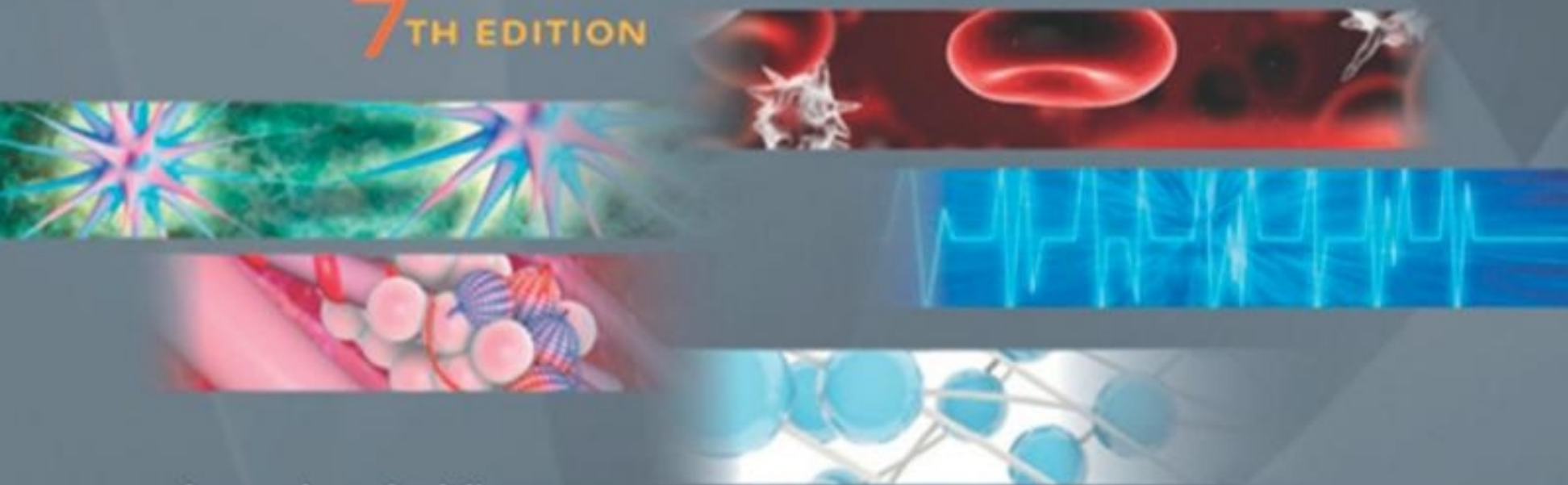


TEXTBOOK OF CRITICAL CARE

7TH EDITION



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TEXTBOOK OF CRITICAL CARE

7th Edition

Textbook of Critical Care, Seventh Edition

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7TH EDITION

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PREFACE

We are pleased to bring you the Seventh Edition of *Textbook of Critical Care*. We've listened to our readers and have retained the acclaimed features that have made this book one of the top sellers in critical care, while also making changes to the organization and content of the book to best reflect the changes in the critical care specialty since the last edition.

Our tables, boxes, algorithms, diagnostic images, and key points, which provide clear and accessible information for quick reference, will continue to be featured prominently throughout the book. The Seventh Edition contains a wealth of new information, including an entirely new section on Common Approaches for Organ Support, Diagnosis, and Monitoring. In addition, we have added new chapters on Extracorporeal Membrane Oxygenation, Biomarkers of Acute Kidney Injury, Antimicrobial Stewardship, Targeted Temperature Management and Therapeutic Hypothermia, Telemedicine in Intensive Care, and many more. Given the increased use of bedside ultrasonography, a new chapter addressing best practices with this now ubiquitous tool has been added. All chapters throughout the book have been revised to reflect new knowledge in the field and, thus, changes in the practice of critical care medicine.

Textbook of Critical Care has evolved with critical care practice over the years and is now known as the reference that successfully bridges

the gap between medical and surgical intensive care practice. Unlike many critical care references, *Textbook of Critical Care* includes pediatric topics, providing a comprehensive resource for our readers who see a broad range of patients. We continue to focus on the multidisciplinary approach to the care of critically ill patients and include contributors trained in anesthesia, surgery, pulmonary medicine, and pediatrics.

The companion online book is more interactive than ever, with 29 procedural videos and 24 e-only procedural chapters, a powerful search engine, hyperlinked references, and downloadable images. The website is mobile optimized for your convenience on all portable devices. Access to the online content is included with your book purchase, so please activate your e-book to take advantage of the full scope of information available to you.

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IN MEMORIAM



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This edition of the *Textbook of Critical Care* is dedicated to the late Mitchell P. Fink, MD. Dr. Fink was Professor of Surgery and Vice Chair for Critical Care at the University of California Los Angeles and an international leader and giant in the field of critical care medicine. He was the lead author of the Fifth Edition of this textbook. In the Fifth Edition, Dr. Fink inspired a novel, informative, user-friendly, and exciting approach to

revising the textbook that served as the backbone for the Sixth and this new Seventh Edition, which he also importantly helped to formulate. Mitch was a great friend and colleague to each of us, and he will be dearly missed by us and by the entire field. We are confident that his visionary work on this book will serve, through its users, to improve the care and outcomes of critically ill adults and children worldwide for many years into the future.

To my family and friends and all who can contribute to make a better world

— *Jean-Louis Vincent*

To Norma-May, my true love. To Claire and Erin, who bring me the greatest joy,
and to my mother, Dale Abraham, for her support throughout my life

— *Edward Abraham*

To my father, Ernest E. Moore, who was a family practitioner for 50 years in Butler,
Pennsylvania. He inspired me by his dedication to self-education, humility,
and service to his community

— *Frederick A. Moore*

To my family, friends, colleagues, and staff for their sacrifices, support, and
dedication, and to the late Dr. Peter Safar for inspiring each of us to bring promising
new therapies to the bedside of the critically ill

— *Patrick M. Kochanek*

Patients admitted to the intensive care unit (ICU) with critical illness or injury are at risk for neurologic complications.¹⁻⁵ A sudden or unexpected change in the neurologic condition of a critically ill patient often heralds a complication that may cause direct injury to the central nervous system (CNS). Alternatively, such changes may simply be neurologic manifestations of the underlying critical illness or treatment that necessitated ICU admission (e.g., sepsis). These complications can occur in patients admitted to the ICU without neurologic disease and in those admitted for management of primary CNS problems (e.g., stroke). Neurologic complications can also occur as a result of invasive procedures and therapeutic interventions performed. Commonly, recognition of neurologic complications is delayed or missed entirely because ICU treatments (e.g., intubation, drugs) interfere with the physical examination or confound the clinical picture. In other cases, neurologic complications are not recognized because of a lack of sensitive methods to detect the problem (e.g., delirium). Morbidity and mortality are increased among patients who develop neurologic complications; therefore, the intensivist must be vigilant in evaluating all critically ill patients for changes in neurologic status.

Despite the importance of neurologic complications of critical illness, few studies have specifically assessed their incidence and impact on outcome among ICU patients. Available data are limited to medical ICU patients; data regarding neurologic complications in general surgical and other specialty ICU populations must be extracted from other sources. In studies of medical ICU patients, the incidence of neurologic complications is 12.3% to 33%.^{1,2} Patients who develop neurologic complications have increased morbidity, mortality, and ICU length of stay. Sepsis is the most common problem associated with development of neurologic complications (sepsis-associated encephalopathy). In addition to encephalopathy, other common neurologic complications associated with critical illness include seizures and stroke. As the complexity of ICU care has increased, so has the risk of neurologic complications. Neuromuscular disorders are now recognized as a major source of morbidity in severely ill patients.⁶ Recognized neurologic complications occurring in selected medical, surgical, and neurologic ICU populations are shown in Table 1-1.⁷⁻⁴¹

■ IMPAIRMENT IN CONSCIOUSNESS

Global changes in CNS function, best described in terms of impairment in consciousness, are generally referred to as *encephalopathy* or *altered mental status*. An acute change in the level of consciousness, undoubtedly, is the most common neurologic complication that occurs after ICU admission. *Consciousness* is defined as a state of awareness (arousal or wakefulness) and the ability to respond appropriately to changes in environment.⁴² For consciousness to be impaired, global hemispheric dysfunction or dysfunction of the brainstem reticular activating system must be present.⁴³ Altered consciousness may result in a sleeplike state (coma) or a state characterized by confusion and agitation (delirium). States of acutely altered consciousness seen in the critically ill are listed in Table 1-2.

When an acute change in consciousness is noted, the patient should be evaluated, keeping in mind the patient's age, presence or absence of coexisting organ system dysfunction, metabolic status and medication list, and presence or absence of infection. In patients with a primary CNS disorder, deterioration in the level of consciousness (e.g., from

stupor to coma) frequently represents the development of brain edema, increasing intracranial pressure, new or worsening intracranial hemorrhage, hydrocephalus, CNS infection, or cerebral vasospasm. In patients without a primary CNS diagnosis, an acute change in consciousness is often due to the development of infectious complications (i.e., sepsis-associated encephalopathy), drug toxicities, or the development or exacerbation of organ system failure. Nonconvulsive status epilepticus is increasingly being recognized as a cause of impaired consciousness in critically ill patients (Box 1-1).⁴⁴⁻⁵³

States of altered consciousness manifesting as impairment in wakefulness or arousal (i.e., coma and stupor) and their causes are well defined.^{42,43,54,55} Much confusion remains, however, regarding the diagnosis and management of delirium, perhaps the most common state of impaired CNS functioning in critically ill patients at large. When dedicated instruments are used, delirium can be diagnosed in more than 80% of critically ill patients, making this condition the most common neurologic complication of critical illness.⁵⁶⁻⁵⁸ Much of the difficulty in establishing the diagnosis of delirium stems from the belief that delirium is a state characterized mainly by confusion and agitation and that such states are expected consequences of the unique environmental factors and sleep deprivation that characterize the ICU experience. Terms previously used to describe delirium in critically ill patients include *ICU psychosis*, *acute confusional state*, *encephalopathy*, and *postoperative psychosis*. It is now recognized that *ICU psychosis* is a misnomer; *delirium* is a more accurate term.⁵⁹

Currently accepted criteria for the diagnosis of delirium include abrupt onset of impaired consciousness, disturbed cognitive function, fluctuating course, and presence of a medical condition that could impair brain function.⁶⁰ Subtypes of delirium include hyperactive (agitated) delirium and the more common hypoactive or quiet delirium.⁵⁸ Impaired consciousness may be apparent as a reduction in awareness, psychomotor retardation, agitation, or impairment in attention (increased distractibility or vigilance). Cognitive impairment can include disorientation, impaired memory, and perceptual aberrations (hallucinations or illusions).⁶¹ Autonomic hyperactivity and sleep disturbances may be features of delirium in some patients (e.g., those with drug withdrawal syndromes, delirium tremens). Delirium in critically ill patients is associated with increased morbidity, mortality, and ICU length of stay.⁶²⁻⁶⁴ In general, sepsis and medications should be the primary etiologic considerations in critically ill patients who develop delirium.

As has been noted, nonconvulsive status epilepticus is increasingly recognized as an important cause of impaired consciousness in critically ill patients. Although the general term can encompass other entities, such as absence and partial complex seizures, in critically ill patients, *nonconvulsive status epilepticus* is often referred to as *status epilepticus of epileptic encephalopathy*.⁵³ It is characterized by alteration in consciousness or behavior associated with electroencephalographic evidence of continuous or periodic epileptiform activity without overt motor manifestations of seizures. In a study of comatose patients without overt seizure activity, nonconvulsive status epilepticus was evident in 8% of subjects.⁵¹ Nonconvulsive status epilepticus can precede or follow an episode of generalized convulsive status epilepticus; it can also occur in patients with traumatic brain injury, subarachnoid hemorrhage, global brain ischemia or anoxia, sepsis, and multiple organ failure. Despite the general consensus that nonconvulsive status

TABLE 1-1 Neurologic Complications in Selected Specialty Populations

| | |
|---|---|
| MEDICAL | |
| Bone marrow transplantation ^{7,8} | CNS infection, stroke, subdural hematoma, brainstem ischemia, hyperammonemia, Wernicke encephalopathy |
| Cancer ⁹ | Stroke, intracranial hemorrhage, CNS infection |
| Fulminant hepatic failure ¹⁰ | Encephalopathy, coma, brain edema, increased ICP |
| HIV/AIDS ^{11,12} | Opportunistic CNS infection, stroke, vasculitis, delirium, seizures, progressive multifocal leukoencephalopathy |
| Pregnancy ^{13,14} | Seizures, ischemic stroke, cerebral vasospasm, intracranial hemorrhage, cerebral venous thrombosis, hypertensive encephalopathy, pituitary apoplexy |
| SURGICAL | |
| Cardiac surgery ¹⁵⁻¹⁹ | Stroke, delirium, brachial plexus injury, phrenic nerve injury |
| Vascular surgery ^{20,21} | |
| Carotid | Stroke, cranial nerve injuries (recurrent laryngeal, glossopharyngeal, hypoglossal, facial), seizures |
| Aortic | Stroke, paraplegia |
| Peripheral | Delirium |
| Transplantation ^{10,22-25} | |
| Heart | Stroke |
| Liver | Encephalopathy, seizures, opportunistic CNS infection, intracranial hemorrhage, Guillain-Barré syndrome, central pontine myelinolysis |
| Renal | Stroke, opportunistic CNS infection, femoral neuropathy |
| Urologic surgery (TURP) ²⁶ | Seizures and coma (hyponatremia) |
| Otolaryngologic surgery ^{27,28} | Recurrent laryngeal nerve injury, stroke, delirium |
| Orthopedic surgery ²⁹ | |
| Spine | Myelopathy, radiculopathy, epidural abscess, meningitis |
| Knee and hip replacement | Delirium (fat embolism) |
| Long-bone fracture/nailing | Delirium (fat embolism) |
| NEUROLOGIC | |
| Stroke ³⁰⁻³⁴ | Stroke progression or extension, reocclusion after thrombolysis, bleeding, seizures, delirium, brain edema, herniation |
| Intracranial surgery ³⁵ | Bleeding, edema, seizures, CNS infection |
| Subarachnoid hemorrhage ^{32,36-38} | Rebleeding, vasospasm, hydrocephalus, seizures |
| Traumatic brain injury ^{32,39,40} | Intracranial hypertension, bleeding, seizures, stroke (cerebrovascular injury), CNS infection |
| Cervical spinal cord injury ⁴¹ | Ascension of injury, stroke (vertebral artery injury) |

CNS, central nervous system; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; ICP, intracranial pressure; TURP, transurethral prostatic resection.

TABLE 1-2 States of Acutely Altered Consciousness

| STATE | DESCRIPTION |
|-----------|--|
| Coma | Closed eyes, sleeplike state with no response to external stimuli (pain) |
| Stupor | Responsive only to vigorous or painful stimuli |
| Lethargy | Drowsy, arouses easily and appropriately to stimuli |
| Delirium | Acute state of confusion with or without behavioral disturbance |
| Catatonia | Eyes open, unblinking, unresponsive |

epilepticus is a unique entity responsible for impaired consciousness in some critically ill patients, there is no general consensus on the electroencephalographic criteria for its diagnosis or the optimal approach to treatment.⁶⁵

STROKE AND OTHER FOCAL NEUROLOGIC DEFICITS

The new onset of a major neurologic deficit that manifests as a focal impairment in motor or sensory function (e.g., hemiparesis) or one that results in seizures usually indicates a primary problem referable to the cerebrovascular circulation. In a study evaluating the value of computed tomography (CT) in medical ICU patients, ischemic stroke and intracranial bleeding were the most common abnormalities associated with the new onset of a neurologic deficit or seizures.⁶⁶ Overall, the frequency of new-onset stroke is between 1% and 4% in medical ICU patients.^{1,2} Among general surgical patients, the frequency of

perioperative stroke ranges from 0.3% to 3.5%.⁶⁷ Patients undergoing cardiac or vascular surgery and surgical patients with underlying cerebrovascular disease can be expected to have an increased risk of perioperative stroke.¹⁹

The frequency of new or worsening focal neurologic deficits in patients admitted with a primary neurologic or neurosurgical disorder varies. For example, as many as 30% of patients with aneurysmal subarachnoid hemorrhage develop delayed ischemic neurologic deficits.³⁶ Patients admitted with stroke often develop worsening or new symptoms as a result of stroke progression, bleeding, or reocclusion of vessels previously opened with interventional therapy. In patients who have undergone elective intracranial surgery, postsurgical bleeding or infectious complications are the main causes of new focal deficits. In trauma patients, unrecognized injuries to the cerebrovascular circulation can cause new deficits. Patients who have sustained spinal cord injuries, and those who have undergone surgery of the spine or of the thoracic or abdominal aorta, can develop worsening or new symptoms of spinal cord injury. Early deterioration of CNS function after spinal cord injury usually occurs as a consequence of medical interventions to stabilize the spine, whereas late deterioration is usually due to hypotension and impaired cord perfusion. Occasionally, focal weakness or sensory symptoms in the extremities occur as a result of occult brachial plexus injury or compression neuropathy. New cranial nerve deficits in patients without primary neurologic problems can occur after neck surgery or carotid endarterectomy.

SEIZURES

The new onset of motor seizures occurs in 0.8% to 4% of critically ill medical ICU patients.^{1,2,68} New-onset seizures in general medical-surgical ICU patients is typically caused by narcotic withdrawal, hyponatremia, drug toxicities, or previously unrecognized structural abnormalities.^{3,68} New stroke, intracranial bleeding, and CNS infection

BOX 1-1**General Causes of Acutely Impaired Consciousness in the Critically Ill****INFECTION**

Sepsis encephalopathy
CNS infection

DRUGS

Narcotics
Benzodiazepines
Anticholinergics
Anticonvulsants
Tricyclic antidepressants
Selective serotonin uptake inhibitors
Phenothiazines
Steroids
Immunosuppressants (cyclosporine, FK506, OKT3)
Anesthetics

ELECTROLYTE AND ACID-BASE DISTURBANCES

Hyponatremia
Hypernatremia
Hypercalcemia
Hypermagnesemia
Severe acidemia and alkalemia

ORGAN SYSTEM FAILURE

Shock
Renal failure
Hepatic failure
Pancreatitis
Respiratory failure (hypoxia, hypercapnia)

ENDOCRINE DISORDERS

Hypoglycemia
Hyperglycemia
Hypothyroidism
Hyperthyroidism
Pituitary apoplexy

DRUG WITHDRAWAL

Alcohol
Opiates
Barbiturates
Benzodiazepines

VASCULAR CAUSES

Shock
Hypotension
Hypertensive encephalopathy
CNS vasculitis
Cerebral venous sinus thrombosis

CNS DISORDERS

Hemorrhage
Stroke
Brain edema
Hydrocephalus
Increased intracranial pressure
Meningitis
Ventriculitis
Brain abscess
Subdural empyema
Seizures
Vasculitis

SEIZURES

Convulsive and nonconvulsive status epilepticus

MISCELLANEOUS

Fat embolism syndrome
Neuroleptic malignant syndrome
Thiamine deficiency (Wernicke encephalopathy)
Psychogenic unresponsiveness

CNS, central nervous system.

are other potential causes of seizures after ICU admission. The frequency of seizures is higher in patients admitted to the ICU with a primary neurologic problem such as traumatic brain injury, aneurysmal subarachnoid hemorrhage, stroke, or CNS infection.⁶⁹ Because nonconvulsive status epilepticus may be more common than was previously appreciated, this problem should also be considered in the differential diagnosis of patients developing new, unexplained, or prolonged alterations in consciousness.

GENERALIZED WEAKNESS AND NEUROMUSCULAR DISORDERS

Generalized muscle weakness often becomes apparent in ICU patients as previous impairments in arousal are resolving or sedative and neuromuscular blocking agents are being discontinued or tapered. Polyneuropathy and myopathy associated with critical illness are now well recognized as the principal causes of new-onset generalized weakness among ICU patients being treated for nonneuromuscular disorders.^{5,70-73} These disorders also may be responsible for prolonged ventilator dependency in some patients. Patients at increased risk for these complications include those with sepsis, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome, as well as those who require prolonged mechanical ventilation. Other risk factors include treatment with corticosteroids or neuromuscular blocking agents. In contrast to demyelinating neuropathies (e.g., Guillain-Barré syndrome), critical illness polyneuropathy is primarily an axonal condition. Critical illness polyneuropathy is diagnosed in a high percentage of patients undergoing careful evaluation for weakness acquired while in the ICU. Because primary myopathy coexists in a large number of patients with critical illness polyneuropathy, *ICU-acquired paresis*⁷² or *critical illness neuromuscular abnormalities*⁵ may be better terms to describe this problem. Although acute Guillain-Barré syndrome and myasthenia gravis are rare complications of critical illness, these diagnoses should also be considered in patients who develop generalized weakness in the ICU.

NEUROLOGIC COMPLICATIONS OF PROCEDURES AND TREATMENTS

Routine procedures performed in the ICU or in association with evaluation and treatment of critical illness can result in neurologic complications.⁴ The most obvious neurologic complications are those associated with intracranial bleeding secondary to the treatment of stroke and other disorders with thrombolytic agents or anticoagulants. Other notable complications are listed in Table 1-3.

EVALUATION OF SUDDEN NEUROLOGIC CHANGE

A new or sudden change in the neurologic condition of a critically ill patient necessitates a focused neurologic examination, review of the clinical course and medications administered before the change, a thorough laboratory assessment, and appropriate imaging or neurophysiologic studies when indicated. The type and extent of the evaluation depend on clinical context and the general category of neurologic change occurring. The history and physical examination should lead the clinician to the diagnostic approach best suited to the individual patient.

Essential elements of the neurologic examination include an assessment of the level and content of consciousness, pupillary size and reactivity, and motor function. Additional evaluation of the cranial nerves and peripheral reflexes and a sensory examination are conducted as indicated by the clinical circumstances. If the patient is comatose on initial evaluation, a more detailed coma examination should be performed to help differentiate structural from metabolic causes of coma.^{43,55} When the evaluation reveals only a change in arousal without evidence of a localizing lesion in the CNS, a search for infection, discontinuation or modification of drug therapy, and a

TABLE 1-3 Neurologic Complications Associated with ICU Procedures and Treatments

| PROCEDURE | COMPLICATION |
|------------------------------------|--|
| Angiography | Cerebral cholesterol emboli syndrome |
| Anticoagulants/antiplatelet agents | Intracranial bleeding |
| Arterial catheterization | Cerebral embolism |
| Bronchoscopy | Increased ICP |
| Central venous catheterization | Cerebral air embolism, carotid dissection, Horner's syndrome, phrenic nerve injury, brachial plexus injury, cranial nerve injury |
| DC cardioversion | Embolic stroke, seizures |
| Dialysis | Seizures, increased ICP (dialysis disequilibrium syndrome) |
| Endovascular procedures (CNS) | Vessel rupture, thrombosis, reperfusion bleeding |
| Epidural catheter | Spinal epidural hematoma, epidural abscess |
| ICP monitoring | CNS infection (ventriculitis), hemorrhage |
| Intraaortic balloon pump | Lower extremity paralysis |
| Intubation | Spinal cord injury |
| Left ventricular assist devices | Stroke, seizures |
| Lumbar puncture or drain | Meningitis, herniation |
| Mechanical ventilation | Cerebral air embolism, increased ICP (high PEEP and hypercapnia), seizures (hypocapnia) |
| Nasogastric intubation | Intracranial placement |

CNS, central nervous system; DC, direct current; ICP, intracranial pressure; ICU, intensive care unit; PEEP, positive end-expiratory pressure.

general metabolic evaluation may be indicated. Lumbar puncture to aid the diagnosis of CNS infection may be warranted in selected neurosurgical patients and immunocompromised individuals. Lumbar puncture to rule out nosocomially acquired meningitis in other patients is generally not rewarding.⁷⁴ Electroencephalography should be performed in patients with clear evidence of seizures, as well as

when the diagnosis of nonconvulsive status epilepticus is being entertained. Continuous electroencephalography should be considered when the index of suspicion for nonconvulsive status epilepticus remains high and the initial electroencephalographic studies are unrevealing.

Computed tomography (CT) is indicated for nonneurologic patients with new focal deficits, seizures, or otherwise unexplained impairments in arousal.⁶⁶ In patients with primary neurologic disorders, CT is indicated if worsening brain edema, herniation, bleeding, and hydrocephalus are considerations when new deficits or worsening neurologic status occurs. In some cases, when the basis for a change in neurologic condition remains elusive, magnetic resonance imaging (MRI) may be helpful. In particular, the diffusion-weighted MRI technique can reveal structural abnormalities such as hypoxic brain injury, fat embolism, vasculitis, cerebral venous thrombosis, or multiple infarcts following cardiopulmonary bypass that are not apparent by standard CT or conventional MRI.⁷⁵⁻⁸⁰ MRI may be the imaging modality of choice in patients with human immunodeficiency virus (HIV) and new CNS complications.⁷⁵ For patients who develop signs and symptoms of spinal cord injury complicating critical illness, MRI or somatosensory evoked potentials can be used to further delineate the nature and severity of the injury. For patients who develop generalized muscle weakness or unexplained ventilator dependency, electromyography and nerve conduction studies can confirm the presence of critical illness polyneuropathy or myopathy.

MONITORING FOR NEUROLOGIC CHANGES

The common occurrence of neurologic changes in critically ill patients emphasizes the need for vigilant monitoring. A variety of clinical techniques such as the Glasgow Coma Scale, National Institutes of Health Stroke Scale, Ramsay Sedation Scale, Richmond Agitation-Sedation Scale, and Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) can be used to monitor clinical neurologic status.^{57,58,81-86} Neurophysiologic methods such as the bispectral index may provide more objective neurologic monitoring in the future for patients admitted to the ICU with and without primary neurologic problems.⁸⁷⁻⁸⁹ For patients admitted to the ICU with a primary neurologic disorder, a variety of monitoring techniques including measurements of intracranial pressure, near-infrared spectroscopy, brain tissue PO_2 , transcranial Doppler, and electroencephalography are available.⁹⁰

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Agitation and delirium are commonly encountered in the intensive care unit (ICU). They are more than just an inconvenience; these conditions can have deleterious effects on patient and staff safety and contribute to poor outcomes. It is therefore important for clinicians to be able to recognize agitation and delirium and to have an organized approach for its evaluation and management.

■ AGITATION

Agitation is a psychomotor disturbance characterized by excessive motor activity associated with a feeling of inner tension.^{1,3} The activity is usually nonproductive and repetitious, consisting of behaviors such as pacing, fidgeting, wringing of hands, pulling of clothes, and an inability to sit still. Careful observation of the patient may reveal the underlying intent. In the ICU, agitation is frequently related to anxiety or delirium. Agitation may be caused by various factors: metabolic disorders (hypo- and hypernatremia), hyperthermia, hypoxia, hypotension, use of sedative drugs and/or analgesics, sepsis, alcohol withdrawal, and long-term psychoactive drug use to name a few.^{4,5} It can also be caused by external factors such as noise, discomfort, and pain.⁶ Associated with a longer length of stay in the ICU and higher costs,⁴ agitation can be mild, characterized by increased movements and an apparent inability to get comfortable, or it can be severe. Severe agitation can be life threatening, leading to higher rates of self-extubation, self-removal of catheters and medical devices, nosocomial infections,⁴ hypoxia, barotrauma, and/or hypotension due to patient/ventilator asynchrony. Indeed, recent studies have shown that agitation contributes to ventilator asynchrony, increased oxygen consumption, and increased production of CO₂ and lactic acid; these effects can lead to life-threatening respiratory and metabolic acidosis.⁵

■ DELIRIUM

Delirium can be defined as follows: (1) A disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention. (2) A change in cognition (e.g., memory deficit, disorientation, language disturbance) or development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia. (3) The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day. (4) There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use, or more than one cause (Fig. 2-1).³ Delirium is commonly underdiagnosed in the ICU and has a reported prevalence of 20% to 80%, depending on the severity of illness and the need for mechanical ventilation.⁷⁻¹⁰ Recent investigations have shown that the presence of delirium is a strong predictor of longer hospital stay, higher costs, and increased risk of death.¹¹⁻¹³ Each additional day with delirium increases a patient's risk of dying by 10%.¹⁴ Longer periods of delirium are also associated with greater degrees of cognitive decline when patients are evaluated after one year.¹³ Thus, delirium can adversely affect the quality of life in survivors of critical illnesses and may serve as an intermediate recognizable step for targeting therapies to prevent poor outcomes in survivors of critical illness.^{13,15}

Unfortunately, the true prevalence and magnitude of delirium have been poorly documented because myriad terms including *acute confusional state*, *ICU psychosis*, *acute brain dysfunction*, and *encephalopathy*,

have been used to describe this condition.¹⁶ Delirium can be classified according to psychomotor behavior into hypoactive delirium, hyperactive delirium, or a mixed subtype. Hypoactive delirium, which is the most prevalent form of delirium, is characterized by decreased physical and mental activity and inattention. In contrast, hyperactive delirium is characterized by combativeness and agitation. Patients with both features have mixed delirium.¹⁷⁻¹⁹ Hyperactive delirium puts both patients and caregivers at risk of serious injury but fortunately only occurs in a minority of critically ill patients.¹⁷⁻¹⁹ Hypoactive delirium might actually be associated with a worse prognosis.^{20,21} The Delirium Motor Subtype Scale may assist in making this diagnosis.²²

Although healthcare professionals realize the importance of recognizing delirium, it frequently goes unrecognized in the ICU.²³⁻³⁰ Even when ICU delirium is recognized, most clinicians consider it an expected event that is often iatrogenic and without consequence.²³ However, it needs to be viewed as a form of organic brain dysfunction that has consequences if left undiagnosed and untreated.

Risk Factors for Delirium

The risk factors for agitation and delirium are many and overlap to a large extent (Table 2-1). Fortunately there are several mnemonics that can aid clinicians in recalling the list; two common ones are IWATCH-DEATH and DELIRIUM (Table 2-2). In practical terms, risk factors can be divided into three categories: the acute illness itself, patient factors, and iatrogenic or environmental factors. Importantly, a number of medications that are commonly used in the ICU are associated with the development of agitation and delirium (Box 2-1). A thorough approach to the treatment and support of the acute illness (e.g., controlling sources of sepsis and giving appropriate antibiotics; correcting hypoxia, metabolic disturbances, dehydration, and hyperthermia; normalizing sleep/wake cycles), as well as minimizing iatrogenic factors (e.g., excessive sedation), can reduce the incidence and/or severity of delirium and its attendant complications. A retrospective study conducted on postoperative delirium, specifically in patients undergoing cardiopulmonary bypass, has alluded to a decreased incidence of delirium in patients pre-treated with statins.³¹ Furthermore, ICU statins have been associated with decreased delirium, most significantly in the early stages of sepsis; in contrast to this, discontinuation of statins has been shown to be associated with increased delirium.^{32,33}

■ PATHOPHYSIOLOGY

The pathophysiology of delirium is poorly understood, although there are a number of hypotheses:

- **Neurotransmitter imbalance.** Multiple neurotransmitters have been implicated, including dopamine (excess), acetylcholine (relative depletion), γ -aminobutyric acid (GABA), serotonin, endorphins, norepinephrine, and glutamate.³⁴⁻³⁷
- **Inflammatory mediators.** Inflammatory mediators, such as tumor necrosis factor alpha (TNF- α), interleukin-1 (IL-1), and other cytokines and chemokines, have been implicated in the pathogenesis of endothelial damage, thrombin formation, and microvascular dysfunction in the central nervous system (CNS), contributing to delirium.³⁷ Recently, a study in the ICU has strengthened the evidence of a role for endothelial dysfunction in increasing the duration of delirium.³⁸

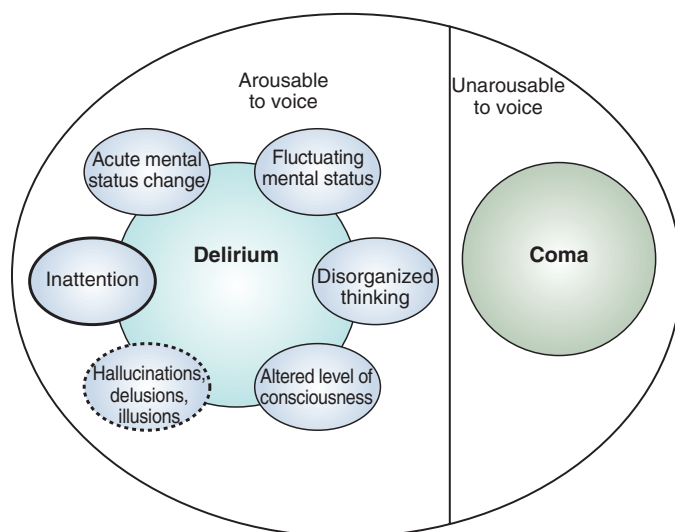


FIGURE 2-1 ■ Acute brain dysfunction. Patients who are unresponsive to voice are considered to be in a coma. Patients who respond to voice can be further evaluated for delirium using validated delirium monitoring instruments. Inattention is a cardinal feature of delirium. Other pivotal features include a change in mental status that fluctuates over hours to days, disorganized thinking, and altered levels of consciousness. While hallucinations, delusions, and illusions may be part of the perceptual disturbances seen in delirium, they on their own are not synonymous with delirium, a diagnosis of which requires the presence of inattention and other pivotal features outlined above. (With permission from E. Wesley Ely and A. Morandi) (www.icudelirium.org).

TABLE 2-1 Risk Factors for Agitation and Delirium

| | |
|--|---------------------------------------|
| Age >70 years | BUN/creatinine ratio ≥ 18 |
| Transfer from a nursing home | Renal failure, creatinine > 2.0 mg/dL |
| History of depression | Liver disease |
| History of dementia, stroke, or epilepsy | CHF |
| Alcohol abuse within past month | Cardiogenic or septic shock |
| Tobacco use | Myocardial infarction |
| Drug overdose or illicit drug use | Infection |
| HIV infection | CNS pathology |
| Psychoactive medications | Urinary retention or fecal impaction |
| Hypo- or hypernatremia | Tube feeding |
| Hypo- or hyperglycemia | Rectal or bladder catheters |
| Hypo- or hyperthyroidism | Physical restraints |
| Hypothermia or fever | Central line catheters |
| Hypertension | Malnutrition or vitamin deficiencies |
| Hypoxia | Procedural complications |
| Acidosis or alkalosis | Visual or hearing impairment |
| Pain | Sleep disruption |
| Fear and anxiety | |

BUN, blood urea nitrogen; CHF, congestive heart failure; CNS, central nervous system; HIV, human immunodeficiency virus.

- **Impaired oxidative metabolism.** According to this hypothesis, delirium is a result of cerebral insufficiency secondary to a global failure in oxidative metabolism.³⁹
- **Large neutral amino acids.** Increased cerebral uptake of tryptophan and tyrosine can lead to elevated levels of serotonin,

TABLE 2-2 Mnemonic for Risk Factors for Delirium and Agitation

IWATCHDEATH

Infection
Withdrawal
Acute metabolic
Trauma/pain
Central nervous system pathology
Hypoxia
Deficiencies (vitamin B₁₂, thiamine)
Endocrinopathies (thyroid, adrenal)
Acute vascular (hypertension, shock)
Toxins/drugs
Heavy metals

DELIRIUM

Drugs
Electrolyte and physiologic abnormalities
Lack of drugs (withdrawal)
Infection
Reduced sensory input (blindness, deafness)
Intracranial problems (CVA, meningitis, seizure)
Urinary retention and fecal impaction
Myocardial problems (MI, arrhythmia, CHF)

CHF, congestive heart failure; CVA, cerebrovascular accident; MI, myocardial infarction.

BOX 2-1

Commonly Used Drugs Associated With Delirium and Agitation

Benzodiazepines
Opiates (especially meperidine)
Anticholinergics
Antihistamines
H₂ blockers
Antibiotics
Corticosteroids
Metoclopramide

dopamine, and norepinephrine in the CNS. Altered availability of these amino acids is associated with increased risk of development of delirium.⁴⁰

ASSESSMENT

Recently, the Society of Critical Care Medicine (SCCM) published guidelines for the use of sedatives and analgesics in the ICU.⁴¹ The SCCM has recommended the routine monitoring of pain, anxiety, and delirium and the documentation of responses to therapy for these conditions.⁴²

There are many scales available for the assessment of agitation and sedation, including the Ramsay Scale,⁴³ the Riker Sedation-Agitation Scale (SAS),⁴⁴ the Motor Activity Assessment Scale (MAAS),⁴⁵ the Richmond Agitation-Sedation Scale (RASS),⁴⁶ the Adaptation to Intensive Care Environment (ATICE)⁴⁷ scale, and the Minnesota Sedation Assessment Tool (MSAT).⁴⁷ Most of these scales have good reliability and validity among adult ICU patients and can be used to set targets for goal-directed sedative administration. The SAS, which scores agitation and sedation using a 7-point system, has excellent inter-rater reliability (kappa = 0.92) and is highly correlated ($r^2 = 0.83$ to 0.86) with other scales. The RASS (Table 2-3), however, is the only method shown to detect variations in the level of consciousness over time or in response to changes in sedative and analgesic drug use.⁴⁸ The 10-point RASS scale has discrete criteria to distinguish levels of agitation and sedation. The evaluation of patients consists of a 3-step process. First, the patient is observed to determine whether he or she is alert, restless, or agitated (0 to +4). Second, if the patient is not alert and does not show positive motoric characteristics, the patient's name is called and his or her sedation level scored based on the duration of eye contact (−1 to −3). Third, if there is no eye opening on verbal

TABLE 2-3 Richmond Agitation-Sedation Scale

| | | |
|----|-------------------|--|
| +4 | Combative | Combative, violent, immediate danger to staff |
| +3 | Very agitated | Pulls or removes tube(s) or catheter(s); aggressive |
| +2 | Agitated | Frequent nonpurposeful movement; fights ventilator |
| +1 | Restless | Anxious, apprehensive, but movements not aggressive or vigorous |
| 0 | Alert and calm | |
| −1 | Drowsy | Not fully alert but has sustained (>10 sec) awakening (eye opening/contact) to voice |
| −2 | Light sedation | Drowsy; briefly (<10 sec) awakens to voice or physical stimulation |
| −3 | Moderate sedation | Movement or eye opening (but no eye contact) to voice |
| −4 | Deep sedation | No response to voice, but movement or eye opening to physical stimulation |
| −5 | Unarousable | No response to voice or physical stimulation |

PROCEDURE FOR ASSESSMENT

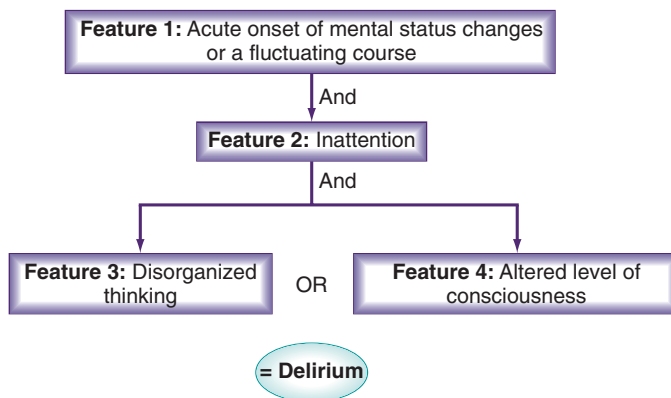
1. Observe patient. Is patient alert, restless, or agitated? (Score 0 to +4)
2. If not alert, state patient's name and tell him or her to open eyes and look at speaker. Patient awakens, with sustained eye opening and eye contact. (Score −1)
3. Patient awakens, with eye opening and eye contact, but not sustained. (Score −2)
4. Patient does not awaken (no eye contact) but has eye opening or movement in response to voice. (Score −3)
3. Physically stimulate patient by shaking shoulder and/or rubbing sternum. No response to voice, but response (movement) to physical stimulation. (Score −4)
4. No response to voice or physical stimulation (Score −5)

From Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166(10):1338-1344.

stimulation, the patient's shoulder is shaken or pressure applied over the sternum by rubbing, and the response noted (−4 or −5). This assessment takes less than 20 seconds in total and correlates well with other measures of sedation (e.g., Glasgow Coma Scale [GCS], bispectral electroencephalography, and neuropsychiatric ratings).⁴⁶

Until recently, there was no valid and reliable way to assess delirium in critically ill patients, many of whom are nonverbal owing to sedation or mechanical ventilation.^{51,58} A number of tools have been developed to aid in the detection of delirium in the ICU. These tools have been validated for use in both intubated and nonintubated patients and measured against a "gold standard," the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria. The tools are the Confusion Assessment Method for the ICU (CAM-ICU)⁵¹⁻⁵⁵ and the Intensive Care Delirium Screening Checklist (ICDSC).⁸

The CAM-ICU (Fig. 2-2) is a delirium measurement tool developed by a team of specialists in critical care, psychiatry, neurology, and geriatrics.^{51,58} Administered by a nurse, the evaluation takes only 1 to 2 minutes to conduct and is 98% accurate in detecting delirium as compared with a full DSM-V assessment by a geriatric psychiatrist.^{51,52}

**FIGURE 2-2** ■ Confusion Assessment Method in the Intensive Care Unit (CAM-ICU).**TABLE 2-4 Intensive Care Delirium Screening Checklist****PATIENT EVALUATION**

| Altered level of consciousness | (A–E)* |
|--------------------------------------|--|
| Inattention | Difficulty in following a conversation or instructions. Easily distracted by external stimuli. Difficulty in shifting focus. Any of these scores 1 point. |
| Disorientation | Any obvious mistake in time, place, or person scores 1 point. |
| Hallucinations-delusions-psychosis | The unequivocal clinical manifestation of hallucination or behavior probably attributable to hallucination or delusion. Gross impairment in reality testing. Any of these scores 1 point. |
| Psychomotor agitation or retardation | Hyperactivity requiring the use of additional sedative drugs or restraints to control potential danger to self or others. Hypoactivity or clinically noticeable psychomotor slowing. |
| Inappropriate speech or mood | Inappropriate, disorganized, or incoherent speech. Inappropriate display of emotion related to events or situation. Any of these scores 1 point. |
| Sleep/wake cycle disturbance | Sleeping less than 4 h or waking frequently at night (do not consider wakefulness initiated by medical staff or loud environment). Sleeping during most of the day. Any of these scores 1 point. |
| Symptom fluctuation | Fluctuation of the manifestation of any item or symptom over 24 h scores 1 point. |

Total Score (0-8)

*Level of consciousness:

A—No response: score 0.

B—Response to intense and repeated stimulation (loud voice and pain): score 0.

C—Response to mild or moderate stimulation: score 1.

D—Normal wakefulness: score 0.

E—Exaggerated response to normal stimulation: score 1.

Available at: <http://www.acgme.org/acgme/web/tabid/445/GraduateMedicalEducation/SingleAccreditationSystemforAOA-ApprovedPrograms.aspx>. Accessed November 12.

To perform the CAM-ICU, patients are first evaluated for level of consciousness; patients who respond to verbal commands (a RASS score of −3 or higher level of arousal) can then be assessed for delirium. The CAM-ICU comprises four features: (1) a change in mental status from baseline or a fluctuation in mental status, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. Delirium is diagnosed if patients have features 1 and 2, and either feature 3 or 4 is positive (see Fig. 2-2).

The ICDSC⁸ (Table 2-4) is a checklist-based assessment tool that evaluates inattention, disorientation, hallucination, delusion or

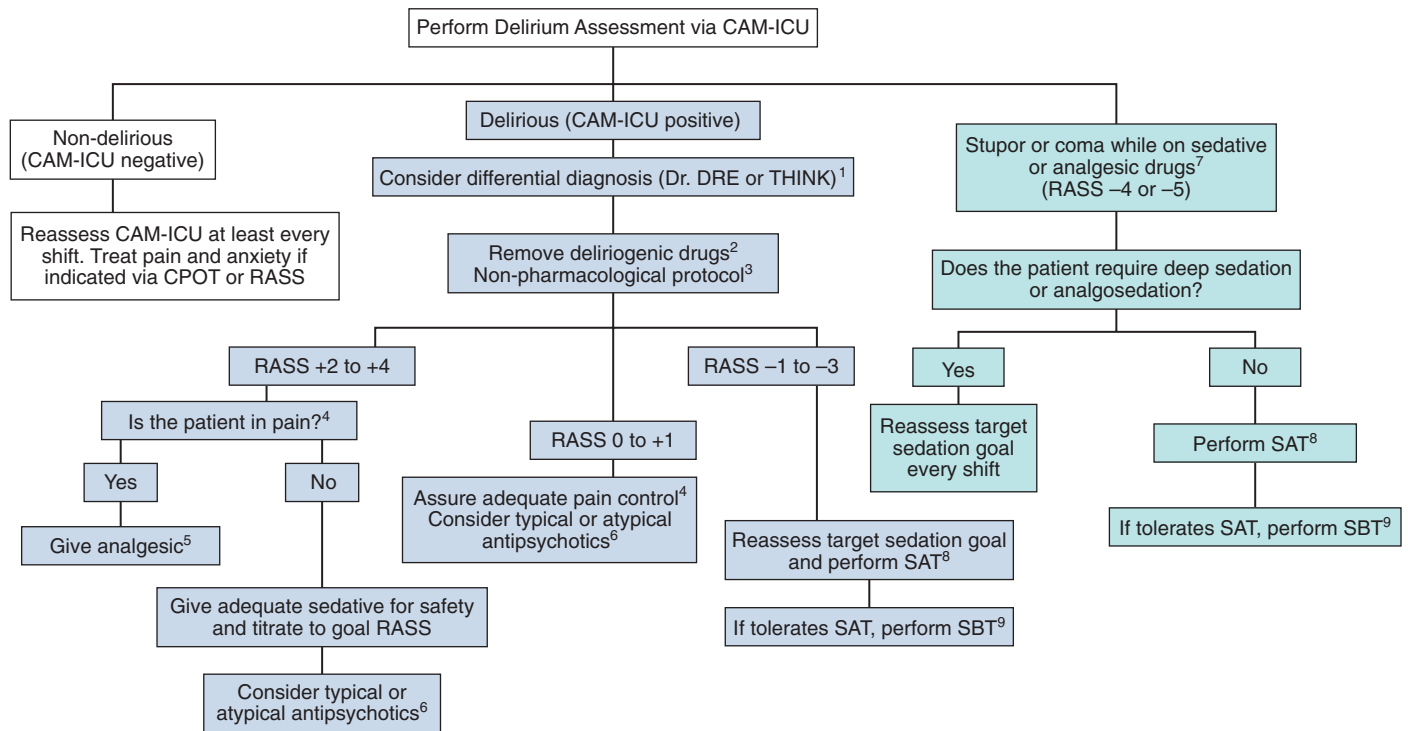
psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbances, and fluctuations in these symptoms. Each of the eight items is scored as absent or present (0 or 1), respectively, and summed. A score of 4 or above indicates delirium, while 0 indicates no delirium. Patients with scores between 1 and 3 are considered to have subsyndromal delirium,⁵⁹ which has worse prognostic implications than the absence of delirium but a better prognosis than clearly present delirium.

Recent studies have called into question the usefulness of delirium evaluations for patients under sedation.^{60,61} A small subset of patients (approximately 10%) were noted to have rapidly reversible sedation-related delirium, but unfortunately in this study the majority of patients

continued to have persistent delirium even after interruption of sedation. Thus, when feasible, delirium evaluation should be performed after interruption of sedation; however delirium evaluations should not be forgone just because a patient is under sedation since the omission of the diagnosis would be far worse than overdiagnosing delirium in a handful of patients.

MANAGEMENT

The development of effective evidence-based strategies and protocols for prevention and treatment of delirium awaits data from ongoing randomized clinical trials of both nonpharmacologic and



1. Dr. DRE:
Diseases: Sepsis, CHF, COPD
Drug Removal: SATs and stopping benzodiazepines/narcotics
Environment: Immobilization, sleep and day/night orientation, hearing aids, eye glasses, noise
THINK:
Toxic Situations – CHF, shock, dehydration – Deliriogenic meds (tight titration) – New organ failure (liver, kidney, etc.)
Hypoxemia
Infection/sepsis (nosocomial), immobilization
Nonpharmacological interventions³
K⁺ or Electrolyte problems
2. Consider stopping or substituting deliriogenic medications such as benzodiazepines, anticholinergic medications (metoclopramide, H2 blockers, promethazine, diphenhydramine), steroids, etc.
3. See non-pharmacological protocol – see below.
4. If patient is non-verbal assess via CPOT, or if patient is verbal assess via visual analog scale.
5. Analgesia – Adequate pain control may decrease delirium. Consider opiates, non-steroidals, acetaminophen, or gabapentin (neuropathic pain).
6. Typical or atypical antipsychotics. Discontinue if high fever, QTc prolongation, or drug-induced rigidity.
7. Consider non-benzodiazepine sedation strategies (propofol or dexmedetomidine)
8. Spontaneous Awakening Trial (SAT) – If meets safety criteria (no active seizures, no alcohol withdrawal, no agitation, no paralytics, no myocardial ischemia, normal intracranial pressure, $\text{FiO}_2 \leq 70\%$)
9. Spontaneous Breathing Trial (SBT) – If meets safety criteria (no agitation, no myocardial ischemia, $\text{FiO}_2 \leq 50\%$, adequate inspiratory efforts, O_2 saturation $\geq 88\%$, no vasopressor use, PEEP ≤ 7.5 cm)

Non-pharmacological protocol³

Orientation

Provide visual and hearing aids
Encourage communication and reorient patient repetitively. Have familiar objects from patient's home in the room
Attempt consistency in nursing staff
Family engagement and empowerment

Environment

Sleep hygiene: Lights off at night, on during day.
Control excess noise (staff, equipment), earplugs
Early mobilization and exercise
Music

Clinical parameters

Maintain systolic blood pressure > 90 mm Hg
Maintain oxygen saturations $> 90\%$
Treat underlying metabolic derangements and infections

FIGURE 2-3 ■ Delirium Protocol as a part of ABCDEF Bundle.

pharmacologic strategies. Refer to Chapter 51 for a detailed description of management strategies of delirium, including an empiric sedation and delirium protocol. A brief overview is provided here.

When agitation or delirium develops in a previously comfortable patient, a search for the underlying cause should be undertaken before attempting pharmacologic intervention. A rapid assessment should be performed, including assessment of vital signs and physical examination to rule out life-threatening problems (e.g., hypoxia, self-extubation, pneumothorax, hypotension), or other acutely reversible physiologic causes (e.g., hypoglycemia, metabolic acidosis, stroke, seizure, pain). The previously mentioned IWATCHDEATH and DELIRIUM mnemonics can be particularly helpful in guiding this initial evaluation.

Once life-threatening causes are ruled out as possible etiologies, aspects of good patient care such as reorienting patients, improving sleep and hygiene, providing visual and hearing aids if previously used, removing medications that can provoke delirium, and decreasing the use of invasive devices if not required (e.g., bladder catheters, restraints), should be undertaken.

The use of ABCDEs (Awakening and Breathing Trials, Choice of appropriate sedation, Delirium monitoring and management, and Early mobility and Exercise) has been shown to decrease the incidence of delirium and improve patient outcome (Fig. 2-3). This algorithm based on the PAD 2013 guidelines⁴¹ involves the following: (1) Routine *assessment* of agitation, depth and quality of sedation and delirium using appropriate scales (RASS and SAS for agitation and sedation and CAM-ICU or ICDSC for delirium). They recommend using protocol target-based sedation and targeting the lightest possible sedation, thus exposing the patient to lower cumulative doses of sedatives⁶² and/or daily awakening trials⁶³ and spontaneous breathing trials⁶⁴ to reduce the total time spent on mechanical ventilation. Coordination of daily awakening and daily breathing was associated with shorter durations of mechanical ventilation, reduction in length of hospital stay, and no long-term neuropsychologic consequences of waking patients during critical illness.^{65,66} (2) *Treatment* should start with treating analgesia first. Choosing the right sedative regimen in critically ill patients is important. Numerous studies have confirmed that benzodiazepines are associated with poor clinical outcomes.^{67,68,69} The guidelines also recommend avoiding rivastigmine and antipsychotics if there is an increased risk of Torsades de Pointes. (3) *Prevention* also plays an important role. Exercise and early mobility in ICU patients is associated with decreased length of both ICU and hospital polypharmacy.^{70,71} Risk factors for delirium need to be identified and eliminated. Promoting sleep and restarting baseline antipsychotic medications are also important. Data from the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS)⁶⁷ study and the Safety and Efficacy of Dexmedetomidine Compared to Midazolam (SEDCOM) trial⁶⁹ also support the view

that dexmedetomidine can decrease the duration and prevalence of delirium when compared to lorazepam or midazolam. Pharmacologic therapy should be attempted only after correcting any contributing factors or underlying physiologic abnormalities. Although these agents are intended to improve cognition, they all have psychoactive effects that can further cloud the sensorium and promote a longer overall duration of cognitive impairment. Patients who manifest delirium should be treated with traditional antipsychotic medication. Newer “atypical” antipsychotic agents (e.g., risperidone, ziprasidone, quetiapine, olanzapine) may decrease the duration of delirium.⁷⁶

Benzodiazepines are not recommended for the management of delirium because they can paradoxically exacerbate delirium. These drugs can also promote oversedation and respiratory suppression. However, they remain the drugs of choice for the treatment of delirium tremens (and other withdrawal syndromes), and seizures.

At times, mechanical restraints may be needed to ensure the safety of patients and staff while waiting for medications to take effect. It is important to keep in mind, however, that restraints can increase agitation and delirium, and their use may have adverse consequences, including strangulation, nerve injury, skin breakdown, and other complications of immobilization.

SUMMARY

Agitation and delirium are very common in the ICU, where their occurrence puts patients at risk of self-injury and poor clinical outcomes. Available sedation and delirium monitoring instruments allow clinicians to recognize these forms of brain dysfunction. Through a systematic approach, life-threatening problems and other acutely reversible physiologic causes can be rapidly identified and remedied. A strategy that focuses on early liberation from mechanical ventilation and early mobilization can help reduce the burden of delirium. Use of antipsychotics should be reserved for patients who pose an imminent risk to themselves or staff.

KEY POINTS

1. Delirium
2. Agitation
3. Confusion
4. Assessment
5. Risk factors
6. Management
7. Sedation

ANNOTATED REFERENCES

- Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004;291(14):1753-1762.
- This large cohort study showed that delirium in the ICU was an independent risk factor for death at 6 months and that each day with delirium increased the hazards of dying by 10%.*
- Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med* 2001;27(5):859-864. (Available at: <http://www.acgme.org/acgme/web/tabid/445/GraduateMedicalEducation/SingleAccreditationSystemforAOA-ApprovedPrograms.aspx>. Accessed November 12.)
- The ICDSC provides health care providers with an easy to use bedside delirium monitoring instrument that can be incorporated into the daily work flow of bedside nurses. It provides the ability to diagnose subsyndromal delirium.*
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This cohort study demonstrated a dose-response curve between days of delirium and the risk of dying at 1 year.

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A landmark study validating for the first time an easy to use bedside delirium-monitoring instrument for nonverbal mechanically ventilated patients. Delirium monitoring with the CAM-ICU can be performed in less than 2 minutes and does not require a psychiatrist.

Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009;373(9678):1874-1882.

This is the only interventional study that tested a nonpharmacologic intervention—early mobility—in ICU patients, and showed a reduction in delirium and improvements in functional outcomes.

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Critically ill patients frequently experience acute pain, which can have multiple causes in the intensive care unit (ICU) setting including surgical and posttraumatic wounds, the use of invasive monitoring devices and mechanical ventilators, prolonged immobilization, and routine nursing care (e.g., dressing changes). The experience of pain differs among patients, but the physiologic consequences of inadequately treated pain are relatively predictable and potentially deleterious. Some physiologic responses to acute pain and stress are mediated by neuroendocrine activation and increased sympathetic tone. Patients may develop tachycardia, increased myocardial oxygen consumption, immunosuppression, hypercoagulability, persistent catabolism, and numerous other metabolic alterations.¹ Additional morbidity may be incurred by pain-related functional limitations such as impaired pulmonary mechanics or delayed ambulation.

ACUTE PAIN ASSESSMENT

The assessment of acute pain in the ICU can be challenging. Unfortunately, many ICU patients cannot provide full or even partial information regarding their pain. However, the inability of ventilated, sedated ICU patients to report pain should not preclude its assessment and management. A number of scales and assessment tools for the evaluation of pain in ICU patients have been developed, such as the visual analog scale, the numeric rating scale, behavioral pain scale, and critical care pain observation scale (Fig. 3-1). In heavily sedated or paralyzed patients, caregivers must use signs of heightened sympathetic activity like hypertension, tachycardia, lacrimation, diaphoresis, and restlessness as surrogate indicators for the presence of pain. Favorable trends in these signs following analgesic administration provide a measure of the success of a given intervention.

OPTIONS FOR ACUTE PAIN THERAPY

Acute pain is triggered by stimulation of peripheral nociceptors in the skin or deeper structures and is a complex process involving multiple mediators at various levels of the neuraxis (Fig. 3-2). Different parts of the pain pathway can be targeted either individually or as part of a comprehensive “multimodal” strategy aimed at multiple sites for additive or synergistic effects. Thus, nociception can be influenced peripherally by the use of nonsteroidal antiinflammatory drugs (NSAIDs) and nerve blocks, at the spinal cord level by the use of epidural or intrathecal medications, and centrally by the use of systemic medications.

Nonsteroidal Antiinflammatory Drugs

Drugs in this class inhibit cyclooxygenase (COX) enzymes, which are involved in synthesis of prostaglandins and related inflammatory mediators in response to injury. COX-1 is a constitutive enzyme that is present in most tissues and, through the production of prostaglandins E₂ and I₂, serves homeostatic and protective functions. COX-2 is an inducible enzyme that is expressed in response to inflammation. As a class, NSAIDs can cause adverse effects that include gastrointestinal (GI) ulceration and GI bleeding, inhibition of platelet function, renal

injury, and bronchospasm in aspirin-sensitive patients (triad of asthma, nasal polypsis, and aspirin allergy).

Ketorolac is one of only two parenteral NSAIDs available in the United States. Although it has been shown to reduce postoperative opioid requirements, prolonged use may be associated with a significant incidence of the aforementioned side effects, primarily GI bleeding and renal injury. Consequently, it is recommended that ketorolac therapy be limited to a maximum of 5 days. In addition, ketorolac, as with all NSAIDs, should be used at decreased dosages or avoided altogether in patients at higher risk of such complications (e.g., advanced age, hypovolemia, or preexisting renal insufficiency).

Intravenous ibuprofen (Caldolor) has recently been approved by the Food and Drug Administration (FDA) as the only other parenteral NSAID for the treatment of pain. It has been demonstrated in several studies to be a safe and well-tolerated adjunctive agent in a multimodal approach of pain management, reducing opioid requirements and decreasing the incidence of opioid-related side effects.²⁻⁴ As with other nonselective NSAIDs, there is risk of GI bleeding and renal injury.

Due to the concern for an increased risk of cardiovascular thrombotic complications, myocardial infarction, and stroke demonstrated with COX-2 selective NSAIDs, there is a Black Box Warning contraindicating the use of both intravenous ibuprofen and ketorolac in perioperative coronary artery bypass graft (CABG) patients. In addition, their use is contraindicated in patients with active or recent GI bleeding or perforation. Unfortunately, the unfavorable adverse effect profile of these agents limits their use in the ICU setting.

Acetaminophen is a para-aminophenol derivative with analgesic and antipyretic properties similar to those of aspirin. The mechanism of action of acetaminophen is still poorly defined. Recent evidence has suggested that it may selectively act as an inhibitor of prostaglandin synthesis in the central nervous system (CNS) rather than in the periphery. When combined with opioids, acetaminophen may be a useful adjunct in pain relief, especially as an alternative to NSAIDs in high-risk patients because of the lower incidence of adverse effects.

An intravenous (IV) form of acetaminophen was approved in 2010 for the management of fever and mild to severe pain. Studies have proven it to be safe and effective in the reduction of pain, leading to decreased opioid requirements and fewer opioid-related side effects.⁴⁻⁷ Compared head-to-head in the setting of acute pain, IV acetaminophen has been shown to be equal and in some cases even more effective than IV morphine.⁸⁻¹⁰ The increased analgesic effects of IV, compared to oral acetaminophen, likely has to do with more favorable pharmacokinetics and avoidance of the hepatic first pass effect. When compared with oral or rectal acetaminophen in equal doses, intravenous administration results in a more rapid elevation in plasma concentrations and higher peak levels of acetaminophen.¹⁰ In fact, the mean peak concentration after infusion of IV acetaminophen is 70% higher than that seen with an equivalent oral dose.¹⁰ These higher plasma concentrations result in a more rapid and significant diffusion across the blood-brain barrier, as demonstrated by significant differences in the peak and total amount of acetaminophen in the cerebrospinal fluid with intravenous versus oral administration.¹¹ Although there are concerns about the use of acetaminophen in patients with liver disease, it has proven to be safe even in this population, although

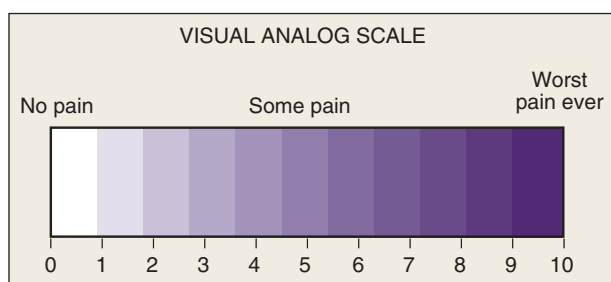


FIGURE 3-1 ■ Visual analog scale. Pain can be rated between 0 (no pain) and 10 (extreme pain). Use of a graphic such as this allows an intubated patient to indicate his or her level of discomfort by pointing. Other scales use cartoon faces that are either smiling or frowning. (From Higgins TL, Jodka PG, Farid A. Pharmacologic approaches to sedation, pain relief and neuromuscular blockade in the intensive care unit. Part II. Clin Intensive Care. 2003;14[3-4]:91-98.)

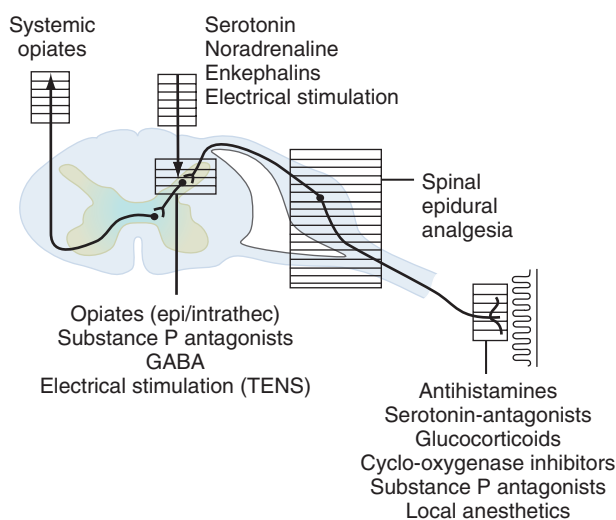


FIGURE 3-2 ■ “Map” of the path of nociceptive information from periphery to central nervous system. Modification of information can occur at any point of information transfer. GABA, gamma-aminobutyric acid; TENS, transcutaneous electrical nerve stimulation. (From Kehlet H. Modification of responses to surgery by neural blockade: clinical implications. In: Cousins MJ, Bridenbaugh PO, editors. Neural blockade in clinical anesthesia and pain management. 2nd ed. Philadelphia: Lippincott; 1988:145.)

a reduction of the daily dosage limit is recommended by the manufacturer in cases of mild to moderate hepatic impairment.¹² Its use is contraindicated, however, in cases of severe hepatic impairment.

Opioid Analgesics

This drug class remains the mainstay of ICU analgesia. Although a number of parenteral opioids are available, morphine, hydromorphone, and fentanyl are most commonly used, often as infusions in intubated patients along with a sedative agent. Opioids bind to a variable degree with opioid receptor subtypes (μ , δ , κ) located in the brain, spinal cord, and peripheral sites and modulate the transmission and processing of nociceptive signals. The clinical and pharmacologic properties of opioids depend on several variables, including chemical and solubility properties, dosing regimen, patient characteristics (e.g., age, tolerance, hepatic or renal dysfunction), and presence of active metabolites.

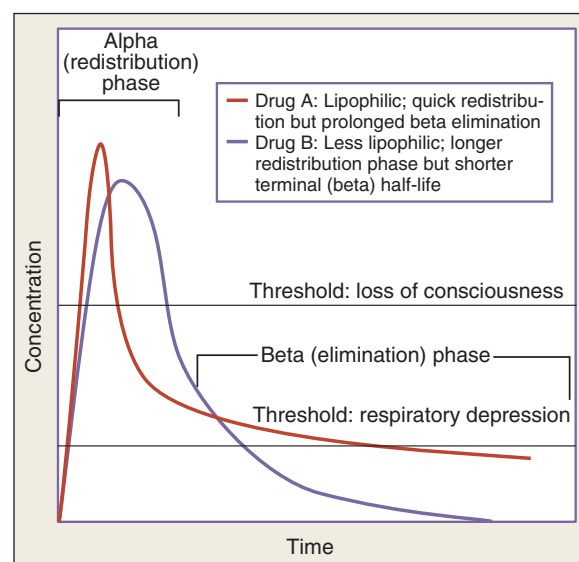


FIGURE 3-3 ■ Pharmacokinetics. A lipophilic drug (drug A) may have a rapid onset and an initially quick distribution, but a prolonged beta-elimination (metabolism) phase resulting in respiratory depression with repeated doses or constant infusion. A less lipophilic drug (drug B) may take longer to redistribute, giving the impression of a prolonged initial duration of action, but it does not accumulate owing to a shorter elimination half-life. Fentanyl is like drug A, whereas morphine is similar to drug B. (From Higgins TL, Jodka PG, Farid A. Pharmacologic approaches to sedation, pain relief and neuromuscular blockade in the intensive care unit. Part II. Clin Intensive Care 2003;14[3-4]:91-98.)

Opioids are excellent analgesics, but they are not amnestic agents. As a class they may suppress respiratory drive and promote sedation, GI symptoms (ileus, nausea and vomiting, constipation), urinary retention, pruritus, or hypotension as a result of the ablation of pain-mediated sympathetic stimulation. In actual practice, however, opioids are relatively neutral in their hemodynamic effects, so long as they are used judiciously in euvolemic patients. Of note, morphine additionally causes hypotension by triggering the release of histamine. This side effect, along with its hepatic metabolism to an active compound, morphine-6-glucuronide, which can accumulate in patients with renal insufficiency, are the main disadvantages of morphine when compared with other parenteral opioids.

Opioids are most commonly administered intravenously in critically ill patients and titrated to effect, either on a scheduled, intermittent basis or as a continuous infusion. This strategy avoids concerns regarding unpredictable bioavailability associated with intramuscular, enteral, or transdermal administration and favors more stable analgesic drug concentrations. The benefits of administering analgesics in this fashion, however, must be balanced against the possibility of unintentional overdosing resulting in excessive sedation, respiratory depression, and in turn, prolonged intubation. To avoid this problem, scheduled daily interruptions of sedative and analgesic drug infusions, often referred to as “sedation vacations” or “sedation holidays,” are recommended as they have been shown to result in shorter durations of mechanical ventilation and ICU stays.¹³ Drugs that are often thought of as short acting, like fentanyl, actually have a markedly prolonged duration of action if given as an infusion, even in patients without significant renal or hepatic dysfunction due to its accumulation in fat (Fig. 3-3). This concept is referred to as the “context-sensitive half-life,” which is defined as the time it takes for the plasma concentration of a drug to decrease by one-half following cessation of a continuous infusion.

Remifentanyl is a potent synthetic opioid with a rapid onset and short duration of action, owing to its unique organ-independent

metabolism and the absence of active metabolites or drug accumulation, even following prolonged infusion. Unlike other opioids that rely heavily on hepatic metabolism, remifentanyl is rapidly hydrolyzed within a matter of minutes by nonspecific plasma and tissue esterases (not plasma cholinesterase or pseudocholinesterase notably, meaning that patients with atypical cholinesterase do not experience a prolonged duration of action). This rapid hydrolysis also prevents drug accumulation during continuous administration. Furthermore, although its major metabolite is renally eliminated, it is virtually devoid of opioid activity, resulting in a stable pharmacokinetic profile even in the presence of severe renal impairment. All of these qualities result in a drug with an extremely short context-sensitive half-life, irrespective of infusion duration. Although this may be particularly useful in critically ill patients who often have comorbid hepatorenal dysfunction and who require prolonged opioid infusions, there are a couple of drawbacks to this drug that limit its widespread use in the ICU setting: First, its potent nature often leads to dose-dependent hypotension and bradycardia if not carefully titrated. Second, its ultra-short duration of action of several minutes can result in abrupt recurrence of pain after an infusion is stopped, which may result in unwanted acute sympathetic stimulation. This may be particularly pronounced in those with a large pain burden, such as postoperative or trauma patients. Other adverse effects of remifentanyl are similar to those of other opioids. Of these, chest wall rigidity resulting in the inability to ventilate is arguably the most worrisome and deserves a brief mention. Although a possible adverse effect of any IV opioid, it may be slightly more common with remifentanyl, particularly when it is given as a bolus or infused at higher rates. This can be treated by administering a neuromuscular blocking agent and reducing or discontinuing the infusion.¹⁴⁻¹⁶

Ketamine

Ketamine is a well-known general anesthetic and analgesic. With the discovery of the *N*-methyl-D-aspartate (NMDA) receptor and its links to nociceptive pain transmission and central sensitization, there has been renewed interest in utilizing ketamine as a potential antihyperalgesic agent. Ketamine is a noncompetitive NMDA receptor antagonist. Although high doses (>2 mg/kg) of ketamine have been implicated in causing psychomimetic effects (excessive sedation, cognitive dysfunction, hallucinations, nightmares), subanesthetic or low doses (<1 mg/kg) of ketamine have demonstrated significant analgesic efficacy without these side effects. Furthermore, there is no evidence to indicate that low doses of ketamine exert any adverse pharmacologic effects related to respiration or cardiovascular function. Low doses of ketamine have not been associated with development of nausea, vomiting, urinary retention, or impaired intestinal motility. Ketamine, in combination with IV opioids, has been shown not only to reduce postoperative opioid consumption but also to improve analgesia.^{5,17}

Methadone

The use of methadone in the outpatient setting in treating opioid addiction and providing relief in chronic pain and palliative care is well established.¹⁸ Its long duration of action (up to 8 hours) compared to other opioids and its dual effects on both opioid and NMDA receptors make it an ideal agent in these settings. In addition to these features, methadone differs pharmacologically from other opioids in several important ways. Its elimination half-life, which is considerably longer than its duration of action, varies dramatically among individuals from 8 to 90 hours, due largely to its highly lipophilic properties leading to drug accumulation.¹⁸ This results in three important considerations regarding drug titration and side effects: First, dosage increases should only be made once every several days, since steady-state plasma concentrations, and therefore full analgesic effects, are not attained until 3 to 5 days after initiation. Second, peak respiratory depressant effects usually occur later and last longer than the peak

analgesic effect, especially during the drug initiation phase. Third, when attempting to discontinue the drug after long-term use the dose should be gradually tapered off, as abrupt discontinuation can lead to withdrawal symptoms. These factors should be kept in mind when dosage adjustments are being made. The delayed respiratory depressant effect is due to drug accumulation rather than the presence of active metabolites as with morphine, since methadone is hepatically metabolized to inactive metabolites. Other than respiratory depression, the most commonly seen serious adverse effect is QT prolongation, which makes regular monitoring of the EKG necessary especially during initiation of therapy, dosage increases, or addition of other medications with QT prolonging effects. Although traditionally used for chronic pain and addiction, there is recent interest in the use of this drug acutely in the inpatient setting in patients who are displaying signs of either opioid tolerance or opioid-induced hyperalgesia.

OPIOID TOLERANCE AND OPIOID-INDUCED HYPERALGESIA

Although at first glance their presentation is quite similar, it is clinically important to distinguish these two situations in terms of the differences in their treatment. Both may result from high-dose opioid consumption and present with uncontrolled pain despite increasing opioid doses. The difference, however, is that patients with opioid-induced hyperalgesia display signs of increasing sensitivity to painful stimuli (hyperalgesia), and the pain is more diffuse (allodynia) and present in an area or distribution that is beyond the initial site. Differentiation of these two scenarios can be difficult, and consultation with a pain management specialist may be necessary.

Opioid tolerance results from repeated exposure to an opioid causing a decreased therapeutic effect through desensitization of antinociceptive mechanisms. Treatment options involve further uptitration of the current opioid regimen, the addition of adjunctive agents with different mechanisms of pain control in a multimodal approach, and attempting an opioid switch or “rotation” to a different opioid analgesic. Although there is debate about the efficacy of the latter approach, methadone in particular has demonstrated particular efficacy when attempting an opioid switch.^{19,20} This is likely due to its dual mechanism of action as an opioid agonist and NMDA receptor antagonist, a quality that is unique among other opioids. Its action at the NMDA receptor not only provides an additional mechanism for pain control but also attenuates hyperalgesia, which arguably also plays a part in many cases of opioid tolerance.^{19,20}

Opioid-induced hyperalgesia, on the other hand, results from repeated exposure to an opioid causing increased pain due to the central sensitization of pronociceptive mechanisms. This has been termed the *wind-up* phenomenon, and presents a challenging problem for the clinician. As its mechanism is different from opioid tolerance, the treatment also differs. Rather than uptitration of opioid agents, attempts should be made to reduce and even discontinue them. This is accomplished through the addition of nonopioid analgesics and through the use of NMDA-receptor antagonists, in particular ketamine. The NMDA receptor is a ligand-gated calcium channel that plays a major role in the development of central sensitization. Through antagonism of this receptor, ketamine has been shown to reverse this phenomenon and effectively treat the hyperalgesia.^{19,20} In addition to its effectiveness in treating opioid-induced hyperalgesia, the use of low-dose ketamine in the treatment of acute pain has been shown to reduce opioid requirements, as previously discussed. This may be particularly beneficial in the postoperative setting.⁵ The opioid-sparing effect of ketamine is partly due to its own intrinsic analgesic effect, but when combined with opioid treatment regimens, it is also likely due to prevention of hyperalgesia.^{17,19} In addition to ketamine, methadone has been shown to improve opioid-induced hyperalgesia, likely in part due to its own action at the NMDA receptor.^{19,20} Initiation of methadone in this setting may also facilitate the tapering and removal of other opioid agents contributing to the hyperalgesia.

Tramadol

Tramadol is a centrally acting synthetic analgesic with two distinct mechanisms of action: It is a weak μ -opioid agonist and a reuptake inhibitor of norepinephrine and, to a lesser extent, serotonin. This results in augmentation of descending inhibitory pathways of pain control. Tramadol has proven to be an effective analgesic, especially when combined with acetaminophen, with fewer opioid-related side effects, most notably gastrointestinal.^{21–24} Tramadol is a racemic mixture of two enantiomers with different pharmacologic effects. One isomer is responsible for the norepinephrine effect and the other the serotonin effect. In addition, its μ -opioid effect is dependent on metabolism by P4502D6 enzyme to an active metabolite. Unfortunately, 5% to 15% of the population are poor metabolizers.²⁵

Tapentadol is a newer agent with a similar dual mechanism of action as a μ -opioid agonist and a norepinephrine uptake inhibitor. Unlike tramadol, it does not require metabolic activation and is a nonracemic molecule, only affecting the reuptake of norepinephrine. These features may increase the efficacy of this agent compared to tramadol. Although tapentadol has 20 times less affinity for the μ -opioid receptor than morphine, it has been demonstrated to have an analgesic effect only three times less than morphine, which is likely explained by its action on norepinephrine.²⁶ When compared with several opioid analgesics including oxycodone in the setting of both acute and chronic pain, tapentadol has shown comparable efficacy with fewer GI adverse effects.^{27–30}

Gabapentin

The gabapentanoids gabapentin and pregabalin are analogs of gamma-aminobutyric acid (GABA). Although initially developed as antiepileptic agents, an indication for which they have not shown great efficacy, these agents have become well established for the long-term treatment of chronic neuropathic pain. Although not completely understood, their mechanism of action involves binding to voltage-gated calcium channels in the central nervous system, downregulating their action and subsequently decreasing neurotransmitter release. This results in inhibition of central sensitization and hyperalgesia, which is responsible for the development of chronic neuropathic pain. Recent studies, however, have investigated the use of these agents as an adjunct to opioid analgesics in the treatment of acute pain, in particular postsurgical pain.

A single preoperative dose of gabapentin has been shown to improve postoperative pain scores and decrease postoperative opioid requirements in a variety of surgical populations.^{31,32} This is theorized to be due to the prevention of surgery-induced central sensitization, which is believed to also play a significant role in acute postoperative pain. There is also evidence that continuation of gabapentanoids in the postoperative period may help to provide increased pain relief and reduce opioid requirements.^{32,33}

Studies using pregabalin in the treatment of acute postoperative pain have demonstrated similar efficacy with this agent.^{5,17,33,34}

Alpha-2 Adrenergic Agonists

In addition to the opiate system, alpha-2 (α_2) adrenergic activation represents another inherent pain-control network in the CNS. The α_2 adrenergic receptor exists in the substantia gelatinosa of the dorsal horn, which is a primary site of action by which this class of drugs can inhibit somatic pain. This receptor system also exists in the brain, where its stimulation can produce sedation. Cardiovascular depression

from α_2 adrenergic agonists can occur at both brain and spinal cord sites. These side effects of sedation and sympathetic inhibition limit α_2 adrenergic agonists to only an adjuvant role as analgesics.

Clonidine was originally used to control blood pressure and heart rate. It binds to α_2 adrenergic and imidazole receptors in the CNS. It has been hypothesized that clonidine acts at α_2 adrenergic receptors in the spinal cord to stimulate acetylcholine release, which acts on both muscarinic and nicotinic receptor subtypes for postoperative pain relief. Clonidine can be administered by oral, IV, or transdermal routes.

A newer centrally acting α_2 agonist is the parenteral agent dexmedetomidine, which possesses a higher affinity for the α_2 receptor than clonidine. Although FDA approved only for sedation, it is being studied as an adjunctive analgesic based on its mechanism and several studies that have demonstrated decreased opioid requirements and improved pain scores with its use.^{35,36}

Neuraxial Analgesic Techniques

The administration of narcotics, local anesthetics, and other agents via intrathecal or epidural catheters targets the processing of pain signals at the level of the spinal cord or nerve root. The use of epidural catheters for regional analgesia in ICU patients may be quite useful, assuming that the pain pattern is regionalized and that there are no contraindications to catheter placement (e.g., coagulopathy, uncontrolled infection, unstable spinal skeletal fractures). In some patients, epidural analgesia may be preferable to IV-administered medications because this approach affords dense regional pain control while largely avoiding the sedative and respiratory side effects of systemic medications. In trauma patients with rib fractures and postsurgical thoracotomy patients, the use of epidural catheters may be particularly helpful in achieving pain control while minimizing respiratory depression in a patient population that is prone to develop respiratory insufficiency and failure due to hypoventilation as a result of uncontrolled pain.

Peripheral Nerve Blocks

Peripheral nerve blocks are an attractive method of providing postoperative analgesia for many orthopedic surgical procedures. The use of peripheral nerve blocks achieved by either a single injection or by continuous infusion via a catheter may provide superior analgesia, reduce opioid consumption, and reduce opioid-related side effects. Unfortunately, this technique is not commonly used in the ICU setting. Due to the aforementioned benefits, however, it should be strongly considered as an alternative to opioids when appropriate.

Multimodal Analgesia

Multimodal analgesia is a concept that was developed as a technique to improve the quality of pain relief while minimizing the adverse effects of opioids. The idea is to use a combination of agents with different mechanisms in an additive and often synergistic effect to achieve adequate analgesia with lower doses of each agent. Utilizing this concept in the ICU can be vitally important, since the adverse effects of drugs are often magnified in the critically ill, especially in the setting of polypharmacy. As we increase our understanding of the etiology of pain, newer agents with different mechanisms of action are being developed, and hopefully one day the concept of treating pain with several agents in a multimodal approach will be common practice in every clinical setting.

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Fever is defined as an increase in body temperature. Normal body temperature is $36.8^{\circ}\text{C} \pm 0.4^{\circ}\text{C}$. Normally, body temperature varies in a circadian fashion by about 0.6°C , being lowest in the morning and highest in the late afternoon or early evening. A core body temperature of $\geq 38.3^{\circ}\text{C}$ is generally accepted to represent fever.¹ In 2008, a task force from the Society of Critical Care Medicine and the Infectious Disease Society of America concluded that “because fever can have many infectious and noninfectious etiologies, a new fever in a patient in the intensive care unit should trigger a careful clinical assessment rather than automatic orders for laboratory and radiologic tests. A cost-conscious approach to obtaining cultures and imaging studies should be undertaken if indicated after a clinical evaluation.”¹

Fever is a common finding in patients admitted to an intensive care unit (ICU), being present at one time or another in almost 50% of cases. Moreover, fever is an independent risk factor for mortality in patients admitted to ICUs.²

The pathogenesis of fever triggered by infectious agents is complex.^{2,3} Classically, fever was thought to be triggered by the peripheral release of various cytokines—notably, interleukin 1-beta (IL-1 β), tumor necrosis factor (TNF), IL-6, and possibly interferon-alpha (IFN- α)—that are capable of up-regulating the expression of two key enzymes that are involved in the production of prostaglandin E₂ (PGE₂), namely: cyclooxygenase (COX)-2 and microsomal prostaglandin E synthase-1 (mPGES-1). The central role of PGE₂ in the pathogenesis of fever is supported by the following findings: first, febrile responses to lipopolysaccharide (LPS) and other inflammatory stimuli are depressed by drugs that inhibit PG synthesis; second, mice that are genetically deficient in either COX-2 or mPGES-1 do not become febrile after an LPS challenge. Although PGE₂ can be produced by immunostimulated macrophages in the periphery, the PGE₂ that is responsible for fever is probably generated in the central nervous system (CNS). PGE₂ binds to prostaglandin receptors located on a cluster of neurons in the pre-optic region of the hypothalamus. Although there are four subtypes of PGE₂ receptors, only one, PGE₂ receptor 3 (EP3), is required for the development of fever in response to IL-1 β , LPS, or PGE₂.⁴ The activation of EP3 triggers a number of neurohumoral and physiologic changes that lead to increased body temperature. The antipyretic effects of various nonsteroidal antiinflammatory drugs (NSAIDs), such as aspirin and ibuprofen, are due to the inhibition of COX-2-dependent PGE₂ biosynthesis in the CNS. The mechanism by which acetaminophen reduces fever might involve COX-2 inhibition in the CNS, but it remains controversial and poorly understood.⁵⁻⁷

The classical view of the pathogenesis of fever associated with infection has been updated by the proposal that pyrogenic stimuli trigger the activation of vagal afferent signals originating from the liver and travelling to the nucleus tractus solitarius in the brainstem. These signals are subsequently transmitted to the hypothalamus, where an early increase in temperature is mediated in a PGE₂-independent fashion via an α_1 -adrenergic receptor-dependent pathway. A secondary (delayed) increase in temperature is mediated via an α_2 -adrenergic-dependent pathway that leads to an increase in PGE₂ production secondary to the increased expression of COX-2.

Body temperature can be measured using an oral, axillary, or rectal mercury-filled glass thermometer. These traditional approaches, however, have been largely replaced by a variety of safer and more

environmentally friendly methods that use thermistors located on catheters or probes placed in the pulmonary artery, distal esophagus, urinary bladder, or external ear canal. Infrared detectors can be used to measure tympanic membrane temperature. Forehead skin temperature can be measured using a temperature-sensitive patch.

Fever is a cardinal sign of infection. Accordingly, any new onset of fever should trigger a careful diagnostic evaluation for investigating the source of infection. The diagnostic evaluation should be thorough and tailored to the recent history of the patient. For example, the possibility of a CNS infection should receive greater attention in a patient with recent or ongoing CNS instrumentation. By the same token, if a patient recently underwent a gastrointestinal surgical procedure, the clinician should have a high index of suspicion for an intraabdominal source of infection. Key elements in the assessment of new-onset fever in the ICU are listed in [Box 4-1](#). Common sources of infection in ICU patients are listed in [Box 4-2](#).

Although fever in the ICU is most commonly due to infection, myriad noninfectious causes of systemic inflammation ([Box 4-3](#)) can also result in hyperthermia. Some authors claim that noninfectious causes of fever rarely result in a core temperature above 38.9°C ,^{8,9} but rigorous data in support of this view are lacking. Still, infections are rarely if ever associated with core temperatures over 41.1°C . When the core temperature is this high, the clinician should suspect malignant hyperthermia, neuroleptic malignant syndrome, or heat stroke.

On theoretical grounds, the routine treatment of fever would seem to be ill-advised. Hyperthermia is an adaptive response that enhances the host's ability to fight infection.¹⁰ In addition, body temperature becomes an unreliable clinical parameter when patients are receiving antipyretic therapy. Still, currently available data are insufficient to determine whether fever should be routinely treated in ICU patients. In one randomized clinical trial that enrolled 82 surgical ICU patients, the protocolized administration of acetaminophen when body temperature exceeded 38.5°C was compared to the treatment of fever only when temperature exceeded 40°C . More aggressive treatment of fever in this study was associated with a trend toward higher mortality ($P = 0.06$).¹¹ In contrast to these findings, Schortgen et al. randomized febrile patients with septic shock requiring vasopressors, mechanical ventilation, and sedation to either external cooling ($n = 101$) for 48 hours to achieve normothermia (36.5°C to 37°C) or no external cooling ($n = 99$).¹² Day 14 mortality was significantly lower in the group randomized to external cooling ($P = 0.013$). In another study, 120 febrile adults (not all critically ill) were randomized to treatment with intravenous ibuprofen (100, 200, or 400 mg) or placebo every 4 hours for a total of 6 doses. There was no significant difference in the rate of serious adverse events, such as acute kidney injury, bleeding, or mortality, between the groups.¹³

Although it is unclear whether hyperthermia should be routinely treated in ICU patients, antipyretics should be administered to selected patients with fever, notably those with acute coronary syndromes (i.e., myocardial infarction or unstable angina), because the tachycardia that usually accompanies the febrile response can exacerbate imbalances between myocardial oxygen delivery and demand. Febrile patients with head trauma, subarachnoid hemorrhage, or stroke should receive cooling (using antipyretics and/or external cooling devices) to prevent temperature-related increases in cerebral oxygen utilization. Children with temperatures higher than 40°C or with a history of seizures should also be treated.

[†] Deceased

BOX 4-1**Key Elements in the Evaluation of New-Onset Fever in ICU Patients**

- Be familiar with the patient's history. Pay particular attention to possible predisposing causes of fever.
- Perform a careful physical examination. Pay particular attention to surgical wounds and vascular access sites. Look for evidence of pressure-induced skin ulceration. In patients with recent median sternotomy, evaluate the stability of the chest closure. Perform a careful abdominal examination.
- Obtain or review a recent chest X-ray, looking for evidence of new infiltrates or effusions.
- Obtain appropriate laboratory studies. At a minimum, these studies should include a peripheral white blood cell count and cultures of blood and urine. If the patient is endotracheally intubated or has a tracheotomy, obtain a sample of sputum for Gram stain. In some centers, sputum is routinely cultured. In other centers, bronchoalveolar lavage or bronchial brushing for quantitative microbiology is performed using blind or bronchoscopic methods.
- In patients receiving antibiotics for more than 3 days, a stool sample should be analyzed for the presence of *Clostridium difficile* toxin, unless a high sensitivity assay for the toxin was performed recently and was negative.
- More extensive diagnostic evaluation should be considered in a graded fashion based on history, physical examination findings, laboratory results, persistence of fever despite presumably appropriate antimicrobial chemotherapy, or clinical instability. These additional tests and procedures include diagnostic thoracentesis, paracentesis, and lumbar puncture. Imaging studies should be considered, including abdominal or cardiac ultrasonography and head, chest, or abdominal computed tomography.

Hypothermia blankets are often used to lower the core temperature in febrile ICU patients, although these blankets are no more effective for cooling patients than antipyretic agents.^{14,15} Hypothermia blankets can cause large temperature fluctuations and are associated with rebound hyperthermia when removed. Additionally, external cooling can augment hypermetabolism and actually promote persistent fever. Lenhardt and colleagues demonstrated that active external cooling in volunteers with induced fever increased oxygen consumption by 35% to 40% and was associated with a significant increase in circulating norepinephrine and norepinephrine concentrations.¹⁶

In view of these phenomena, the administration of an antipyretic agent is the recommended approach when the treatment of fever is warranted. Commonly used antipyretics include isoform nonselective COX inhibitors, such as ibuprofen or aspirin, or acetaminophen. Because corticosteroids (hydrocortisone, methylprednisolone) are potent antiinflammatory agents, these drugs can suppress the febrile response to infection. Other antiinflammatory agents have a similar effect, so absence of fever should not be used to rule out infection, especially in patients receiving corticosteroids or other potent antiinflammatory drugs.

A reasonable approach for evaluating fever in ICU patients was described by Marik.⁸ Blood cultures should be obtained whenever an ICU patient develops a new fever. The sensitivity of blood cultures for detecting bacteremia depends to a large extent on the volume of blood inoculated into culture media. Whenever possible, at least 10 to 15 mL of blood should be withdrawn and inoculated into 2 or 3 bottles or tubes at a ratio of 1 mL of blood per 5 mL of medium.¹

A comprehensive physical examination should be carried out, and a chest X-ray obtained and reviewed. Noninfectious causes of fever should be excluded. In patients with an obvious focus of infection, a directed diagnostic evaluation is necessary. However, if there is no obvious source of infection and the patient is not clinically deteriorating, it is reasonable to obtain blood cultures and observe the patient for 48 hours before ordering additional diagnostic studies or starting empirical antibiotics. This approach is not reasonable, however, if new fever is accompanied by other signs of worsening clinical status such as arterial hypotension, oliguria, increasing confusion, rising serum lactate concentration, falling platelet count, or worsening coagulopathy. Nor is this approach reasonable if the core temperature is above

BOX 4-2**Common Infectious Causes of Fever****CENTRAL NERVOUS SYSTEM**

Meningitis
Encephalitis
Brain abscess
Epidural abscess

HEAD AND NECK

Acute suppurative parotitis
Acute sinusitis
Parapharyngeal and retropharyngeal space infections
Acute suppurative otitis media

CARDIOVASCULAR

Catheter-related infection
Endocarditis

PULMONARY AND MEDIASTINAL

Pneumonia
Empyema
Mediastinitis

HEPATOBIILIARY AND GASTROINTESTINAL

Diverticulitis
Appendicitis
Peritonitis (spontaneous or secondary)
Intraperitoneal abscess
Perirectal abscess
Infected pancreatitis
Acute cholecystitis
Cholangitis
Hepatic abscess
Acute viral hepatitis

GENITOURINARY

Bacterial or fungal cystitis
Pyelonephritis
Perinephric abscess
Tubo-ovarian abscess
Endometritis
Prostatitis

BREAST

Mastitis
Breast abscess

CUTANEOUS AND MUSCULAR

Cellulitis
Suppurative wound infection
Necrotizing fasciitis
Bacterial myositis or myonecrosis
Herpes zoster

OSSEOUS

Osteomyelitis

39°C but below 41.1°C. Patients in this category should receive empirical antimicrobial chemotherapy while aggressive attempts are made to diagnose the source of infection. All febrile neutropenic patients should receive broad-spectrum empirical antimicrobial chemotherapy after appropriate cultures are obtained.

Intravascular catheters are commonly suspected as a source of infection and fever in ICU patients and can cause fever due to localized or systemic (bloodstream) infection. In patients with a new onset of fever but without other ominous signs (e.g., hypotension, profound thrombocytopenia, acute respiratory distress syndrome), it is unnecessary to remove all intravascular catheters. In contrast, if one or more of these (or other) ominous signs are present, the most prudent course of action is to remove all vascular access catheters, including tunneled and/or cuffed devices. In many institutions, routine culturing of catheter tips (using semiquantitative methods on solid media) is no longer thought to be cost effective because the results of such studies rarely change the subsequent therapy strategy.^{17,18}

BOX 4-3 Noninfectious Causes of Fever**CENTRAL NERVOUS SYSTEM**

Subarachnoid hemorrhage
Intracerebral hemorrhage
Infarction

CARDIAC

Myocardial infarction
Pericarditis

PULMONARY

Atelectasis
Pulmonary embolism
Fibroproliferative phase of acute respiratory distress syndrome

HEPATOBIILIARY AND GASTROINTESTINAL

Acalculous cholecystitis
Acute pancreatitis
Active Crohn's disease
Toxic megacolon
Alcoholic hepatitis

RHEUMATOLOGIC SYNDROMES

Vasculitides (e.g., polyarteritis nodosa, temporal arteritis, Wegener's syndrome)
Systemic lupus erythematosus
Rheumatoid arthritis
Goodpasture's syndrome

ENDOCRINE

Hyperthyroidism
Adrenal insufficiency
Pheochromocytoma

OTHER

Drug reactions ("drug fever")
Transfusion reactions
Neoplasms (especially lymphoma, hepatoma, and renal cell carcinoma)
Malignant hyperthermia
Neuroleptic malignant syndrome
Serotonin syndrome
Opioid withdrawal syndrome
Ethanol withdrawal syndrome
Transient endotoxemia or bacteremia associated with procedures
Devitalized tissue secondary to trauma
Hematoma

Fever is a common feature of the systemic inflammatory response syndrome (SIRS), irrespective of whether the underlying cause is infectious or noninfectious.¹⁹ Procalcitonin, a precursor of the polypeptide hormone, calcitonin, has been studied extensively as a circulating marker that can be used to differentiate infectious from noninfectious causes of SIRS in ICU or emergency department patients. A recent meta-analysis concluded that "procalcitonin represents a good biological diagnostic marker for sepsis, severe sepsis, or septic shock."²⁰ Several randomized controlled trials have investigated the feasibility of using the results of procalcitonin assays for making decisions regarding starting or stopping antibiotics for patients with proven or suspected

respiratory infections. According to a recent meta-analysis of these studies, the "use of procalcitonin to guide the initiation and duration of antibiotic treatment was not associated with higher mortality rates or treatment failure, [and] antibiotic consumption was significantly reduced."²¹ Thus, measurements of procalcitonin can be a useful adjunct for the evaluation of fever in ICU patients, but this assay is not a replacement for other key diagnostic modalities: careful physical examination, chest X-ray, assessment of sputum Gram stain findings, and appropriate cultures of blood, urine, sputum, or bronchoalveolar lavage fluid.

■ References for this chapter can be found at expertconsult.com.

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An acute elevation in systemic blood pressure is termed a *hypertensive crisis*, a clinical condition that includes both *hypertensive urgency* (HU) and *hypertensive emergency* (HE). HE is characterized by a severe elevation in systemic blood pressure combined with new or progressive end-organ damage most frequently in the cardiac, renal, and/or central nervous system.¹ HE is an infrequent clinical presentation of acute hypertension that requires immediate, titrated, blood pressure reduction. Although HE is typically associated with a blood pressure elevation > 180/110 mm Hg, the diagnosis of HE is based upon the patient's clinical signs and symptoms rather than a specific blood pressure level. Clinical conditions associated with HE might include hypertensive encephalopathy, intracranial hemorrhage, acute coronary syndrome, acute pulmonary edema, aortic dissection, acute renal failure, and eclampsia.

In contrast, HU is characterized by a critically elevated blood pressure (>180/110 mm Hg) without evidence for acute and progressive dysfunction of target organs. In HU, a more gradual reduction of blood pressure over several hours to days is the therapeutic target. A rapid reduction in blood pressure in HU has no proven benefit, and cerebral or myocardial ischemia can be induced by aggressive antihypertensive therapy if the blood pressure falls below a level needed to maintain adequate tissue perfusion. HU is not to be ignored, however, as it can progress to end-organ damage if blood pressure remains uncontrolled over a sustained interval.

In the current treatment era for HE, a 25-institution U.S. analysis reported a hospital mortality rate of 6.9% with an aggregate 90-day mortality rate of 11% and a 90-day readmission rate of 37%.² While the frequency of hospitalization for hypertensive emergency may be increasing, the all-cause hospital mortality for these patients continues to decrease.

■ PATHOPHYSIOLOGY

An acute elevation in systemic arterial blood pressure (BP) most fundamentally involves an increase in systemic vascular resistance. This increase in vascular resistance is attributed to a complex interaction of vascular mediators with a triggering factor in the setting of preexisting hypertension. Vasoconstriction can be promoted by circulating catecholamines, angiotensin II (ATII), vasopressin, thromboxane (TxA₂), and/or endothelin-1 (ET1). In contrast, compensatory production of local counterregulatory vasodilators including nitric oxide (NO) and prostacyclin (PGI₂) is inadequate to maintain homeostatic balance. The early stages of HE are associated with a naturesis that further stimulates the release of vasoconstrictor substances from the kidney.

Specific cellular mechanisms of vascular injury in HE appear to involve proinflammatory responses incorporating cytokine secretion, monocyte activation, and upregulation of endothelial adhesion molecules.³ These proinflammatory factors extend the endothelial injury by promoting endothelial permeability and activating the coagulation cascade.

This cascade of intravascular events leads to the characteristic pathologic findings of obliterative vascular lesions. The vascular changes, evident to the clinician during examination of the retina, are mirrored by similar changes in the kidney, leading to a proliferative arteritis and, in advanced stages of the process, fibrinoid necrosis. A state of relative ischemia results in the affected organs, leading to end-organ dysfunction. The thrombotic microangiopathy (TMA) that characterizes the advanced stages of HE is a prothrombotic state characterized

by endothelial dysfunction, platelet activation, and thrombin generation, with enhanced fibrinolytic activity.³

The potential adverse effects of aggressive blood pressure control have been most carefully studied in the cerebral circulation. Cerebrovascular arteriolar tone is adjusted over a range of cerebral perfusion pressures (CPP) to maintain a constant cerebral blood flow (CBF). Increases in CPP promote an increase in vascular resistance, whereas decreases in CPP act to vasodilate the cerebral vasculature. Constant flow is therefore maintained over a range of mean arterial pressure (MAP) from approximately 60 mm Hg to 150 mm Hg.⁴ As MAP increases to values >180 mm Hg or above the upper limit of autoregulation, cerebral hyperperfusion can occur, resulting in cerebral edema. Conversely, when CPP falls below the lower limit of autoregulation, CBF decreases, and tissue ischemia may occur. In patients with longstanding hypertension, a rightward shift of the CPP-CBF relationship occurs such that the lower limit of autoregulation occurs at a value higher than that in normal subjects. Comparative studies in hypertensive and normotensive patients suggest that the lower limit of autoregulation is about 20% below the resting MAP for both, although the absolute value is higher for the hypertensive patient. These data support the common recommendation that a safe level of blood pressure reduction in the HE setting is a 10% to 20% reduction of MAP from the highest values on clinical presentation, or a diastolic blood pressure typically in the 100- to 110-mm Hg range.

■ CLINICAL PRESENTATION

According to the STAT registry, the most common presenting symptoms in HE include shortness of breath (29%), chest pain (26%), headache (23%), altered mental status (20%), and a focal neurologic deficit (11%).² The most common admitting diagnoses are severe hypertension (27%), subarachnoid hemorrhage (11%), acute coronary syndrome (10%), and heart failure (8%). In approximately 25% of patients with HE, there is a history of either chronic or current medication nonadherence, and 11% of patients are current drug abusers. No specific blood pressure level defines HE, but the mean systolic blood pressure in the STAT registry was 200 mm Hg (IQR, 186-220), and the median diastolic blood pressure (DBP) was 110 mm Hg (IQR, 93-123).²

A detailed history is indicated, with some attention to the use of prescription medications associated with hypertension. Hypertensive emergencies may also develop as secondary hypertension in association with such diverse etiologies as renal vascular disease, sleep apnea, hyperaldosteronism, pheochromocytoma, and pregnancy (preeclampsia). In addition, illicit drug use is a major risk factor for the development of hypertensive emergencies.

Blood pressure should be measured in both arms using an appropriately sized cuff. Repeated blood pressure measures are indicated, as a significant fraction of patients will resolve hypertension with bed rest and initial observation. Physical examination including a fundoscopic examination should focus on identification of signs suggesting end-organ dysfunction.

Hypertension and Cerebrovascular Disease Hypertensive Encephalopathy

Acute elevations in systemic arterial blood pressure can lead to hypertensive encephalopathy (HEN). The clinical manifestations include headache, confusion or a depressed level of consciousness, nausea and

vomiting, visual disturbances, or seizures (generalized or focal). Patients may present with focal neurologic deficits, although this finding is more common in cerebrovascular accidents. Rarely, HEN can present with brainstem involvement manifesting as ataxia and/or diplopia.⁵ If left untreated, the condition can progress to coma and death. Retinal findings, including arteriolar spasm, exudates or hemorrhages, and papilledema may be present but are not a requirement. MRI studies show edema involving the subcortical white matter of the parieto-occipital regions best seen on T2 and FLAIR imaging, a finding termed *posterior leukoencephalopathy*. Approximately two-thirds of patients will also have hyperintense lesions on T2 and FLAIR imaging in the frontal and temporal lobes, and one-third will have brainstem, cerebellum, or basal ganglia involvement.⁶ The imaging findings are typically bilateral but can be asymmetric. HEN is the most common cause of posterior reversible encephalopathy syndrome (PRES).⁶ An improvement or resolution of the radiographic findings is delayed often in comparison to clinical improvement. Seizures can occur in patients with PRES and may include both focal and generalized features.⁷

The diagnosis of HEN is confirmed by the absence of other conditions and the prompt resolution of symptoms and neuroimaging abnormalities with effective blood pressure control. The failure of a patient to improve within 6 to 12 hours of blood pressure reduction should suggest an alternative cause of the encephalopathy. The condition is typically reversible with no observable adverse outcomes.

Acute Stroke

The majority of patients with acute stroke have an elevated systolic blood pressure on presentation to the hospital that often declines to normal within 48 hours of presentation. Current data are contradictory whether hypertension in the early phase of acute stroke contributes to a worse patient outcome or is a surrogate marker of stroke severity.

During acute stroke, cerebral autoregulation may be compromised in ischemic tissue, and lowering of blood pressure may further compromise cerebral blood flow and extend ischemic injury. Medications used to treat hypertension may lead to cerebral vasodilation, augmenting cerebral blood flow and leading to progression in cerebral edema. Ideally, a "correct" level of MAP should be maintained in each patient to maintain cerebral perfusion pressure without worsening cerebral edema or progression of the lesion, but the clinical determination of this ideal value is often difficult.

Consensus guidelines recommend that blood pressure not be treated acutely in the patient with ischemic stroke unless the hypertension is extreme (systolic blood pressure >220 mmHg or diastolic blood pressure >120 mm Hg) or the patient has active end-organ dysfunction in other organ systems.⁸ When treatment is indicated, cautious lowering of blood pressure by approximately 15 percent during the first 24 hours after stroke onset is suggested. Antihypertensive medications can be restarted at approximately 24 hours after stroke onset in patients with preexisting hypertension who are neurologically stable, unless a specific contraindication to restarting treatment exists. Special considerations are patients with extracranial or intracranial stenosis and candidates for thrombolytic therapy. The former group may be critically dependent on perfusion pressure, so blood pressure therapy may be further delayed. In contrast, treatment is recommended before lytic therapy is started, so that systolic blood pressure is ≤ 185 mm Hg and diastolic blood pressure is ≤ 110 mm Hg before lytic therapy administration.⁸ The blood pressure should be stabilized and maintained below 180/105 mm Hg for at least 24 hours after intravenous lytic therapy.

Blood pressure is frequently elevated in patients with acute intracranial hemorrhage (IH), often to a greater degree than seen in ischemic stroke. Theoretically, severe elevations in blood pressure may worsen IH by creating a continued force for bleeding. However, the increased arterial pressure may also be necessary to maintain cerebral perfusion in this setting, and aggressive blood pressure management could lead to worsening cerebral ischemia. For patients with suspected elevated intracranial pressure (ICP), ICP monitoring may be indicated to help maintain cerebral perfusion pressure during therapeutic interventions. American Heart Association guidelines, admittedly arbitrary

and not evidenced based, suggest a target MAP of less than 110 mm Hg or a blood pressure of less than 160/90 mm Hg while maintaining a reasonable cerebral perfusion pressure in patients with suspected elevated ICP.⁹ Based upon the results of INTERACT 1 and 2, which showed a decreasing trend in the primary outcome of death or severe disability, significant improvements in secondary functional outcomes, and reassuring safety data, many investigators advocate acute blood pressure reduction to a target systolic blood pressure of 140 mm Hg for patients with spontaneous IH.¹⁰

Hypertension and Cardiovascular Disease

Acute Coronary Syndrome

Patients presenting with acute myocardial ischemia and/or infarction frequently suffer from elevated MAP. The increased afterload raises the myocardial oxygen demand. Decreasing the heart rate and blood pressure in these patients will favorably decrease the myocardial oxygen demand and infarct size. However, a reduction in arterial pressure in this setting should be done cautiously. Potent systemic vasodilation without coronary vasodilation can lead to a decrease in coronary artery perfusion pressure and infarct extension. For this reason, nitroglycerin, a potent coronary vasodilator, is often the antihypertensive agent of choice in acute coronary syndromes. In combination with beta-blocker therapy, this approach can reduce cardiac workload significantly in the setting of ischemia.

Acute Left Ventricular Dysfunction

Hypertension in acute left ventricular dysfunction (LVD) may be the inciting event with secondary myocardial dysfunction, or alternatively a secondary component of acute pulmonary edema due to the sympathoadrenal response to hypoxemia, increased work of breathing, and anxiety. Regardless, efforts to control hypertension in LVD are essential to resolve increased myocardial workload and diastolic dysfunction. However, the use of vasodilators in patients with LVD and normal to low blood pressure can lead to hemodynamic instability, impaired organ perfusion, and, potentially, shock.

Intravenous vasodilators, including nitroglycerin and calcium channel antagonists, which permit rapid titration of blood pressure, are generally preferred in the setting of acute LVD. The dihydropyridine calcium antagonists nifedipine and clevidipine have been associated with reduced systemic arterial pressure with preservation of coronary blood flow. Patients with LVD may be initially hypertensive secondary to high initial catecholamine levels. With effective treatment or control of hypoxemia and anxiety, blood pressure may fall rapidly, especially in the setting of concomitant diuresis. Thus, longer-acting medications such as ACE inhibitors or ARB therapy are avoided early in the treatment period.

Patients with HE in particular may have suffered a natriuresis resulting in elevated levels of renin production by the kidney and, hence, increased circulating levels of the potent endogenous vasoconstrictor angiotensin II. Further reductions in intravascular volume and renal perfusion can lead to further increases in circulating angiotensin II levels. Therefore, aggressive diuresis before blood pressure control is not advised. Medications that increase cardiac work (e.g., hydralazine) or impair cardiac contractility (e.g., labetalol) are contraindicated as primary therapy for hypertension in the setting of LVD.

Acute Aortic Dissection

Aortic dissection results from an intimal tear in the aortic wall. The primary morbidity and mortality result from extension of that tear. Extension is promoted by factors that increase the rate of change of aortic pressure (dp/dt), including elevation in blood pressure, heart rate, and myocardial stroke volume. A high clinical suspicion is required, as the classic triad of chest pain, arm-leg BP differential, and a widened mediastinum is present in only one-quarter of cases.

Blood pressure in aortic dissection should be promptly reduced to near-normal levels. Combined modality therapy to promote vasodilation (nifedipine) and control cardiac contractility (beta-blocker) is

advocated for this disorder, with initial aggressive control of the heart rate (~60 beats per min). Isolated treatment with a vasodilator alone could precipitate a reflex tachycardia, increasing dp/dt.

Hypertension and Renovascular Disease

The kidney is both a source of mediators that promote hypertension (i.e., angiotensin II) and a target of high systemic arterial pressure. Chronic hypertension is second to diabetes mellitus as a primary cause of renal insufficiency. Elevated systemic arterial pressure should be regulated in patients with underlying renal insufficiency and a comprehensive workup initiated to determine the cause and effect relationship. Traditional vasodilator medications are preferred to ACE inhibitors in the acute setting because ACE inhibitors can compromise renal function.

Scleroderma Renal Crisis

Scleroderma renal crisis (SRC) is characterized by acute renal failure associated with moderate to severe hypertension and a normal to minimally abnormal urine sediment. Significant risk factors for SRC are the presence of diffuse scleroderma skin involvement and recent treatment with high-dose corticosteroids.¹¹ SRC results in marked activation of the renin-angiotensin system. Aggressive control of blood pressure using ACE inhibitors, particularly early in the disease process, controls blood pressure in up to 90% of patients and promotes recovery in renal function.¹¹

Hypertension in Excess Catecholamine States

Pheochromocytoma

Pheochromocytoma results in the production of circulating catecholamines, which causes hypertension, diaphoresis, tachycardia, and paresthesias of the hands and feet. These attacks can last from minutes to days and occur as frequently as several times a day or as infrequently as once per month. Operative manipulation of the tumor can result in perioperative hypertension. Hypertension therapy in this disorder must avoid the use of isolated therapy with a beta-blocker, a strategy that can lead to unopposed alpha-adrenergic stimulation with the risk of further vasoconstriction and blood pressure elevation. The preferred agents for treatment of hypertension due to pheochromocytoma are nitroprusside, nicardipine, and phentolamine, a potent alpha-adrenergic antagonist. If necessary, phentolamine can be combined with a beta-blocker or a combined alpha/beta-blocker such as labetalol, which can be used safely.

Pharmacologically Mediated Hypertension

The administration of exogenous substances (medications or illicit drugs) and/or abrupt withdrawal of substances can be associated with a hypertensive crisis. Rapid withdrawal or tapering of clonidine has been associated with a hyperadrenergic state characterized by hypertension, diaphoresis, headache, and anxiety. The syndrome is best treated by restarting the clonidine. If the symptoms are extreme, treatment is similar to that for the patient with pheochromocytoma. Hypertension can also occur during the withdrawal phase of alcohol abuse.

Monoamine oxidase (MAO) inhibitors can be associated with hypertension if the patient consumes foods or medications containing tyramine or other sympathomimetic amines. MAO inhibitors interfere with the degradation of tyramine in the intestine, leading to excess absorption and tyramine-induced catecholamine activity in the circulation.

Medications including metoclopramide, calcineurin inhibitors, cyclosporine, tacrolimus, and drugs of abuse, such as cocaine, phenylpropanolamine, phencyclidine, and methamphetamine must all be considered as possible factors in the intensive care patient with elevated systemic arterial pressure.

Hypertensive states may occur following spinal cord injury, particularly with stimulation of dermatomes and muscles below the level

of the injury. The blood pressure elevation is believed to result from excess stimulation of sympathetic neurons. The hypertension is accompanied by bradycardia through stimulation of the baroreceptor reflex. Treatment is focused on minimizing stimulation and providing medical therapy as necessary. Patients with Guillain-Barré can manifest a similar syndrome.

Hypertension and Miscellaneous Conditions

Preeclampsia/Eclampsia

Hypertension can occur in pregnant women or women in the postpartum period. Acute severe hypertension in the second half of gestation may occur in preeclampsia, gestational hypertension, or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. Hypertension occurs as one manifestation of preeclampsia in the pregnant patient; the other key features are proteinuria and edema. Severe hypertension, particularly systolic hypertension in pregnancy, can be associated with central nervous system injury including cerebral infarction and hemorrhage.

The optimal treatment of preeclampsia is delivery of the fetus, an approach that prevents progression to eclampsia. However, blood pressure should be regulated to prevent end-organ damage. The treatment goal is to achieve a range of 140-150/90-100 mm Hg.¹² Intravenous (IV) labetalol and hydralazine have been considered the first-line medications for the management of severe hypertension in pregnant and postpartum women, although more recent guidelines have included nifedipine.¹² Magnesium sulfate is not considered an antihypertensive agent but rather is administered for seizure prophylaxis in severe preeclampsia and eclampsia. Sodium nitroprusside (fetal defects), ACE inhibitors (renal dysfunction in fetus), and trimethaphan (meconium ileus) should be avoided.

Postoperative Hypertension

Postoperative hypertension most often occurs following vascular surgery procedures in patients with a background history of hypertension. The duration of postoperative hypertensive crisis is often brief (2-6 hours) but has been linked to postoperative cardiac and renal complications including bleeding from suture lines, intracerebral hemorrhage, stroke, and left ventricular dysfunction.¹³

Factors such as pain, anxiety, hypervolemia, hypoxemia, hypercarbia, and nausea are reversible factors that can contribute to postoperative hypertension and should be addressed. Postoperative hypertension is often limited in duration (2 to 12 hours), and aggressive attempts to lower blood pressure acutely can lead to delayed hypotension.

■ ANTIHYPERTENSIVE MEDICATIONS

A summary of the medications available for the treatment of elevated systemic arterial pressure is outlined in Table 5-1. Currently, the clinician has very limited comparative data to guide initial therapy for the patient with hypertension. Patients without end-organ dysfunction (HU) are best treated with oral agents, allowing a gradual reduction in blood pressure over 24 to 48 hours. In contrast, for patients with hypertensive emergency (HE), short-acting titratable medications provided in a monitored environment are preferred, as hypotension and compromised organ perfusion must be avoided. The sublingual and intramuscular routes should be avoided due to unpredictable pharmacokinetics. The conversion to oral therapy is timed to stable BP readings and no further progression in end-organ dysfunction.

Patients receiving nicardipine were more likely to have their BP controlled to prospectively defined target ranges at 30 min compared to those receiving labetalol in one of the few comparative effectiveness trials of nicardipine versus IV labetalol in the ED management of acute hypertension.¹⁴

Clevidipine was compared to three commonly employed medications for the treatment of postoperative hypertension (nitroglycerin (NTG), sodium nitroprusside (SNP), and nicardipine (NIC)).¹⁵ The

TABLE 5-1 Intravenous Antihypertensive Therapy

| MEDICATION (ROUTE) | PHARMACOLOGY | DOSING | INDICATION | CONTRAINDICATION |
|----------------------------------|--------------------------------------|---|--|---|
| NITRIC OXIDE VASODILATORS | | | | |
| Nitroprusside (IV infusion) | Onset: 2-3 min Duration: 2-3 min | Init: 0.25 to 0.5 mcg/kg/min Max: 2 mcg/kg/min | Most hypertensive emergencies | Contraindication in pregnancy. Caution with use in the settings of cerebral edema, acute coronary syndrome, or azotemia |
| Nitroglycerin (IV infusion) | Onset: 2-5 min Duration: 5-10 min | Init: 5 mcg/min Max: 200 mcg/min | Acute coronary syndromes | Contraindication in pregnancy. Caution with use in a volume-contracted patient |
| CALCIUM CHANNEL BLOCKERS | | | | |
| Nicardipine (IV infusion) | Onset: 5-15 min Duration: 4-6 h | Init: 5 mg/h Max: 15 mg/h | Most hypertensive emergencies | |
| Clevidipine (IV infusion) | Onset: 2-4 min Duration: 5-15 min | Init: 1-2 mg/h Max: 32 mg/h | Most hypertensive emergencies | Contraindicated with allergy to soybean or egg products. Contraindicated with defective lipid metabolism |
| MISCELLANEOUS MEDICATIONS | | | | |
| Labetalol (IV infusion, oral) | Onset: 2-5 min Duration: 2-4 h | Init: IV bolus 20 mg Repeat bolus 20-80 mg q 10 min Infusion: 1 to 2 mg/min | Most hypertensive emergencies | Contraindication in airflow obstruction, acute heart failure, or in patients nontolerant of beta-blockers |
| Phentolamine (IV) | Onset: 1-2 min Duration: 10-30min | Test dose: 1 mg Repeat 5 mg boluses or continuous infusion may be provided. | Pheochromocytoma Catecholamine withdrawal Catecholamine excess | |
| Enalapril | Onset: 15 min Duration: 12-24 h | 1.25-5 mg q 6 h | Scleroderma renal crisis | Caution with use in acute coronary syndrome. Not titratable |
| Hydralazine (IV, oral) | Onset: 10-20 min Duration: 2-4 h | Init: 10 mg q 20 min Max: 20 mg | Pregnancy | |

primary end point was safety as assessed by the incidence of death, stroke, myocardial infarction (MI), and renal dysfunction from the initiation of study drug infusion through postoperative day 30. There was no difference in the CLV-treated patients compared with the other treatment groups. However, mortality was significantly higher for SNP-treated patients compared to CLV-treated patients.

Nitric Oxide Vasodilators

Sodium nitroprusside (SNP) is a potent arterial and venous vasodilator that reduces preload and afterload. SNP was once the gold standard for the treatment of HE due to its short duration of action, allowing careful titration. The blood pressure response to SNP is rapid and mandates its use in a well-monitored environment with frequent blood pressure monitoring. The arteriolar and venous vasodilating activity of SNP may not be uniform, however. Redistribution of oxygenated blood flow from nonresponsive ischemic regions to vasodilated nonischemic coronary arteries can reduce coronary perfusion pressure, resulting in a "coronary steal" syndrome. A similar "cerebral steal" syndrome has been suggested with the use of SNP due to preferential vasodilation in systemic vascular beds versus cerebral vessels. Through dilation of large capacitance vessels, SNP can increase cerebral blood volume, leading to an increase in intracranial pressure that raises additional concerns in patients with increased ICP. SNP is rarely associated with cyanide or thiocyanate toxicity, occurring primarily in patients receiving infusions for greater than 24 to 48 hours, in the setting of underlying renal insufficiency, and/or the use of doses that exceed the capacity of the body to detoxify cyanide (more than 2 µg/kg per min). Despite the marked potency and rapidly titratable characteristics of SNP, the recognized adverse effects on cerebral and coronary blood flow combined with the potential toxicities have made newer alternative agents favored over SNP for the treatment of HE.

Nitroglycerin (NTG) is a coronary vascular dilation and a systemic venodilator that reduces myocardial preload. NTG demonstrates arterial smooth muscle effects only at higher dose infusions. The drug is

contraindicated in patients with significant volume depletion, as vasodilation in these patients will further lower preload, reduce cardiac output, and compromise overall systemic perfusion. When administered by the intravenous route, the medication has a relatively short duration of action. The drug has favorable effects for patients with acute coronary syndromes, including reducing myocardial oxygen demand via its effects on preload and afterload and augmenting myocardial oxygen delivery through its effects on the coronary circulation. Headache is the most common adverse effect of NTG, and methemoglobinemia is a rare complication of prolonged nitroglycerin therapy.

Calcium Channel Blockers

Calcium channel blockers (CCB) are a heterogeneous class of medications used in the treatment of hypertension emergency. Dihydropyridines, a specific class of CCB (e.g., nicardipine and clevidipine), are selective for vascular smooth muscle over the myocardium, with little if any activity in cardiac muscle or the sinoatrial node; thus, they have little effect on heart rate and no effect on myocardial contractility.¹⁶ The vascular smooth muscle relaxation without associated cardiac effects makes this class favorable for the treatment of hypertensive emergencies.

Nicardipine hydrochloride is a dihydropyridine CBB that acts primarily as a systemic, cerebral, and coronary artery vasodilator. The greater water solubility of this drug compared to other calcium channel blockers (e.g., nifedipine) allows intravenous administration with a short onset (5-15 min) and short duration of action; therefore, titration to a therapeutic effect is easy. Nicardipine readily crosses the blood-brain barrier and relaxes vascular smooth muscle, especially in regions of ischemic tissue. The medication acts as a vasodilator of small resistance cerebral arterioles but does not change intracranial volume or intracranial pressure with preservation of cerebral oxygenation.¹⁷ In comparison to SNP, nicardipine appears to offer equal efficacy with the advantage of avoiding the toxic metabolites of SNP, less frequent dose adjustments, and a decreased risk of increased intracranial pressure as

reported with SNP. Nicardipine has been shown to increase coronary blood flow with a favorable effect on myocardial oxygen demand.¹⁸ Nicardipine is metabolized by the liver, and excretion can be impaired in patients with liver disease.

Clevidipine is a third-generation dihydropyridine CCB available as a racemic mixture with poor water solubility, so the drug is administered by continuous IV infusion in a lipid emulsion. A new formulation of clevidipine has been available in the United States since 2011 and contains a retardant (0.005% disodium edetate) that inhibits microbial growth for up to 12 hours. Clevidipine reduces afterload without adversely affecting cardiac filling pressures or causing reflex tachycardia.¹⁹ Clevidipine has a rapid onset (~2-4 min) and offset of action (~5-15 min). It undergoes rapid ester hydrolysis by arterial blood esterases to form inactive metabolites, making medication clearance independent of renal or hepatic functional status.

Clevidipine is contraindicated in patients with allergies to soybeans, soy products, eggs, or egg products and in patients with defective lipid metabolism. Due to lipid-load restrictions, no more than 1000 mL or an average of 21 mg/h of clevidipine infusion is recommended per 24-hour period.

Clevidipine has shown favorable results in adult cardiac surgery patients with acute perioperative or postoperative hypertension, in acute hypertensive heart failure, and in patients with intracranial hemorrhage.^{20,21} Elevated triglyceride levels have been reported in patients who received clevidipine but these resolved with discontinuation of the medication.

Beta-Blockers

Esmolol is a short-acting, cardioselective beta-blocker with a rapid onset (<1 min) and short duration of action (10-20 min) that is only administered by continuous infusion. The short half-life requires bolus administration with each infusion titration. Esmolol reduces blood pressure, heart rate, and cardiac output and must be avoided in patients with bradycardia or impaired left ventricular function. Esmolol is optimally used in patients with tachycardia, hypertension, and normal to elevated cardiac output. Esmolol is rapidly cleared by red blood cell esterases and is independent of renal or hepatic function.

Labetalol is an oral and parenteral agent that acts as an alpha- and nonselective beta-adrenergic blocker with an alpha-to-beta blocking ratio of 1:7.²² The blood pressure-lowering effect is produced through a reduction in systemic vascular resistance without a compensatory increase in heart rate. In contrast to traditional beta-blockers, labetalol is associated with preservation of cardiac output. The hypotensive effect of labetalol has an onset of 2-5 min, peak effect at 5-15 min, and duration of ~2-6 hours. Labetalol has very little effect on cerebral circulation and is thus not associated with an increase in intracranial pressure in the normal brain. The drug has minimal placental transfer and has been used effectively in pregnancy-associated hypertension. The drug has been used effectively in patients with end-organ dysfunction in the setting of acute neurologic injury, pheochromocytoma, dissecting aneurysm, and eclampsia. The primary contraindication to the use of the medication relates to its nonselective beta-blocking

properties. The drug should be used cautiously in patients with reactive airway disease and heart block.

Miscellaneous Medications

Enalapril is an intravenously administered angiotensin converting enzyme (ACE) inhibitor. This medication reduces renin-dependent vasopressor activity, blocks the conversion of angiotensin I to angiotensin II, and blocks the degradation of bradykinin. ACE inhibitor administration is associated with a decrease in systemic vascular resistance, with minimal change in heart rate, cardiac output, or left ventricular filling pressure. Enalapril is effective in patients with low to normal renin levels and hypertension. The peak effect of enalapril may not be seen for up to 4 hours, with a duration of 12-24 hours. These pharmacokinetic parameters limit the drug titration in the acute setting of hypertensive emergency. ACE inhibitors are contraindicated in the setting of renal artery stenosis and pregnancy.

Phentolamine is a rapid-acting, alpha-adrenergic blocker. Phentolamine is often considered the drug of choice for hypertensive emergencies secondary to pheochromocytoma, MAO-tyramine interactions, and clonidine rebound hypertension.

Hydralazine is a direct-acting vasodilator with a latent onset (5-15 min) and a prolonged effect (~12-hour half-life) that can be highly variable. Because of hydralazine's prolonged and unpredictable antihypertensive effects, this medication is best avoided in the management of hypertensive emergency.

Diuretics should be avoided initially in the acute management of hypertensive emergency in the absence of pulmonary edema or renal parenchymal disease. Volume depletion is typical in HE patients and these patients are susceptible to hypotension and compromised perfusion if vasodilators and diuretics are initiated together.

KEY POINTS

1. Although hypertensive emergency (HE) is typically associated with a blood pressure elevation >180/110 mm Hg, the diagnosis of HE is based on the patient's clinical signs and symptoms rather than a specific blood pressure level.
2. Clinical conditions associated with HE include hypertensive encephalopathy, intracranial hemorrhage, acute coronary syndrome, acute pulmonary edema, aortic dissection, acute renal failure, and eclampsia.
3. Patients with hypertensive urgency (without end-organ dysfunction) are best treated with oral agents, allowing a gradual reduction in the blood pressure over 24-48 hours.
4. Patients with hypertensive emergency (HE), should be treated with short-acting titratable medications that are administered in a monitored environment, as hypotension and compromised organ perfusion must be avoided.

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Assessment of hemodynamics is an important skill in the critical care setting. The goal of hemodynamic monitoring in a critically ill patient is to ensure adequate tissue oxygen delivery and end organ perfusion. Low systemic arterial blood pressures are commonly encountered in the clinical setting, and a thoughtful, systematic approach should be utilized.

INITIAL EVALUATION

Initial evaluation usually begins with assessment of blood pressure (BP) readings. However, one should not rely solely on these readings, as there is no “normal” BP for all patients, and a BP value in the “normal” range does not always equate with adequate tissue perfusion. For example, a patient with a history of poorly controlled chronic hypertension may be normotensive, not yet in critical condition, but cannot meet his or her body’s oxygen demand, resulting in evidence of significant anaerobic metabolism referred to as *cryptic shock*.¹ Conversely, a patient with cirrhosis or a pregnant patient may have adequate perfusion despite having a lower than normal BP.

Additionally, attention should also be given to the mean arterial pressure (MAP). It is important to keep in mind that the MAP is the sum of 2/3 diastolic and 1/3 systolic pressure. The MAP is the main determinant of the perfusion pressure or what pressure the organ sees. Safe levels of hypotension have historically been estimated to be anything greater than 2/3 MAP.^{2,3} Even more recently, it was found that an MAP less than 55 mm Hg during noncardiac surgery is independently associated with an increased risk of kidney and myocardial injury and has a moderate association with duration of surgery.⁴ A good initial goal should be to restore the patient to an MAP of 65 to 70 mm Hg, but the level should be adjusted to restore tissue perfusion as assessed on the basis of mental status, appearance, urine output, etc.⁵ Therefore, hypotension triage needs to be quick and purposeful in order to prevent potentially damaging long-term sequelae.

An initial bedside assessment of tissue perfusion should include evaluation of mental status, urine output, and skin findings (e.g., temperature, diaphoresis, mottling, and capillary refill). If any of these parameters is abnormal, a more urgent approach to treatment must be taken. A focused cardiac and pulmonary examination is essential: presence of jugular venous distention, an S₃ or S₄ heart sound, new or worsening murmurs, or muffled heart sounds, crackles or rales. Furthermore, a finding of absent breath sounds could be equally important, suggesting a pneumothorax.

All patients should have adequate IV access, preferably two patent 18-gauge or larger catheters. The patient should be monitored using a standard ECG monitor and pulse oximetry. A 12-lead ECG should be performed looking for evidence of myocardial ischemia. Chest radiography should be done and supplemental oxygen should be given. Complete blood counts, serum chemistry, lactate, arterial blood gas, random cortisol, coagulation panels, and cardiac enzymes should be drawn as part of the initial workup.

WHAT IS THE CAUSE?

A review of cardiovascular physiology is essential in order to help focus the differential diagnosis of a hypotensive patient. A clinician’s initial evaluation should be a global assessment (Fig. 6-1) of systemic vascular resistance (SVR) and cardiac output (CO). It is important to recall that $\text{pressure} = \text{flow} \times \text{resistance}$, where flow is CO and resistance is SVR.

Because CO is determined by stroke volume (SV) \times heart rate (HR), the presence of hypotension means that at least one of these parameters (e.g., SV, SVR, or HR) is abnormal.⁶ Assessment of HR is obvious by palpation of pulses or cardiac monitoring; however, assessing SV and SVR can be more challenging. Attention should be paid to systolic (SBP) and diastolic (DBP) blood pressures in the context of pulse pressure (PP = SBP – DBP). Diastolic pressure is a reasonable surrogate for systemic vascular resistance (SVR).

During systole, the SV is ejected into the proximal arterial conduits. Because more blood is being ejected than the peripheral circulation can accommodate in the arterioles, the arterial walls distend, increasing SBP in a way that is directly proportional to the SV and indirectly proportional to the capacitance (C) of the arterial wall. This relationship is represented by the following formula⁶:

$$\text{SBP} = \text{SV} \div C$$

That is, for a fixed SV, if capacitance is higher, the SBP is lower.

During diastole, the portion of the SV that was “stored” by the distention of the arterial walls during systole fills the peripheral arterioles, leading to a progressive decrease in BP until the next systolic phase. This is the diastolic pressure, a parameter that is directly related to the SVR and capacitance (i.e., low diastolic pressure = low SVR and/or capacitance).⁶ When using these basic cardiovascular principles to understand the cause of hypotension, it is important to remember the following: (1) capacitance does not change from heartbeat to heartbeat and (2) SV depends on preload, afterload, and contractility.

Low SVR is characteristic of a number of pathologic conditions, including sepsis, adrenal insufficiency, vasodilating medications, neurogenic shock, post-cardiopulmonary bypass (CPB) vasoplegia, and severe liver dysfunction. Decreased SVR should be suspected in the presence of a widened pulse pressure and low diastolic pressure.^{7,8}

Reduced SV can be due to decreased preload, decreased contractility, or increased afterload. The most common cause of inadequate preload is hypovolemia. Other causes of inadequate preload include increased intrathoracic pressure due to dynamic hyperinflation in mechanically ventilated patients^{9,10} or tension pneumothorax, pulmonary embolism,¹¹ mitral valve stenosis,¹² cardiac tamponade,¹³ and right ventricular failure.¹⁴ Decreased contractility can be caused by myocardial ischemia or infarction, cardiomyopathy, myocarditis, negative inotropic drugs, myocardial stunning after CPB, and direct myocyte toxins such as chemotherapeutic agents and inflammatory mediators (e.g., tumor necrosis factor [TNF] and interleukin 1-beta [IL-1 β]).¹⁵ A reduction in SV can be identified by decreased systolic BP and normal or narrow pulse pressure.

TREATMENT

Hypotension has been associated with higher morbidity and mortality in a variety of disease states, so until proven otherwise, hypotension should be considered synonymous with hypoperfusion and thus treated aggressively. A trial of at least 1.0 L of crystalloid should be infused to treat hypotension; the fear of pulmonary edema should not preclude the use of volume expanders in a patient who is not perfusing adequately.¹

There are several tools that aid in the workup of the hypotensive patient. The use of ultrasound at the bedside to evaluate inferior vena cava diameter (IVCd) has proven to be an accurate metric of volume responsiveness in mechanically ventilated and spontaneously

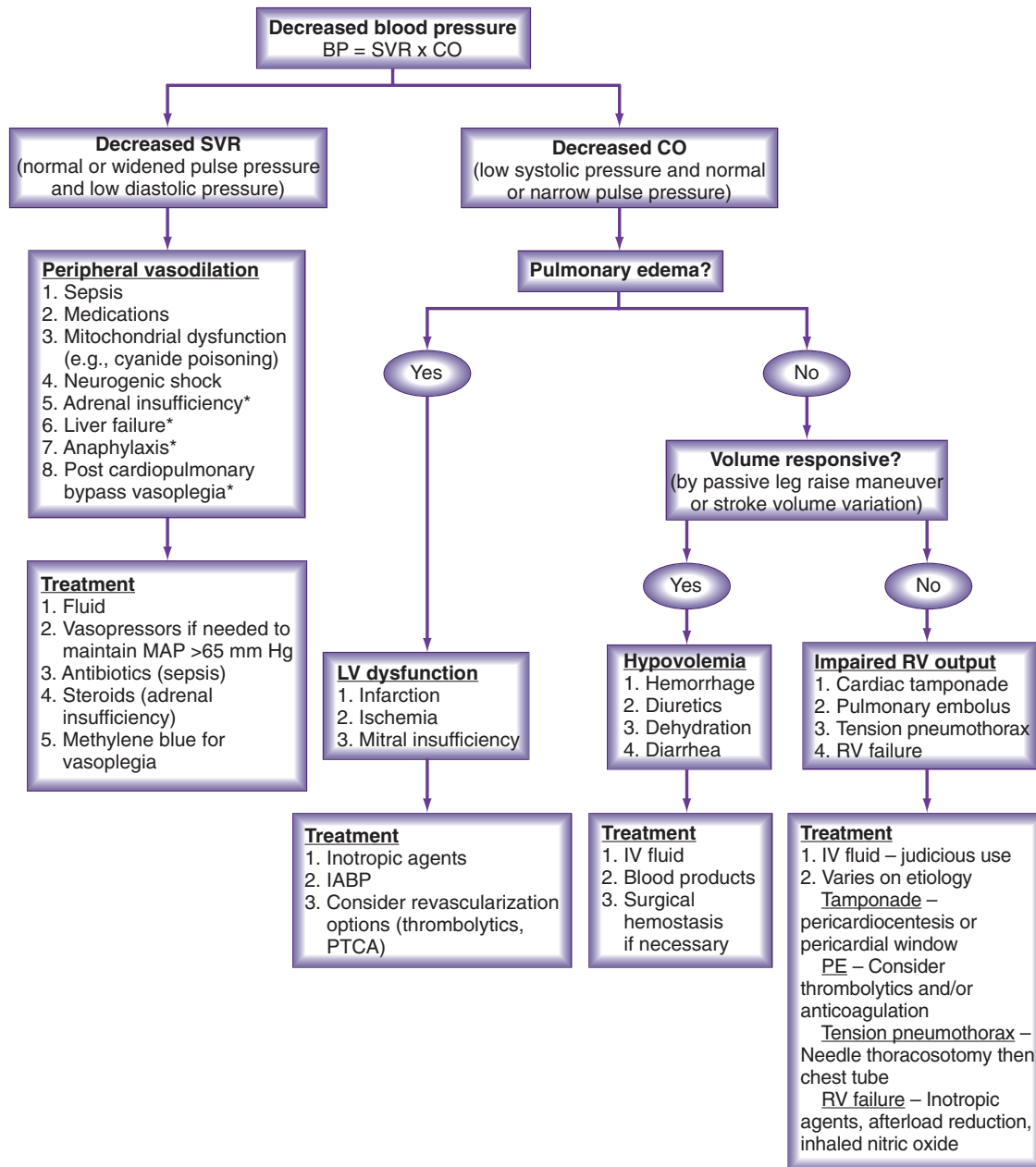


FIGURE 6-1 ■ Initial approach to a patient with low systemic arterial blood pressure. *Adrenal insufficiency, liver failure, post-cardiopulmonary bypass vasoplegia, and anaphylaxis are commonly listed as vasodilatory shock; however, data are inconclusive, and components of other types of shock (hypovolemic, cardiogenic) may also be present. BP, blood pressure; CO, cardiac output; IABP, intraaortic balloon pump; IV, intravenous; LV, left ventricle; MAP, mean arterial pressure; PE, pulmonary embolism; PTCA, percutaneous transluminal coronary angioplasty; RV, right ventricle; SVR, systemic vascular resistance.

breathing patients.¹⁶ IVCd is measured subcostally, approximately 0.5–4.0 cm below the junction of the IVC and right atrium, in the longitudinal direction at a perpendicular angle to the IVC, and is calculated as “the change” in IVCd during inspiration as compared with baseline (expiration).¹⁶ Patients with a large variation (>50%) will most likely respond to additional volume.¹⁷ Also, using ultrasound to perform a focused cardiac examination can identify the global quality of contractility, ventricular size and volume, obvious wall motion abnormalities, significant valvular abnormalities, and the presence of a pericardial effusion.¹⁸

Another method by which the clinician can evaluate “volume responsiveness” is the passive leg raise (PLR) test. In the nonintubated, supine patient, elevating the patient’s legs at a 45-degree angle above the plane of the bed will cause a rapid temporary increase in venous return to the heart and an increase in CO, which has been shown to correlate with a 500-cc bolus of normal saline.¹⁶ This maneuver increases pulse pressure in “responders.” An increase in pulse pressure of more than 9% noted before and after the passive leg lifts will identify patients who are likely to respond to additional IV fluid administration.^{19,20}

While more invasive than the above, pulse contour analysis (PCA) has emerged as an accurate method for measuring cardiac performance (SV, CO, CI) and also measures pulse pressure or stroke volume variation in the intubated and mechanically ventilated patient. By observing the undulation of the arterial line monitor for 30 seconds and observing the variability throughout the respiratory cycles, a decrease of 13% or more in stroke volume during the inspiratory cycle correlates with preload responsiveness of stroke volume. This variation represents a decrease in venous return in conjunction with the increased intrathoracic pressure during the inspiratory phase of ventilation. This measurement is only accurate when the heart rhythm is regular, so it is an unreliable index of preload responsiveness in patients with many kinds of arrhythmias, in the presence of an intraaortic balloon pump, or when there is loss of integrity in the arterial wave-

form. It is also only accurate in mechanically ventilated patients who are not experiencing large variations in intrathoracic pressures.^{21,22}

In those patients where a low SVR is suspected as the primary cause of hypotension, the treatment is different. Large amounts of additional IV fluid alone will not adequately increase the BP to maintain tissue perfusion. Vasoconstrictor agents (e.g., norepinephrine, dopamine, phenylephrine, and vasopressin) will be required in these patients. In certain specific cases, other pharmacologic adjuncts may be helpful. Low-dose hydrocortisone in vasoconstrictor-resistant septic shock²³ and methylene blue in post-CPB vasoplegia are two examples.²⁴

Many occurrences of hypotension may have some qualities of both decreased SV and decreased SVR. However, by using a systematic approach, the clinician can rapidly start diagnostic and therapeutic measures needed to treat tissue hypoperfusion.

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Cardiac arrhythmias are common in the intensive care unit (ICU), and the incidence can approach 40%. Critically ill patients are at a greater risk for developing arrhythmias because of elevated catecholamine levels, electrolyte imbalances, metabolic disturbances, the presence of invasive lines, polydrug therapy, and rapidly changing intravascular volume status.¹ Depending on the type of arrhythmia and the degree of physiologic reserve, patients can be asymptomatic or present with profound hemodynamic instability, including cardiopulmonary arrest. The presence of arrhythmias has been associated with prolonged hospital stays, increased risk of neurologic deficits, and greater in-hospital mortality rates.^{1,2} While definitive diagnosis requires an electrocardiogram (ECG), arrhythmias are generally classified according to their heart rate into one of two categories: tachycardias (heart rate > 100 beats per minute [bpm]) and bradycardias (heart rate < 60 bpm).

TACHYCARDIA

A key principle in managing the patient with tachycardia is to determine whether end-organ perfusion is being compromised as a result of the tachycardia or if the increase in heart rate represents a normal physiologic response to hemodynamic instability. Further evaluation includes identification of the type of tachycardia based on morphologic features. Specifically, tachycardias can be classified as supraventricular or ventricular in origin on the basis of the QRS complex. Tachycardia with a narrow QRS complex (<120 milliseconds [ms]) denotes a supraventricular tachycardia (SVT), while wide complex tachycardias (>120 ms) indicate either ventricular tachyarrhythmias or SVTs with associated conduction abnormalities.³

Sinus Tachycardia

Sinus tachycardia represents a form of SVT that occurs as a result of the impact of various stimuli on sinus node pacemaker cells.⁴ In critically ill patients, common causes of sinus tachycardia include hypoxia, acidosis, hyperthermia, pain, hypovolemia, and hyperthyroidism.³ Furthermore, a number of medications including inotropes, vasopressors, and anticholinergics can produce sinus tachycardia. Often sinus tachycardia is the appropriate physiologic response to an ongoing disease process, and treatment should be directed toward the underlying cause. Inappropriate treatment of sinus tachycardia may lead to hemodynamic collapse in situations where the tachycardic response was appropriate in order to compensate for hypovolemia or low cardiac output states. Conversely, sinus tachycardia can produce myocardial ischemia and decrease diastolic filling in patients with coronary artery disease. In these situations, β -blocker administration may decrease myocardial oxygen demand and mitigate the development of ischemia.³ The development of sinus tachycardia in a critically ill patient should prompt both a thorough review of medications and evaluation for evolving disease processes.

Supraventricular Tachycardia

Aside from sinus tachycardia, regular narrow complex SVT is typically associated with a reentry pathway. In hemodynamically stable patients, exercises that increase vagal tone will slow conduction through the

atrioventricular (AV) node and can effectively terminate many SVTs.⁴ Sequential carotid sinus massage (e.g., application of unilateral pressure on the carotid artery) and Valsalva techniques (e.g., expiration against a closed glottis) are examples of vagal maneuvers that can produce rapid arrhythmia resolution in the absence of pharmacologic therapy.⁵ If the arrhythmia is refractory to these interventions, the administration of an AV nodal blocking agent (e.g., adenosine, calcium channel blockers, and β -blockers) can be both diagnostic and therapeutic. Non-AV nodal dependent SVTs can be identified as conduction through the AV node is blocked, allowing visualization of the underlying atrial rhythm. Adenosine has the advantage over other AV nodal blockers as having the shortest onset and half-life times, although episodes of severe bronchospasm and degeneration into ventricular arrhythmias have been reported.^{3,5} For recurrent episodes of SVT following the use of adenosine, non-dihydropyridine calcium channel blockers or β -blockers can be used for both termination and suppression therapy. If the SVT remains refractory to AV nodal blockade, antiarrhythmic therapy with amiodarone or procainamide or catheter ablation may be required for definitive management.^{1,3}

Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia both in the general population and among adult ICU patients.^{1,6} AF occurs in up to 31% of critically ill patients, and ICU-specific risk factors include hypotension, the use of vasopressors or inotropes, septic shock, hypervolemia, heart failure, electrolyte derangements, and postoperative status.¹ Electrocardiographic features of AF include the lack of organized P waves, high-frequency fibrillation waves, and an irregular ventricular response.⁷ Physiologically, AF is characterized by the loss of the atrial contribution to ventricular filling, which normally accounts for approximately 25% of left ventricular end-diastolic volume.¹ This loss can be especially significant in patients with diastolic dysfunction, and pulmonary edema can develop as a result of the acute rise in left atrial pressure. Additionally AF is associated with increased risks of non-ST elevation myocardial infarction (NSTEMI), stroke, heart failure, longer hospital stays, reduced quality of life, and increased mortality.^{6,7,8}

In unstable patients with hemodynamic instability, AF should be treated with immediate synchronized cardioversion. Management of the hemodynamically stable patient with AF involves three treatment principles: rate control, rhythm control (cardioversion), and systemic anticoagulation. When comparing these strategies, rate control is not inferior to rhythm control for the management of AF.⁹ Rate control can be accomplished with the use of a number of medications, and β -blockers should be considered first-line agents. They provide more successful rate control than calcium channel blockers, and they may be especially effective in the postoperative period when sympathetic tone is high.^{1,3} If β -blockers are contraindicated or ineffective, non-dihydropyridine calcium channel blockers can be used as alternatives. Given their negative inotropic effects, calcium channel blockers should be avoided in patients with reduced ejection fraction. Amiodarone is an effective option for cardioversion in patients with depressed ejection fraction or those who are receiving inotropic support; however, pulmonary and thyroid toxicity can develop following its administration. Cardioversion rates with the use of amiodarone can approach 80%. The

time period between amiodarone administration and cardioversion can be prolonged, making amiodarone a poor choice if rapid conversion is needed.³ Digoxin has been traditionally recommended as an option for rate control; however, it is less efficacious in patients with high sympathetic tone, making its effectiveness in the ICU setting often marginal.³ Furthermore, the use of digoxin in patients with AF is associated with an increased risk for mortality.¹⁰ If AF persists for greater than 48 hours, systemic anticoagulation should be considered. The risk of stroke in nonanticoagulated patients with AF is 0.05% per day, but the risk of bleeding should be weighed against the risk of stroke for each patient before anticoagulation is initiated.³

Atrial Flutter

Atrial flutter is a reentry-mediated, narrow complex tachycardia that is characterized by a sawtooth pattern on the ECG. Atrial rates typically range from 250 to 350 bpm, and patients often present with 2:1 AV conduction with a corresponding ventricular rate of approximately 150 bpm.³ In critically ill patients with high levels of sympathetic tone, ventricular rates may be more rapid. Pharmacologic and anticoagulation management principles for atrial flutter are similar to those for AF, although it may be more difficult to achieve rate control in atrial flutter.¹ Furthermore, electrical cardioversion of atrial flutter can often be accomplished with lower energies than those required for AF. Success rates of electrical cardioversion in atrial flutter can range from 95% to 100%.³

Ventricular Tachycardia

Ventricular tachycardia (VT) accounts for 80% of all wide complex tachycardias.¹ VT can be classified as either monomorphic or polymorphic on the basis of the QRS morphology. Monomorphic VT is characterized by a uniform QRS morphology, and the approach to treatment is based on the presence or absence of hemodynamic instability.³ If the patient is unstable or manifesting with evidence of hypoperfusion, then synchronized cardioversion is indicated. If the patient presents with pulseless VT, then unsynchronized cardioversion should be performed. Stable monomorphic VT can be managed with antiarrhythmics, and the choice of agent depends on the degree of left ventricular dysfunction. Procainamide, amiodarone, sotalol, and lidocaine are treatment options for patients with preserved function. Sotalol and procainamide should be avoided in patients with impaired left ventricular function.^{3,5} Because of its superior efficacy, amiodarone is typically the drug of choice for stable monomorphic VT.¹ In addition to pharmacologic therapy, correction of electrolyte abnormalities and discontinuation of proarrhythmic agents are important management principles and should be performed concurrently.

Polymorphic ventricular tachycardia (PVT) is characterized by beat-to-beat variations in QRS morphology.¹ Unlike its monomorphic counterpart, PVT is almost never asymptomatic, and synchronized cardioversion should be performed immediately.³ PVT can occur in the setting of either a normal (<460 ms) or prolonged QT interval (>460 ms). When associated with QT prolongation, the syndrome is termed *torsades de pointes*, and management should be directed toward correcting the QT interval. Discontinuation of QT-prolonging medications, correction of electrolyte abnormalities, and magnesium administration should be performed in patients with PVT.^{1,5} If the arrhythmia persists, isoproterenol administration or overdrive pacing can be performed to increase the heart rate and shorten the QT interval.³

BOX 7-1

Common Causes of Bradycardia in the ICU

Medications: antiarrhythmics, β -blockers, calcium channel blockers, clonidine, dexmedetomidine, digoxin, lithium, opioids, phenytoin, and propofol
 Age-related degeneration
 Cardiac ischemia
 Electrolyte abnormalities
 Elevated intracranial pressure
 Elevated vagal tone
 Endotracheal intubation
 Hypertension
 Hypothermia
 Hypothyroidism
 Hypoxia
 Inflammatory disease
 Obstructive sleep apnea
 Post cardiac surgery

BRADYCARDIA

In general, bradyarrhythmias arise from abnormalities in impulse generation or impulse conduction. Diminished sinus node function manifests with sinus bradycardia, while heart block occurs as a result of disease in the AV node or His-Purkinje system.¹¹ The degree of heart block is determined by the extent of AV impulse conduction. In first-degree heart block, all impulses are conducted, but the rate of conduction is slowed. This condition is reflected by a prolonged PR interval (>200 ms) on the ECG. Second-degree heart block is characterized by intermittent AV conduction and can be divided into two types. Type I second-degree block presents with progressive PR interval prolongation prior to a nonconducted P wave. Type II second-degree block presents with constant PR intervals before and after a nonconducted P wave. Third-degree heart block presents with absent AV conduction.¹¹ In critically ill patients, bradycardia is often a consequence of pharmacologic therapy, underlying comorbid disease, or progressive respiratory failure. Scenarios associated with the development of bradyarrhythmias include elevated intracranial pressure, high vagal tone, hypothyroidism, hypothermia, and cardiac ischemia (Box 7-1). As with tachycardia, the most important principle in evaluating the patient with bradycardia is to determine if perfusion is being compromised as a result of the arrhythmia. Ultimately, appropriate treatment is dependent both on the type of bradycardia and the context in which it arises.

No treatment is indicated for asymptomatic bradycardia. Bradycardia may decrease cardiac output in patients with fixed stroke volumes, and the initial treatment for bradycardia-induced hypoperfusion is intravenous atropine.³ Medications with β -agonist activity (e.g., dopamine, dobutamine, isoproterenol, and epinephrine) can provide temporary support if the bradyarrhythmia is refractory to atropine administration. Concurrent investigation into the underlying cause of the bradycardia should be performed, especially focusing on medication side effects and declining respiratory status. The ECG should then be evaluated for the presence of myocardial ischemia and heart block. Patients with first-degree and type I second-degree blocks can often be managed conservatively. Type II second-degree and third-degree blocks require pacemaker placement.¹¹ In the acute setting, temporary pacing may be required to restore end-organ perfusion.¹ Depending on the clinical scenario, temporary pacing in the ICU can be accomplished using transcutaneous, transvenous, and epicardial modalities.

KEY POINTS

1. Determination of whether tachycardia is the cause of hemodynamic instability or the physiologic response to instability is important.
2. Sinus tachycardia is often a manifestation of an ongoing disease process and is best managed by treating the underlying cause.
3. Management of the hemodynamically stable patient with atrial fibrillation involves three treatment principles: rate control, rhythm control, and systemic anticoagulation.
4. Discontinuation of QT-prolonging medications, correction of electrolyte abnormalities, and magnesium administration should be performed in patients with polymorphic ventricular tachycardia.
5. No treatment is indicated for asymptomatic bradycardia. The initial treatment for symptomatic bradycardia is intravenous atropine.
6. Bradycardia that is refractory to atropine administration can be treated with inotropes and temporary pacing.

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To allow for normal aerobic cellular metabolism, oxygen needs to be transported from ambient air into the circulatory system before it is delivered to the end organs. Reduced arterial oxygen levels either in dissolved form (partial pressure of oxygen [PaO_2] less than 80 mm Hg) or percent bound to hemoglobin (SaO_2 less than 95%) define *hypoxemia*. In contrast, inadequate oxygen content of the tissue beds of organs defines *hypoxia*. Since the lungs facilitate the transport of oxygen from ambient air to the circulatory system, respiratory failure commonly results in hypoxemia and often requires intensive care management. Left unchecked, arterial hypoxemia can lead to end-organ hypoxia and dysfunction, most devastatingly anoxic brain injury and cardiac arrest.

SaO_2 varies with PaO_2 in a nonlinear relationship, affected by temperature, partial pressure of carbon dioxide in arterial blood (PaCO_2), pH, and 2,3-diphosphoglycerate concentration (Fig. 8-1). As a result, patients can have a higher or lower SaO_2 for a given PaO_2 , depending on the existing metabolic conditions. The critical threshold of PaO_2 is 60 mm Hg, below which further decrements in PaO_2 result in more significant reductions in SaO_2 compared to when PaO_2 is >60 mm Hg.

Because arterial oxygen is overwhelmingly bound to hemoglobin (Hb) instead of being dissolved in plasma, SaO_2 is considered a better reflection of arterial oxygen content (CaO_2) compared to PaO_2 :

$$\text{CaO}_2 = (\text{SaO}_2 \times \text{Hb} \times 1.34) + (0.003 \times \text{PaO}_2),$$

where 1.34 is the amount of oxygen (mL) per gram of hemoglobin. While PaO_2 is less of a factor for CaO_2 compared to SaO_2 , increasing supplemental oxygen to increase PaO_2 to supranormal levels can improve the time window for medical interventions that may result in hypoxemia, such as endotracheal intubation or bronchoscopy.

PaO_2 and SaO_2 are measured by arterial blood gas analysis, which is invasive and not measured continuously. Peripheral oxygen saturation (SpO_2) serves as a surrogate measure of SaO_2 and can be measured noninvasively and continuously with a pulse oximeter. Pulse oximetry determines SpO_2 using spectrophotometry to detect oxyhemoglobin (peak absorption at 940 nm) and deoxyhemoglobin (peak absorption at 660 nm) isolated to the pulsatile signal through tissue (e.g., fingertip or earlobe). As a result, its accuracy may be affected by various factors. The SpO_2 can present a falsely low reading if there is a poor pulsatile waveform, which can occur when there is poor cutaneous perfusion. Light transmission through the tissues of the fingertip can be decreased by dark blue or black nail polish. Methemoglobinemia can result in a falsely low SpO_2 reading, whereas carboxyhemoglobinemia can result in a falsely elevated SpO_2 reading.¹

It takes seconds to minutes for the SpO_2 to reflect treatment changes for arterial hypoxemia (e.g., increase or decrease of supplemental oxygen). Longer response times are expected if the probe is placed farther away from the heart, when the blood flow to the area of the probe is reduced, and when there is reduced cardiac output.^{2,3} The delay between a treatment intervention and the SpO_2 response needs to be considered when making decisions regarding the escalation and de-escalation of oxygen therapy.

CAUSES OF ARTERIAL HYPOXEMIA

Once hypoxemia is detected, in addition to initiating oxygen therapy, the cause for hypoxemia must be determined. Etiologies for hypoxemia can be categorized as follows:

1. Reduced fraction of inspired oxygen (FiO_2) or partial pressure of oxygen (e.g., breathing at elevation)
2. Hypoventilation (e.g., central respiratory depression, neuromuscular weakness, and chest wall deformity)
3. Diffusion impairment
4. Ventilation/perfusion mismatch
5. Presence of a pulmonary shunt

Reduced Alveolar Oxygenation and Hypoventilation

Alveolar oxygenation (PAO_2) is defined by the equation:

$$\text{PAO}_2 = \text{FiO}_2 (\text{Patm} - \text{PH}_2\text{O}) - \text{PaCO}_2 / \text{RQ},$$

where FiO_2 is the concentration of inspired oxygen, P_{atm} is the atmospheric pressure, PH_2O is the partial pressure of water, and RQ is the respiratory quotient.^{4,5} RQ represents the amount of oxygen consumed relative to the amount of carbon dioxide produced when nutrients are metabolized. RQ is generally assumed to be 0.8, under the assumption that glucose is the predominant metabolic fuel. Under normal conditions at sea level,

$$\text{PAO}_2 =$$

$$0.21 (760 \text{ mm Hg} - 47 \text{ mm Hg}) - (40 \text{ mm Hg} / 0.8) \approx 100 \text{ mm Hg}.$$

According to the equation, PAO_2 decreases with decreased FiO_2 and/or decreased Patm , which can occur when climbing at high altitudes.⁶ PAO_2 can also be reduced with increased PaCO_2 , which in turn is determined by the following equation:

$$\text{PaCO}_2 =$$

$$\text{CO}_2 \text{ production} \div (\text{respiratory rate} \times [\text{tidal volume} - \text{dead space}]).$$

Thus, PaCO_2 increases with an increase in production, a decrease in the minute ventilation, and/or an increase in dead space ventilation. Hypoventilation from central respiratory depression, neuromuscular weakness, or other conditions that decrease minute ventilation or increase dead space ventilation can therefore lead to hypoxemia from reduced PAO_2 .

To summarize, reduced inspired oxygen content and reduced ventilation can both contribute to arterial hypoxemia. However, in the case where neither of these is a contributing factor, hypoxemia must be the result of either diffusion impairment or more commonly a ventilation/perfusion mismatch.

Diffusion Impairment

Diffusion impairment is the least likely cause of hypoxemia in the intensive care unit and can result from an increase in the diffusion distance between the alveolar space and the capillary lumen, a reduction in the total alveolar surface area, or a reduction in the capillary transit time. Increases in sympathetic tone due to fever, anemia, work of breathing, or sepsis can each increase the cardiac output and heart rate, resulting in faster transpulmonary transit times. With less opportunity for alveolar oxygen to diffuse into the red blood cells, diffusion capacity is reduced and hypoxemia ensues.

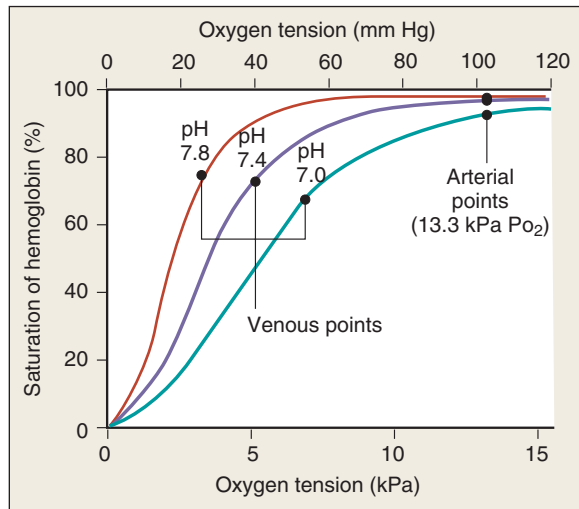


FIGURE 8-1 ■ Oxygen saturation varies with the PaO_2 in a nonlinear relationship and is affected by temperature, PaCO_2 , pH, and 2,3-diphosphoglycerate (2,3-DPG) concentration.

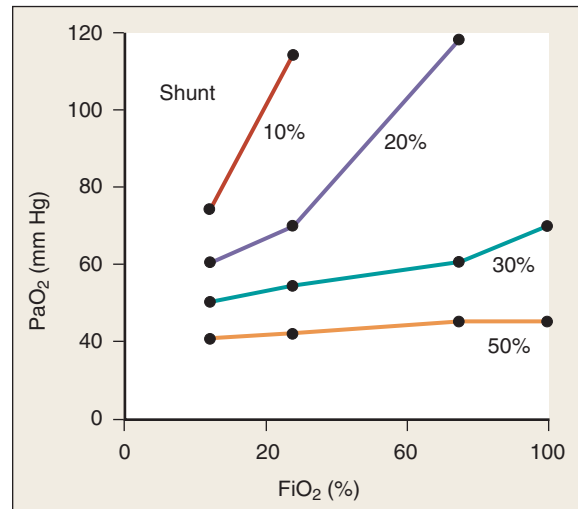


FIGURE 8-3 ■ Blunted response to increasing inspired oxygen concentration. A patient with a shunt greater than 50% has little response to increasing FiO_2 .

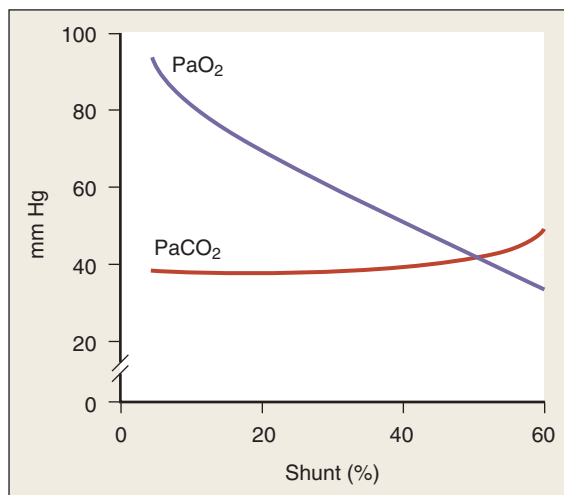


FIGURE 8-2 ■ Decrease in PaO_2 with increasing shunt fraction.

Ventilation/Perfusion Mismatch and Shunting

The most common cause of hypoxemia is ventilation/perfusion mismatch, specifically when areas of reduced alveolar ventilation have relatively preserved or even supranormal levels of blood perfusion. Typically, alveolar filling or collapse (due to edema, pneumonia, hemorrhage, tumor, or atelectasis) results in unventilated or poorly ventilated areas of lung. Under normal conditions, the hypoxic pulmonary vasoconstriction reflex reduces perfusion to under-ventilated areas of lung to minimize hypoxemia, but if the adaptive mechanisms that are responsible for hypoxic vasoconstriction are dysfunctional, then perfusion of under-ventilated areas can continue. As a consequence, an increased fraction of the cardiac output will not participate in gas exchange. The portion of cardiac output that does not participate in gas exchange is called the shunt fraction. The normal shunt fraction is approximately 3%, and this small amount of shunt is due to the bronchial arterial circulation. Reduced ventilation of perfused alveoli increases the shunt fraction. As the shunt fraction increases, PaO_2 decreases (Fig. 8-2), and there is a blunted response to increases of FiO_2 . When the shunt fraction is $>50\%$, there is little response to increases of FiO_2 (Fig. 8-3). As such, severe ventilation/perfusion mis-

matching can result in a shunt where hypoxemia is refractory to treatment with supplemental oxygen.

Anatomic right-to-left shunts, such as intracardiac shunts and intrapulmonary shunts resulting from either arterial-venous malformations or end-stage liver disease, can also result in hypoxemia refractory to supplemental oxygen.

Pulmonary perfusion is normally distributed in a dependent manner, with dependent areas preferentially perfused compared to nondependent areas. As a result, changes in the patient's physical position can lead to changes in arterial oxygenation, depending on the location and distribution of the under-ventilated lung areas or the regions of intrapulmonary shunt. If the patient is positioned such that the under-ventilated areas of the lung or the regions with the intrapulmonary shunt are located in a more dependent way, then preferential perfusion of these areas will result in an increased shunt fraction and worse hypoxemia. For example, an intrapulmonary shunt in the bases of the lungs can lead to platypnea-orthodeoxia, i.e., dyspnea and hypoxemia that are worse in the upright position compared to the supine position.

While reduced ventilation with preserved perfusion typically causes hypoxemia, preserved alveolar ventilation with reduced perfusion typically results in increased functional dead space, and thus hypercarbia, which is usually overcome by increased minute ventilation. Areas of reduced perfusion can result from pulmonary vascular disease such as pulmonary emboli, pulmonary arterial hypertension, or reduced cardiac output. Pulmonary vascular disease per se does not result in hypoxemia unless there is also reduced alveolar ventilation or diffusion impairment. Another way pulmonary vascular disease can lead to hypoxemia is if high pulmonary vascular resistance results in elevated right heart pressures and an intracardiac right-to-left shunt via, for example, a patent foramen ovale.

MEASURES OF ARTERIAL HYPOXEMIA

Aside from PaO_2 , SaO_2 , and SpO_2 , hypoxemia can be assessed by other measures. The difference between the PAO_2 and the PaO_2 , termed the *A-a gradient*, is used to estimate the extent of pulmonary pathophysiology and to exclude the effects of hypercarbia on PaO_2 .^{4,5} However, the A-a gradient increases with age or increasing FiO_2 , limiting its reliability.^{7,8} Nevertheless, the upper limit of the normal A-a gradient can be estimated using the following equation:

$$\text{A-a gradient} < (\text{age} \div 4) + 4.$$

The $\text{PaO}_2/\text{FiO}_2$ ratio and $\text{PaO}_2/\text{PAO}_2$ ratio are also used to describe the severity of hypoxemia. They both are influenced by increasing FiO_2 .^{7,9}

MANAGEMENT OF ARTERIAL HYPOXEMIA

If a patient has low SpO_2 , the initial treatment is supplemental oxygen with observation of the response, pending evaluation of the hypoxemia. If the response to the initial increase in FiO_2 is poor, a better response may be achieved by increasing the flow rate of supplemental oxygen (e.g., using a high-flow nasal cannula or Venturi mask) or using

a reservoir of 100% oxygen (i.e., using a “nonrebreather mask”). If the response to the escalation of FiO_2 is poor, then the patient likely has severe ventilation/perfusion mismatching or a true right-to-left shunt. Satisfactory improvement in arterial oxygenation under these conditions usually requires positive pressure ventilation and the application of positive end-expiratory pressure (PEEP) using noninvasive ventilation or endotracheal intubation. If the patient has severe hypoxemia and is unstable, immediate bag-and-mask ventilation and early endotracheal intubation should take precedence over establishing a diagnosis.

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Acute respiratory failure (ARF) is defined by the sudden onset of severe impairment of pulmonary gas exchange and is characterized by the inability of the lungs to meet the body's metabolic needs for the transport of oxygen (O_2) into the blood and/or removal of carbon dioxide (CO_2) from the blood. The diagnosis of ARF is based on the measurements of arterial blood gas (ABG) parameters (i.e., PaO_2 , $PaCO_2$, and pH). These values must be interpreted in relation to the patient's baseline status. As a final common pathway for a variety of illnesses, ARF is one of the most frequently encountered diagnoses in the intensive care unit (ICU), and its management represents one of the key aspects of critical care medicine. This chapter aims to tie together the physiology of breathing to the pathological processes that lead to ARF and to discuss the clinical approach to the patient with ARF.

ARF is one of the most common reasons for admission to the ICU, and almost 330,000 patients in the United States are annually diagnosed with this disorder.¹ More than half of the patients admitted to the ICU with stays >48 hours have ARF at some point during their hospitalization,² with overall mortality rates quoted as being $\geq 34\%$.²⁻⁵ Mortality significantly increases with age, preexisting comorbidities, and the presence of shock or multisystem organ failure.⁶ With the aging population in the United States, the incidence of patients with ARF is expected to increase by 80% over the next two decades.

COMPONENTS OF THE RESPIRATORY SYSTEM

Understanding the process of respiration is a key step in understanding and managing ARF. Respiratory control is established by the tight coordination of three groups of neurons in the medulla oblongata: a dorsal respiratory center that controls inspiration, a ventral respiratory group that controls expiration, and a pneumotaxic center that controls the rate and depth of breathing. In addition to neurons in the brainstem, a peripheral chemoreceptor system is located outside the brain in the form of carotid bodies and aortic bodies and detects subtle changes in PaO_2 . The neural impulses from the central nervous system (CNS) traverse the spinal cord and motor neurons, reaching and activating the diaphragm and other respiratory muscles. Contraction of the respiratory muscles creates negative pleural pressure by expanding the chest cavity and pushing the abdominal contents down. The negative pressure created in the thorax during inspiration leads to subatmospheric pressure in the alveoli, creating a gradient for the flow of inspired air toward the alveoli. Oxygen-rich inspired air allows the diffusion of O_2 from the alveoli to the blood through the alveolar-capillary membrane, where deoxygenated hemoglobin becomes saturated with O_2 and forms oxyhemoglobin.

O_2 is consumed by all human tissues, and oxygen consumption (QO_2) is dependent on gas exchange in the lungs. The average O_2 uptake of an adult is approximately 250 mL/min, although this depends upon numerous factors.⁷ Most (~98.5%) O_2 is carried to peripheral tissues via oxyhemoglobin, whereas the remainder is transported as O_2 dissolved in the fluid phase of blood. The total transport of O_2 by the arterial system is termed *oxygen delivery* (DO_2) and is normally several-fold higher than the O_2 demand of the peripheral tissues. However, O_2 utilization (VO_2) can become dependent on DO_2 in pathological conditions such as ARF.⁷⁻⁹ In these states, the relationship between oxygen delivery and oxygen demand can be disrupted due to decreased delivery or increased demand (Fig. 9-1).

DO_2 is dependent on cardiac output and arterial oxygen content (CaO_2), a value determined by the concentration of hemoglobin (Hgb) and oxygen saturation (SaO_2) (Fig. 9-2). The adequate perfusion of capillaries in the peripheral tissues allows for the liberation of O_2 from oxyhemoglobin.

PATHOPHYSIOLOGICAL PROCESSES LEADING TO ARF

It is important to understand the various etiologies and mechanisms leading to hypoxemia (Table 9-1), since interventions may vary and oxygen support may have different effects in different situations.

CLASSIFICATION OF ARF

Respiratory failure can be classified as acute or chronic. The clinical presentation of ARF is typically dramatic and obvious, often with profound derangements in ABG values. "Acute on chronic" respiratory failure represents an acute deterioration in the presence of preexisting chronic pulmonary disease and chronic respiratory dysfunction. Chronic respiratory dysfunction may present with markers of chronic hypoxemia (e.g., polycythemia or *cor pulmonale*) and may or may not require ICU care. Regardless of acuity, respiratory failure represents a life-threatening group of disorders for which inadequate management may lead to rapid clinical deterioration.

ARF has been classically described as one of two types: hypoxemic or hypercapnic failure. More recent classifications categorize ARF into four different types, based on the mechanism of hypoxemia.¹⁰ Table 9-2 describes differences among the four types of ARF with regard to the mechanism of hypoxemia, location of the abnormality, and most commonly seen clinical syndromes. Despite these categories, there exists considerable overlap in the different types of ARF. Furthermore, a given patient can have multiple types of ARF contributing to his or her clinical representation.

Type I or Classic "Hypoxemic" Respiratory Failure

Type I ARF is the most common form of respiratory failure and is defined by $PaO_2 < 60$ mm Hg, with normal or decreased $PaCO_2$. The primary abnormality is located in one of three sites: 1) inadequately oxygenated alveoli (due to low FiO_2 and/or alveolar collapse and/or the presence of alveoli filled with fluid, cells, debris, or blood); 2) compromised transition of oxygen from the alveoli to the blood (due to interstitial processes or pulmonary vascular disease); or 3) compromised ability of the blood to become oxygenated (due to obstructed blood flow, shunting, low Hgb concentration, or the presence of dysfunctional Hgb). The analysis of ABG values and calculation of the alveolar-arterial (A-a) gradient are important for the assessment of type I ARF.

Type II or "Hypercapnic" Respiratory Failure

Type II ARF ($PaCO_2 > 45$ mm Hg) represents the failure of the lungs to remove a sufficient amount of CO_2 and is characterized by decreased alveolar minute ventilation. An increase in $PaCO_2$ leads to hypoxemia because CO_2 displaces O_2 and effectively reduces the alveolar partial pressure of oxygen (PAO_2). In contrast to some cases of type I ARF,

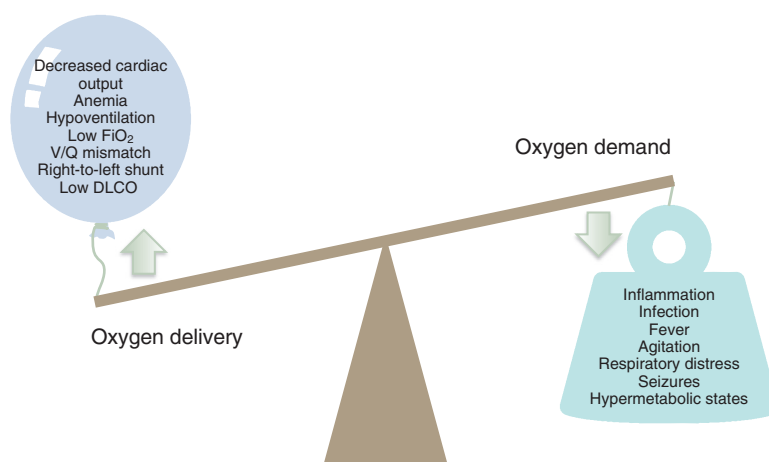


FIGURE 9-1 ■ Compromised oxygenation of peripheral tissues may be the consequence of inadequate O_2 delivery or increased O_2 demand.

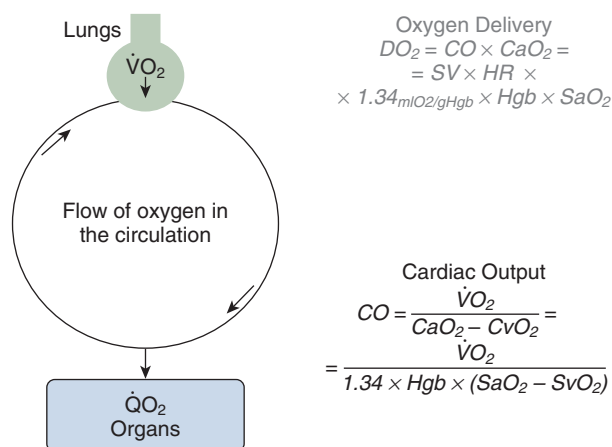


FIGURE 9-2 ■ The Fick principle establishes the relationship of O_2 uptake/consumption by peripheral tissues, cardiac output, and oxygen content in arterial and venous compartments ($\dot{V}O_2$, oxygen uptake; $\dot{Q}O_2$, oxygen consumption rate; DO_2 , oxygen delivery; CO , cardiac output; CaO_2 , arterial oxygen content; SV , stroke volume; HR , heart rate; Hgb , hemoglobin; SaO_2 , arterial oxygen saturation; SvO_2 , mixed venous oxygen saturation).

hypoxemia in type II ARF is easily corrected with supplemental oxygen. This type of respiratory failure is frequently due to acute or chronic neuromuscular dysfunction or the inability of the airways or lungs to ensure adequate ventilation and CO_2 exchange.

Type III or “Perioperative” Respiratory Failure

Type III respiratory failure is synonymous with perioperative respiratory failure and is related to atelectasis of the lung. It is often a consequence of abnormal abdominal and chest wall mechanics in the setting of surgery or trauma, especially with intrapleural or subdiaphragmatic pathologies. The patient usually splints the chest to limit involuntary movement of the injured region, leading to inadequate expansion of the dependent parts of the lungs, with resultant regional atelectasis and hypoventilation. As a result, type III ARF shares features with both type I (hypoxemic) and type II (hypercapnic) ARF. This type of ARF can be prevented or ameliorated by certain anesthetic strategies as well as perioperative measures such as elevating the head of the bed, early

TABLE 9-1 Pathophysiological Mechanisms That Lead to Hypoxia and Respiratory Insufficiency

- Extrapulmonary processes including chest wall and skeletal abnormalities (hypoxic hypoxia)
 - Deficiency of oxygen in inspired air (high altitude, suffocation)
 - Hypoactive hypoventilation (central nervous system trauma, drug toxicities, and neuromuscular and skeletal disorders)
 - Upper airway obstruction leading to hypoventilation (trauma and angioedema)
- Pulmonary etiologies (hypoxic hypoxia)
 - Hypoventilation caused by increased airway resistance (chronic obstructive pulmonary disease and asthma)
 - Abnormal alveolar ventilation-perfusion ratio (pulmonary embolism, pneumonia, aspiration, and emphysema)
 - Diminished diffusing capacity via the alveolar-capillary membrane (interstitial lung disease and pulmonary vascular disease)
 - Pulmonary shunting (atelectasis, pneumonia, hepatopulmonary syndrome, and arteriovenous malformations)
- Cardiac right-to-left shunts; e.g., atrial septal defect (hypoxic hypoxia)
- Inadequate capacity of blood to transport oxygen (anemic hypoxia)
 - Anemia
 - Hemoglobinopathies (methemoglobinemia and carbon monoxide poisoning)
- Inadequate oxygen transport due to a circulatory defect (static hypoxia)
 - General circulatory deficiency or collapse (shock or cardiac failure)
 - Localized circulatory deficiency (peripheral, cerebral, and coronary vessels)
- Abnormal tissue capability for using oxygen (histotoxic hypoxia)
 - Late-stage irreversible shock
 - Poisoning of cellular oxidation enzymes (cyanide or arsenic toxicity and heavy ethanol intoxication)
 - Diminished cellular metabolic capacity for using oxygen (severe vitamin deficiencies; e.g., beri-beri)

ambulation, incentive spirometry, avoiding excessive sedation, and lowering intraabdominal pressure.

Type IV or “High-demand” Respiratory Failure

Type IV respiratory failure is related to an inability of (normal or relatively normal lungs) to keep up with increased ventilatory demands associated with systemic hypermetabolism (e.g., secondary to sepsis). Under these conditions, respiratory muscle fatigue can lead to a

TABLE 9-2 Classification of Acute Respiratory Failure (Modified From¹⁰)

| | TYPE I | TYPE II | TYPE III | TYPE IV |
|---|--|---|---|--|
| MECHANISM OF HYPOXEMIA | Low FiO ₂ ventilation/perfusion (V/Q) mismatch Shunting Reduced diffusing capacity | Hypoventilation | Shunting Hypoventilation V/Q mismatch | Hypoperfusion or inadequate oxygenation of peripheral tissues |
| LOCATION OF PATHOLOGICAL PROCESS | Inhaled air composition Alveolar-capillary unit Oxygen-carrying capacity of blood | Airway Central nervous system (CNS) Neuromuscular system Chest wall | Alveolar-capillary unit collapse with regional hypoventilation | Cardiovascular system Peripheral tissues |
| CLINICAL SYNDROMES | Cardiogenic pulmonary edema Acute respiratory distress syndrome Pneumonia Interstitial lung disease Pulmonary embolism Pulmonary hypertension Atelectasis Alveolar hemorrhage Carbon monoxide poisoning Anatomic shunts | Chronic obstructive pulmonary disease Asthma CNS depression (intoxication) CNS trauma or injury Neuromuscular disorders Skeletal disorders Obesity-hypoventilation syndrome | Thoracic or upper abdominal surgery or trauma Inadequate postoperative analgesia Pleural tumor or inflammation Trapped lung Subdiaphragmatic tumor or inflammation Obesity | Septic (distributive) shock Hypovolemic shock Cardiogenic shock Compromised cellular oxidation Hypermetabolic states |

TABLE 9-3 Common Clues Obtained from the History, Symptoms, and Clinical Examination Findings That Can Help in the Initial Diagnostic Workup and Management of Acute Respiratory Failure

| HISTORY AND SYMPTOMS | SIGNS ON PHYSICAL EXAMINATION | DIAGNOSIS |
|--|---|--|
| Cough, sputum, secretions | Rales or wheezing | Pneumonia, chronic obstructive pulmonary disease (COPD) exacerbation, bronchiectasis |
| Sudden onset of shortness of breath | Normal auscultation and percussion, possible signs of leg swelling to suggest deep vein thrombosis | Pulmonary embolism |
| History of heavy smoking | Wheezing, rhonchi | Emphysema, chronic bronchitis |
| Orthopnea, chest pain, paroxysmal nocturnal dyspnea | Arrhythmia, peripheral edema, jugular venous distention, peripheral hypoperfusion | Congestive heart failure or acute coronary syndrome |
| Trauma, aspiration, blood transfusions | Diffuse crackles | Acute respiratory distress syndrome |
| History of allergies, wheezing or airway disease | Wheezing | Asthma, COPD |
| Exposure to heavy metals, handling of animals, dust or other significant environmental exposures | "Velcro" rales, clubbing | Chronic interstitial lung disease |
| Choking, aspiration, vomiting, dental procedures | Inspiratory stridor, poor air entry | Foreign body |
| Drug abuse | Constricted or dilated pupils, altered mental status, skin marks, perforated nasal septum, hypersalivation, decreased respiratory frequency | Central nervous system depression, intoxication |
| Exposure to a new drug/chemical or foods known to be allergenic | Swollen oral mucosa and tongue; stridor or wheezing | Angioedema, anaphylaxis |
| Progressive muscle weakness or immobility | Sensory abnormalities | Neuromuscular disorders |
| Trauma, procedures, inhalational injury | Absent breath sounds unilaterally, hypertympanic, tracheal deviation | Pneumothorax |
| Trauma, procedures | Absent breath sounds, dull on percussion, tracheal deviation | Hemothorax |

requirement for mechanical ventilation (MV) to support adequate minute ventilation.

■ DIAGNOSTIC WORK-UP

Obtaining a history is crucial in narrowing down the etiology of ARF. A focused physical examination also helps to assess the severity of respiratory failure and to determine the need for immediate interventions. Common signs include tachypnea, the use of accessory respiratory muscles, nasal flaring, abdominal paradoxical breathing, and retractions in the intercostal, suprasternal, or supraclavicular areas. One can also see irregular breathing patterns or poor chest wall excursion

in addition to cough, wheezing, copious secretions, or cyanosis. A detailed examination of the upper airway and chest, as well as a careful neurologic, cardiovascular, abdominal, skin, and musculoskeletal system examination, may also help to narrow the differential diagnosis. Table 9-3 lists common clues obtained from the history and physical examination of the patient, which can help to diagnose the etiology of respiratory failure.

Prior to the comprehensive diagnostic work-up, it is important to remember that a diagnostic procedure should not be a reason for delayed intervention in cases of severe ARF. ABG analysis should be obtained in all patients with suspected ARF. ABG helps to determine the chronicity of the respiratory failure and, more importantly, the

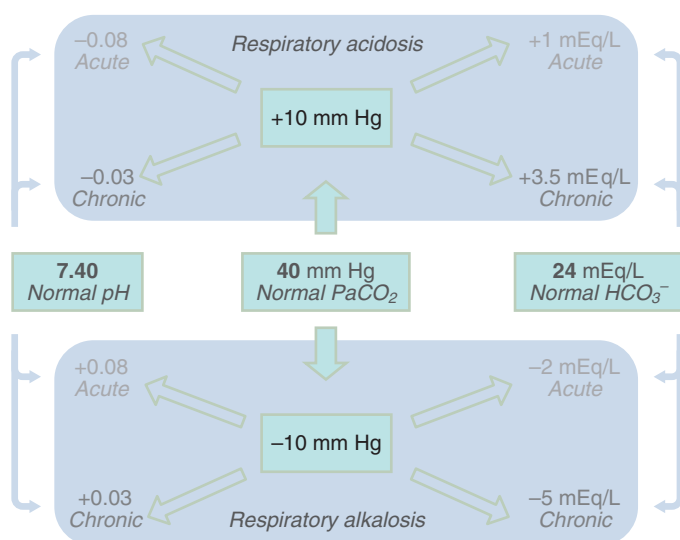


FIGURE 9-3 ■ Interpretation of an arterial blood gas in the setting of respiratory failure.

extent and severity of the ARF. Fig. 9-3 schematically displays the changes in ABG parameters in acute and chronic respiratory disorders. Laboratory work-up should also include complete blood count, basic metabolic profile, cardiac enzymes, and microbiological evaluation. Chest imaging, including computerized tomography when needed, can help with the diagnosis of a pulmonary pathology. Evaluating cardiac function with echocardiography can significantly narrow the diagnostic differential in patients with systemic disease and shock. With the increasing availability of the critical care bedside ultrasound, familiarization with the Rapid Ultrasound for Shock and Hypotension (RUSH) examination is recommended as a rapid tool for the assessment of patients with ARF.¹¹ Laryngoscopy or bronchoscopy may be necessary for the evaluation of airway patency in scenarios such as fixed obstruction, aspiration, foreign bodies, or severe secretions.

MANAGEMENT

Appropriate management of a patient with ARF usually requires admission to the ICU, where adequate support and close monitoring are available. Management should focus on both stabilization of the patient's ventilatory and hemodynamic status as well as correction of the pathophysiologic process underlying the respiratory failure. The "ABC" approach, which prioritizes airway, breathing, and circulation, has long been a basic tenet in the management of ARF.

Airway Patency

Securing airway patency is the first step in the management of ARF. This usually requires interventions such as positioning, the suctioning of secretions, treatment with bronchodilators, and/or the placement of an oral airway. When physical obstruction of the upper airway by a foreign body or mass is suspected, advanced invasive procedures, such as laryngoscopy or bronchoscopy, may be necessary. In cases of severe respiratory compromise that require more invasive ventilatory management, endotracheal intubation is indicated. This can be achieved via orotracheal or nasotracheal intubation or, in difficult cases when an endotracheal tube cannot be advanced through the vocal cords, emergency cricothyroidotomy. The inability of a patient to protect his or her airway because of compromised mental status (usually with a Glasgow Coma Scale score of <8) also warrants endotracheal intubation to secure the airway. The process of securing the airway in ARF requires an understanding of the ongoing pathologic process, as well as an advanced knowledge of the anatomy of the upper airway.

Breathing

Breathing assistance is required in both oxygenation and ventilation disorders. Treating hypoxemia should be the first step, which can be achieved with supplemental oxygen. Oxygen can be provided via nasal cannula, face mask, Venturi mask, nonrebreather mask, or high-flow oxygen delivery devices. When hypoxemia cannot be corrected with supplemental oxygen only, or ventilation is compromised, transition to MV may be necessary. MV may be provided via noninvasive positive pressure ventilation (NIPPV) or via invasive MV through an endotracheal tube. Severe respiratory failure with an inability to oxygenate and/or ventilate despite MV may occasionally require transition to extracorporeal membrane oxygenation (ECMO).¹²

Circulation

Normal breathing with negative pressure ventilation not only provides gas exchange but also affects hemodynamics on a breath-to-breath basis, helping to optimize venous return and cardiac output. Circulation affects our respiratory patterns, and they are also affected by ventilatory mechanics. Treating hypotension or hypertension and optimizing the cardiac output may help treat the underlying etiology of ARF and may also be necessary given the potential adverse effects of positive pressure ventilation on cardiac preload and afterload. In addition, anesthetics and sedatives used for mechanically ventilated patients, as well as paralytics used for intubation, have significant hemodynamic effects that should be anticipated and aggressively corrected as necessary.

Further Management and Monitoring

Along with focusing on the "ABC" of ARF, the treatment of its underlying cause is of paramount importance to the patient's outcome. Antibiotics and source control for the management of infections, cardiac or inotropic medications, revascularization, air or fluid evacuation, anticoagulation or thrombolysis, fluid expansion, diuretics, vasodilators, bronchodilators, glucocorticoids as well as many other medications and interventions may be required to treat the underlying etiology of ARF.

The success and adequacy of the management of ARF should be continuously monitored. Multiple blood gas analyses may be required to ensure that both oxygenation and ventilation are maintained within desired limits. In general, PaO₂ should be maintained at >55 to 60 mm Hg, a range that represents a threshold for severe hypoxemia. Arterial blood oxygen saturation (SpO₂) can be tested and correlated to PaO₂ and can be used as a surrogate marker for the adequacy of oxygenation with a general recommended goal of >88%. pH and PaCO₂ values reflect the adequacy of MV and are also useful in the setting of a metabolic acid-base disorder. ABG goals should in general be individualized. For example, permissive hypercapnia may be appropriate for some patients, whereas other patients may benefit from therapeutic hyperventilation.

MV

The purpose of MV is to improve oxygenation and ventilation while correcting respiratory acidosis and hypoxemia, meeting metabolic demands, resting respiratory muscles, and optimizing cardiac function and blood circulation. MV allows for augmented minute ventilation and the provision of high concentrations of oxygen and positive end expiratory pressure (PEEP). MV has also been shown to have a positive effect on gas exchange and the regional distribution of lung aeration and ventilation.¹³ MV can be *noninvasive*, involving a variety of interfaces such as nasal or face masks, or *invasive*, involving endotracheal intubation. General indications for intubation and invasive MV are described in Table 9-4.

Noninvasive positive pressure ventilation (NIPPV) has been increasingly utilized in the past two decades as an alternative to

TABLE 9-4 General Indications for Intubation and Mechanical Ventilation

| |
|--|
| Cardiorespiratory arrest or impending arrest |
| Respiratory distress/tachypnea with increased ventilatory demand and breathing effort leading to respiratory muscle fatigue |
| Severe hypercapnic respiratory failure with either poor candidacy for nasal intermittent positive pressure ventilation (NIPPV) or failure of NIPPV |
| Severe refractory hypoxemia with failure of noninvasive oxygen delivery devices |
| Severe refractory metabolic acid-base disorder |
| Inability to protect the airway |
| Inability to clear secretions |
| Need for therapeutic hyperventilation or hypoventilation |
| Upper airway obstruction with poor airway patency |
| Decreased respiratory drive with bradypnea |
| Coma with Glasgow Coma Scale score of <8 |
| Severe trauma |
| Surgery requiring general anesthesia |

endotracheal intubation and MV in appropriate clinical settings.¹⁴ NIPPV with continuous (CPAP) or bi-level positive airway pressure (BiPAP) modalities have been shown to be beneficial in selected cases of COPD exacerbation, cardiogenic pulmonary edema, obesity hypoventilation syndrome or decompensated obstructive sleep apnea, and neuromuscular disease.^{14,15} It has also been successfully used for respiratory failure in postoperative patients,¹⁶ immunocompromised patients,¹⁷ or in patients with a do-not-intubate (DNI) code status.¹⁸

NIPPV requires the patient's cooperation and an anatomically preserved upper airway. It is not a replacement for invasive MV and is not suitable for all patients with respiratory failure. Significantly depressed mental status, copious secretions with an inability to protect the airway, massive hemoptysis or hematemesis, recent upper gastrointestinal surgery or bowel obstruction, and cardiorespiratory arrest or severe arrhythmias are contraindications to its use.¹⁵ NIPPV is not widely recommended for use in advanced hypoxemic respiratory failure as its use may lead to a more difficult transition to MV in cases of NIPPV failure,¹⁹ although there is some evidence that it can be beneficial in the setting of severe hypoxemia during the process of transitioning to invasive MV.²⁰ Its use in shock states leading to type IV ARF may adversely affect venous return and pulmonary hemodynamics in volume-depleted patients.²¹

Invasive MV requires an endotracheal or tracheostomy tube as an interface between the patient and the ventilator. Prior to the initiation of invasive MV, a careful assessment of risks and benefits needs to be undertaken as both intubation and MV carry risks of potentially fatal complications. Though it is clearly a life-saving measure when appropriately utilized, invasive MV may lead to significant hemodynamic compromise that results from the sedative effects of medications used for intubation and MV, abrogation of the patient's inspiratory drive, and changes in cardiac preload, afterload, and interventricular dependence.^{22,23} MV also increases the risks of ventilator-associated lung

injury, dynamic hyperinflation, and ventilator-associated pneumonia, as well as discomfort due to patient-ventilator asynchrony. Importantly, in situations involving terminal illnesses or irreversible etiologies of ARF, a discussion with the patient and family regarding the appropriateness and expectations of invasive MV is warranted.

Evaluation of the patient's anatomy, such as the presence of facial hair; oral cavity inspection, including dentition, neck shape, and mobility; and the presence of secretions or obstruction, is helpful for predicting the odds of a difficult intubation and for planning of the specific intubation approach. Prior to intubation, the operator needs to carefully choose sedatives and anesthetics, secure vascular access and prepare hemodynamic support, and adequately pre-oxygenate the patient and prepare for supportive manual bag-valve mask ventilation.¹⁹ It is important to remember that every intubation in the setting of ARF may become a difficult intubation,²⁴ and experienced operators and rescue strategies for securing the airway need to be available. Upon endotracheal intubation, the tube position should be confirmed and secured to avoid accidental extubation.

While on a ventilator, the patient's comfort, gas exchange, mechanics, and ventilator waveforms need to be continuously monitored. The least amount of sedation required to achieve comfort and ventilator synchrony should be utilized.²⁵⁻²⁷ Spontaneous breathing trials should be initiated daily, once the patient's condition is stable.²⁷⁻²⁹ The patient's head should be elevated to >30°, and prophylaxis for deep venous thrombosis and peptic ulcer disease should be administered daily.

In patients with or at high risk for acute lung injury and acute respiratory distress syndrome (ARDS), a lung-protective ventilation strategy should be utilized. This entails low tidal volumes (~6 mL/kg of ideal body weight), permissive hypercapnia, and the maintenance of adequate static inspiratory or plateau pressures (<30 cm H₂O).^{30,31} Neuromuscular paralysis may be needed in cases of severe ARDS or ventilator dyssynchrony despite high doses of sedatives.³² In cases of refractory hypoxemia in severe ARDS, additional strategies,³³ including prone positioning,³⁴ pulmonary vasodilators (such as inhaled nitric oxide),³⁵ recruitment maneuvers,³⁶ high-frequency oscillatory ventilation,³⁷ or airway pressure release ventilation (APRV or bi-level ventilation),³⁸ have been utilized with variable success rates. Patients with profound nonresolving ARF despite the above mentioned strategies should be considered for ECMO if the underlying etiology is considered reversible.³⁹

CONCLUSION

ARF is one of the most common conditions encountered in the ICU and is associated with significant morbidity and mortality. Understanding the pathophysiology of ARF with regard to oxygen consumption, delivery, and transport; the etiologies of ARF (types I to IV); and the clinical presentation (acute or acute on chronic) is essential for the management of these patients. The priority in the management of ARF is to focus on the "ABC" approach, with efficient and effective decision making regarding the use of either NIPPV or invasive MV. Finally, therapies need to be directed at both the ARF itself as well as the underlying condition in order to optimize patient outcomes.

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BACKGROUND AND EPIDEMIOLOGY OF PULMONARY EDEMA

Pulmonary edema (PE) is an emergency that demands immediate medical attention. PE is broadly classified into cardiogenic (increased hydrostatic pressure) or noncardiogenic (increased microvascular permeability) causes; however, it is common for critically ill patients to present with PE arising from a combination of cardiogenic and noncardiogenic etiologies. PE is a major health problem accounting for ~10% of intensive care unit (ICU) admissions¹ and associated with an estimated acute hospital mortality of ~10% to 25%²⁻⁴ and 1-year mortalities exceeding 40%.^{3,5,6}

PATHOPHYSIOLOGY OF PE

Normal pulmonary physiology favors a small net influx of fluid from the alveolar capillaries into the lung interstitial space (IS) that is facilitated by hydrostatic forces and by the presence of microscopic gaps between the capillary endothelial cells. The rate of fluid influx is mitigated by a protein osmotic pressure gradient favoring movement of fluid from the IS back into the circulating plasma. The resulting relatively small physiological fluid movement from the vasculature into the lungs is normally offset by fluid efflux from the lung IS via the pulmonary lymphatic system, which ultimately drains back into the systemic venous circulation. As fluid passes through the lung IS it is excluded from the alveolar space by occlusive tight junctions between alveolar epithelial cells.⁷ In the absence of acute lung injury (e.g., capillary damage), changes in the rate of fluid flux through the lungs are dictated primarily by changes in hydrostatic pressure. The pulmonary capillary wedge pressure (PCWP), derived from a pulmonary artery catheter balloon wedged into a pulmonary artery segment, is a reflection of left atrial filling pressure and is thought to most reliably estimate the hydrostatic pressure of the lung microcirculation.^{8,9}

The Starling equation for filtration mathematically represents the fluid balance between the pulmonary vasculature and IS, which “depends on the net difference in hydrostatic and protein osmotic pressures and permeability of the capillary membrane.”¹⁰

$$Q = K[(P_{mv} - P_{pmv}) - (\pi_{mv} - \pi_{pmv})]^9$$

where:

Q = net transvascular filtration of fluid into the IS

K = filtration coefficient

Ppmv = hydrostatic pressure in perimicrovascular IS

Pmv = hydrostatic pressure within the capillaries (e.g., the PCWP)

π_{mv} = protein osmotic pressure in the circulation

π_{pmv} = protein osmotic pressure in the perimicrovascular IS

While the Starling equation is useful in understanding the mechanisms favoring PE formation, it is impractical to accurately measure most of these parameters clinically. Nonetheless, a basic understanding of this equation is helpful to clinicians caring for patients with PE.

Cardiogenic PE (Increased Hydrostatic Pressure)

Increased hydrostatic pressure in the pulmonary capillaries results in increased transvascular fluid filtration and is most often caused by

volume overload or impaired left ventricular function resulting in elevated pulmonary vascular pressures. Mild elevations of left atrial pressure reflected by PCWPs of 18–25 mm Hg cause edema formation in the perimicrovascular and peribronchovascular IS. As left atrial pressure rises further (PCWP > 25 mm Hg), the capacitance of the lymphatics and IS (estimated at ~500 mL fluid)⁹ is exceeded and fluid overwhelms the lung epithelial barrier, flooding the alveoli with protein-poor fluid.^{9,11} Hypoxemia results clinically due to the development of alveolar fluid accumulation, destabilization of alveolar units (impaired surfactant function), and consequent ventilation-perfusion (V/Q) mismatching.

Noncardiogenic PE (Increased Vascular Permeability)

Noncardiogenic PE refers to any condition promoting abnormal increases in the vascular permeability of the lung, thereby promoting greater fluid and protein flux into the lung IS and air spaces. In terms of the Starling equation, pulmonary vascular damage equates with an increase in the filtration coefficient and an increase in the protein osmotic pressure in the lung IS, both of which favor lung edema formation. Another factor contributing to impaired gas exchange during noncardiogenic PE relates to the disruption of the alveolar epithelial barrier, such as occurs when lung IS pressure is severe enough to disrupt tight junctions, or when direct inflammatory or toxic injury to the epithelial lining of the alveoli occurs. Damaged alveolar epithelium has a reduced capacity for the active transport of fluid from the alveolar space into the lung IS and causes impaired surfactant production (reduced surface activity) favoring alveolar collapse during normal tidal breathing. Examples of direct injury to the alveolar epithelium include gastric aspiration or pneumonia. Conditions that promote acute lung capillary endothelial injury include systemic infections (sepsis), severe burns, trauma, and other systemic inflammatory conditions. Injury to the lung capillary endothelium and/or alveolar epithelium is the hallmark of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), which represent a spectrum of progressive noncardiogenic lung injury associated with impaired gas exchange (shunting, V/Q mismatching) and reduced lung compliance (increased work of breathing).^{9,11}

ESTABLISHING THE ETIOLOGY OF PE IN THE CLINICAL SETTING

It is important for care providers to quickly establish the cause of acute PE such that appropriate therapy can be rapidly initiated to avoid serious, life-threatening complications. For instance, a patient with an acute rupture of mitral valve *chordea tendineae* would benefit from afterload reduction (e.g., peripheral vasodilators, intraaortic balloon pump [IABP]), and immediate mitral valve surgery,¹² whereas a patient with ARDS related to sepsis would benefit from high concentrations of inspired oxygen, positive pressure ventilation, and early antibiotics. Unfortunately, the cause of PE can be difficult to establish in the critical care setting and requires a skilled clinician with appropriate diagnostic tools.

Common clinical manifestations of PE (of any cause) include the acute onset of dyspnea, anxiety, orthopnea, and in some cases pink (blood-tinged) frothy sputum. On examination, patients have signs of

increased sympathetic tone (tachycardia, hypertension), increased work of breathing (e.g., accessory muscle use and diaphoresis), inspiratory crackles of the lung, and peripheral cyanosis.

Clinical Features Favoring Cardiogenic PE

Beyond the clinical features of PE previously mentioned, historical information, such as a recent myocardial infarction, new onset of cardiac arrhythmias, and exam findings of elevated jugular venous pressures, a third heart sound (S3), new murmurs, and/or dependent edema would favor the diagnosis of cardiogenic over noncardiogenic PE. CXR findings of cardiomegaly, a centralized pattern of interstitial and alveolar opacities, and/or the presence of pleural effusions further support the diagnosis of cardiogenic PE.¹³ Other supporting evidence includes elevated brain natriuretic peptide (BNP > 1200 pg/mL), or troponin, a marker of acute myocardial injury. However, these biomarkers lack diagnostic specificity.¹⁴ Cardiac imaging, particularly echocardiography, is very useful diagnostically, and is shown to alter the management of a high percentage of critically ill patients presenting with acute PE.^{15,16} The use of invasive means to measure left ventricular filling pressures may be useful in complex cases (e.g., treatment-refractory PE)¹⁷ but has been largely replaced by less invasive approaches (e.g., central venous pressure [CVP] monitoring, transpulmonary thermodilution).¹⁷⁻¹⁹

Clinical Features Favoring Noncardiogenic PE

ALI and ARDS encompass a spectrum of moderate to severe gas exchange abnormalities developing consequent to altered pulmonary vascular permeability, which is often further complicated by alveolar epithelial damage. The differential diagnosis of ALI/ARDS is broadly categorized as processes causing direct versus indirect lung injury (Box 10-1), the most common direct causes being severe pulmonary infections and gastric aspiration pneumonia, whereas severe infections (sepsis), multiple transfusions, and trauma are common causes of indirect ALI.

Highly specific diagnostic tests for ALI/ARDS are lacking, and the differentiation of ALI/ARDS from cardiogenic PE largely relies on the clinical acumen of the critical care providers. In this regard, details of the present illness as it relates to the known risk factors for ALI often provide important clues (see Box 10-1), and certain objective examination and test results (e.g., BNP < 200 pg/mL)¹⁴ support the diagnosis of ALI/ARDS (Table 10-1).

Certain causes of noncardiogenic PE deserve special consideration because of their unique clinical presentations.

Neurogenic PE

It occurs following a significant central nervous system insult²⁰ and is most often triggered by conditions associated with rapid and extreme elevations in intracranial pressure (ICP)^{20,21} as well as in the setting of acute spinal cord injury, intracranial hemorrhage, or during status epilepticus. Sympathetic nervous system activation and catecholamine release are primary mechanisms.²² The condition typically resolves within 48 hours of ICP normalization.^{20,23}

Transfusion-Related Acute Lung Injury (TRALI)

It is an adverse response to transfusion of blood products containing plasma characterized by the acute (within 6 hours) onset of dyspnea, hypoxemia, and bilateral pulmonary infiltrates that is mediated mechanistically by anti-HLA antibodies, neutrophil activation, and related endothelial barrier damage.^{24,25} The diagnosis of TRALI is made

BOX 10-1

Common Causes of Cardiogenic and Noncardiogenic Pulmonary Edema

CARDIOGENIC PULMONARY EDEMA

- Acute exacerbation of heart failure
- Acute valve dysfunction (e.g., mitral valve chordae tendineae rupture)
- Arrhythmia/Myocardial infarction
- Hypertensive crisis
- Fluid overload following aggressive volume resuscitation (e.g., postoperative)
- Ventricular septal rupture
- Pericardial tamponade

NONCARDIOGENIC PULMONARY EDEMA

- Direct lung injury
 - Pneumonia
 - Gastric aspiration
 - Toxic inhalation
 - Negative pressure related (e.g., strangulation)
- Indirect causes of lung injury
 - Sepsis
 - Trauma
 - Pancreatitis
 - Multiple blood transfusions
 - Burn injury

TABLE 10-1 Distinguishing Cardiogenic and Noncardiogenic Pulmonary Edema

| | HISTORY | EXAM | LABS | IMAGING | PULMONARY ARTERY CATHETER |
|----------------|--|--|---|---|---|
| Cardiogenic | Heart disease Renal disease Uncontrolled HTN Edema Orthopnea Recent administration of IV fluids or blood products | Heart failure exam findings: Distended neck veins S3 heart sound Dependent edema Elevated blood pressure Cool extremities | *↑BNP > 1200 pg/mL ↑Creatinine (in setting of volume overload) ↑↑Troponin | CXR: CMG Pleural effusions #Kerley B lines TEE: ↓LVEF Diastolic filling defect Severe mitral or aortic valvular disease Pericardial effusion with tamponade VSD | PCWP > 18 mm Hg Prominent V-waves (mitral regurgitation) Elevation and equilibration of right atrial pressure, pulmonary artery diastolic and PCWP (tamponade physiology) CVP > 12 mm Hg |
| Noncardiogenic | Sepsis Aspiration event Trauma (long bone fractures) Burn injury Pancreatitis Multiple transfusions | Signs of active infection Extensive burn injury Evidence of trauma (absence of heart failure exam findings) | ↑WBC *BNP < 200 pg/mL | CXR: Diffuse central and peripheral infiltrates Normal heart size No or minimal pleural effusions TEE: Normal LV and valvular function No evidence of volume overload | PCWP < 18 mm Hg CVP < 12 mm Hg |

clinically and by the exclusion of cardiogenic edema or fluid overload. Thus, a low BNP (<250 pg/mL) supports the diagnosis.²⁶ Treatment includes immediate discontinuation of any transfusing blood products and supportive care, which often requires intubation and mechanical ventilation. Duration of symptoms is typically limited (48–96 hours).²⁵

Re-expansion Pulmonary Edema

It typically occurs within hours of draining a large pleural effusion in cases of sustained (>72 hours) lung collapse. Associated symptoms range from mild to life-threatening, including dyspnea, cough with frothy sputum production, chest discomfort, and hypoxemic respiratory failure. A unilateral edema pattern of the re-expanded lung is typical on CXR but occasionally can occur in the contralateral lung or in both lungs.^{27,28} Most patients completely recover with supportive care within a few days. Preventative strategies include discontinuation of pleural fluid removal at the onset of any signs of chest discomfort, limiting volume removal to <1.5 L, and avoidance of high negative pressure (less than −20 cm H₂O).²⁹

Negative Pressure PE (NPPE)

It rarely presents in the immediate postextubation period following the acute development of negative intrathoracic pressure generated during respiratory efforts against an obstructed upper airway. NPPE occurs in less than 0.1% of all elective surgeries and is most common in young, healthy and athletic patients during postextubation laryngospasm. Other causes of NPPE include strangulation (or hanging), severe sleep apnea, endotracheal tube occlusion, or epiglottitis.³⁰ As with re-expansion PE, the condition typically resolves within several days.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF PULMONARY EDEMA

Table 10-1 summarizes the typical clinical findings that distinguish cardiogenic from noncardiogenic PE. Ironically, pulmonary artery (PA) catheterization, the most definitive diagnostic modality, is no longer routinely used because of frequent complications (e.g., bleeding,

pneumothorax, arrhythmias, infections, vessel trauma) and its unreliability due to improper calibration or misinterpretation of the data.^{31–33} Thus, less invasive techniques have largely replaced PA catheters for the routine evaluation of cardiogenic causes of PE in the ICU setting.

Transesophageal echocardiography (TEE) is the most widely used tool for the evaluation of critically ill patients with suspected cardiac disease. In the context of PE, TEE can rapidly detect serious cardiac diseases associated with elevated left ventricular filling pressures, including impaired left ventricular ejection fraction due to ischemic (typically causing regional wall motion abnormalities) or nonischemic (diffuse wall motion abnormalities) muscle disease, significant valvular disease, or pericardial effusions causing tamponade physiology.³⁴

Two alternative modalities have emerged to evaluate PE. The pulse indicator continuous cardiac output (PiCCO) system estimates the pulmonary vascular permeability index in critically ill patients.³⁵ Quantitative computed tomography (QCT) analysis with single-indicator thermodilution has also been used to detect PE in the setting of ARDS.³⁶ To date, no study has shown superiority of PiCCO or QCT compared to conventional approaches (e.g., CVP-guided) for PE assessment in the context of ARDS.^{36,37}

MANAGEMENT OF PE

Therapeutic approaches are classified as either cardiovascular or pulmonary interventions. Cardiovascular interventions aim to reduce transcapillary fluid flux into the lung by reducing pulmonary capillary pressures. As shown in Fig. 10-1 and Box 10-2, such interventions aim to reduce preload (e.g., loop diuretics, nitrates, or ultrafiltration in renal failure), reduce afterload (systemic vasodilating agents including nitrates, angiotensin converting enzyme [ACE] inhibitors, phosphodiesterase inhibitors), or optimize cardiac contractility during impaired left ventricular function (catecholamines, phosphodiesterase [PDE] inhibitors, intraaortic balloon pump). Although most effective in the setting of cardiogenic PE, pulmonary capillary hydrostatic pressure reduction can also mitigate the severity of PE during noncardiogenic PE.

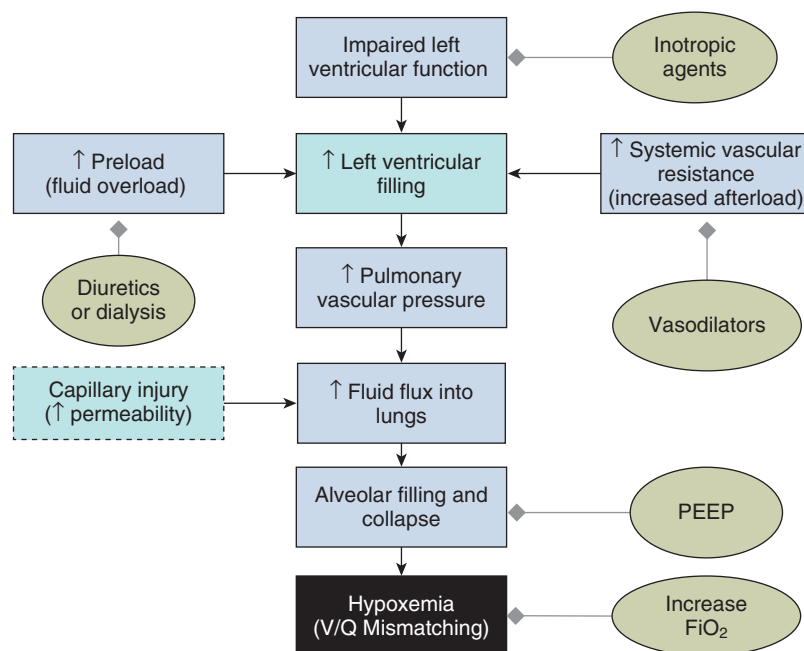


FIGURE 10-1 ■ Acute management of pulmonary edema. This schematic represents basic mechanisms distinguishing cardiogenic and noncardiogenic pulmonary edema (red boxes) and the contributing factors (blue boxes) that ultimately lead to impaired gas exchange (black box). The green circles represent treatments that are available in the intensive care unit setting to reduce pulmonary edema or to mitigate its adverse consequences.

BOX 10-2**Management of Cardiogenic Pulmonary Edema****DECREASE PRELOAD**

- Diuretics (e.g., furosemide): decrease systemic venous tone and extracellular volume/volume overload⁶
- Opiates (e.g., morphine sulfate): reduces sympathetic tone.
- Nitrates (e.g., nitroglycerin): venous and arterial vasodilator,³¹ reduces myocardial oxygen demand⁴²
- Nesiritide: recombinant BNP that results in vasodilation and diuresis³¹
- Ultrafiltration (volume removal)

AFTERLOAD REDUCTION

- ACE inhibitor/ARB: reduce preload and afterload^{42,43}
- Nitroprusside (decreases venous return and afterload)
- Intraaortic balloon pump

INOTROPIC SUPPORT

- Dobutamine
- Dopamine
- Phosphodiesterase inhibitors (e.g., milrinone)
- Vasopressin (e.g., tolvaftan)

Pulmonary interventions are designed to optimize gas exchange, particularly oxygenation, by recruiting unstable, collapsed or fluid-filled alveolar units primarily through the administration of positive end expiratory pressure (PEEP). PEEP, typically 5-15 cm H₂O, counteracts alveolar collapse during the ventilator cycle to enhance V/Q matching and consequently oxygen diffusion from the alveoli to the blood. Alveolar stabilization also reduces the work of breathing by improving CO₂ exchange (i.e., lower ventilatory rates) and lung compliance. In addition to PEEP, it is often necessary to increase the fractional inspired oxygen concentration (Fio₂) to maintain adequate oxygenation (see Fig. 10-1). PEEP may be provided by a tight-fitting, occlusive face mask in the form of continuous positive airway pressure (CPAP) or by noninvasive positive pressure ventilation (NIPPV) wherein inspiratory support is added to PEEP (bilevel ventilation). Positive pressure ventilation further mitigates cardiogenic PE by decreasing both preload and afterload.⁹ Early use of NIPPV for respiratory distress in cardiogenic PE should be strongly considered as it provides support while awaiting the benefits of the aforementioned medical interventions. NIPPV has been shown to reduce both the need for endotracheal intubation and early mortality, as well as decrease

ICU length of stay.³⁸ NIPPV is a helpful adjunct to medical therapy; however, it is unclear if bilevel NIPPV is superior to CPAP in improving dyspnea, work of breathing, oxygenation, and Paco₂ retention.^{39,40} Endotracheal intubation and sedation may be required for patients with intolerably high work of breathing or altered mental status.

When ventilator support is required in the setting of noncardiogenic PE, a lung-protective ventilation strategy using lower tidal volumes (6 mL/kg ideal body weight or less) is highly recommended to minimize lung injury and PE severity.⁴¹

KEY POINTS

1. Pulmonary edema is broadly classified into cardiogenic (increased hydrostatic pressure) or noncardiogenic (increased microvascular permeability) causes; however, it is common for critically ill patients to present with pulmonary edema arising from a combination of cardiogenic and noncardiogenic etiologies.
2. Common clinical manifestations of pulmonary edema (of any cause) include the acute onset of dyspnea, anxiety, orthopnea, and in some cases pink (blood-tinged) frothy sputum. On examination, patients have signs of increased sympathetic tone (tachycardia, hypertension), increased work of breathing (e.g., accessory muscle use and diaphoresis), inspiratory crackles of the lung, and peripheral cyanosis.
3. In addition to the history and physical exam, laboratory testing (troponin, BNP) and imaging (CXR, echocardiogram) may be helpful in differentiating between cardiogenic and noncardiogenic causes of the pulmonary edema.
4. Management should be directed at the cause(s) of the pulmonary edema. In addition, early use of NIPPV for respiratory distress in cardiogenic PE should be strongly considered because it provides support while awaiting the benefits of the medical interventions described above.

■ References for this chapter can be found at expertconsult.com.

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Although polyuria in critically ill patients is less common than oliguria, it is an important manifestation of a number of important clinical conditions. Unless it is recognized and appropriately managed, polyuria can rapidly lead to the development of intravascular volume depletion and/or severe hyponatremia. Generally, urine flow varies depending on fluid intake, insensible losses (e.g., perspiration), and renal function. The average person excretes about 600 to 800 mOsm of solutes per day, and average urine output is about 1.5 to 2.5 L/day.

Polyuria has been variably defined in the literature. The most commonly used definition is entirely based upon the absolute urine volume and arbitrarily defines polyuria as a urine volume of more than 3 L/day. However, some authors prefer to define polyuria as “inappropriately high urine volume in relation to the prevailing pathophysiologic state,” regardless of the actual volume of urine.^{1,2}

■ CLASSIFICATION

Polyuria is broadly classified into *water diuresis* or *solute diuresis*, depending upon whether water or solute is the primary driving force for the increased urine output. However, some patients have mixed water and solute diuresis.

Water Diuresis

Definition and Pathophysiology

If urine output is greater than 3 L/day, and the urine is dilute (urine osmolality < 250 mOsm/L), total solute excretion is relatively normal, and polyuria occurs due to the excessive excretion of water. In general, diuresis is marked, and urine osmolality (Uosm) is often less than 100 mOsm/L. Water diuresis is usually secondary to excess water intake (as in primary polydipsia) or inability of the renal tubules to reabsorb free water, as in central or nephrogenic diabetes insipidus (DI). A good understanding of water homeostasis is critical for recognizing and managing water diuresis.

The normal plasma osmolality is 275 to 285 mOsm/L. To maintain this steady state, water intake must equal water excretion. The primary stimulus for water ingestion is thirst, mediated either by an increase in effective osmolality or a decrease in blood pressure or effective circulating volume. Under normal circumstances, water intake generally exceeds physiologic requirements.

Unlike water intake, water excretion is very tightly regulated by multiple factors. The most dominant regulating factor affecting water excretion is arginine vasopressin (AVP), a polypeptide synthesized in the hypothalamus and secreted by the posterior pituitary gland. Once released, AVP binds to vasopressin-2 (V2) receptors located on the basolateral membranes of renal epithelial cells lining the collecting ducts. Binding of AVP to V2 receptors initiates a sequence of cellular events, ultimately resulting in the insertion of water channels into the luminal cell membrane. The presence of these water channels permits passive diffusion of water (hence its reabsorption) across the collecting duct. Any derangement in this process results in a lack of or inadequate water reabsorption by the collecting duct, resulting in water diuresis. The major stimulus for AVP release is plasma hypertonicity. AVP release is also affected by other nonosmotic factors, such as the effective circulating volume, hypoglycemia, and drugs. In summary, water diuresis occurs either because of excessive water intake sufficient to

overwhelm the renal excretory capacity (primary polydipsia) or the impairment of renal water reabsorption itself (central or nephrogenic DI). Impaired renal water reabsorptive capacity (leading to water diuresis) in turn can occur either as a result of failure of AVP release in response to normal physiologic stimuli (central or neurogenic DI) or failure of the kidney to respond to AVP (nephrogenic DI). In most patients, the degree of polyuria is primarily determined by the degree of AVP deficiency or AVP resistance.

Primary Polydipsia

Primary polydipsia can be clinically recognized based on the history of the patient. Usually there is a history of psychiatric illness along with a history of excessive water intake. Many patients with chronic psychiatric illnesses have a moderate to marked increase in water intake (up to 40 L/day).^{3,4} It is presumed that a central defect in thirst regulation plays an important role in the pathogenesis of primary polydipsia. In some cases, the osmotic threshold for thirst is reduced below the threshold for the release of AVP. The mechanism responsible for abnormal thirst regulation in this setting is unclear. There is evidence that these patients have other defects in central neurohumoral control as well.⁵ Hyponatremia, when present, also points to the diagnosis of primary polydipsia. The diagnosis of primary polydipsia is usually evident from low urine and plasma osmolalities in the face of polyuria. Hypothalamic diseases such as sarcoidosis, trauma, and certain drugs, (e.g., phenothiazines) can lead to primary polydipsia (Table 11-1). There is no proven specific therapy for psychogenic polydipsia. Free water restriction is the mainstay of therapy.

Central Diabetes Insipidus

Inadequate secretion of AVP (central DI) can be caused by a large number of disorders that act at one or more of the sites involved in AVP secretion, interfering with the physiologic chain of events that lead to the release of this hormone. However, the most common causes of central DI account for the vast majority of cases. These common causes include neurosurgery, head trauma, brain death, primary or secondary tumors of the hypothalamus, and infiltrative diseases such as Langerhans cell histiocytosis (see Table 11-1).

Nephrogenic Diabetes Insipidus

Nephrogenic DI refers to a decrease in urinary concentrating ability due to renal resistance to the action of AVP. In some cases, collecting duct cells fail to respond to AVP. Other factors that can cause renal resistance to AVP are problems that interfere with the renal counter-current concentrating mechanism, such as medullary injury or decreased sodium chloride reabsorption in the medullary aspect of the thick ascending limb of the loop of Henle. In children, nephrogenic DI is usually hereditary. Congenital or hereditary nephrogenic DI is an X-linked recessive disorder resulting from mutations in the V2 AVP receptor gene.⁶ The X-linked inheritance pattern means that males tend to have marked polyuria. Female carriers are usually asymptomatic but occasionally have severe polyuria. In addition, different mutations are associated with different degrees of AVP resistance. Nephrogenic DI can also be inherited as an autosomal recessive disorder due to mutations in the aquaporin gene that result in absent or defective water channels, thereby causing resistance to the action of AVP.⁷

TABLE 11-1 Causes of Polyuria

1. Polyuria secondary to water diuresis
 - a. Excessive intake of water
 - i. Psychogenic polydipsia
 - ii. Drugs—anticholinergic drugs, thioridazine
 - iii. Hypothalamic diseases—trauma, sarcoidosis
 - b. Defective water reabsorption by the kidney
 - i. Central diabetes insipidus (vasopressin deficiency)
 - ii. Renal tubular resistance to AVP
2. Congenital nephrogenic diabetes insipidus
3. Acquired nephrogenic diabetes insipidus
 - a. Hypercalcemia
 - b. Hypokalemia
 - c. Drugs—lithium, demeclocycline
 - d. Chronic renal diseases—postobstructive diuresis, polyuric phase of ATN
 - e. Other systemic diseases—amyloidosis, sickle cell anemia
4. Polyuria secondary to solute diuresis
 - a. Electrolyte-induced solute diuresis
 - i. Iatrogenic—excessive sodium chloride load, loop diuretic use
 - ii. Salt-wasting nephropathy (rarely causes polyuria)
 - b. Nonelectrolyte solute-induced diuresis
 - i. Glucosuria—diabetic ketoacidosis, hyperosmolar coma
 - ii. Urea diuresis—high-protein diet, ATN
 - iii. Iatrogenic—mannitol

ATN, acute tubular necrosis; AVP, arginine vasopressin.

The most common cause of nephrogenic DI in adults is chronic lithium ingestion (see Table 11-1). Polyuria occurs in about 20% to 30% of patients on chronic lithium therapy. The impairment in the nephron's concentrating ability is thought to be due to decreased density of V2 receptors or decreased expression of aquaporin-2, a water channel protein. Other secondary causes of nephrogenic DI include hypercalcemia, hypokalemia, sickle cell disease, and other drugs (see Table 11-1). Water diuresis can also follow relief of obstructive nephropathy. Hypercalcemia-induced nephrogenic DI occurs when the plasma calcium concentration is persistently above 11 mg/dL (2.75 mmol/L). This defect is generally reversible with correction of hypercalcemia. The mechanism(s) responsible for hypercalcemia-induced nephrogenic DI remain incompletely understood. Compared to hypercalcemia-induced DI, hypokalemia-induced nephrogenic DI is less severe and often asymptomatic. A rare form of nephrogenic DI can occur during the second half of pregnancy (gestational DI). This condition is thought to be caused by release of a vasopressinase from the placenta, leading to rapid degradation of endogenous or exogenous AVP.⁸

Approach to Hypotonic Polyuria (Water Diuresis)

The accurate diagnosis of hypotonic polyuria is often indicated by the plasma sodium concentration and the patient history. When the problem is primary polydipsia, the plasma sodium concentration is usually low (dilutional hyponatremia), whereas when the problem is central or nephrogenic DI, the plasma sodium concentration is typically normal or high (due to the loss of solute-free water in excess of solutes). The rate of onset of polyuria can sometimes provide a clue about the diagnosis; when central DI is the problem, the onset of polyuria is generally abrupt, whereas when nephrogenic DI or primary polydipsia is the problem, the onset of polyuria tends to be more gradual. When the diagnosis of central versus nephrogenic DI is unclear, the diagnosis can be confirmed by determining the urinary response to an acute increase in plasma osmolality induced either by water restriction or, less commonly, by administration of hypertonic saline (Fig. 11-1).

Comparing urinary osmolality after dehydration with that after vasopressin administration can help differentiate DI due to vasopressin deficiency from other causes of water diuresis (see Fig. 11-1). In this test, fluids are withheld long enough to result in stable hourly urinary osmolality values (<30 mmol/kg rise in urine osmolality for 3 consecu-

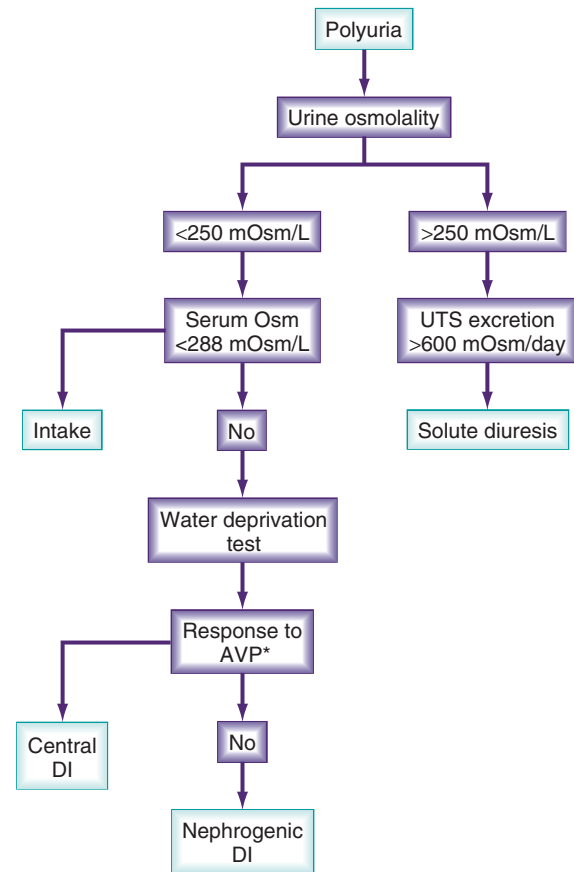


FIGURE 11-1 ■ Approach to polyuria. *Response to AVP is defined as a greater than 9% increase in urine osmolality between 30 and 60 minutes after vasopressin administration (see text for details). AVP, arginine vasopressin; DI, diabetes insipidus; UTS, urine total solute concentration.

tive hours). Plasma osmolality and urine osmolality are measured at this time point, and then the patient is intravenously (IV) administered 5 units of aqueous vasopressin. The clinician subsequently measures the osmolality of a urine sample collected during the interval from 30 to 60 minutes after the administration of vasopressin. In subjects with normal pituitary function, urinary osmolality does not rise by more than 9% after vasopressin injection. However, in central DI, the increase in urine osmolality after vasopressin administration exceeds 9%. To ensure the adequacy of dehydration, plasma osmolality prior to vasopressin administration should be greater than 288 mmol/kg. There is little or no increase in urine osmolality with dehydration in patients with nephrogenic DI, and there is no further change after vasopressin injection. In the future, a novel method to confirm the results of the water restriction test will be to measure the urinary excretion of aquaporin-2, the collecting tubule water channel that normally fuses with the luminal membrane of the collecting tubule cells under the influence of AVP. In one study, urinary aquaporin-2 excretion substantially increased to a comparable extent after the administration of vasopressin in normal subjects and in those with central DI.⁹ However, in patients with hereditary nephrogenic DI, urinary aquaporin-2 excretion was unchanged after vasopressin administration.

Treatment of Water Diuresis

Central diabetes insipidus can be treated by replacing AVP. The agent of choice is desmopressin, since it has prolonged antidiuretic activity and a very minimal vasopressor effect. It is usually administered intranasally at doses of 10 to 20 µg once or twice a day. Patients with central

DI with some residual releasable AVP can be treated with drugs, such as carbamazepine (100 to 300 mg twice daily), clofibrate (500 mg every 6 hours), or chlorpropamide (125 to 250 mg once or twice a day), that stimulate AVP release.

Primary polydipsia can only be treated by eliminating the underlying cause. In patients with schizophrenia and polydipsia, clozapine has been shown to have a beneficial effect.

The mainstay of treatment of nephrogenic DI is solute restriction and diuretics. Thiazide diuretics in combination with a low-salt diet can diminish the degree of polyuria in patients with persistent and symptomatic nephrogenic DI. Thiazide diuretics (e.g., hydrochlorothiazide) act by inducing mild volume depletion. Hypovolemia induces an increase in proximal sodium and water reabsorption, thereby diminishing water delivery to AVP-sensitive sites in the collecting tubules and reducing the urine output. The potassium-sparing diuretic, amiloride, also may be helpful.¹⁰

Solute Diuresis

Solute diuresis causing polyuria is due to solute excretion in excess of the usual excretory rate.¹¹ Total daily urinary solute excretion widely varies among different ethnicities, cultures, and dietary habits. The average urinary solute excretion in a healthy American adult is between 500 and 1000 mOsm/d. Solute diuresis can be very severe and can be caused by more than one solute concurrently. Solute diuresis is a relatively common clinical condition and one with important clinical implications. Unless there is an adequate replacement of solute and water, a persistent solute diuresis contracts extracellular volume, leading to severe dehydration and hypernatremia. Although glucosuria is the major cause of an osmotic diuresis in outpatients, other conditions are often responsible when polyuria develops in the hospital. These conditions include administration of a high-protein diet, in which case urea acts as the osmotic agent, and volume expansion due to saline loading or the release of bilateral urinary tract obstruction. Multiplying urine osmolality by the 24-hour urine volume gives an estimate of total urine solute concentration. If urinary total solute concentration is abnormally large, a solute diuresis is present.

Solute diuresis can be due to either excessive electrolyte excretion or excessive nonelectrolyte solute excretion. If the total urinary elec-

trolyte excretion exceeds 600 mOsm/d, then an electrolyte diuresis is present. The total urinary electrolyte excretion (in mOsm/d) can be estimated as $2 \times (\text{urine } [\text{Na}^+] + \text{urine } [\text{K}^+]) \times \text{total urine volume}$.^{1,12}

Electrolyte diuresis is usually driven by a sodium salt, usually sodium chloride (NaCl).¹³ Common causes of NaCl-induced diureses are iatrogenic administration of excessive normal saline solution, excessive salt ingestion, and repetitive administration of loop diuretics. Most often, NaCl-induced diuresis is accompanied by water diuresis, causing a mixed solute-water diuresis. Also, more than one electrolyte may be responsible for the diuresis.

A clearly excessive value for urine nonelectrolyte excretion (i.e., >600 mOsm/d) implies that nonelectrolytes are the predominant solutes contributing to the diuresis. The urinary nonelectrolyte excretion can be calculated by subtracting urine electrolyte excretion from the total urine solute excretion. The urine osmolality in these disorders is usually above 300 mOsm/kg, the high osmolality contrasting with the dilute urine typically found with a water diuresis. Furthermore, total solute excretion (calculated as the product of urine osmolality and the urine output over a 24-hour urine collection period) is normal with a water diuresis (600 to 900 mOsm/d) but markedly increased with an osmotic diuresis. The most common nonelectrolyte solute causing excessive diuresis is glucose. Conditions associated with glucose-induced diuresis include diabetic ketoacidosis or hyperosmolar coma.¹⁴ Excessive excretion of urea is another important cause of solute diuresis. This problem can occur following relief of urinary tract obstruction, as a consequence of enteral nutrition using a high-protein tube feeding formula, or during recovery from acute tubular necrosis.¹⁵ Mannitol administration (e.g., as a therapy for intracranial hypertension) also can lead to significant solute diuresis. This issue is pertinent because mannitol is often administered to patients with head trauma, who are at risk for development of nephrogenic DI. The correct diagnosis of solute diuresis depends on a clear systematic approach (see Fig. 11-1). Management usually involves treatment of the underlying disorder and repletion of extracellular volume by hydration. Since solute diuresis is often accompanied by hypernatremia, and very rapid correction of hypernatremia can have disastrous consequences (e.g., cerebral herniation), it is crucial to carefully monitor serum Na^+ . The serum Na^+ should not be permitted to decrease more than 0.5 to 1 mEq/L per hour.

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Oliguria is an exceedingly common diagnostic problem faced on a daily basis by the critical care practitioner. The goal of this chapter is to provide a practical, physiology-based approach to diagnosing and treating oliguria.

DEFINITIONS AND EPIDEMIOLOGY

A number of definitions for oliguria can be found in the literature. An average person excretes 600 mOsm of solute/day. The maximal urinary concentration that can be achieved, however, is 1200 mOsm/L. Hence a urine output of at least 500 mL per day is obligatory for excreting the daily solute load. Therefore oliguria has generally been defined as urine output less than 500 mL per 24 hours. In order to standardize the use of the term across different studies and populations, the Acute Dialysis Quality Initiative (ADQI) adopted a definition of *oliguria* as urine output of less than 0.3 mL/kg/h for at least 24 hours (www.ADQI.org). For all practical purposes, however, urine output under 0.5 mL/kg/h is usually considered inadequate for most critically ill patients. This is in part because fluid input due to medications, nutrition, and other reasons typically exceeds this threshold in critically ill patients, and fluid overload may result if urine output is inadequate to maintain fluid balance.

Given the historical lack of consensus over definitions, it has been difficult to determine the incidence of oliguria. Some studies have estimated that up to 18% of medical and surgical intensive care unit (ICU) patients with intact renal function exhibit episodes of oliguria.¹ Furthermore, 88% of ICU patients who develop acute kidney injury (AKI) have a urine output of <0.5 mL/kg/h for 6 hours or more, and 18% have a urine output of <0.3 mL/kg/h for 24 hours or longer.² Overall, AKI in the ICU has a poor prognosis (hospital mortality rates range from 12% for stage 1 to >40% for stage 3), and yet when oliguria is also present along with increased creatinine (at any stage), mortality and the use of renal replacement therapy increase² (Fig. 12-1). Thus, it is essential to understand the physiologic derangements leading to this exceedingly common and serious problem.

PATHOPHYSIOLOGY

Urine output is a function of glomerular filtration, tubular secretion, and tubular reabsorption. Glomerular filtration is directly dependent on intravascular volume and renal perfusion. Renal perfusion in turn is a function of arterial pressure and renal vascular resistance. The intrarenal vasculature is capable of preserving glomerular filtration rate (GFR) in the face of varying systemic pressure through important neurohumoral autoregulating mechanisms that affect the afferent and efferent arterioles. The most important of these neurohumoral mechanisms is the renin-angiotensin-aldosterone system. Oliguria can be due to decreased GFR, increased tubular reabsorption of filtrate, or a combination of both. Oliguria also can be caused by mechanical obstruction to urine flow. It is important to note that AKI need not manifest as oliguria in the intensive care setting, and oliguria is an insensitive clinical manifestation of AKI. Moreover, other factors, such as profound hypokalemia, hypothermia, hyperglycemia, and medications, can all lead to good urine output even in the presence of AKI, confounding the assessment of AKI severity.

Reduction in Glomerular Filtration Rate

Oliguria secondary to a decrease in GFR is usually related to one of the following conditions:

1. Absolute decrease in intravascular volume, which can be due to myriad causes, including trauma, hemorrhage, burns, diarrhea, excessive administration of diuretics, or sequestration of so-called third space fluid, as occurs in acute pancreatitis or abdominal surgery.
2. A relative decrease in blood volume in which the primary disturbance is an alteration in the capacitance of the vasculature due to vasodilation. This abnormality is commonly encountered in sepsis, hepatic failure, nephrotic syndrome, and use of vasodilatory drugs, including anesthetic agents.
3. Decreased renal perfusion in the critical care setting often occurs due to intravascular volume depletion, systemic vasodilation, or impaired cardiac contractility or a combination of the above. Left ventricular dysfunction, either due to underlying coronary artery disease or myocardial depression from sepsis, is the leading cause of impaired cardiac contractility. Decreased renal perfusion due to various other causes, such as thromboembolism, atherosclerosis, aortic dissection, or inflammation (vasculitis, especially scleroderma), affecting either the intra- or extrarenal circulation can also occur but is not common. Although renal arterial stenosis presents as subacute or chronic renal insufficiency, renal atheroembolic disease can present as AKI with acute oliguria. Renal atheroemboli (usually due to cholesterol emboli) usually affect older patients with a diffusive erosive atherosclerotic disease. The condition is most often seen after manipulation of the aorta or other large arteries during arteriography, angioplasty, or surgery.³ It also may occur spontaneously or after treatment with heparin, warfarin, or thrombolytic agents. Drugs such as cyclosporine, tacrolimus, and angiotensin-converting enzyme (ACE) inhibitors, as well as toxins, including radiocontrast dye, cause intrarenal vasoconstriction, resulting in reduced renal plasma flow and consequent oliguria. Decreased renal perfusion can also occur as a result of an outflow problem, such as with abdominal compartment syndrome or (rarely) renal vein thrombosis. Patients who receive massive volume resuscitation (e.g., burns, pancreatitis) and those who undergo major abdominal surgeries are at high risk for intraabdominal compartment syndrome.
4. Acute tubular necrosis (ATN). While this is often an end result of the listed factors, it may also be due to direct nephrotoxicity of agents such as antibiotics, heavy metals, solvents, contrast agents, crystals like uric acid or oxalate, or myoglobinuria.

Mechanical Obstruction

Oliguria secondary to mechanical obstruction can be further classified according to the anatomic site of the obstruction:

1. Tubular-ureteral obstruction may be caused by stones, papillary sloughing, crystals, or pigment.
2. Urethral or bladder neck obstruction, which is usually more common in men and typically due to prostatic hypertrophy or malignancy.

| KDIGO Stage | | UO Only | | | | |
|-------------|---------|---------|---------|---------|---------|--------|
| | | No AKI | Stage 1 | Stage 2 | Stage 3 | Total |
| SC Only | No AKI | 8,179 | 3,158 | 5,421 | 440 | 17,198 |
| | Dead | 4.3% | 5.3% | 7.9% | 17.7% | 5.9% |
| | RRT | 0.0% | 0.0% | 0.1% | 1.1% | 0.1% |
| | Stage 1 | 1,889 | 1,262 | 3,485 | 842 | 7,478 |
| | Dead | 8.0% | 11.3% | 13.0% | 32.1% | 13.6% |
| | RRT | 0.3% | 0.7% | 0.6% | 10.9% | 1.7% |
| | Stage 2 | 618 | 476 | 1,533 | 831 | 3,458 |
| | Dead | 11.3% | 23.9% | 21.5% | 44.2% | 25.5% |
| | RRT | 1.0% | 1.3% | 1.7% | 21.7% | 6.3% |
| | Stage 3 | 371 | 321 | 1,019 | 2,200 | 3,911 |
| | Dead | 11.6% | 38.6% | 28.0% | 51.1% | 40.3% |
| | RRT | 3.2% | 17.8% | 14.2% | 55.3% | 36.6% |
| | Total | 11,057 | 5,217 | 11,458 | 4,313 | 32,045 |
| | Dead | 5.6% | 10.5% | 13.0% | 42.6% | 14.0% |
| | RRT | 0.3% | 1.4% | 1.7% | 34.6% | 5.6% |

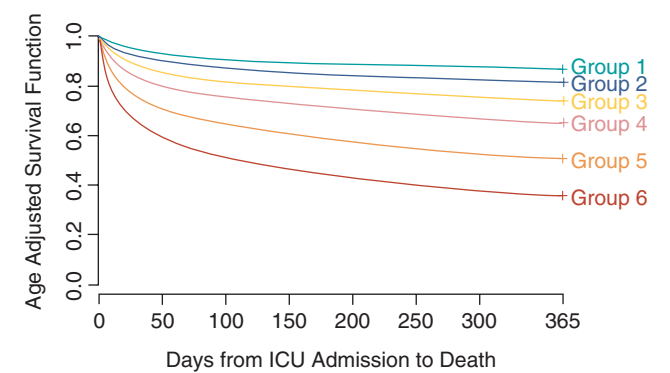


FIGURE 12-1 ■ Relationship Between Urine Output (UO) and Serum Creatinine (SC) Criteria and Clinical Outcomes. Top Panel: Results of a large observational study of critically ill patients. Presented are the number of patients, percentage of hospital mortality, and percentage of renal replacement therapy (RRT) for patients by maximum AKI criteria (urine output, serum creatinine, or both). Colors denote similar outcome patterns. Bottom Panel: Corresponding 1-year survival for patients classified as per top panel. (Source: Kellum JA, Sileanu FE, Murugan R, et al. Classifying AKI by urine output versus serum creatinine level. *J Am Soc Nephrol* 2015 January 7, Online. ASN.2014070724 (Permission requested).

3. A malpositioned or obstructed urinary catheter. Oliguria from mechanical obstruction of a urinary catheter should be suspected in any patient who develops oliguria with no predisposing events such as hypotension, shock, or use of nephrotoxins.

■ DIAGNOSTIC APPROACH TO OLIGURIA

Transient oliguria may not be an independent risk factor for morbidity and mortality in critically ill or injured patients, but sustained oliguria (>6 hours) often indicates AKI and has been shown to be independently associated with hospital mortality. Oliguria if not corrected will lead to worsening azotemia, fluid overload, and tissue edema, all of which can cause a variety of adverse outcomes in critically ill patients. Although treating oliguria may confer important physiologic benefits and allow for easier fluid management in intensive care patients, it does not improve important clinical outcomes such as the need for renal replacement therapy, the number of dialysis sessions, survival, or renal recovery. Thus, rapidly determining the cause of oliguria and correcting the underlying cause(s) are crucial to halt the progression of kidney injury.

Rule out Urinary Obstruction

The first step in the approach to a patient with oliguria is to rule out urinary obstruction. A prior history of prostatic hypertrophy may provide some clues to the presence of distal obstruction. However, in the ICU setting, distal obstruction presenting as oliguria is commonly due to obstruction of the urinary catheter (especially in male patients). Hence, in patients with new-onset oliguria, the urinary catheter must be flushed or changed in order to rule out obstruction, especially when no inciting factors are identified. Although uncommon in the acute setting, complete or severe partial bilateral ureteral obstruction may also lead to acute, “acute on chronic,” or chronic renal failure. Early diagnosis of urinary tract obstruction (UTO) is important, since in many cases it can be corrected, and a delay in therapy can lead to irreversible renal injury. Renal ultrasonography is usually the test of choice to exclude UTO,⁴ since this is noninvasive, can be performed by the bedside, and also carries the advantage of avoiding the potential allergic and toxic complications of radiocontrast media. In the majority of affected patients, ultrasonography can establish the diagnosis of hydronephrosis and often establish its cause. Ultrasonography also can be useful to assess the presence of a chronic component to the kidney injury (decreased size of kidney and cortical thinning) and for detecting other causes of renal disease such as polycystic kidney disease. However, under some circumstances, renal ultrasound may not yield good results. For example, in early obstruction or obstruction associated with severe dehydration, hydronephrosis may not be seen on the initial ultrasound examination but may appear later in the course of the disease. Computed tomography (CT) scanning should be performed if the ultrasound results are equivocal or if the kidneys are not well visualized. CT also is indicated if the cause of the obstruction cannot be identified by ultrasonography.

Laboratory Indices

Although most authorities advocate examining the urine sediment, the yield of urine microscopy in the ICU is very low. Urine sediment is typically bland or reveals hyaline and fine granular casts in a prerenal state. By contrast, ATN is often associated with coarse granular casts and tubular epithelial casts. However, the discrimination of these findings is limited, and AKI may be present in the absence of changes in urinary sediment, particularly with sepsis-induced AKI. The main utility of examining the urine sediment is for the detection of red cell casts, which indicate primary glomerular disease. Although rare, these can be present in patients with other systemic illnesses such as systemic lupus erythematosus (SLE). The urine sediment in postrenal failure is often very bland; casts or sediment typically are absent. Occasionally a few red cells and white cells may be seen. Eosinophilia, eosinophiluria, and hypocomplementemia, if present (although insensitive and nonspecific), point to the diagnosis of atheroembolic etiology of acute oliguria.⁵

Table 12-1 lists laboratory values that have been traditionally thought to help in the differentiation of prerenal and intrarenal causes of oliguria. The fractional excretion of filtered sodium (FE_{Na}) is calculated according to the following formula:

$$FE_{Na} = \frac{(\text{urine sodium} \times \text{plasma creatinine})}{(\text{plasma sodium} \times \text{urine creatinine})} \times 100$$

If the calculated FE_{Na} is <1%, a prerenal cause of oliguria is generally suspected. Importantly, interpretation of the FE_{Na} is difficult or impossible if the patient has received diuretic or natriuretic agents (including dopamine and/or mannitol). Interpretation of the FE_{Na} also can be affected by the presence of large amounts of endogenous osmotically active substances in the urine, such as glucose or urea. Drugs that interfere with the renin-angiotensin-aldosterone axis, such as ACE inhibitors or nonsteroidal antiinflammatory agents, also confound the interpretation of FE_{Na}. Several nephrotoxic factors, such as aminoglycosides, cyclosporine, and contrast media, cause afferent arteriolar

TABLE 12-1

Biochemical Indices Useful to Distinguish Prerenal from Intrarenal Acute Renal Failure

| | PRERENAL | RENAL |
|------------------------|----------|-------|
| Osm u (mOsm/kg) | >500 | <400 |
| Na u (mmol/L or mEq/L) | <20 | >40 |
| urea/creatinine | >0.1 | <0.05 |
| u/s creatinine | >40 | <20 |
| u/s osmolality | >1.5 | >1 |
| FE _{Na} (%)* | <1 | >2 |
| FE _{urea} (%) | <25 | >25 |

*[(u Na/s Na)/(u creatinine/s creatinine)] × 100

ARF, acute renal failure; S, serum; U, urine.

vasoconstriction and are hence associated with FE_{Na} values below 1%, mimicking prerenal azotemia. Furthermore, sepsis may result in urine chemistries that resemble prerenal physiology even when renal blood flow is normal or increased.⁶

A low fractional excretion of urea (FE_{urea} < 35%) has been proposed to be more sensitive and specific than FE_{Na} in differentiating between prerenal and renal causes of AKI, especially when diuretics have been administered.⁷ However, numerous studies have demonstrated the limited diagnostic and prognostic utility of urine biochemistry in AKI.⁸⁻⁹

Clinical Parameters

Traditional indicators of fluid status and tissue perfusion—systemic arterial blood pressure, heart rate, body weight, presence of jugular-venous pulsations (JVP), and peripheral edema—can provide important clues about the etiology of oliguria. In the ICU, however, some of these indicators are less useful for a variety of reasons.

The presence or absence of JVP is not an accurate way to assess right ventricular or central venous pressures in the presence of positive pressure ventilation and positive end-expiratory pressure (PEEP). Similarly, peripheral edema is often due to coexistent hypoalbuminemia and decreased oncotic pressure in critically ill patients. Thus, patients can have an excessive volume of total body water and yet be intravascularly volume depleted. BP and heart rate are affected by numerous physiologic and treatment variables and are unreliable measures of volume status.

It is common to assume that one can obtain a more accurate assessment of preload by measuring the central venous pressure (CVP) or pulmonary capillary occlusion pressure (PAOP). However, these parameters do not provide reliable estimates of preload or preload responsiveness.¹⁰ Static measures such as CVP are affected by the presence of atrioventricular valve abnormalities, compliance of the ventricle, and pericardial and abdominal pressures. Even when CVP is low, the value of CVP does not give any information on whether the patient will improve his or her cardiac output to a fluid bolus (i.e., being preload responsive). A cardiac index greater than 3.0 L/min/m² generally suggests adequate preload, but it may not reflect optimal preload.¹¹ The mixed venous oxygen saturation (SvO₂) can serve as a surrogate for cardiac output but again does not define optimal filling. Moreover, SvO₂ can be altered by the ability of tissues to extract and subsequently utilize delivered oxygen. In patients on mechanical ventilation and without spontaneous triggering of the ventilator, an arterial pulse-pressure variation of >13% is strongly predictive of preload responsiveness.¹² However, the use of pulse contour analysis is limited in that it is applicable only in patients who receive >8 mL/kg tidal volume on the ventilator, who do not have arrhythmias, and in whom lung compliance is >30 cm of water. An easier and more applicable test of

preload responsiveness in the ICU setting would be passive leg raising (PLR), which can be done in spontaneously breathing patients and in those with arrhythmias.¹³ A detailed discussion on how to perform this test and its interpretation is beyond the scope of this chapter. In other cases, critical care echocardiography looking at inferior vena cava collapsibility, contractility of the heart, and presence or absence of B lines on lung ultrasound may provide reliable guides to fluid therapy optimization.

Abdominal Compartment Syndrome

Another important and often overlooked reason for acute oliguria is abdominal compartment syndrome (ACS). ACS is defined as symptomatic organ dysfunction that results from an increase in intra-abdominal pressure. Although this condition was initially described in trauma patients, ACS occurs in a wide variety of medical and surgical patients. ACS is sometimes seen after acute severe pancreatitis and major abdominal surgeries requiring large-volume resuscitation, emergent laparotomies with tight abdominal wall closures, or abdominal wall burns with edema. ACS leads to AKI and acute oliguria mainly by directly increasing renal outflow pressure and thus reducing renal perfusion. Other mechanisms include direct parenchymal compression and arterial vasoconstriction mediated by stimulation of the sympathetic nervous and renin-angiotensin systems. Cardiac output also can be compromised by impaired venous return. These factors lead to decreased renal and glomerular perfusion and acute oliguria on this basis. Intraabdominal pressures over 15 mm Hg can lead to oliguria, and pressures over 30 mm Hg can cause anuria.¹⁴

ACS should be suspected in any patient with a tensely distended abdomen, progressive oliguria, and increased airway pressures (transmitted across the diaphragm). The mainstay of diagnosis is the measurement of intraabdominal pressure, and the most common way to assess intraabdominal pressure is to measure the pressure within the urinary bladder. Bladder pressure, obtained by transducing a fluid-filled Foley catheter, has been shown to correlate well with intraabdominal pressure over a wide range of pressures. Decompression of the abdomen with laparotomy, sometimes requiring that the abdomen be left open for a time, is the only definitive treatment for oliguria secondary to ACS.

TREATMENT OF OLIGURIA

Ensuring Adequate Renal Perfusion but Avoiding Fluid Overload

The mainstays of treatment of oliguria are identification and correction of precipitating factors. Hypovolemia should be rectified promptly, but care should be taken to avoid fluid overload. Oliguria should prompt an investigation as to the cause and not just a reflex administration of fluids. In addition, both the volume and type of fluid have been shown to influence the renal function. Too little or too much fluid worsens renal function. Although hypovolemia leading to AKI is intuitive, it is crucial to realize that fluid overload has been consistently shown to impair renal function in several studies.¹⁵⁻¹⁷ Fluid overload impairs renal function by several mechanisms, including increase in the interstitial pressure within the kidney and renal venous pressure, both of which impair the GFR.

Hyperoncotic colloids (20% albumin)¹⁸⁻¹⁹ and hydroxyethyl starch (HES)²⁰⁻²¹ have been shown to worsen renal function, increase the need for renal replacement therapy, and increase patient mortality. These agents should usually be avoided in oliguric patients with or at increased risk of AKI. Although RCTs are lacking, there is considerable observational^{22,23} and experimental²⁴ evidence documenting an association between fluids containing high chloride content (e.g., 0.9% saline) and development or worsening of AKI. Both lactated Ringer's and newer isotonic balanced salt solutions are therefore preferable in patients with or at significant risk of AKI.

Instituting appropriate supportive measures, such as avoidance of nephrotoxic agents and adjustment of doses of renally excreted drugs, is also important. Renal perfusion should be ensured both by correcting hypotension and by supporting appropriate intravascular volume expansion but also by ensuring that intraabdominal and right heart pressures are appropriately managed. The correction of hypotension is especially crucial in sepsis and ischemic AKI, where some of the important autoregulating mechanisms that help preserve GFR in the face of fluctuating BP are disrupted. Vasoactive drugs may be necessary in the ICU setting to maintain adequate renal perfusion pressure and adequate urine output. In general, a target mean arterial pressure (MAP) of 65 mm Hg should be adequate. However, in patients with chronic hypertension and renal vascular disease, the autoregulation curve can be shifted to the right, and higher than normal MAP may be required to ensure adequate renal perfusion.²⁵

Role of Diuretic Agents

The use of diuretic agents in oliguric renal failure is widespread despite the lack of convincing evidence supporting their efficacy. Traditionally, diuretics have been used in the early phases of oliguria to “jump start” the kidney and establish urine flow. Many clinicians believe that the absence of oliguria makes it easier to regulate intravascular volume status. Moreover, nonoliguric renal failure generally has a better prognosis than oliguric renal failure, and clinicians frequently use diuretics in an effort to avoid development of a low urine output state. A large observational study (BEST kidney study) showed that use of diuretics has no beneficial effect on clinical outcomes.²⁶ Furthermore, high doses of loop diuretics can be associated with ototoxicity. Although a cautious trial of diuretics is a reasonable approach in an oliguric patient, and may even be helpful in discerning the cause of oliguria (e.g., furosemide stress test²⁷), this should not be done unless hypovolemia is ruled out and care taken to ensure diuretic usage does not delay initiation of renal replacement therapy when indicated.

Vasoactive Agents

Other agents that have been used to treat oliguria include dopamine and related compounds. Because urine output often increases with the

addition of low-dose dopamine, many intensivists assume that it has a beneficial effect. Indeed, low-dose dopamine had been advocated for nearly 30 years as therapy for oliguric renal failure on the basis of its action on DA1 receptors at doses of <5 µg/kg/min. However, this is now of historical interest only, with there being abundant evidence that low-dose dopamine does not afford any renal protection in oliguria.²⁸

Furthermore, there are important physiologic considerations that argue against a protective role for dopamine or any other dopamine receptor agonists (e.g., fenoldopam, dopexamine) in oliguric states. First, the effect of dopamine agonists on urine output may be merely the natriuretic response mediated by inhibition of sodium/potassium-adenosine triphosphatase (Na⁺/K⁺-ATPase) at the tubular epithelial cell level. In other words, dopamine increases urine output because it is a diuretic. Second, administration of dopaminergic antagonists (e.g., metoclopramide) has not been associated with loss of renal function. Third, the effect of dopamine may be counteracted by increased plasma renin activity in critically ill patients. Fourth, a significant hysteresis effect has been shown for the action of dopamine on renal blood flow. Finally, although dopamine increases renal blood flow, it does not increase medullary oxygenation. Indeed, by increasing solute delivery to the distal tubule, dopamine agonists actually worsen medullary oxygen balance.²⁹ Despite claims to the contrary, newer dopaminergic agonists (e.g., fenoldopam, dopexamine) not only suffer from these limitations but also can induce hypotension, thereby further increasing the risk of renal injury; hence, these should not be used to treat oliguria.³⁰

CONCLUSION

The presence of oliguria should alert the clinician to undertake a diligent search for any correctable underlying causes. The mainstay of treatment is to ensure adequate renal perfusion through optimization of cardiac output and intravascular volume status while avoiding over-resuscitation. The use of diuretics should be limited to treatment of fluid overload, not for treatment of oliguria per se.

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A systematic review of studies examining urine chemistries in acute kidney injury in patients with sepsis. The authors conclude that urine chemistries are unreliable as a means to distinguish prerenal physiology from kidney damage.

Kellum JA, Sileanu FE, Murugan R, et al. Classifying AKI by urine output versus serum creatinine level. *J Am Soc Nephrol* 2015 January 7; On Line. ASN.2014070724.

Analysis of over 32,000 ICU patients of whom 23,866 (74.5%) developed AKI by urine output or creatinine criteria or both. Short- and long-term outcomes were worse when patients had any stage of AKI defined by both criteria compared to either criterion alone.

Uchino S, Doig GS, Bellomo R, et al. Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Diuretics and mortality in acute renal failure. *Crit Care Med* 2004;32(8):1669-77.

A large multicentered, multinational observational study examining the impact of diuretic therapy on outcomes in acute kidney injury. No clinical benefit could be demonstrated from the use of these agents.

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Disorders of osmoregulation resulting in dysnatremia—namely, *hypernatremia and hyponatremia*—are exceedingly common clinical problems observed in the critically ill. These abnormalities are usually asymptomatic although at times they can manifest with symptoms ranging from minor to life-threatening. Dysnatremias present at hospitalization or of iatrogenic origin are individual risk factors for increased morbidity and mortality. Dysnatremias present at the time of intensive care unit (ICU) admission were associated with a higher risk of death compared with ICU-acquired dysnatremia. Fluctuations in serum sodium concentrations were independently associated with an increased risk of in-hospital death, even in patients who remained normonatremic during the ICU stay.¹ The key to treatment in an individual patient involves differentiating between acute and chronic disorders and subsequently in balancing the risks of treatment and risks of the disorder.

■ HYPERNATREMIA

Hypernatremia is defined as a serum sodium concentration exceeding 145 mmol/L. It usually affects individuals who have restricted access to water, decreased thirst, or both. In addition, the situation may be exacerbated by pathologic conditions such as acute illnesses that result in increased fluid loss. In the ICU setting, this is a fairly common situation with ongoing fluid loss and inadequate/restricted free water replacement.

In outpatient settings, hypernatremia is mainly found in the geriatric population, whereas in the hospital environment, it is seen in all age groups. The observed incidence is up to 2% of all inpatients, increasing up to 15% among patients admitted to the ICU.^{2,3,4,5} Mortality rates in ICU patients with hypernatremia are reported to be around 32%.⁴ Whereas the increased incidence of hypernatremia in the ICU and increased mortality in these patients is indicative of the underlying disease severity, hypernatremia itself is an independent risk factor of hospital mortality and ICU mortality.^{1,7}

Hypernatremia is usually not a problem of sodium homeostasis but rather a free water deficit resulting from a negative balance between water intake and water excretion. Rarely, hypernatremia can result from increased sodium intake, such as administration of hypertonic saline. Depending on the relative balance of salt and free water intake/loss, hypernatremia can be classified as hypovolemic, euvoletic, or hypervolemic.

Water moves through semipermeable cell membranes to equalize the concentration of solutes in intra- and extracellular fluids. Hypernatremia always causes hypertonicity with extracellular movement of water, leading to cell shrinkage. Sodium can freely cross the systemic capillary membranes, resulting in the same sodium concentration in all extracellular fluids. In contrast, the blood-brain barrier, with its tight endothelial junctions lined by astrocytic foot processes, restricts this sodium movement.⁷ Hypernatremia can therefore cause net loss of brain volume leading to mechanical stress on cerebral vessels leading to intracranial hemorrhage.⁸ Hypernatremia has also been used therapeutically to prevent brain herniation in patients with increased intracranial pressure.⁶

Regulation of water balance is controlled by osmoreceptors present in the hypothalamus. These cells express transient receptor potential time channel subfamily member 1 (TRPV 1) and member 4 (TRPV 4)

channels on the cell membranes^{9,10} and release vasopressin in a linear relationship with increasing plasma sodium concentration above 135 mmol/L.¹¹ Vasopressin binds to V2 receptors on the basolateral membrane of principal cells lining the renal collecting duct⁹ and causes retention of free water, resulting in concentrated urine. Chronic hypernatremia leads to the development of idiogenic osmoles in brain cells. This cellular adaptation prevents cell shrinkage but can lead to idiopathic cerebral edema if the hypernatremia is corrected rapidly with free water replacement.

Symptoms of hypernatremia are mainly neurologic and can range from confusion, weakness, and lethargy in the early stages, progressing to seizures, coma, and even death. Cardiovascular symptoms may relate to volume status, depending upon the cause of hypernatremia. Acute hypernatremia may also cause brain demyelination syndrome.^{12,13}

Prevention of iatrogenic hypernatremia should always be a consideration while treating patients in the ICU. Since the ICU is a monitored environment, predisposed patients should be recognized and identified before the serum sodium rises to an abnormal level. ICU hypernatremia has been proposed as an indicator of quality of care.⁴

Hypernatremia should be aggressively managed in patients having symptoms or when the increase in serum sodium is acute. The basic principle in treatment of hypernatremia is water replacement. Water deficit can be estimated as follows:

$$\text{Water deficit} = (0.6 \times \text{total body weight in kg}) \times (\text{patient's serum sodium concentration} / 140 - 1)$$

where $0.6 \times \text{total body weight in kg}$ is total body water, and 140 is the desired serum sodium concentration. The percentage of water relative to total body weight is actually closer to 50% in women and about 50% in the elderly of both genders.

Since this formula assumes the body to be a closed space, consideration needs to be given for ongoing fluid losses. Another simplified method for calculating free water deficit is 3 mL/kg (elderly woman) to 4 mL/kg (young man) for every 1 mmol/L increase in serum sodium concentration.¹⁴

In chronic hypernatremia, defined as hypernatremia lasting for more than 48 hours or of an unknown duration, the initial therapeutic goal is to decrease the plasma sodium concentration by not more than 10 mmol/L per day.¹⁴ In acute hypernatremia, the rate of decrease in plasma sodium concentration should not exceed 2 mmol/L per hour until the plasma concentration reaches 145 mmol/L. Hyperacute hypernatremia, such as with accidental salt ingestion, manifesting as seizures or intracranial hemorrhage should be aggressively treated with 5% dextrose in water and emergency hemodialysis to restore the normal sodium concentration. Typically, hypernatremia is often undertreated, and there is little risk of inadvertent overcorrection.^{16,17}

■ HYPONATREMIA

Hyponatremia, defined as serum sodium concentration below 136 mmol/L, is the most common electrolyte problem seen in hospitalized patients.¹⁸ The incidence of hyponatremia in hospitalized patients ranges from 30% to 36%.^{19,20} Advanced age is an independent risk factor for the development of hyponatremia due to decreased ability of the body to handle stresses related to salt and water balance.¹⁹

In an aging population, this electrolyte abnormality is increasingly important to understand. Moreover, drugs such as thiazides and non-steroidal antiinflammatory agents commonly used in this age group contribute to decreased renal ability to excrete free water. Critically ill patients also demonstrate impaired renal capacity to excrete free water. In the ICU settings, hyponatremia was noted to be present in 14% of patients at admission²¹ with an overall incidence of 11% to 29%.^{22,23,24} Hyponatremia is also associated with prolonged hospital stay and is an independent predictor of patient mortality. Severe hyponatremia (serum sodium less than 125 mmol/L) has an estimated risk of death of 27% to 40%.^{21,25}

Sodium is the main electrolyte responsible for serum osmolarity. Hyponatremia causes hyposmolarity and intracellular efflux of water. This cellular swelling is most prominent in brain cells, manifesting as varying degrees of cerebral edema with resulting neurologic symptoms. Two mechanisms compensate for cellular swelling. First, increased interstitial hydrostatic pressure due to cerebral edema causes displacement of fluid from the interstitial space into the cerebrospinal fluid (CSF) where some of it may get resorbed. Second, loss of intracellular electrolytes (mainly potassium) and cell-to-cell transfer of osmolytes (taurine, glutamate, etc.) takes place between neurons and the astrocytes that surround them. As a result, the astrocytes swell instead, protecting the neurons from osmotic stress.²⁶ With osmolyte and accompanying water loss, the brain volume returns to normal over time. This adaptive strategy can be harmful at times. In acute hyponatremia, the release of osmolytes such as glutamate may result in seizures; this adaptive mechanism may account for neurologic symptoms such as weakness and lethargy seen in chronic hyponatremia.²⁷ Rapid correction of chronic hyponatremia can cause acute cellular dehydration, with changes similar to those seen in hypernatremia. Once hyponatremia is corrected, the regeneration of osmolytes is slow and can take many days, although intracellular electrolyte accumulation is faster.²⁷

Although mild chronic hyponatremia is often thought to be asymptomatic, it has been associated with an increased incidence of falls, impaired memory, and gait abnormalities.²⁸ Hyponatremia has also been associated with osteoporosis.^{29,30,31} Both these factors add up to an increase in the risk of fractures, especially in the elderly. The major clinical symptoms are neurologic and present more commonly in acute hyponatremia, especially when the serum sodium decreases to less than 120 mmol/L. Initial nonspecific symptoms such as headache, lethargy, and nausea can progress to depressed reflexes, seizures, coma, and death.³² Patients at increased risk of developing encephalopathy are postmenopausal women,³³ children younger than 16 years,³⁴ and those with a preexisting central nervous system (CNS) disorder or space-occupying brain lesion and hypoxemia.³⁵ Increased mortality after developing neurologic symptoms has also been noted in menstruating females.³³ Hyponatremic encephalopathy and increased intracranial pressure can trigger the development of noncardiogenic pulmonary edema.³⁶ This condition is secondary to a CNS-mediated increase in pulmonary vascular permeability and catecholamine release, leading to pulmonary vasoconstriction and hydrostatic edema.³⁵

Treatment of hyponatremia must focus on increasing the sodium concentration and addressing the precipitating cause of the hyponatremia, while preventing any iatrogenic injury related to correction of the sodium level. Restriction of hypotonic fluids, regardless of the cause of hyponatremia, is a basic step/mainstay of such management. Water restriction must be sufficient to achieve negative free water balance (the difference between the total intake and excretion of water) for effective correction of hyponatremia. Urinary sodium and osmolarity should also be measured, especially if the urine is noted to be hypertonic. In patients with syndrome of inappropriate antidiuretic hormone (SIADH) secretion, renal excretion of sodium is increased in response to volume expansion. Therefore administration of normal saline may result in hyponatremia in these patients and should be avoided.

Symptomatic hyponatremia, whether acute (<48 hours) or chronic (>48 hours), needs emergency therapy. Experts agree that the first line of treatment of symptomatic hyponatremia is the administration of 3%

hypertonic saline.³⁷ However, controversy exists regarding the optimal rate of correction of hyponatremia. Each mL of 3% saline will increase the serum sodium concentration by 1 mEq/L. Initial administration of 2 mL/kg of 3% hypertonic saline up to 100 mL should be initially given and repeated every 10-15 minutes if the symptoms persist. Increasing the sodium concentration by 4-6 mEq/L with hypertonic saline is usually sufficient to prevent life-threatening neurologic symptoms of hyponatremia.³⁷

The amount of hypertonic saline necessary to correct the serum sodium concentration to a safe level (e.g., 120 mEq/L) can be estimated by calculating the sodium deficit as follows:

$$\text{Sodium deficit} = 0.5 \times \text{Lean body weight in kg} \times (120 - \text{Observed serum sodium concentration})$$

Cautious correction of hyponatremia and avoidance of iatrogenic neurologic injury is important. The increase in serum sodium concentration should not exceed 10 mEq/L per 24 hours and 18 mEq/L in any 48-hour period.³⁸ Electrolytes should be frequently checked to ensure that the rate of correction is not too high. Resolution of symptoms should be followed by a decrease in the rate of correction.

Unintended overcorrection of hyponatremia is common.³⁹ This result can occur with simultaneous administration of 3% hypertonic saline along with correction of the underlying cause (such as volume administration in dehydration, discontinuation of thiazide diuretics, or correction of the underlying cause of SIADH). Administration of desmopressin every 6-8 hours has been used to therapeutically re-lower the serum sodium concentration in patients who are at risk or who start developing signs and symptoms of osmotic demyelination syndrome (ODS).⁴⁰

In addition to the correction of serum sodium, any coexisting hypokalemia should be simultaneously corrected. Increasing the potassium concentration will indirectly increase serum sodium levels because sodium concentration is a function of exchangeable cations divided by the total body water.⁴¹

Rapid correction (>2 mEq/L per hour) has been linked to ODS in some cases. Other risk factors for ODS are overcorrection and large corrections of hyponatremia (>12 to 25 mEq/L per 24 hours).^{42,43,44,45} Classically, ODS affects the pons (central pontine myelinolysis), but extrapontine lesions are equally common.⁴⁶ In patients who develop this complication, correction of hyponatremia leads to an initial improvement in encephalopathic symptoms followed by a delayed deterioration and development of new permanent neurologic symptoms, including pseudobulbar palsy, quadriparesis, and coma.

Increasing evidence indicates that mild chronic hyponatremia is related to gait and cognition disturbances, thereby increasing the risk of falls and fractures.⁴⁷ Therefore, correction of hyponatremia should be attempted in every ICU patient. Hypertonic saline is rarely recommended in these cases. Besides water restriction, the volume status of the patient should be assessed. In euvolemic patients, SIADH is the most common cause of chronic hyponatremia. ADH restricts free water excretion by the kidneys. Although water restriction is a mainstay of therapy, it may be important to measure the urine osmolarity. In cases of high urine osmolarity, negative free water balance can be promoted by the use of a loop diuretic or demeclocycline (300-600 mg twice a day) that blocks the action of vasopressin on the kidneys. Vasopressin antagonists (vaptans) are a relatively new category of drugs used for the treatment of euvolemic and hypervolemic hyponatremia. Two drugs in this category, tolvaptan and conivaptan, have been approved by the Food and Drug Administration (FDA) in the United States. These drugs are not recommended for the treatment of acute symptomatic hyponatremia, given the failure of some patients to respond.⁴⁸ For chronic hyponatremia patients, these drugs are most effective in hypervolemic hyponatremia of congestive heart failure (CHF) and cirrhosis. Given the lack of mortality benefit and prohibitive cost of treatment, they are not recommended for routine use.⁴⁹

Hypervolemic hyponatremia is associated with the presence of edema and low "effective" volume states, such as CHF. Diminished

effective circulating volume causes release of ADH, causing water retention. Besides correcting the underlying disease process to correct the low “effective” circulating volume, specific treatment includes sodium and water restriction and use of loop diuretics to promote free water loss.

Hypovolemic hyponatremia is usually the result of volume depletion (both salt and water) combined with consumption of hypotonic

fluids. In response to hypovolemia, ADH is released, which further causes free water retention via the kidneys. This positive free water balance results in hypovolemic hyponatremia. Treatment involves intravenous replacement with normal saline to correct the volume depletion that subsequently decreases ADH hormone secretion, thereby allowing kidneys to excrete excess free water, thus correcting the hyponatremia.

KEY POINTS

1. Dysnatremias are risk factors for increased mortality and morbidity.
2. Treatment should be based on differentiating between acute and chronic dysnatremia.
3. Signs and symptoms of dysnatremias are mostly neurologic and primarily are due to the restricted movement of sodium across the blood-brain barrier.
4. Rapid correction of chronic hypernatremia and hyponatremia can predispose a person to cerebral edema and acute demyelination syndrome.
5. Hyponatremia is the most common electrolyte problem seen in hospitalized patients.
6. Vasopressin antagonists (vaptans) are a relatively new category of drugs used for the treatment of euvoletic and hypervolemic hyponatremia.

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Potassium is the most abundant intracellular cation and is involved in the regulation of a number of biological functions.¹ Alterations in electrolyte homeostasis frequently occur in critically ill patients, which are likely the result of comorbid disease, prolonged malnutrition, organ dysfunction, and polydrug therapy. Both hyperkalemia and hypokalemia are associated with an increased risk of mortality for intensive care unit (ICU) patients; accordingly, prompt recognition and treatment are essential.²

■ HYPERKALEMIA

Hyperkalemia is defined as a serum potassium concentration of $K^+ > 5.0$ mEq/L.³ As both serum and plasma samples can be used to measure K^+ levels, it is important to know which laboratory specimen is being analyzed. During the clotting process, platelets release K^+ , resulting in higher concentrations in serum as compared to plasma samples.⁴ Elevated K^+ may be due to either true hyperkalemia or pseudohyperkalemia.⁵ *Pseudohyperkalemia* is defined as when serum K^+ exceeds plasma K^+ by >0.4 mEq/L.⁶ Other potential causes of falsely elevated K^+ include cell lysis, thrombocytosis, leukocytosis, delayed processing times, and cold specimen temperatures.^{4,6}

True hyperkalemia occurs as a result of impaired K^+ excretion or transcellular K^+ shifts (Box 14-1). In the absence of renal failure, the kidneys account for approximately 90% of K^+ excretion. Serum K^+ begins to rise only when renal function falls to $<25\%$ of normal.⁵ Factors that have been associated with a greater risk of hyperkalemia include advanced stages of kidney disease, concomitant diabetes mellitus, and the use of agents that impair K^+ elimination, especially drugs that affect the renin-angiotensin-aldosterone system.^{7,8} Aldosterone stimulates the secretion of K^+ into the urine; thus, the deficiency of aldosterone or relative resistance to the effects of aldosterone may result in hyperkalemia.⁹

There are a number of drugs commonly used in the ICU that can cause hyperkalemia by altering K^+ elimination. Potassium-sparing diuretics (e.g., spironolactone, amiloride, and triamterene) inhibit urinary K^+ excretion and increase the risk of hyperkalemia in patients with impaired renal function.¹ Because treatment with spironolactone was found to reduce morbidity and mortality among patients with severe heart failure, the use of this drug has substantially increased in recent years.¹⁰ As a result, hospital admissions for hyperkalemia are more common now than in the past, and deaths in the hospital related to hyperkalemia have increased.¹¹ Angiotensin-converting enzyme inhibitors (ACEIs) reduce aldosterone levels and are associated with a high prevalence of hyperkalemia. Angiotensin receptor blockers (ARBs), when compared to ACEIs, may be associated with a greater risk of hyperkalemia.¹² Due to the inhibition of the cyclooxygenase-2 (COX-2) enzyme, nonsteroidal antiinflammatory drugs (NSAIDs) cause a reduction in renal prostaglandin synthesis. As prostaglandins stimulate the release of renin, NSAIDs may induce relative hyporeninemic hypoaldosteronism, manifesting as hyperkalemia and acidosis.^{13,14} The degree of NSAID-associated hyperkalemia is likely greater in patients with baseline renal insufficiency or those taking other medications that alter K^+ elimination.¹⁵ It has not been firmly established whether the degree of selectivity of COX inhibition impacts the development of hyperkalemia with NSAID administration.^{16,17} Heparin induces reversible hypoaldosteronism and hyperkalemia via a reduc-

tion in the number and affinity of angiotensin II receptors. This effect is independent of the route of heparin administration or the level of anticoagulation achieved.¹⁸ The calcineurin inhibitors, cyclosporine and tacrolimus, impair renal tubular hydrogen ion (H^+) secretion and cause hyperkalemia in the absence of significant renal injury.¹⁹ Other drugs that may alter urinary K^+ excretion and produce hyperkalemia include pentamidine and trimethoprim. The structure of trimethoprim is similar to that of the potassium-sparing diuretic amiloride, and it may reduce urinary K^+ elimination by approximately 40%.²⁰

Changes in transcellular K^+ relationships may lead to severe hyperkalemia in critically ill patients. These may be caused by the release of large amounts of intracellular K^+ or the prevention of extracellular-to-intracellular K^+ shifts. The pH-related effects on transcellular K^+ dynamics are complex as a number of direct and indirect physiologic responses occur simultaneously.¹ Serum hypertonicity causes the movement of water out of the intracellular space, and K^+ follows as a result of solvent drag, increasing K^+ .²¹ As K^+ is primarily an intracellular cation, massive tissue damage from rhabdomyolysis, burns, or trauma can lead to the release of K^+ into the extracellular space, producing hyperkalemia.²² Familial hyperkalemic periodic paralysis is a rare autosomal dominant disorder of ion channel function that presents as episodic weakness and elevations in K^+ .²³

A number of medications affect transmembrane K^+ shifts. β -adrenergic blockers reduce the movement of K^+ into cells and can promote hyperkalemia in patients with renal failure. The development of hyperkalemia with these agents may depend on their relative α - and β -receptor selectivity.²⁴ Succinylcholine is commonly used for paralysis in the ICU and promotes K^+ efflux from myocytes. In the setting of denervation, burns, trauma, or prolonged immobility, the hyperkalemic response can be severe.^{22,25} Digoxin is a cardiac glycoside that inhibits the cell membrane-bound sodium/potassium-adenosine triphosphatase (Na^+ - K^+ -ATPase). Inhibition of this pump leads to a release of K^+ into the extracellular space. Digoxin does not produce hyperkalemia in therapeutic doses but may cause hyperkalemia with toxic levels.²⁶ Insulin promotes the uptake of K^+ into the intracellular space, so insulin resistance or deficiency can result in hyperkalemia.

Clinical Effects

Many of the manifestations of K^+ abnormalities reflect the importance of normokalemia for maintaining membrane potential functionality.² Neuromuscular and cardiac cells are most affected by changes in K^+ homeostasis.²⁷ Hyperkalemia is often asymptomatic but can present as weakness, fatigue, paresthesia, motor paralysis, or quadriplegia.^{2,5} These symptoms are not specific to hyperkalemia and usually occur only in severe cases. The most important consequence of hyperkalemia is a reduction in the myocardial resting membrane potential. Alterations in K^+ result in conduction system abnormalities, with characteristic changes observed on the electrocardiogram (ECG) (Table 14-1). The ECG abnormalities associated with hyperkalemia are often progressive. The first and most common change observed is symmetrical peaking of the T wave. Other abnormalities associated with ongoing hyperkalemia include widening of the QRS complex and reduction in P wave amplitude with its eventual disappearance from the ECG.⁵ Further increases in K^+ can cause the QRS complex to merge with the T wave, resulting in a sine wave pattern. This may eventually

BOX 14-1 Causes of Hyperkalemia**IMPAIRED K⁺ EXCRETION**

Renal failure
 Mineralocorticoid deficiencies
 Renal tubular acidosis (type 4)
 Enzyme deficiencies
 Aldosterone resistance
 Drugs: potassium-sparing diuretics, ACEIs, ARBs, NSAIDs, heparin, trimethoprim, cyclosporine, tacrolimus, pentamidine

SHIFTS OF K⁺ OUT OF CELLS

Hypertonicity
 Tissue breakdown: rhabdomyolysis, burns, trauma
 Drugs: β -adrenergic blockers, digoxin, succinylcholine, arginine, lysine
 Familial hyperkalemic periodic paralysis
 Insulin deficiency or resistance

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; NSAIDs, nonsteroidal antiinflammatory drugs.

TABLE 14-1 Electrocardiogram Changes Caused by Abnormal K⁺

| HYPERKALEMIA | HYPOKALEMIA |
|-------------------------|--------------------------|
| Peaked T waves | Flat T waves |
| Widening QRS complexes | ST segment depression |
| Loss of P waves | U waves |
| Sine wave | QT interval prolongation |
| Ventricular arrhythmias | Ventricular arrhythmias |
| Asystole | |

degenerate into ventricular arrhythmias or asystole. It is important to note that there is significant variability in the K⁺ that results in a particular ECG abnormality, and hyperkalemia does not always present with cardiac manifestations.²⁸

Treatment

The most important goal of treating hyperkalemia is to prevent life-threatening cardiac arrhythmias. Therapeutic strategies are directed at antagonizing the effects of hyperkalemia at the cellular level, shifting K⁺ from the extracellular to the intracellular space, and removing K⁺ from the body. While there is no consensus as to what level of hyperkalemia mandates intervention, patients with serum K⁺ \geq 6.0 mEq/L or those with ECG abnormalities should be emergently treated.^{3,29}

Antagonizing the Effects of Hyperkalemia at the Cellular Level

Calcium chloride and calcium gluconate are salts that antagonize hyperkalemia-induced cardiac membrane excitability. Calcium chloride has greater bioavailability and contains more calcium than calcium gluconate. Despite their beneficial effects on cell membrane excitability, calcium salts do not lower K⁺. Furthermore, the use of calcium in the setting of digoxin toxicity is contraindicated as it may potentiate the drug's negative effects.⁵

Shifting K⁺ From the Extracellular to the Intracellular Space

Insulin increases the cellular uptake of K⁺ by stimulating the Na⁺-K⁺-ATPase pump.³ It is the most effective agent to facilitate transcellular shift, providing the fastest and largest reduction in K⁺.²² The potassium-lowering effect occurs within 15 minutes following administration and

is sustained for 2 to 4 hours. The recommended dose is 10 units of intravenous (IV) regular insulin with 12.5 to 25 g of dextrose to avoid hypoglycemia. This dose will decrease the K⁺ by 0.5 to 1.0 mEq/L.²⁹ β_2 -receptor agonists will also decrease K⁺ by stimulating the Na⁺-K⁺-ATPase pump. Nebulized albuterol is an effective treatment option, lowering K⁺ within 30 minutes.²⁸ Albuterol's reduction in K⁺ is dose dependent. Insulin and β_2 -receptor agonists can each be used as monotherapy, but when these agents are co-administered, a synergistic effect occurs.²⁹ Sodium bicarbonate buffers extracellular H⁺ and promotes the shift of K⁺ into cells. This provides the smallest reduction in K⁺, and its administration should be limited to situations with concurrent metabolic acidosis.^{5,29}

Removal of K⁺ From the Body

A number of diuretics stimulate urinary K⁺ excretion; however, no clinical trials have supported the use of these medications in the treatment of hyperkalemia.²⁸ Cation exchange resins, such as sodium polystyrene sulfonate (Kayexalate), exchange sodium for K⁺ in the colon.³ Each 1 gram of resin removes approximately 1 mEq of K⁺ over 24 hours.⁵ Kayexalate's potassium-lowering effect is slow and may not be appropriate in emergency situations. Furthermore, its use has been associated with intestinal necrosis and bowel perforation.²² Recent studies evaluating newer cation exchange compounds, such as sodium zirconium cyclosilicate (ZS-9) and patiomer, have shown promising results; however, further investigation is needed.^{7,8} Dialysis is the most reliable way of removing K⁺. Both peritoneal dialysis and hemodialysis are options, but hemodialysis is more effective. The speed of K⁺ removal can be adjusted with changes in dialysate K⁺ and the blood flow rate.²⁹ Table 14-2 summarizes these hyperkalemia treatment options.

HYPOKALEMIA

Hypokalemia is defined as serum K⁺ < 3.5 mEq/L.¹ Common causes of hypokalemia include decreased dietary intake, increased excretion, and shifts into the intracellular compartment (Box 14-2). Hypokalemia is often iatrogenic. Diuretic therapy is a well-documented cause of hypokalemia in critically ill patients. Thiazide diuretics indirectly stimulate K⁺ secretion by increasing sodium and fluid delivery to the collecting duct.³⁰ Loop diuretics directly inhibit the Na-K-2Cl transporter in the thick ascending limb of the loop of Henle. Acetazolamide decreases bicarbonate reabsorption in the proximal tubule and increases K⁺ excretion in the distal nephron.³¹ Through their mineralocorticoid effects, fludrocortisone and hydrocortisone can lead to excessive urinary K⁺ wasting. Aminoglycosides, amphotericin B, cisplatin, tenofovir, and foscarnet all promote renal K⁺ loss and can be causes of hypokalemia.³² Penicillin and its synthetic derivatives act as nonreabsorbable anions, enhancing K⁺ secretion.²² A number of drugs promote hypokalemia by altering transcellular K⁺ homeostasis. β_2 -receptor agonists, catecholamines, insulin, and xanthines all stimulate the intracellular uptake of K⁺. Overdoses of thyroxine, risperidone, and quetiapine have all been associated with the development of hypokalemia.^{22,32}

The K⁺ of stool is approximately 55 to 75 mEq/L.³³ As the volume of stool is normally low, fecal K⁺ losses are only 10 mEq/day.³⁴ With increased stool output seen with laxatives, diarrhea, or enemas, K⁺ losses can be significant. The K⁺ in gastric secretions is 5 to 10 mEq/L; thus, vomiting or excessive nasogastric suctioning usually do not directly cause hypokalemia. However, the loss of gastric acid will induce metabolic alkalosis that indirectly stimulates renal K⁺ excretion, possibly exacerbating hypokalemia.³³ The ultimate effect of alkalemia on K⁺ depends on the nature of the underlying disorder, the chronicity, and the degree of renal dysfunction.³¹ Some forms of renal tubular acidosis can promote urinary K⁺ loss. Magnesium deficiency may further exacerbate hypokalemia by increasing distal K⁺ secretion.³⁵ Barium poisoning from radiopaque contrast agents reduces the efflux of K⁺ from muscle cells, causing hypokalemia.³⁶ Delirium tremens is associated with both an increase in renal K⁺ secretion and shifts into the intracellular space.³⁷

TABLE 14-2 Treatment of Hyperkalemia

| TREATMENT | MECHANISM | DOSAGE/COMMENT | ONSET | DURATION |
|--------------------------|------------------------------------|--|--------------|-----------|
| Calcium | Stabilizes myocardial excitability | 10 mL of 10% solution IV (calcium gluconate or calcium chloride) | Minutes | 30-60 min |
| Insulin (regular) | Shifts K ⁺ into cells | 10 U IV + glucose (12.5-25 g) | 15-30 min | 2-4 h |
| Albuterol | Shifts K ⁺ into cells | 10-20 mg inhaled over 10 min | 30 min | 2-3 h |
| Sodium bicarbonate | Shifts K ⁺ into cells | In cases of acidosis | Delayed | — |
| Kayexalate with sorbitol | Removes K ⁺ from body | Oral: 15-30 g Retention enema: 30-50 g | 4-6 h 1 h | — — |
| Loop diuretics | Removes K ⁺ from body | IV, varies by drug and renal function | 15-60 min | — |
| Dialysis | Removes K ⁺ from body | Hemodialysis preferred over peritoneal dialysis in acute cases | 15-30 min | — |

BOX 14-2 Causes of Hypokalemia**DECREASED K⁺ INTAKE****INCREASED K⁺ EXCRETION**

Diarrhea, laxative, enema abuse

Increased renal losses:

Drugs: diuretics, glucocorticoids, aminoglycosides, amphotericin B, cisplatin, tenofovir, foscarnet, penicillin derivatives

Alkalemia

Osmotic diuresis (uncontrolled hyperglycemia)

Renal tubular acidosis

Mineralocorticoid excess:

Primary hyperaldosteronism

Congenital adrenal hyperplasia

Other causes:

Liddle's disease

Enzyme deficiencies

Bartter's syndrome

Magnesium deficiency

SHIFTS OF K⁺ INTO CELLS

Drugs: β -adrenergic agonists, catecholamines, insulin, xanthines, risperidone, quetiapine

Delirium tremens

Hyperthyroidism

Familial hypokalemic periodic paralysis

Barium poisoning

ally, serum K⁺ decreases by approximately 0.3 mEq/L for every 100-mEq reduction in total body K⁺, although this depends on body mass. The presence of ECG abnormalities or respiratory muscle paralysis mandates immediate treatment with IV K⁺. In order to minimize the risk of iatrogenic hyperkalemia, the maximum rate of K⁺ repletion should not exceed 20 mEq/h. In the presence of unstable arrhythmias, more rapid infusions are indicated.³ IV administration of K⁺ should ideally be performed using a central venous catheter as peripheral infusions may cause phlebitis.²² The use of infusion pumps and continuous ECG monitoring is mandatory. IV bolus administration of K⁺ can induce cardiac arrest. In the absence of a medical emergency, oral repletion is the preferred method of administration as it minimizes the risk of rebound hyperkalemia.³⁸ A number of potassium-salt compounds can be used to replenish total body stores. In most cases of hypokalemia, potassium chloride is preferred. Potassium phosphate administration is recommended in patients with concomitant hypophosphatemia, and potassium bicarbonate is preferred in patients with accompanying metabolic acidosis.³⁸ Correction of any coexisting magnesium deficiency is important in treating hypokalemia. Hypomagnesemia promotes renal K⁺ wasting, and the repletion of magnesium will allow for more rapid correction of hypokalemia. Finally the use of protocol-based algorithms for K⁺ replacement may reduce the prevalence of hypokalemia in the ICU.³⁹

KEY POINTS

1. Hyperkalemia and hypokalemia are common electrolyte abnormalities found in ICU patients. Early recognition and intervention are essential to prevent life-threatening complications.
2. ECG changes associated with hyperkalemia include peaked T waves, widening of the QRS complex, loss of P waves, appearance of a sine wave pattern, and ventricular arrhythmias.
3. Calcium salts reduce cardiac membrane excitability and should be given to patients with hyperkalemia and ECG changes.
4. Insulin and β -agonists are effective treatments to shift K⁺ into the intracellular compartment.
5. ECG changes associated with hypokalemia include flattened T waves, ST segment depression, the appearance of U waves, QT interval prolongation, and ventricular arrhythmias.
6. IV K⁺ administration is associated with complications and should be reserved for patients with ECG abnormalities or respiratory muscle paralysis.

Clinical Effects

Hypokalemia is reported to be the most common electrolyte disorder in hospitalized patients, and most cases are asymptomatic.³ Mild effects include fatigue, weakness, nausea, vomiting, and constipation.²² Ongoing reductions in K⁺ result in rhabdomyolysis, ascending paralysis, and respiratory insufficiency.³ The most serious and potentially fatal consequences related to hypokalemia are cardiac. These effects are especially pronounced in patients with hypertension, coronary artery disease, or heart failure.²² Hypokalemia is associated with characteristic ECG changes (Table 14-1). Progressive reductions in K⁺ produce T-wave flattening, ST depression, U waves, QT interval prolongation, ventricular arrhythmias, and cardiac arrest.¹

Treatment

The most important goals in the management of hypokalemia are to recognize and correct life-threatening reductions in serum K⁺. Gener-

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Derangements in the metabolism of phosphate commonly affect patients in the intensive care unit (ICU) and can cause significant multiorgan system sequelae, leading to increased morbidity and mortality. For instance, severe hypophosphatemia by itself is a reliable predictor of increased mortality in the septic patient.¹ An approach to recognizing and identifying the causes and clinical implications of this electrolyte disturbance follows; this chapter will provide an overview of phosphate homeostasis, the etiologies, classification, clinical manifestations, and treatment modalities of hypo- and hyperphosphatemic states.

■ PHOSPHATE HOMEOSTASIS

Phosphorus, the essential mineral found in the body, combined with oxygen as phosphate (PO_4) serves a number of crucial physiologic functions. Intracellularly, phosphate mostly exists in organic compounds such as creatine phosphate, 2,3-diphosphoglycerate, and adenosine triphosphate. Phosphorus is a substrate for kinase and phosphatase enzymatic processes critical in intracellular signaling; it is a component of the cell membrane lipid bilayer, a component of hydroxyapatite, the structural matrix of bone, and it serves as a buffer against acid-base derangements.

There is an important distinction between low serum phosphate, referred to as *hypophosphatemia*, and low total body phosphorus stores, referred to as *phosphate depletion*. *Hypophosphatemia* can occur in the setting of normal or even high total body phosphate due to a shift from the extracellular to intracellular compartment. Conversely, phosphate depletion may exist with normal or even elevated levels of serum phosphate in certain conditions such as in diabetic ketoacidosis. There is no common laboratory test to accurately measure total phosphorus stores. In a healthy 70-kg adult, the total body phosphorus content is estimated to be around 700 g (23,000 mmol).²

Laboratory tests instead measure the free inorganic phosphate ions (HPO_4^{2-} , H_2PO_4^- , and PO_4^{3-}), which do not directly reflect total body phosphorus stores because (1) about 80% of total body phosphorus is present in the skeleton as hydroxyapatite; (2) phosphorus is mostly intracellular, with an estimated intracellular to extracellular ratio of 100:1; and (3) transcellular shifts will alter serum phosphate levels without significantly changing total body phosphorus content. Phosphate homeostasis relies on the complex interplay between the gastrointestinal, renal, parathyroid (PTH), and bone axis. PTH increases intestinal phosphate absorption by its effect on vitamin D. Under low serum calcium levels, PTH is secreted and acts on the kidneys to increase 1,25-dihydroxyvitamin D₃ synthesis, which in turn augments both phosphate and calcium transport across the intestinal epithelium. Low serum phosphate levels also stimulate the kidneys to increase hydroxylation of vitamin D to its active form. Under steady-state circumstances, the kidneys regulate phosphate homeostasis by matching urinary excretion with net intake.

Emerging evidence describes a class of regulatory peptides called *phosphatonins*. These peptides decrease serum phosphorus levels by acting on the renal-skeletal-gut axis. Fibroblast growth factor-23 (FGF-23) appears to be the key phosphatonin produced by osteoblasts and osteocytes in response to elevated calcitriol. FGF-23 is secreted into the systemic circulation, decreases renal phosphate resorption, and increases excretion.³

■ HYPOPHOSPHATEMIA

Hypophosphatemia is typically classified as mild (serum phosphate concentration 2.5–3 mg/dL), moderate (1–2.5 mg/dL), or severe (<1 mg/dL). The prevalence of moderate hypophosphatemia ranges between 2.2% and 3.1%, and severe hypophosphatemia between 0.2% and 0.4% in the general hospital population.⁴ Critically ill patients, especially those with diabetic ketoacidosis and sepsis, have a high incidence of hypophosphatemia. Up to 34% of post-elective cardiac surgery patients and nearly all patients after major hepatic procedures develop hypophosphatemia within the first week.^{5,6} Although mild to moderate hypophosphatemia is often subclinical, severe hypophosphatemia can be associated with significant morbidity. All-cause mortality in patients with serum phosphate concentrations less than 1 mg/dL is as high as 30%.⁷

Common causes of hypophosphatemia are summarized in Box 15-1. Respiratory alkalosis can induce intracellular shifts of phosphate. Certain therapies instituted in the ICU, including overly aggressive diuresis, renal replacement therapy,⁸ and erythropoietin therapy,⁹ increase the risk of hypophosphatemia. Hyperparathyroidism and proximal renal tubular disorders impair phosphate resorption. Total body phosphate depletion also follows extreme catabolic states such as burns or sepsis.

Total body phosphate stores become depleted during a state of severe starvation, despite lab values that may show normal serum phosphate levels. Initially, the body adapts to a fasting state by glycogenolysis of the liver stores, which deplete after 24 hours. The body then decreases insulin secretion, shifting from glycogen to protein and fat catabolism as a source of glucose. Reintroduction of nutrition, especially a high carbohydrate load, increases insulin levels; anabolic pathways are activated, and lipolysis reverts to lipogenesis. The subsequent *refeeding syndrome* precipitates from low phosphate supply to high anabolic demand, as well as an intracellular compartment shift caused by insulin. Therefore, identifying high-risk patients, anticipating these changes before initiating feeding, slowly increasing nutritional intake, and close monitoring of electrolytes with appropriate repletion is imperative.^{10,11}

The patient in diabetic ketoacidosis is also at serious risk for phosphate depletion. Although plasma levels may be normal, total body stores are often depleted first due to the acidemia, which promotes transcellular phosphate shift and then through high renal losses through osmotic diuresis. Once insulin therapy is initiated, the acidemia is corrected, which pushes phosphate from the serum back into the cell, further exacerbating the problem.¹²

Development of the cardiac, respiratory, or neurologic manifestations of hypophosphatemia depends on the severity (typically serum levels below 1.0 mg/dL) and chronicity (Box 15-2). Proximal and/or diffuse skeletal muscle weakness with or without bone pain or rhabdomyolysis can be profound.¹³ ATP depletion in myocardial cells results in a well-described reduction in cardiac contractility that corrects with phosphate repletion. Hypophosphatemia can also cause a reversible depression in diaphragmatic contractility associated with respiratory failure and ventilator dependence.¹⁴ Neurologically, a wide spectrum of disorders such as peripheral or central neuropathy, tremors, paresthesias, encephalopathy, and seizures has been reported.

BOX 15-1**Common Causes of Hypophosphatemia**

Trans-cellular shift
 Refeeding syndrome
 Respiratory alkalosis
 Insulin administration
 Renal losses
 Diuretic therapy
 Volume expansion
 Osmotic diuresis
 Hyperparathyroidism (primary or secondary)
 Proximal renal tubular dysfunction
 Fanconi syndrome
 Insufficient intestinal absorption
 Malnutrition
 Phosphate-binding antacids
 Vitamin D deficiency
 Chronic diarrhea
 Steatorrhea
 Nasogastric suctioning
 Vomiting
 Malabsorption syndromes
 Extreme catabolic states
 Burns
 Trauma
 Sepsis

BOX 15-2**Clinical Manifestations of Severe Hypophosphatemia**

Respiratory
 Acute respiratory failure
 Ventilator dependence
 Musculoskeletal
 Muscle weakness
 Rhabdomyolysis
 Bone demineralization
 Hematologic
 Hemolysis
 Disorders of leukocyte phagocytosis or chemotaxis
 Neurologic
 Altered mental status
 Gait disturbance
 Paresthesias
 Cardiovascular
 Cardiomyopathy
 Decreased inotropy
 Cardiac dysrhythmias

Because phosphate serves as a buffer against acid-base derangements, hypophosphatemia influences the interpretation of acid-base status. The anion gap used to estimate unmeasured anions is typically lower for a patient with low measurable anions (i.e., either hypophosphatemia or hypoalbuminemia, or both). Therefore, the presence of a “normal” value for the calculated anion gap, under 10 or 12, in the setting of profound hypophosphatemia can actually suggest the presence of unmeasured anions. As a rule, the expected anion gap (in mEq/L) equals twice the serum albumin concentration (in g/dL) plus half the serum phosphate concentration (in mM/L).

Severe hypophosphatemia (phosphate concentration <1 mg/dL) mandates intravenous replacement, which has been found to vary widely from clinician to clinician in regard to dosages and speeds of infusion.¹⁵ One common regimen recommends continuous infusion of potassium phosphate 9 mmol (279 mg) given over 12 hours. Depending on the severity of phosphate deficit a weight-based regime ranging from 0.08 mmol/kg (2.5 mg/kg) or 0.16 mmol/kg (5 mg/kg) over 6 hours can be infused.¹⁶ Phosphate should *not* be administered by the

BOX 15-3**Common Causes of Hyperphosphatemia**

Renal
 Acute or chronic renal failure
 FGF-23 Deficiency
 Increased renal resorption:
 Hypoparathyroidism
 Thyrotoxicosis
 Cellular injury
 Rhabdomyolysis
 Tumor lysis syndrome
 Hemolysis
 Medication related
 Abuse of phosphate-containing laxatives
 Excessive (iatrogenic) phosphate administration
 Bisphosphonate therapy

IV route to patients with renal failure, and in every patient, close attention must be paid to the side effects of IV phosphate repletion; namely, metastatic calcification, hypocalcemia, hyperkalemia associated with potassium-containing supplements, volume excess, hyponatremia, metabolic acidosis, and hyperphosphatemia.

HYPERPHOSPHATEMIA

Hyperphosphatemia is defined as a serum phosphate level above 4.5 mg/dL; symptoms may be clinically significant at levels over 5 mg/dL. Causes of hyperphosphatemia are summarized in **Box 15-3**. Because of the kidney's high capacity to excrete phosphorus, hyperphosphatemia rarely occurs in the absence of kidney disease or from high intake alone. Instead, the most common cause of hyperphosphatemia in the critically ill patient is renal failure. Renal insufficiency impairs phosphate excretion and results in a positive phosphate balance, especially in stage IV and V of chronic kidney disease. Kidney injury also affects the normal adaptive bone mineralization process through hormonal and metabolic mechanisms (i.e., renal osteodystrophy).¹⁷ Bone normally acts as the body's primary phosphate reservoir; renal disease causes an increase in net bone resorption, releasing phosphate from the skeleton into the serum.

Iatrogenic hyperphosphatemia has been reported in the literature, most commonly with the use of phosphate-containing laxatives, bisphosphonate therapy, liposomal amphotericin B, or overly generous phosphate replacement. The use of phosphate-containing colorectal laxatives has been reported to cause clinically significant hyperphosphatemia and even cardiac arrest.¹⁸ Bisphosphonate therapy has been reported to cause hyperphosphatemia in the setting of renal insufficiency.¹⁹ Treatment of invasive fungal infections with liposomal amphotericin B has also been associated with hyperphosphatemia, which resolves after transition to amphotericin B lipid complex.²⁰

Hyperphosphatemia and hypocalcemia are often found together as a result of changes in the renal-parathyroid-bone axis. Loss of calcitriol production capacity in kidney disease leads to decreased intestinal calcium absorption and stimulation of parathyroid hormone production (i.e., secondary hyperparathyroidism). At the same time, however, normal bone resorption is impaired by high levels of phosphate.²¹

The two main approaches to managing hyperphosphatemia include limiting intake and enhancing urinary excretion (**Box 15-4**). In the absence of end-stage renal disease, phosphate excretion can be optimized with saline infusion (volume diuresis) and diuretic administration. Any patient with life-threatening hyperphosphatemia should be considered for dialysis. Oral phosphate binders decrease the absorption of phosphate in the gut and are a mainstay for preventing and treating hyperphosphatemia in patients with chronic renal failure. Calcium and aluminum salts are widely used. Calcium salts such as calcium acetate can produce hypercalcemia and metastatic calcification from a high

BOX 15-4 Treatment of Hyperphosphatemia

Decreased absorption/intake:

- Avoid oral intake of phosphate
- Avoid iatrogenic causes (i.e., phosphate-containing enemas, liposomal amphotericin B)
- Oral phosphate binders (i.e., calcium acetate, sevelamer)
- Slow and cautious repletion of phosphate

Increased excretion:

- Intravenous fluids (volume diuresis)
- Diuretic therapy
- Hemodialysis

calcium-phosphorus ($\text{Ca} \times \text{PO}_4$) product, however, in the patient with concomitant hypocalcemia they become the best choice. For patients requiring renal replacement therapy, chronic management of hyperphosphatemia with calcium-free phosphate binders (e.g., sevelamer hydrochloride [Renagel]) may reduce long-term mortality by preventing cardiovascular complications associated with a high $\text{Ca} \times \text{PO}_4$ product.²² However, these investigations have been observational in nature, and to date, data are lacking to convincingly show that normalization of phosphate in chronic hyperphosphatemia decreases morbidity of chronic kidney disease.

KEY POINTS

1. Phosphate has crucial physiologic functions in cell metabolism, oxygen delivery, enzymatic processes, energy metabolism, and bone integrity.
2. Derangements in phosphate balance have serious clinical sequelae in the critically ill. Severe hypophosphatemia is independently associated with increased mortality in the septic patient.
3. Phosphate regulation relies on the renal-gastrointestinal, parathyroid, and bone axis.
4. Hypophosphatemia is caused by reduced intake/intestinal malabsorption, transcellular shifts, and/or excessive renal excretion. Phosphate repletion regimens are varied in dosing and duration.
5. The kidney has a high capacity to eliminate phosphate. Hyperphosphatemia is rare in the absence of renal insufficiency.

ANNOTATED REFERENCES

Byrnes MC, Stangenes J. Refeeding in the ICU: an adult and pediatric problem. *Curr Opin Clin Nutr Metab Care* 2011;14(2):186–192.

This comprehensive review of refeeding syndrome takes an organ-system approach to the constellation of signs and symptoms that develop from the abrupt provision of nutrition after a period of malnutrition. The diagnostic and treatment modalities, including laboratory studies and electrolyte repletion as well as clinical pathways for correcting undernutrition, are explained.

Cavalli L, Mazzotta C, Brandi ML. Phosphatonins: physiological role and pathological changes. *Clin Cases Miner Bone Metab* 2012;9(1):9–12.

This article describes role of phosphatonins on phosphate homeostasis via their action on the bone-parathyroid-kidney axis, specifically via the peptide FGF23 and its cofactor Klotho. The clinically relevant pathologies related to altered expression of FGF23, either from mutations of the FGF23 gene or other genes that regulate its signaling pathway, are also described.

Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. *Am J Med* 2005;118(10):1094–1101.

This article describes the spectrum of physiologic processes affected by phosphate homeostasis. It reviews phosphate imbalance, its relevance in patient care, as well as its appropriate management.

The RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009;361(17):1627–1638.

A multicenter, randomized trial to assess whether higher intensity of continuous renal replacement therapy decreases all-cause mortality at 90 days. The study found no difference in the primary outcome of mortality, but did note a significantly increased incidence of hypophosphatemia (65.1% versus 54%; $P < 0.0001$) in intensive renal replacement therapy.

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Magnesium is an important ion that participates as a cofactor in over 300 enzymatic reactions, especially in those involving adenosine triphosphate (ATP). Hypomagnesemia is common in critically ill patients and is associated with increased mortality.¹

CELLULAR PHYSIOLOGY AND METABOLISM OF MAGNESIUM

Magnesium is a divalent cation (Mg^{++}) that is predominantly localized to the intracellular compartment (99%). It is the second most abundant intracellular cation after potassium and plays an important role in cellular metabolism and homeostasis. At the cellular level, Mg^{++} influences membrane function by regulating ion transport; Mg^{++} is required for sodium/potassium-adenosine triphosphatase (Na^+/K^+ -ATPase) activity, which maintains transmembrane gradients for Na^+ and K^+ .^{2,3} Mg^{++} also regulates intracellular calcium (Ca^{++}) flux by competing for Ca^{++} binding sites and influencing intracellular Ca^{++} transport.^{2,3} It is also an essential cofactor for most ATP-requiring processes. Intracellular Mg^{++} is required for numerous critical biochemical processes, including DNA synthesis, activation of gene transcription, initiation of protein synthesis, and regulation of energy metabolism.^{2,3}

Total body magnesium (21 to 28 g) is distributed in bone (53%), muscle (27%), soft tissue (19%), and blood (0.8%).² The normal concentration of total magnesium in serum is 1.5 to 2.3 mg/dL. Approximately 19% of circulating magnesium is bound to proteins, whereas 14% is complexed to plasma anions (citrate, phosphate, and bicarbonate). The majority of magnesium in plasma exists in its ionized form (67%), which represents the physiologically active species.² Consequently, the measurements of total serum magnesium may not accurately reflect the relative abundance of circulating Mg^{++} .^{1,2}

Magnesium homeostasis is maintained by the small intestine, kidney, and bone.^{2,4} Unlike calcium, there are no hormonal mechanisms for regulating Mg^{++} . Consequently, normal renal filtration and the reabsorption of Mg^{++} represent important regulatory mechanisms for Mg^{++} homeostasis.^{2,4} Non-protein-bound Mg^{++} is filtered by the glomerulus. Under normal conditions, up to 95% of filtered Mg^{++} is reabsorbed either in the proximal tubule (35%) or in the thick ascending loop of Henle (60%). Mg^{++} reabsorption in the loop of Henle is linked to sodium chloride ($NaCl$) transport and is inversely related to flow. Consequently, diuretic use and other conditions associated with increased tubular flow result in decreased Mg^{++} reabsorption.^{2,4} Under conditions of persistent Mg^{++} deficiency, the mobilization of Mg^{++} from bone also represents a potential homeostatic mechanism.²

PREVALENCE AND ETIOLOGY OF HYPOMAGNESEMIC IN PATIENTS IN THE INTENSIVE CARE UNIT

The reported prevalence of hypomagnesemia in adult intensive care unit (ICU) admissions ranges from 15% to 60% of cases.^{1,2} Most commonly, severe ionized hypomagnesemia in ICU settings is encountered following liver transplantation and in patients with severe sepsis,¹ but many conditions encountered in ICU patients can be associated with hypomagnesemia (Table 16-1). Hypomagnesemia is associated with an increased risk of mortality.¹

CLINICAL SIGNS AND SYMPTOMS OF HYPOMAGNESEMIC

Hypomagnesemia is frequently asymptomatic in critically ill patients and is commonly identified through routine laboratory studies.^{4,5} However, the relationship between hypomagnesemia and intracellular magnesium depletion is complex. Hypomagnesemia is most commonly seen in conjunction with hypokalemia, hypocalcemia, and/or other electrolyte abnormalities. Consequently, determining the clinical consequences of isolated hypomagnesemia has been difficult. In most instances, symptoms were attributed to Mg^{++} deficiency only after other electrolyte abnormalities had been corrected.^{2,4,5} As summarized in Table 16-2, the clinical sequelae of Mg^{++} deficiency are most commonly related to the cardiovascular, metabolic, and neuromuscular systems.

Hypomagnesemia is associated with electrocardiogram (ECG) changes similar to those observed in patients with hypokalemia: flattened T-waves, U-waves, and a prolonged QT interval. Magnesium is a cofactor for Na^+/K^+ -ATPase in cardiac tissue.^{2,4-6} Hypomagnesemia is associated with a variety of dysrhythmias, including atrial fibrillation, multifocal atrial tachycardia, ventricular tachycardia, and torsades de pointes.⁴⁻⁶ The administration of intravenous magnesium sulfate ($MgSO_4$) should be the initial therapy for torsades de pointes and should be used as an adjunctive treatment for refractory ventricular dysrhythmias.^{2,4-6} Magnesium administration during acute myocardial infarction is not recommended in the latest guidelines.⁷⁻⁹

Hypomagnesemia is commonly associated with both hypokalemia and hypocalcemia.⁴ The medications and homeostatic changes that affect magnesium handling often affect K^+ handling as well. In addition, hypomagnesemia promotes the renal losses of K^+ . Thus, hypokalemia can be refractory to potassium supplementation unless magnesium is replaced first.^{2,4} A somewhat similar condition is noted for hypocalcemia because hypomagnesemia suppresses parathyroid hormone release and activity.¹⁰ Consequently, hypocalcemia can be refractory to Ca^{++} replacement unless Mg^{++} is replaced as well.^{2,4} Hypomagnesemia has been shown to be associated with an increased incidence and degree of lactic acidosis.¹¹

Magnesium produces a depressant effect on the nervous system through its ability to cause presynaptic inhibition.^{2,4,6} It may also depress the seizure threshold by its ability to competitively inhibit N-methyl-D-aspartate receptors.^{2,4-6} The neurologic and neuromuscular manifestations of hypomagnesemia include coma, seizures, weakness, and signs of muscular irritability. The supplementation of magnesium might provide neuroprotective properties in patients with traumatic brain injury and prevent cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage.^{12,13} In addition, the administration of Mg^{++} therapy is commonly used in pregnant patients with preeclampsia or eclampsia.^{4,5}

Magnesium replacement has been used to treat bronchospasm in patients with asthma.^{4,5} The proposed mechanism of action for the therapeutic benefit of Mg^{++} in bronchospasm involves its relaxant effects on smooth muscle. Some studies have demonstrated improved forced expiratory volume in the first second of expiration (FEV₁) following intravenous magnesium administration or improved peak flow rates with nebulized magnesium, but these findings have not been confirmed.⁵

TABLE 16-1 Etiology of Hypomagnesemia in the ICU^{1,2,4-6}

| | |
|--------------------------------|---|
| Decreased GI intake | Magnesium-poor diet or total parenteral nutrition; malabsorption syndrome; short bowel syndrome |
| Increased GI losses | Chronic diarrhea; intestinal and biliary fistulae; nasogastric suctioning; vomiting |
| Intrinsic renal losses | Interstitial nephropathy; postrenal transplantation; postobstructive or postacute kidney injury diuresis |
| Drug-induced renal losses | Loop and thiazide diuretics; aminoglycosides; amphotericin B; cyclosporine; cisplatin; granulocyte colony-stimulating factor |
| Endocrine and metabolic causes | Hyperaldosteronemia; hyperparathyroidism; hyperthyroidism; SIADH; diabetic and alcoholic ketoacidosis; hypophosphatemia; hypercalcemia; hypoalbuminemia |
| Magnesium redistribution | Acute pancreatitis; administration of epinephrine, insulin; refeeding syndrome; massive blood transfusion |
| Other causes | CRRT; CPB; severe burns |

GI, gastrointestinal; SIADH, syndrome of inappropriate antidiuretic hormone; CRRT, continuous renal replacement therapy; CPB, cardiopulmonary bypass.

TABLE 16-2 Clinical Signs and Symptoms of Magnesium Deficiency

| CARDIOVASCULAR | METABOLIC | NEUROLOGIC | NEUROMUSCULAR |
|---|--------------------|-----------------------|------------------|
| Atrial fibrillation, flutter | Hypokalemia | Seizures | Chvostek sign |
| Ventricular tachycardia, esp. torsades de pointes | Hypocalcemia | Nystagmus | Muscle cramps |
| Supraventricular tachycardia | Hypophosphatemia | Delirium | Carpopedal spasm |
| ECG changes (↑ PR, wide QRS, ↑ QT) | Insulin resistance | Coma | Muscle weakness |
| Hypertension | Athetoid movements | Muscle fasciculations | |
| Risk of digitalis toxicity | | | |

ECG, electrocardiogram.

TREATMENT OF HYPOMAGNESEMIA

The management of hypomagnesemia should include the identification and correction of underlying causes and the replacement of magnesium. The degree of hypomagnesemia, severity of clinical symptoms, associated electrolyte abnormalities, and renal function should be assessed prior to initiating Mg^{++} therapy.

In general, intravenous administration of Mg^{++} is preferred in symptomatic critically ill patients. However, caution must be used with Mg^{++} replacement when renal dysfunction is present, since severe hypermagnesemia may result. Current recommendations for Mg^{++} replacement therapies are of somewhat limited value owing to the lack of adequately controlled studies. Magnesium may be administered intravenously as $MgSO_4$ (1 g = 4 mmol) or $MgCl_2$ (1 g = 4.5 mmol) and orally as magnesium gluconate (500 mg = 1.2 mmol) or magnesium oxide (400 mg = 6 mmol). When intravenous Mg^{++} replacement is used, a bolus followed by continuous infusion or infusion alone is preferred, since renal filtration and excretion may limit Mg^{++} retention. For the management of torsades de pointes, 1 to 2 g of intravenous

$MgSO_4$ over 5 minutes is recommended. For the urgent treatment of hypomagnesemia, an intravenous bolus of 8 to 12 mmol of Mg^{++} (2-3 g $MgSO_4$), followed by an infusion of 40 mmol Mg^{++} (10 g $MgSO_4$) over the next 5 hours should be considered.

KEY POINTS

1. Hypomagnesemia is one of the most common electrolyte disturbances encountered in ICU patients.
2. Hypomagnesemia is frequently asymptomatic; however, in ICU patients it is associated with increased mortality.
3. Hypomagnesemia in ICU patients manifests as disturbances in the cardiovascular, neuromuscular, and metabolic systems.
4. Aggressive intravenous administration of magnesium is indicated in cardiac arrhythmias, including torsades de pointes, preeclampsia/eclampsia, and status asthmaticus.

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Abnormal serum calcium concentration is a common finding in critically ill patients. The prevalence of hypocalcemia in intensive care unit (ICU) patients ranges from 70% to 90% when total serum calcium is measured and from 15% to 50% when ionized calcium is measured.¹ Hypercalcemia less frequently occurs, with a reported incidence of <15% in critically ill patients.² Hypocalcemia is associated with injury severity and mortality in critically ill patients.^{1,3-5} However, whether low serum calcium is protective, harmful, or simply prognostic in critical illness is unclear. Therefore, in most instances, the management of hypocalcemia involves treating the underlying medical condition(s), except when patients are symptomatic or hemodynamically unstable.

CALCIUM PHYSIOLOGY AND METABOLISM

Calcium is a divalent ion (Ca^{2+}) involved in critical biologic processes like muscle contraction, blood coagulation, neuronal conduction, hormone secretion, and the activity of various enzymes.³⁻⁵ Therefore, it is not surprising that intracellular and extracellular calcium levels, like pH, are tightly regulated. A normal adult contains approximately 1 to 2 kg of total body calcium, which is primarily located in bone (99%) as hydroxyapatite.^{1,3,5} Skeletal stores of calcium represent an unlimited reservoir that is predominantly regulated by extracellular Ca^{2+} , parathyroid hormone (PTH), and calcitonin. Extracellular concentrations of Ca^{2+} are typically 1 to 10,000 times greater than cytoplasmic Ca^{2+} levels.^{1,3} Similarly, the majority of intracellular calcium (>90%) is found in subcellular organelles (e.g., mitochondria, microsomes, and endoplasmic or sarcoplasmic reticulum) as opposed to in the cytoplasmic compartment. Ca^{2+} -mediated cell signaling involves rapid changes in cytoplasmic Ca^{2+} from both internal and external stores.^{6,7} Cytoplasmic Ca^{2+} influx occurs through cell membranes by receptor-activated, G-protein-linked channels and the release of internal Ca^{2+} from endoplasmic or sarcoplasmic reticulum (ER/SR) by second messengers.⁶ The efflux of cytoplasmic Ca^{2+} involves the transport of Ca^{2+} across the cell membrane and into the ER/SR via specific transporters.⁶⁻⁸ These tightly controlled pulsations of cytoplasmic Ca^{2+} thus regulate signal strength and frequency for calcium-mediated cellular functions. Alterations in Ca^{2+} signaling have been identified in myocytes, hepatocytes, neutrophils, and T lymphocytes during sepsis and may contribute to the development of organ dysfunction during catabolic illness (for review see Ref. 7).

Extracellular calcium homeostasis is maintained by the coordinated actions of the gastrointestinal tract, kidneys, and bone.^{1,3} Levels of extracellular Ca^{2+} are detected by calcium-sensing receptors on parathyroid cells.⁸ In response to low serum Ca^{2+} , the parathyroid glands secrete PTH, which reduces the renal reabsorption of phosphate, increases renal calcium reabsorption, and stimulates renal hydroxylation of vitamin D.^{1,3} PTH and 1,25-dihydroxy vitamin D (calcitriol) promote the release of calcium from bone by activating osteoclasts.^{1,3} Calcitriol also stimulates intestinal absorption of dietary calcium and regulates PTH secretion by inhibiting PTH gene transcription. PTH secretion is also influenced by serum phosphate concentration. High circulating phosphate levels stimulate PTH secretion by lowering extracellular Ca^{2+} . Magnesium is required for the release of PTH from parathyroid cells and may explain the occurrence of hypocalcemia in

patients with magnesium deficiency. Calcitonin is a calcium-regulating hormone secreted by the parafollicular C-cells of the parathyroid gland during hypercalcemia. Although calcitonin inhibits bone resorption and stimulates the urinary excretion of calcium, this hormone does not appear to play a major role in calcium homeostasis in humans.^{1,3}

The normal concentration of ionized calcium in the extracellular space (plasma and interstitium) is 1.2 mmol/L and represents 50% of the total extracellular calcium. The remaining 40% is bound to plasma proteins, and 10% is combined with citrate, phosphate, or other anions. Total serum calcium normally ranges from 9.4 to 10.0 mg/dL (2.4 mmol/L). The distribution of ionized and bound calcium may be altered in critically ill patients. Chelating substances like citrate and phosphate may influence the abundance of ionized Ca^{2+} . Increased free fatty acid levels caused by lipolysis or parenteral nutrition result in increased binding of calcium to albumin.⁹ Protein-bound calcium is also increased during alkalosis and reduced during acidosis.^{1,3} Correcting total serum calcium for albumin and pH does not accurately estimate ionized Ca^{2+} .^{10,11} Therefore, a direct measurement of ionized serum calcium has been found to be the most accurate way to determine the concentration of this cation, and hence this approach is indicated in critically ill patients.¹²

HYPOCALCEMIA IN CRITICALLY ILL PATIENTS

Ionized hypocalcemia is frequently seen in critically ill patients with sepsis, pancreatitis, severe traumatic injuries, or following major surgery. The incidence of hypocalcemia ranges from 15% to 50%.³ The degree of hypocalcemia correlates with illness severity as measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II score and is associated with increased mortality in critically ill patients.⁴ In particular, the degree of systemic inflammation, as measured by cytokine, tumor necrosis factor (TNF)-alpha, and pro-calcitonin levels, appears to correlate with hypocalcemia in ICU patients.¹¹ Potential etiologies for the hypocalcemia of critical illness include impaired PTH secretion or action, vitamin D deficiency or resistance, calcium sequestration or chelation, or impaired mobilization of Ca^{2+} from bone (Table 17-1).

Hypocalcemia in the ICU is rarely caused by primary hypoparathyroidism. However, sepsis and systemic inflammatory response syndrome (SIRS) are commonly associated with hypocalcemia, which is caused in part by the impaired secretion and action of PTH and the failure to synthesize calcitriol.^{1,3,11} Hypomagnesemia may contribute to hypocalcemia during critical illness via inhibitory effects on PTH secretion and target organ responsiveness.^{1,3,5} However, the presence of hypomagnesemia only weakly correlates with hypocalcemia in ICU patients.⁴

In many instances, the hypocalcemia of critical illness is multifactorial in etiology. Elderly patients are at an increased risk for vitamin D deficiency due to malnutrition, poor intestinal absorption, and hepatic or renal dysfunction.³ In obese patients with previous gastric bypass, the intestinal absorption of calcium dramatically decreases despite reasonable vitamin D levels and recommended calcium intake.¹³ Renal failure may precipitate hypocalcemia via the decreased formation of calcitriol and hyperphosphatemia and the chelation of ionized calcium.^{1,3} The use of continuous renal replacement therapy in critically ill patients is associated with significant magnesium and calcium

TABLE 17-1 Causes of Hypocalcemia**IMPAIRED PARATHYROID HORMONE SECRETION OR ACTION**

Primary hypoparathyroidism
Secondary hypoparathyroidism

IMPAIRED VITAMIN D SYNTHESIS OR ACTION

Poor intake
Malabsorption
Liver disease
Renal disease
Hypomagnesemia
Sepsis

CALCIUM CHELATION/PRECIPITATION

Hyperphosphatemia
Citrate
Pancreatitis
Rhabdomyolysis
Ethylene glycol

DECREASED BONE TURNOVER

Hypothyroidism
Calcitonin
Cis-platinum
Diphosphonates
Mithramycin
Phosphates

From Zaloga GP. Hypocalcemia in critically ill patients. *Crit Care Med* 1992;20(2).

losses. This results in electrolyte replacement requirements that often exceed the calcium and magnesium supplementation provided in standard parenteral nutrition formulas.¹⁴ Other potential causes of ionized hypocalcemia in critically ill patients include alkalosis (increased binding of Ca^{2+} to albumin), medications (anticonvulsants, antibiotics, diphosphonates, and radiocontrast agents), massive blood transfusion, sepsis, and pancreatitis.^{1,3-5} More recently, the infusion of high doses of propofol have been shown to reduce circulating calcium concentrations by elevating serum PTH levels, but the physiologic significance of this phenomenon is unclear.¹⁵ Ionized hypocalcemia (<1.0 mmol/L) is associated with prehospital hypotension and represents a better predictor of mortality in severely injured patients than base deficit.¹⁶ The exact reasons for this observation are unclear but potentially relate to head injury and/or the presence of hemorrhagic shock. Injured patients receiving blood transfusions may develop hypocalcemia as a consequence of Ca^{2+} chelation by citrate, which is used as an anticoagulant in banked blood.¹⁷⁻¹⁹ The incidence of transfusion-related hypocalcemia is related to both the rate and volume of blood transfusion.^{17,18} When blood transfusions are administered at a rate of 30 mL/kg/h (e.g., 2 L/h in a 70-kg patient) and hemodynamic stability is maintained, ionized Ca^{2+} levels are preserved by physiologic compensatory mechanisms.¹⁹ Transient hypocalcemia may be observed with rapid transfusion and can be prolonged or exacerbated by hypothermia, renal failure, or hepatic failure.¹⁷⁻¹⁹ Consequently, ionized calcium should be monitored and replaced when clinically indicated during massive transfusion. However, hypocalcemia tends to normalize within four days after ICU admission, and failure to normalize in severely hypocalcemic patients may be associated with increased mortality. Calcium replacement does not typically improve normalization or reduce mortality.²⁰

HYPOCALCEMIA IN SEPSIS AND PANCREATITIS

Hypocalcemia is especially common in critically ill patients with systemic infection or pancreatitis.^{1,3,4,7,11} In animal models, serum calcium concentrations decrease following endotoxin infusion.^{7,11,21,22} When septic patients with hypocalcemia were compared with nonseptic controls, increased TNF- α and interleukin-6 levels correlated with ionized hypocalcemia.²³ Septic patients with hypocalcemia may

demonstrate increased or decreased PTH levels; however, urinary excretion of calcium and bone resorption appear to be preserved when compared to controls.^{11,21} Procalcitonin levels are increased during sepsis-induced hypocalcemia, but mature calcitonin only exerts a weak and transient effect on circulating calcium level.^{23,24} Collectively, the results suggest that hypocalcemia during severe infection has a multifactorial etiology but that inflammatory cytokines, impaired activation of vitamin D, and elevated procalcitonin are contributory.

It remains unclear whether sepsis-induced hypocalcemia is pathologic or protective. Calcium administration in experimental sepsis has been shown to increase or have no effect on mortality.^{21,22} Similarly, investigations on the effects of Ca^{2+} blockade on septic mortality demonstrate conflicting results.²³⁻²⁵ Therefore, although sepsis-induced hypocalcemia is commonly seen in critically ill patients, neither routine replacement of calcium nor the use of calcium channel blockers is supported by the existing literature. As with most situations, sepsis-induced hypocalcemia should be treated if patients are symptomatic.

Pancreatitis represents another inflammatory condition that is associated with hypocalcemia in critically ill patients.^{1,3,25,26} Saponification of retroperitoneal fat contributes to the development of hypocalcemia in patients with pancreatitis.^{3,25,26} In rats with experimental pancreatitis, injection of free fatty acids into the peritoneum induces hypocalcemia.²⁵ However, the amount of calcium chelated is relatively small compared to the calcium stores in the bone reservoir available for exchange. Interestingly, elevated levels of PTH seen in pancreatitis, like sepsis, do not result in normalized ionized calcium levels.²⁵⁻²⁷ Although the resistance of bone and kidney to PTH may be a factor, it is likely that inflammatory pathways identical to those in sepsis are responsible. In pancreatitis, like sepsis, hypocalcemia is an indicator of disease severity. As with most clinical conditions, calcium replacement during pancreatitis should be reserved for the symptomatic or hemodynamically unstable patient.

SIGNS AND SYMPTOMS OF HYPOCALCEMIA

Hypocalcemia is frequently asymptomatic and attributable signs or symptoms may be difficult to elucidate in critically ill patients. In general, the signs and symptoms of hypocalcemia correlate with both the magnitude and rapidity of onset of the condition. Neurologic (paresthesias, seizures, dementia) and cardiovascular (hypotension, impaired cardiac contractility, dysrhythmias) signs may be seen with ionized hypocalcemia $\text{Ca}^{2+} < 1.0$ mmol/L.^{3,5} Neuromuscular symptoms of profound hypocalcemia include muscle spasms and tetany. Psychiatric disturbances (dementia, psychosis, depression) also may be attributable to hypocalcemia.^{3,5}

Classic signs of hypocalcemia include the Chvostek and Trousseau signs, which test for latent tetany. The Chvostek sign is an involuntary twitching of facial muscles in response to light tapping of the facial nerve. It is nonspecific and is present in 10% to 25% of normal adults, and may be completely absent in chronic hypocalcemia. The Trousseau sign is a carpal spasm induced by reduced blood flow to the hand in the presence of hypocalcemia when a blood pressure cuff is inflated to 20 mmHg for 3 min. The Trousseau sign is also nonspecific and may be absent in one-third of patients with hypocalcemia.

Cardiac dysrhythmias, such as ventricular tachycardia, prolonged QT interval, and heart block are more serious complications of hypocalcemia.^{3,5} In addition, decreased cardiac output and hypotension, especially where refractory to vasopressors and volume, should prompt calcium replacement when hypocalcemia is present.^{3,5}

TREATMENT OF HYPOCALCEMIA

Critical thresholds for calcium replacement vary, but severe ionized hypocalcemia < 0.8 mmol/L and symptomatic hypocalcemia should be replaced in critically ill patients.^{1,3,5} Treatment of asymptomatic ionized hypocalcemia > 0.8 mmol/L is usually unnecessary and may be potentially harmful in conditions such as sepsis and cellular hypoxia.^{1,3,5,27}

Treatment of hypocalcemia requires intravenous calcium replacement. The two solutions most commonly used are 10% calcium chloride and 10% calcium gluconate. Each solution contains 100 mg/mL of calcium salt and is provided in 10-mL ampules. Ten percent calcium chloride contains 27 mg/mL of elemental calcium (1.36 mEq/mL); 10% calcium gluconate contains 9 mg/mL (0.46 mEq/mL). Typically, 10 mL of 10% calcium gluconate solution is infused over 10 min. A total of 200 mg of elemental calcium may be necessary to raise the total serum calcium by 1 mg/dL. Since the effect of calcium infusion is usually brief, a continuous infusion may be necessary. Calcium chloride should not be infused peripherally if calcium gluconate is available, since the former can produce tissue necrosis and thrombophlebitis if extravasation occurs.

Hemodynamically unstable patients in the ICU who are hypocalcemic may show a transient increase in blood pressure and/or cardiac output with calcium administration. This is probably due to increased cardiac performance.²⁷ However, in the presence of tissue hypoxia, calcium administration may aggravate the cellular injury.^{9,24} Nonetheless, calcium administration is probably warranted in the hypocalcemic, hemodynamically unstable patient, especially those requiring adrenergic support.

Despite the prevalence of hypocalcemia in critically ill patients, there is a paucity of evidence on the benefit of calcium supplementation in this population. Other than elevating systemic ionized calcium, there is no clear evidence that calcium supplementation impacts the outcome in critically ill ICU patients.²⁸ Collectively, these data suggest that hypocalcemia is a metabolic derangement associated with severe illness as opposed to a correctable condition resulting in a poor outcome.

HYPERCALCEMIA

Hypercalcemia is rare in critically ill patients, estimated to be present in between 1% and 15% of ICU patients.² Defined as an increase in serum calcium above 10.4 mg/dL (2.60 mmol/L), hypercalcemia usually is caused by excessive bone resorption. Hyperparathyroidism and humoral hypercalcemia of malignancy are the most common causes of hypercalcemia in hospitalized patients.^{2,5,29} Less common causes of hypercalcemia include sarcoidosis, prolonged immobilization, and medications (e.g., thiazide diuretics).

Mild hypercalcemia is usually asymptomatic. However, patients with circulating Ca^{2+} above 12 mg/dL may manifest symptoms of confusion, delirium, psychosis, and coma.^{2,5,29} Patients with hypercalcemia also may experience nausea, vomiting, constipation, abdominal pain and ileus. Cardiovascular effects of hypercalcemia include hypotension, hypovolemia, and shortened QT interval. Profound skeletal muscle weakness may result. Seizures, however, are rare.

The treatment of hypercalcemia should be directed at the underlying medical condition. Saline infusion and diuresis are indicated in symptomatic patients and when the serum calcium level rises above 14 mg/dL (3.5 mmol/L). For patients with underlying malignancy, treatment with salmon calcitonin, pamidronate, or plicamycin may be necessary. These agents act to inhibit bone resorption. Hydrocortisone can also be used in combination with calcitonin to treat hypercalcemia associated with multiple myeloma.

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Hypoglycemia is associated with increased mortality in critically ill patients.^{1,2} The single largest factor limiting the achievement of adequate glycemic control in the intensive care unit (ICU) is the occurrence of hypoglycemia and the consequent increase in mortality. This chapter will discuss the definitions of hypoglycemia, its incidence, risk factors, physiology, symptomatology, evaluation, outcomes, and management.

■ DEFINITION OF HYPOGLYCEMIA

Traditionally, the American Diabetes Association (ADA) has defined hypoglycemia in five categories³:

- Severe hypoglycemia (symptoms requiring assistance from another person, neuroglycopenic symptoms, seizures or coma, and reversal of these symptoms with the administration of glucose). Glucose measurements may not be available, but neurologic recovery after glucose administration is diagnostic.
- Documented symptomatic hypoglycemia (with a measured plasma glucose of <70 mg/dL [3.9 mmol/L]).
- Asymptomatic hypoglycemia (no symptoms of hypoglycemia but measured plasma glucose is <70 mg/dL [3.9 mmol/L]).
- Probable symptomatic hypoglycemia (symptoms of hypoglycemia not accompanied by a plasma glucose measurement but are presumed to be caused by a plasma glucose concentration <70 mg/dL [3.9 mmol/L]);
- Relative hypoglycemia (symptoms of hypoglycemia in a person with diabetes but with a measured plasma glucose concentration >70 mg/dL [3.9 mmol/L]).

The definition of hypoglycemia in a critically ill patient is challenging because of a lack of symptom reporting in sedated or critically ill patients. The definition and recognition of hypoglycemia in this group of patients is dependent on close monitoring of measured blood glucose. Landmark studies, which have resulted in current glucose management strategies in the ICU, have repeatedly used previously defined severe hypoglycemia values (blood glucose <40 mg/dL [2.2 mmol/L]) for the diagnosis of hypoglycemia in the ICU.^{4,6}

Likewise, the ADA in 2016 defined hypoglycemia as follows⁷:
Moderate hypoglycemia: 40–70 mg/dL (2.2–3.9 mmol/L)
Severe hypoglycemia: <40 mg/dL (2.2 mmol/L).

■ INCIDENCE OF HYPOGLYCEMIA IN THE CRITICALLY ILL

The reported incidence of hypoglycemia is variable and depends on the definition used, the glycemic target, and the admission diagnosis. In a retrospective study conducted by Bagshaw et al. from the Australia New Zealand Intensive Care Society adult patient database, the incidence of hypoglycemia (lowest blood sugar observed during the first 24 hours of ICU stay) ranged from 1.5% to 13.8% depending on the definition used (<82 mg/dL [4.5 mmol/L] versus <44 mg/dL [2.4 mmol/L]).⁸

An interesting study by Niven et al. examined the impact of two major landmark trials (Leuven 1 and NICE-SUGAR) on glycemic management in 195 adult ICUs over 80 hospitals from January 1, 2001, to December 31, 2012, using the APACHE database. At the start of the study the incidence of hypoglycemia was 3%. This increased to 5.8% after the Leuven study, which advocated tight glycemic control, was published and then slightly dropped to 5.2% after the NICE-SUGAR

investigators published their results recommending a more liberal target.⁹

■ THE GLYCEMIC DOMAINS AND THE INFLUENCE OF PREEXISTING DIABETES DIAGNOSIS ON OUTCOMES IN THE ICU

The three domains of glycemic control are hyperglycemia, hypoglycemia, and glucose variability. Each of these has independently been shown to increase mortality in critically ill patients.^{2,10–13} Two large studies evaluated these three domains and the approach to glycemic management in the ICU, as well as the role of diabetes in this complex milieu. The results of both studies are strikingly similar. Hyperglycemia and an increase in glucose variability were associated with an increase in mortality in nondiabetic but not in diabetic patients. On the other hand, hypoglycemia was associated with an increase in mortality in both groups. Furthermore, in diabetic patients, premonitory glycemic control has been shown to play an important role in outcomes based on the glycemic goals. In patients with poor preadmission glycemic control, mortality was higher with lower ICU blood glucose levels (than their own “normal”—i.e., relative hypoglycemia). Conversely, in patients with good preadmission glycemic control, survival was higher when ICU blood glucose levels were maintained closer to the normal range. Plummer et al. in 2014¹⁴ further substantiated previous observations by Egi et al.¹⁵ in their study where they observed an 18% increase in the risk of mortality for every 20 mg/dL (1.1 mmol/L) increase in maximum blood glucose in nondiabetic and diabetic patients with good preadmission glycemic control. The data from these studies further emphasizes that having one glycemic goal for all critically ill patients is probably not appropriate.^{14–17}

■ GLYCEMIC GOAL IN THE ICU

Based on the NICE-SUGAR trial, most centers target a blood glucose level of <180 mg/dL (10 mmol/L) for critically ill patients in an attempt to reduce the incidence of hypoglycemia and subsequent mortality⁶ noticed with the application of tight glycemic control. The ADA also recommends a goal of 140–180 mg/dL (7.7–10 mmol/L) in ICU patients.⁷

■ MEASUREMENT OF BLOOD GLUCOSE IN THE ICU

Most ICUs use point-of-care (POC) glucometers to determine blood glucose concentration. The accuracy of these glucometers, measurements of capillary blood glucose, and the titration of insulin infusions based on these values has been questioned. Several factors that are commonly present in critically ill patients, like anemia, hypoxia, medications, and acidosis, may lead to POC glucometer inaccuracy. Furthermore, these patients may be significantly volume overloaded, and capillary blood glucose may not reflect the whole blood glucose concentration accurately. Laboratory whole blood glucose is the gold standard for blood glucose measurement. Nevertheless, it is labor-intensive, time-consuming, and costly and thus not practical when hourly blood glucose concentrations need to be monitored. Hence glucometers have been used widely in ICUs for this purpose. Arterial whole blood samples drawn via the arterial line using a blood gas analyzer (BGA) have been found to be associated with fewer errors (1% outside the allowed 20% error zone) when compared to capillary samples (27%

outside the 20% error zone) or arterial samples (12% outside the 20% error zone) using a glucometer.¹⁸ Arterial blood samples have thus been recommended for measurement of blood glucose using a BGA, and this has also been extended to POC testing when used, as opposed to capillary blood samples. Since the inaccuracies of POC testing are more pronounced in the hypoglycemic range, it may be prudent to confirm the blood glucose concentration using another method when near the hypoglycemic range.

Due to the high incidence of dysglycemic episodes in the ICU, continuous glucose monitoring (CGM) techniques are being pursued as the potential future method to consistently recognize dysglycemic and hypoglycemic episodes. CGM techniques could be either subcutaneous or intravenous and have proven to be as effective and safe as POC techniques, reducing nursing burden and detecting more dysglycemic/hypoglycemic episodes, especially during the night, as compared to POC testing.¹⁹⁻²¹ Although promising, the routine use of CGM in ICUs would need more trials demonstrating their safety and efficacy.⁷

RISK FACTORS AND BARRIERS TO RECOGNITION OF HYPOGLYCEMIA IN THE ICU

Identified predictors of hypoglycemia in the ICU include female gender, APACHE 2 score, continuous veno-venous hemodialysis (CVVHD), use of bicarbonate substitution solutions, diagnosis of sepsis, use of vasopressors/inotropes, prior diagnosis of diabetes mellitus, serum creatinine >3 mg/dL, insulin therapy, discontinuation of nutrition therapy without an adjustment in insulin therapy, mechanical ventilation, and ICU length of stay.²²⁻²⁴ There are several barriers to the recognition of hypoglycemia in a critically ill patient—sedation, absence of symptoms, reduced oral intake, frequent change in rate of enteral or parenteral nutrition, and inappropriate timing of insulin. Even a single episode of severe hypoglycemia (<45 mg/dL [2.5 mmol/L]) has been associated with increased mortality.²⁴ Increased vigilance and relaxation of the glycemic target is warranted in patients with risk factors so as to reduce the incidence of hypoglycemia.

OUTCOMES OF HYPOGLYCEMIA IN THE CRITICALLY ILL

In a post hoc analysis of the NICE-SUGAR trial, severe hypoglycemia (<40 mg/dL [2.2 mmol/L]) and moderate hypoglycemia (41-70 mg/dL [2.3-3.9 mmol/L]) occurred in 3.7% and 45% of the studied patients, respectively. Although hypoglycemia was more common in the intensive insulin therapy group (93.3% severe hypoglycemia; 82.4% moderate hypoglycemia), the association of hypoglycemia with death was similar in both groups. Moderate hypoglycemia was associated with a 40% increase in the risk of death, and severe hypoglycemia doubled this risk. For both groups, the strongest association with death was from distributive shock. This was probably related to impairment of autonomic function, white cell activation, and release of inflammatory mediators.²⁵ In a recent systematic review and meta-analysis of longitudinal follow-up cohort studies investigating the association between hypoglycemia and adverse outcomes, a dose-dependent relationship between the severity of hypoglycemia and adverse vascular events, and mortality was found.²⁶ In some circumstances, hypoglycemia is a consequence of severe underlying disease and serves as a marker of death and not necessarily the cause. From prospectively collected data from two observational cohorts, patients with hypoglycemia had a higher mortality in comparison with those without hypoglycemia, even after stratification by severity of illness, diagnostic category, diabetic status, mean blood glucose during ICU admission, and coefficient of variation as an index of glycemic variability.¹³ In a retrospective cohort study from the Netherlands, Hermanides et al. corrected for the severity of disease using the SOFA (Sequential Organ Failure Assessment) score and in spite of the adjustment for disease severity, the incidence of death in patients exposed to hypoglycemia (<45 mg/dL [2.5 mmol/L]) was 40 per 1000 ICU days

compared to 17 per 1000 ICU days in patients without an exposure to hypoglycemia, indicating a possible causal relationship.²⁷

PHYSIOLOGY AND SYMPTOMATOLOGY OF HYPOGLYCEMIA

During an episode of hypoglycemia, below a blood glucose concentration of 65 mg/dL (3.6 mmol/L), the secretion of counter regulatory hormones, glucagon and epinephrine, increases. Both glucagon and epinephrine increase blood glucose concentrations by increasing gluconeogenesis and glycogenolysis, glucagon to a much greater degree than epinephrine. Free fatty acids are mobilized from the adipose tissue and converted to ketone bodies to be utilized as an energy source when there is a decrease both in insulin and in the ratio of insulin to glucagon.²⁸ The brain and heart are two organs that are dependent on glucose for energy utilization and function. Consequently, most of the symptoms of hypoglycemia are related to these two organ systems.

The brain utilizes glucose and ketone bodies as fuel, especially during starvation.²⁹ Brain glucose concentrations drop close to zero when blood glucose concentration falls below 36 mg/dL (2 mmol/L). This can result in irreversible brain injury in cases of severe and prolonged hypoglycemia.³⁰ Patients experiencing hypoglycemia present with either adrenergic (tremors, palpitations, anxiety), cholinergic (sweating, paresthesias), or neuroglycopenic symptoms (cognitive, behavioral, psychomotor changes, seizures, coma).³¹⁻³³ Hypoglycemic coma may occur when glucose levels are below 40-50 mg/dL (2.2-2.3 mmol/L).³³ The neurons most sensitive to hypoglycemia are located in the superficial layers of the cortex, the hippocampus, the caudate nucleus, and the subiculum.^{28,34,35} Even in the absence of cell death, mild recurrent hypoglycemia can cause dysfunction in the hippocampus.³⁶

The myocardial cells can utilize either fatty acids or glucose as fuel. During episodes of hypoxia or ischemia, myocardial cells preferentially use glucose as substrate for ATP generation.³⁷ Hypoglycemic episodes stimulate the sympathoadrenal system, which can be proarrhythmic.³⁸ Various rate and rhythm disturbances including sinus tachycardia, sinus bradycardia, atrial and ventricular ectopics, and ventricular repolarization abnormalities have been observed during acute hypoglycemic episodes.³⁹⁻⁴¹

MANAGEMENT OF HYPOGLYCEMIA

Management of hypoglycemia involves recognition, development of a differential diagnosis and treatment.

Recognition of Hypoglycemia (Fig. 18-1)

- Hypoglycemia is usually recognized using the Whipple's triad: symptoms of hypoglycemia, documented low blood glucose concentration, and resolution of symptoms when plasma glucose is raised. This is not always possible in critically ill patients. The diagnosis of hypoglycemia is established when the measured plasma glucose is less than 70 mg/dL (3.9 mmol/L).

Differential Diagnosis

- In a critically ill patient, hypoglycemia may be a consequence of therapy with insulin for the management of hyperglycemia, especially when there is a change in nutritional support. Other insulin secretagogues, oral hypoglycemic agents, and several other non-antihyperglycemic agents⁴² are frequent culprits as well. The commonly cited nonantihyperglycemic drugs responsible for inducing hypoglycemia are quinolones, pentamidine, quinine, beta blockers, angiotensin converting enzyme (ACE) inhibitors, and insulin-like growth factor (IGF).⁴² Critical illness or sepsis leading to hepatic, renal and cardiac dysfunction in and by itself can cause hypoglycemia. Rarely tumors (islet and non-islet cell), hormonal deficiencies and development of antibodies to either insulin or the insulin receptor may be the cause of hypoglycemia in critically ill patients.⁴³

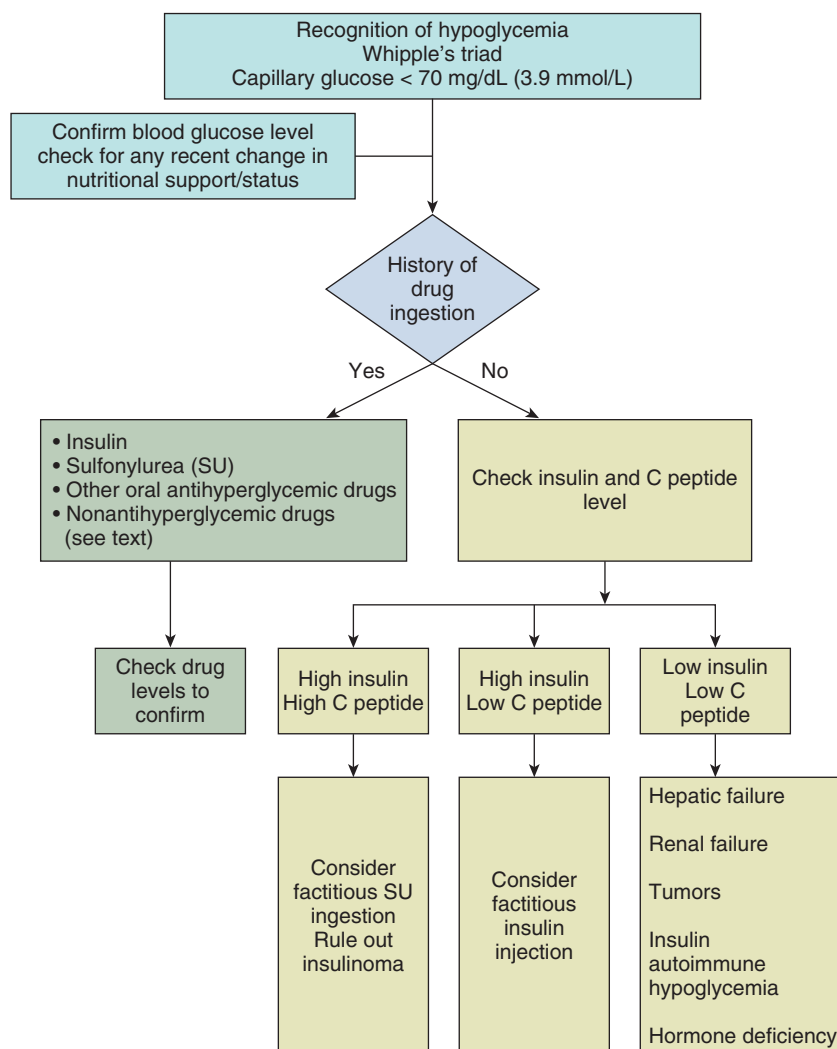


FIGURE 18-1 ■ Recognition and evaluation of hypoglycemia.

Evaluation

- When blood glucose concentration is indicative of hypoglycemia, if there is no obvious medication-related cause, measurement of insulin and C peptide levels can be helpful.
- Make sure that no sudden change in nutritional status has been made (nil per oral (NPO) status/change in rate of enteral/parenteral feed).
- If sulfonylurea is suspected as the cause, radioimmunoassay can detect sulfonylurea levels.
- Check all medications to look for medication-induced hypoglycemia (nonantihyperglycemic).
- Evaluate for deterioration in renal or hepatic function.
- Evaluate for hormonal deficiencies: thyroid hormone, cortisol.

Management (Fig. 18-2)

- Depending on the extent of neurologic or neuroglycopenic symptoms, make sure that airway protection is ensured.
- Supplementing glucose is paramount once a diagnosis of hypoglycemia is established. Patients with mild to moderate symptoms of hypoglycemia are effectively treated with oral glucose tablets or carbohydrate-rich food supplements. A response is usually seen in 15-20 minutes. Continued monitoring and supplementation with glucose (as needed) is recommended as the response to oral glucose may be transient.^{43,44}

- In patients who have severe symptoms or are unable to take glucose orally, intravenous dextrose is supplemented. An initial dose of 25 g of 50% dextrose is given. Similar to oral glucose, the effect is transient and may need a continuous dextrose infusion.
- Glucagon can either be given intravenously or subcutaneously at a dose of 1 mg in adults when hypoglycemia is severe or refractory. This can cause transient hyperglycemia.⁴⁴
- Depending on the cause, an extended period of treatment may be necessary such as in the case of sulfonylurea-induced hypoglycemia or inadvertent administration of a large dose of insulin.
- In cases of sulfonylurea-induced hypoglycemia, octreotide may be used.⁴⁵⁻⁴⁷

CONCLUSION

Although glycemic control and avoidance of hyperglycemia is important in critically ill patients, very close attention should be paid to prevent hypoglycemia and its related adverse outcomes. Hypoglycemia is more detrimental than hyperglycemia. Even mild hypoglycemia in the critically ill is associated with increased mortality.¹³ An association has been found between the adoption of tight glucose control strategies in the ICU and the development of hypoglycemia. Current evidence suggests moving toward more moderate targets that have been shown to improve outcomes and are associated with fewer hypoglycemic episodes, until further evidence emerges.

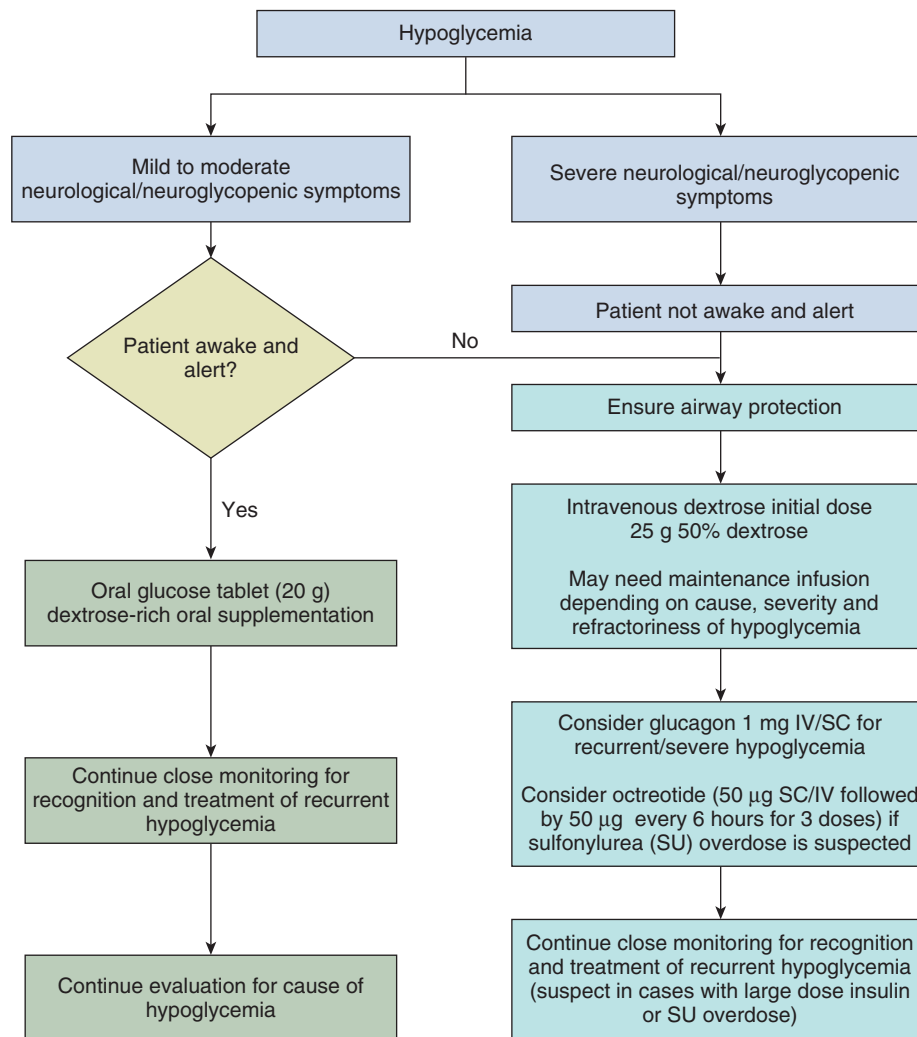


FIGURE 18-2 ■ Management of hypoglycemia.

KEY POINTS

1. Hypoglycemia, and the subsequent increase in mortality, is the single largest factor limiting achievement of glycemic control in the ICU.
2. ADA defines moderate hypoglycemia as a blood glucose level of 40-70 mg/dL (2.2-3.9 mmol/L) and severe hypoglycemia as a blood glucose < 40 mg/dL (2.2 mmol/L).
3. Mild, moderate and severe hypoglycemia are associated with increased mortality in the critically ill and any blood sugar less than 70 mg/dL (3.9 mmol/L) warrants aggressive evaluation and management.
4. The ADA standards of medical practice 2016 recommend a goal of 140-180 mg/dL (7.7-10 mmol/L) in critically ill patients although the goal may vary from patient to patient based on the admission diagnosis, a preadmission diagnosis of diabetes, and chronic glycemic state.
5. Although laboratory whole blood glucose is the gold standard for blood glucose measurement, it is time-consuming, labor-intensive, and thus not practical when hourly blood glucose measurements are required. Hence measurements using arterial blood samples via the arterial line (vs. capillary blood) utilizing preferably a BGA or a POCT have been successful.
6. Identified predictors of hypoglycemia in the ICU include female gender, APACHE 2 score, CVVHD, use of bicarbonate substitution solutions, diagnosis of sepsis, use of vasopressors/inotropes, prior diagnosis of diabetes mellitus, serum creatinine > 3 mg/dL, insulin therapy, discontinuation of nutrition therapy without an adjustment in insulin therapy, mechanical ventilation, and ICU length of stay.
7. Patients experiencing hypoglycemia present with either adrenergic (tremors, palpitations, anxiety), cholinergic (sweating, paresthesias), or neuroglycopenic symptoms (cognitive, behavioral, psychomotor changes, seizures, coma). Various heart rate and rhythm disturbances have also been observed during acute hypoglycemic episodes.
8. Once hypoglycemia is recognized, various possible causes should be evaluated and immediate management initiated. Depending on the cause, an extended duration of treatment may be required.

ANNOTATED REFERENCES

NICE-SUGAR Study Investigators, Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C, et al. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med* 2012;367:1108-18.

This study done by the NICE-SUGAR investigators is a post-hoc analysis of the original study done in 2009 that showed that intensive glucose therapy in critically ill patients posed an increased risk of death in addition to an increased incidence of hypoglycemia. With this analysis they demonstrated that, although not causal, both moderate and severe hypoglycemia was associated with an increased risk of death.

Krinsley JS, Schultz MJ, Spronk PE, Harmsen RE, van Braam Houckgeest F, et al. Mild hypoglycemia is independently associated with increased mortality in the critically ill. *Crit Care* 2011;15:R173.

This paper reports the results of the analysis of data from an international cohort of patients (N=6240). They found a significantly increased risk of death with even mild hypoglycemia in critically ill patients.

American Diabetes Association. 13. Diabetes Care in the Hospital. *Diabetes Care* 2016;39(Suppl 1):S99-S104.

This paper is the statement of the American Diabetes Association on the standards for managing blood glucose and diabetes in the hospital, focusing on critically ill patients.

Niven DJ, Rubenfeld GD, Kramer AA, Stelfox HT. Effect of published scientific evidence on glycemic control in adult intensive care units. *JAMA Intern Med* 2015;175:801-9.

This paper talks about the rapid adoption of tight glucose control when positive scientific evidence was published but not effectively de-adopted when evidence to the contrary was brought to light. It reinforces the need to promote the de-adoption of ineffective clinical practices.

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This paper is a systematic review of literature to identify drugs causing hypoglycemia and to assess the quality of the evidence supporting association. Although it was well known that diabetic drugs can induce hypoglycemia, the study was able to list the most common offending nondiabetic agents.

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Hyperglycemia is by far the most common metabolic abnormality in the intensive care unit. The adverse effects of uncontrolled hyperglycemia, especially in a critically ill patient, are fairly well described.¹⁻³ The management of hyperglycemia in the critically ill patient has gone through substantial changes over the past decade. Although hyperglycemia is associated with adverse clinical outcomes, trying to achieve euglycemia may not be the solution. While the initial landmark randomized controlled trial showed remarkable benefits to tight glycemic management in the intensive care unit (ICU),¹ a somewhat similar strategy did not improve clinical outcomes. On the contrary, it resulted in an increase in hypoglycemic episodes and consequently mortality according to the largest multicenter randomized controlled trial to date.^{4,5} It is worth noting that there is an exceedingly large body of evidence from observational and retrospective studies shedding light on the various glycemic domains that clinicians should keep in mind while achieving glycemic control.⁶⁻⁸ The presence or lack of a history of diabetes and extent of a patient's chronic glycemic state if they were diabetic would probably play a role in determining the glycemic target.^{9,10} Furthermore, glycemic variability of whatever target is chosen may also have an impact on glycemic management outcomes.¹¹

This chapter gives an overview of hyperglycemia in the critically ill patient and current management strategies, including a summary of investigations that led to the development of these strategies.

DEFINITION OF HYPERGLYCEMIA

When a critically ill patient is hyperglycemic, it is important to delineate the clinical group to which the patient belongs. These include the following:

- A known diabetic
- Undiagnosed diabetic
- New-onset hyperglycemia (stress-induced)

The American Diabetes Association has published criteria for the diagnosis of diabetes mellitus.¹² A diagnosis of diabetes is established when any one of the following criteria is met:

- Fasting plasma glucose greater than 126 mg/dL (7 mmol/L)
- Postprandial plasma glucose >200 mg/dL (11.1 mmol/L) after 2 hours of a 75-g glucose oral glucose tolerance test
- HbA1C >6.5%
- Classic symptoms of hyperglycemic crisis with a random glucose >200 mg/dL (11.1 mmol/L)

Unfortunately, there is no set definition for hyperglycemia in the critically ill patient as it is confounded by the presence of multiple variables including the severity of illness, concurrent medication such as catecholamine infusions, feeding, etc. When a patient presents with new-onset hyperglycemia (NOH), either critically or noncritically ill, it is prudent to rule out the presence of undiagnosed diabetes mellitus. The presence of an HbA1C >6.5% might aid in making this diagnosis. The ADA/ACCE in their consensus statement recommend that any blood glucose >180 mg/dL (10 mmol/L) be treated in patients who are critically ill in an attempt to reduce the adverse outcomes associated with hyperglycemia.¹³

STRESS-INDUCED HYPERGLYCEMIA

Hyperglycemia was initially considered to be a normal adaptive response in a critically ill patient to survive a period of acute stress. An increase in the levels of catecholamines, growth hormone, exogenous and endogenous glucocorticoids and glucagon, along with an increase in circulating cytokines and peripheral insulin resistance, may play an important role in the genesis of stress-induced hyperglycemia.^{14,15} However, stress hyperglycemia in the presence of previously normal glucose homeostasis has been associated with an increase in adverse outcomes in critically ill patients. These adverse outcomes were attributed to hyperglycemia per se and/or free radical injury and its related adverse coronary and intracranial events.¹⁶ That being said, hyperglycemia during acute illness may not be the causative agent behind the increase in morbidity and mortality but rather only represents a correlation with disease severity.

DIABETIC VERSUS NON-DIABETIC BLOOD GLUCOSE MANAGEMENT IN THE ICU

Recently, it has been advocated that glycemic targets in the ICU should probably vary based on the presence of a history of diabetes and a chronic glycemic state prior to ICU admission.^{6,9,10,17,18} The diabetic patient can probably tolerate or might even do better with a higher-than-normal glycemic target and reduced glycemic variability. Egi et al. studied 450 critically ill diabetic patients, with a total of 9946 glucose measurements in the study cohort. The median HbA1C was 7%. They found that patients who had higher (>7%) preadmission HbA1C levels had a lower mortality when the ICU time-weighted glucose concentration was higher (>180 mg/dL [10 mmol/L]), as compared to patients who had lower HbA1C (<7%).¹⁹ Similar findings were reported in larger patient cohorts.^{9,20,21} In 2012, Tayek et al. performed a meta-analysis of nine studies with regard to hyperglycemia and in-hospital mortality, measuring unadjusted ICU mortality in five of the nine studies. They observed an increase in ICU mortality and a 2.7-fold increase in hospital mortality in patients with new-onset hyperglycemia as opposed to diabetic patients with hyperglycemia.²² This difference may be due to the fact that in a previously uncontrolled diabetic, the organs and immune system may have been accustomed to higher blood glucose concentrations, and a sudden attempt at euglycemia will represent a relative hypoglycemia for them. Furthermore, if such an attempt at euglycemia is associated with moderate or severe hypoglycemia as is the case with many tight glycemic control algorithms, such dangerously low concentrations would also represent a significant increase in glycemic variability that is thought to be harmful as well.¹¹ In one of the largest database studies evaluating the effect of diabetes on outcomes in critically ill patients, Graham et al. found that hyperglycemia was more detrimental in nondiabetics and was potentially protective in diabetics. There was an increased risk of mortality exclusively in diabetic patients in the normoglycemic/hypoglycemic

glucose range suggesting a relative intolerance to relative and absolute hypoglycemia in this subset of patients.²³ In light of these findings, we probably should seek different glycemic targets (and more robust insulin protocols to achieve such targets) that vary based on the presence of a diagnosis of diabetes and previous chronic glycemic states. An example of such variable glycemic targets has recently been proposed by Marik et al. based on the patient's clinical condition, history of diabetes, and HbA1C signifying the extent of glycemic control.²⁴

LANDMARK INVESTIGATIONS STUDYING HYPERGLYCEMIA IN THE CRITICALLY ILL PATIENT

The Leuven 1 Trial, Surgical ICU, 2001¹

One of the first investigators to research into the field of hyperglycemia and its management in critically ill patients were Van Den Berghe and colleagues from Leuven, Belgium. This was a landmark study which brought about a significant practice change at that time, or at least raised an important question for which researchers were seeking answers.

The study involved 1548 surgical ICU patients of whom 63% were routine cardiac surgical patients. They were randomized to either intensive insulin therapy (IIT) (80-100 mg/dL [4.4-5.5 mmol/L]) or conventional (180-200 mg/dL [10-11.1 mmol/L]) glucose management. Interestingly, both groups received 200 mg of glucose on postoperative day 1 followed by nutrition either enteral or parenteral, started on postoperative day 2. Total parenteral nutrition was initiated on postoperative day 2 if enteral nutrition was found to be inadequate. In hindsight, this probably played a big role in most of the results that were generated. Their results were significant and resulted in a practice change in ICUs across the globe given the mortality benefit of the suggested regimen:

- As expected, mean glucose levels were lower in the IIT group compared to the conventional group; however, hypoglycemia was seen more often in the IIT group.
- ICU and hospital mortality were lower in the IIT group as compared to the conventional management group (4.6% vs. 8% and 7.2% vs. 10.9%, respectively).
- Decreased critical illness, polyneuropathy, acute kidney injury (AKI), and transfusion requirements were observed in the IIT group.

The Leuven II Trial Medical ICU Patients, 2006²

The same investigators from the Leuven I trial studied the effects of IIT versus conventional management in medical ICU patients through a randomized controlled trial. They randomized 1200 patients to either IIT or conventional therapy. Again, as expected, there was an increase in the occurrence of hypoglycemia in the IIT group. They found that IIT did not alter hospital mortality but there was a reduction in ICU length of stay, mechanical ventilation, and AKI.

The VISEP Trial, 2008²⁵

In a multicenter trial from Germany, patients with severe sepsis were assigned to receive either IIT to maintain a blood sugar of 80 to 100 mg/dL (4.4-5.5 mmol/L), or conventional insulin therapy to maintain a blood sugar of 180 to 200 mg/dL (10-11.1 mmol/L). They randomized patients to receive 10% hetastarch, a low-molecular-weight hydroxyethyl starch (HES), or lactated Ringer's solution as the resuscitation fluid. Primary end points were death at 28 days and mean organ failure scores. This trial had to be terminated prematurely due to the unacceptably higher incidence of severe hypoglycemia (<40 mg/dL) (17% vs. 4.1%) and serious adverse events (10.9% vs. 5.2%) in the IIT group as compared to conventional therapy. They also found that HES therapy was associated with a higher incidence of acute renal

failure and renal replacement therapy compared to lactated Ringer's therapy.

The Glucontrol Trial, 2009²⁶

This was a prospective randomized controlled trial to evaluate the effects of IIT versus moderate glucose control on ICU mortality. Patients were randomly assigned to either group 1 (target blood glucose 140-180 mg/dL [7.8-10 mmol/L]) or to group 2 (target blood glucose approximately 80-110 mg/dL [4.4-6.1 mmol/L]). This study had to be terminated prematurely due to an unacceptable number of protocol violations. Nevertheless, the major finding from this study was a lack of clinical benefit, and an increased incidence of hypoglycemia (8.7% in group 2 vs. 2.7% in group 1) in the IIT group as compared to the intermediate glucose control group.

NICE-SUGAR Trial, 2009⁴

This is the largest multinational randomized trial comparing IIT (target blood sugar 81-108 mg/dL [4.5-6 mmol/L]) to moderate target (less than 180 mg/dL [10 mmol/L]) in critically ill adult patients. The primary end point was death due to any cause within 90 days of randomization. There was an increased incidence of mortality in the IIT group (27.5%; odds ratio 1.14), as compared to the conventional group (24.9%). There was no difference in mortality between surgical and nonsurgical patients. Similar to prior studies, the incidence of severe hypoglycemia (<40 mg/dL [2.2 mmol/L]) was higher (6.8%) in the IIT group as compared to the conventional group (0.5%). They concluded that intensive glucose control increased mortality among critically ill adult patients and that a blood glucose target of 180 mg/dL (10 mmol/L) or less would result in lesser mortality.

The COITSS Trial, 2010²⁷

This multicenter randomized controlled trial was done to test the efficacy of IIT in patients with septic shock who were being treated with hydrocortisone and also to assess the benefit of fludrocortisone in these patients. They concluded that there was no mortality benefit in using IIT and tight glucose control in patients with septic shock. The mortality rate in the IIT group was 45.9% versus 42.9% in the conventional group ($P = 0.50$). Of the patients receiving IIT, 16.4% experienced severe hypoglycemia versus 7.8% in the conventional group ($P = 0.003$), which was significant.

GLUCOSE MONITORING IN THE ICU

In current day practice, most ICUs use bedside glucometers for monitoring, reporting, and managing blood glucose in critically ill patients. Bedside glucometers were introduced in an attempt to improve outpatient diabetes control (i.e., for patient self-monitoring of blood glucose). They are probably not very accurate for intensive monitoring and treatment of hyperglycemia in critically ill patients.²⁸⁻³¹ There are multiple variables that can affect the accuracy of a bedside glucometer, such as rapidly changing hematocrit, hypoxia, acidosis, use of vasopressors, and peripheral edema, which make measuring capillary blood glucose using a bedside glucometer less than ideal in the monitoring of patients who need titration of insulin infusions. The Central Laboratory and Standards Institute (CLSI), and the FDA require that 95% of the meter readings are within 20% of the reference value. While such monitors may meet this standard, the issue remains that allowing even that much of a variation in a critically ill patient on an infusion can lead to dangerous insulin therapy.³¹ Laboratory whole blood glucose measurement is the gold standard in blood glucose measurement but is labor intensive and not very practical when hourly glucose measurements are required. Another option is to monitor blood glucose using a blood gas analyzer (BGA), which is close to laboratory standards.³⁰ Blood glucose measurement from arterial whole blood samples drawn via an arterial line using a BGA is associated with fewer

errors (1% outside the permitted 20% error zone) when compared to capillary samples (27% outside the 20% error zone) or arterial samples (12% outside the 20% error zone) using a glucometer.³² Arterial blood samples have been recommended for the measurement of blood glucose using a BGA, and this has also been extended to point-of-care (POC) testing when used, as opposed to capillary blood samples. In critically ill patients who are dysglycemic, hourly blood glucose measurements are recommended.³³ Although POC testing has been largely used for this purpose, there are continuous glucose monitoring (CGM) techniques being developed to consistently recognize dysglycemic episodes.³⁴ CGM techniques could be either subcutaneous or intravenous. Subcutaneous CGM devices have been studied more extensively. The accuracy and reliability of these subcutaneous devices have been demonstrated in critically ill patients in circulatory shock and on vasopressor infusions.³⁵ In a randomized trial evaluating the impact of CGM on glycemic control and the occurrence of hypoglycemia in critically ill patients, CGM did not improve overall glycemic control but did reduce the occurrence of hypoglycemic events.³⁶ Another interesting extension of CGM is in the implementation of fully automated closed-loop glucose control. This system automatically modulates insulin (or dextrose) delivery based on glucose measurements using a CGM device without nurse input. Leelarathna et al. evaluated the feasibility of an automated closed-loop glucose control system using continuous subcutaneous glucose measurements in critically ill patients and were able to demonstrate an increased duration in the target range without the occurrence of hypoglycemia.³⁷ CGM techniques are probably as effective and safe as POC testing. In addition, they reduce nursing burden and detect more dysglycemic/hypoglycemic episodes, especially during the night.^{36,38,39} Although the technology seems very promising, routine use of CGM techniques in ICUs would need more trials demonstrating their safety and efficacy.⁴⁰

Irrespective of the method of blood glucose monitoring or target blood glucose used, there is a requirement to implement a systematic algorithm for insulin infusion titration in the critically ill patient to reduce the occurrence of adverse incidents, primarily hypoglycemia and glucose variability, as suggested by Preiser et al.^{41,42} Although this was suggested at a time when tight glucose control was still in vogue, it still holds true when we target a more moderate blood glucose as well. They suggested that ICUs should develop protocols in collaboration with nursing and medical staff, which are locally applicable. These systematic algorithms should suggest adaptation of the rate of insulin using a dynamic rather than a sliding scale (e.g., adapting rate of infusion to nutritional support), the time for next glucose check, types of devices to be used for sampling, and sites of sampling. Once a protocol has been developed, all ICU healthcare providers should be educated on it. On implementation, the quality of this protocol can be evaluated by the incidence of hypoglycemia divided by the frequency of blood glucose checks, proportion of time in the target range, and blood glucose variability.⁴¹ By implementing such robust algorithms and protocols, we can strive to achieve better glycemic control in critically ill patients and at the same time reduce glucose variability and the occurrence of hypoglycemia.

These issues led to the consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults.³¹

Excerpts from the Consensus Recommendations on Measurement of Blood Glucose and Reporting Glycemic Control in Critically Ill Patients

- All patients whose severity of illness warrants an invasive vascular monitor should have blood glucose samples drawn from an arterial

line. If not available, as a second option, samples can be drawn from a central line. Only when severity of illness does not warrant an invasive line should capillary blood be used for sampling.

- Samples taken from arterial or central lines should be analyzed either in the central lab or using a blood gas analyzer. If delay with the central lab is unacceptable, blood gas analyzers should be the default analyzer. A glucometer is acceptable only when a capillary sample is taken from a patient considered to be too well to need invasive vascular access.

ADA Recommendations for Management of Blood Glucose in Critically Ill Patients

The American Diabetes Association in 2016 issued recommendations for the management of blood glucose in a critically ill adult based on the evidence available thus far⁴⁰:

- Continuous intravenous insulin infusion has been shown to be the best method for achieving glycemic targets in the critical care setting.
- Insulin therapy should be initiated for persistent hyperglycemia starting at a threshold greater than 180 mg/dL (10 mmol/L). Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for the majority of critically ill and noncritically ill patients.
- More stringent goals such as 110–140 mg/dL (6.1–7.8 mmol/L) may be appropriate for selected critically ill patients, as long as this can be achieved without significant hypoglycemia.
- Intravenous insulin should be administered based on validated written or computerized protocols that allow for predefined adjustments in the infusion rate, accounting for glycemic fluctuations and insulin dose.
- A hypoglycemia management protocol should be adopted and implemented by each hospital. A plan for preventing and treating hypoglycemia should be established for every patient. Episodes of hypoglycemia in the hospital should be documented and tracked.
- The treatment regimen should be reviewed and changed if necessary to prevent further hypoglycemia when the blood glucose value is less than 70 mg/dL (3.9 mmol/L).

THE FUTURE

Recently, several investigators have substantiated the existence of three domains that clinicians need to consider when attempting to achieve a glycemic target: treatment of hyperglycemia, prevention of hypoglycemia, and the reduction of glycemic variability.^{6,9,10,21} Each one of these factors weighs in on improving outcomes in these patients. As clinicians, it is of paramount importance that we tailor insulin protocols based on the clinical picture of the patient to achieve an appropriate target glycemic control. Further research should be directed toward developing such protocols. The process may be labor intensive, but this, coupled with a standardized method for glucose measurement in the ICU, could provide us with data for further clinical research on the impact of glycemic control on outcomes in critically ill patients.

KEY POINTS

1. An increase in the levels of catecholamines, growth hormone, exogenous and endogenous glucocorticoids, and glucagon, along with an increase in circulating cytokines and peripheral insulin resistance, may play an important role in the genesis of stress-induced hyperglycemia.
2. In an attempt to reduce adverse outcomes associated with hyperglycemia, the ADA/ACCE recommend treating any blood glucose >180 mg/dL (10 mmol/L) in the critically ill.
3. Continuous intravenous insulin infusion has been shown to be the best method for achieving glycemic targets in the critical care setting.
4. Once insulin therapy is started, a target glucose range of 140-180 mg/dL (7.8-10.0 mmol/L) is recommended for the majority of critically ill and noncritically ill patients.
5. One glycemic target may not suit all ICU patients. We should probably seek different glycemic targets (and more robust insulin protocols to achieve such targets) that vary based on the presence of a diagnosis of diabetes and a previous chronic glycemic state.
6. Adaptive insulin infusion algorithms are recommended for the critically ill patient to reduce hypoglycemia and glucose variability.
7. Although laboratory blood glucose measurement is the gold standard, it is labor intensive and not practical for hourly measurements. Blood glucose measurement from arterial whole blood samples via an arterial line (vs. capillary blood), preferably using a blood gas analyzer (BGA) or a POCT, has been used successfully.

■ References for this chapter can be found at expertconsult.com.

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Anemia is a common clinical problem in critically ill patients. A large proportion of these patients are anemic on admission, and the majority of the remainder becomes anemic during their intensive care unit (ICU) stay. The likelihood of becoming anemic increases with the duration of stay in the ICU.

The traditional approach for the management of anemia in the ICU has been the administration of packed red blood cell (PRBC) transfusions. On average, about 40% of ICU patients are transfused (a mean of 5 units of PRBCs) in response to a mean pretransfusion hemoglobin (Hb) concentration of 8.5 g/dL.¹ Over the past decade, several studies have suggested that PRBC transfusion is independently associated with worse clinical outcomes, independent of the degree of anemia or the severity of illness. Myriad complications resulting from PRBC transfusion are increasingly being recognized, and the scarcity of blood (expected annual shortfall of 4 million units by 2030²) and economic impact of PRBC transfusion (approximately \$270 per unit transfused³ in the United States) have prompted a paradigm change for managing anemia in the ICU.

Current approaches include recognition of absolute indications for PRBC transfusion, avoidance of transfusions based on “transfusion triggers” alone, prevention of anemia in critically ill patients, use of PRBCs that have been stored in blood banks for shorter periods, and increasing acceptance of anemia. Many of these changes in approach are now evidence-based.

Future directions focus on the prevention of anemia, conservation of blood, and evaluation of blood substitutes.

EPIDEMIOLOGY

Anemia is defined as an Hb level less than 13 g/dL for adult males and less than 12 g/dL for adult nonpregnant females.⁴ Using this definition, more than 60% of all patients are anemic at admission, and the majority of those with normal Hb levels at admission become anemic while in the ICU.^{5,6} Given enough time, virtually all patients will become anemic during their ICU stay. In the anemia and blood transfusion in critically ill patients study (the ABC trial), 63% of patients had Hb levels below 12 g/dL, and 29% had Hb levels below 10 g/dL.⁵ Similarly, in the Transfusion Requirements in Critical Care (CRIT) study, the mean Hb level at baseline was 11 g/dL.⁶

The most frequent strategy for treatment of anemia is the transfusion of PRBCs. As a consequence, more than 14 million units are transfused annually in the United States.⁷ In patients with malignancy at their admission, the prevalence and incidence of anemia are 68% and 47%, respectively.⁸ Each day spent in the ICU increases the chance of being transfused by about 7%.⁹

ETIOLOGY

The etiology of anemia in the ICU is most often multifactorial, belonging to one or more of three major classes:

1. Hypoproliferative anemia due to bone marrow production defects
2. Ineffective erythropoiesis due to red cell maturation defects
3. Decreased survival of red cells secondary to blood loss, hemolysis, or both (Fig. 20-1)

The most common causes of anemia include phlebotomy for diagnostic laboratory testing, acute hemorrhage due to trauma,

gastrointestinal (GI) bleeding, or surgery—often exacerbated by the presence of coagulation abnormalities, treatment with chemotherapeutic agents, underlying chronic diseases such as renal and hepatic failure, reduced erythropoiesis, and shortened red cell survival.

Blood loss due to phlebotomy is an often unrecognized, yet significant, cause of anemia in the ICU, where patients are phlebotomized 4.6 times a day on average, with removal of 40 to 60 mL of blood daily.^{5,6,10,11} The volume of blood removed varies with the test being ordered, but average volumes typically drawn are presented in Table 20-1. The presence of an arterial line further increases the phlebotomized blood volume.¹¹ Approximately half of all patients are transfused as a direct result of phlebotomy.¹¹

Although rare since the advent of effective GI prophylaxis, GI bleeding can be a serious problem in the ICU. The overwhelming majority of critically ill patients demonstrates evidence of mucosal damage within the first 24 hours of admission. Overt anemia occurs in 5% of patients with stress-related GI bleeding, and clinically important bleeding necessitating transfusion is observed in 1% to 4% of critically ill patients.¹² Bleeding secondary to erosive gastritis is predominantly seen in patients on mechanical ventilation, those with coagulopathy, those with head injury, and/or those receiving corticosteroids.¹³

Reduced erythropoietin production is a key feature of anemia of critical illness, a distinct clinical entity similar to anemia of chronic disease. This blunted erythropoietic response to low Hb concentration in the face of apparently adequate iron stores is due to a failure to produce appropriate levels of erythropoietin.^{14,15} Blunted erythropoietin production in critically ill patients is probably mediated by proinflammatory cytokines such as tumor necrosis factor, interleukin (IL)-1, and IL-6, which downregulate expression of the gene encoding erythropoietin.¹⁶ IL-6 inhibits renal erythropoietin production.¹⁷ Additional contributory effects of these proinflammatory cytokines include induction of a state of relative iron deficiency, vitamin deficiency, and altered iron metabolism in the bone marrow.^{6,18} Therefore, anemia is a result of both a blunted response to erythropoietin and abnormalities in iron metabolism.

LABORATORY EVALUATION OF ANEMIA IN THE INTENSIVE CARE UNIT

A comprehensive treatise on the evaluation of anemia is beyond the scope of this chapter. Discussion here is limited to pertinent iron studies that aid in the diagnosis of anemia of critical illness. A brief review of iron metabolism is essential to understanding the rationale behind the laboratory tests ordered.

Iron absorbed from food or released from stores circulates in plasma as bound to transferrin, the iron transport protein. This iron-transferrin complex interacts with a specific transferrin receptor protein on the surface of early erythroid cells. This complex is then internalized and the iron released intracellularly. Within the erythroid cells, iron in excess of that needed for Hb synthesis binds to the storage protein apoferritin, forming ferritin. Iron in the ferritin pool can be released and reused in the iron metabolism pathway. The levels of ferritin in serum correlate with total body iron stores and are therefore a suitable laboratory estimate of iron stores.¹⁹ During maturation of reticulocytes to erythrocytes, the cells lose all activities of the Hb-synthesizing system, including surface expression of the

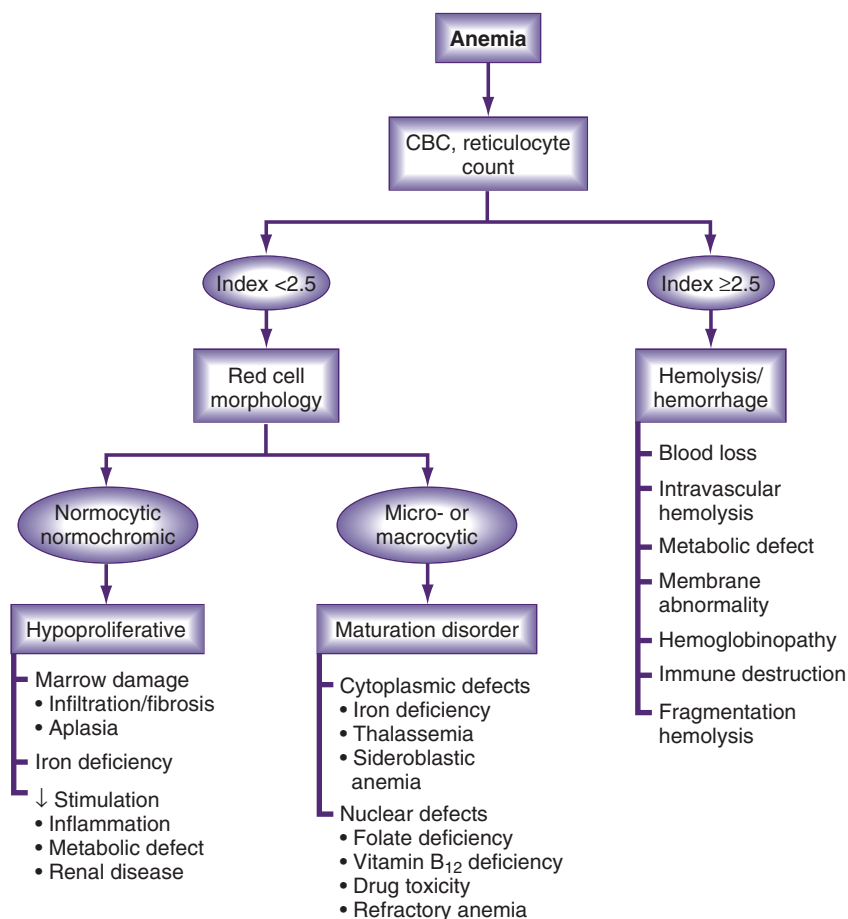


FIGURE 20-1 ■ Physiologic classification of anemia. CBC, complete blood count. (From Adamson JW, Longo DL. Anemia and polycythemia. In: Kasper DL, Hauser SL, Jameson JL, et al., editors. Harrison's principles of internal medicine, 19th ed. New York: McGraw-Hill, 2015. Fig. 77-17.)

TABLE 20-1

Average Volumes of Blood Drawn for Diagnostic Testing⁸⁷

| | |
|-------------------------|--------|
| Arterial blood gas | 2 mL |
| Chemistry | 5 mL |
| Coagulation studies | 4.5 mL |
| Complete blood counts | 5 mL |
| Blood culture | 10 mL |
| Drug levels | 5 mL |
| Standard discard amount | 2 mL |

transferrin receptors, which are released into circulation.²⁰ Levels of transferrin receptor protein in circulation provide a quantitative measure of total erythropoiesis and can be used to measure the expansion of the erythroid marrow in response to recombinant erythropoietin therapy. Serum iron levels represent the amount of circulating iron bound to transferrin. The total iron-binding capacity is an indirect measure of the circulating transferrin concentration.

Key tests necessary for establishing a complete diagnosis of anemia of critical illness include serum iron concentration, serum transferrin concentration, transferrin receptor protein concentration, total iron-binding capacity, and serum ferritin concentration.

Anemia of critical illness is caused by impaired iron release, reduced production of erythropoietin, and a blunted response to erythropoietin; thus, this syndrome is characterized by a low serum iron concentra-

tion, low total iron-binding capacity, low transferrin saturation, normal transferrin-receptor protein levels, and a normal to high ferritin level. In contrast, iron-deficiency states are associated with transferrin saturation less than 18%. Consequently, critically ill patients may develop iron-deficiency anemia, anemia of chronic disease, or a combination of both.

MANAGEMENT

Red Cell Transfusion

Transfusion of PRBCs remains the standard approach for the management of anemia in critically ill patients. Most transfusions are administered in response to a particular Hb level, known as the *transfusion trigger*. Historically, transfusion was indicated for Hb concentrations below 10 g/dL. However, several considerations led to the critical reevaluation of this approach. First, scientific evidence suggests that most critically ill patients safely tolerate lower Hb levels. Second, PRBC transfusions are associated with numerous potential complications. Third, blood is a scarce and costly resource that may not always be available²¹; hence, its use must be limited to those most likely to benefit. Transfusion of PRBCs must therefore be used for a physiologic indication and not only in response to a transfusion trigger.

In recent years, evidence has led us to reconsider the traditional liberal strategy of transfusion. In the ABC trial, a prospective observational study of 3534 patients from 146 western European ICUs, 37% of all patients were transfused while in the ICU. A majority of transfusions were performed during the first week of ICU stay.

Transfusion was more common in the elderly and in those with ICU stays longer than 1 week. Notably, mortality was significantly higher in the transfused than in the nontransfused group. The differences persisted even after the patients were matched for the degree of organ dysfunction.⁵ The CRIT study was a prospective, multicenter, observational study of 284 ICUs in 213 hospitals in the United States. Overall, 44% of patients were transfused, most often within the first week of ICU admission; transfusion was independently associated with longer ICU and hospital stays and increased mortality.⁶ Walsh and colleagues prospectively collected data on 1023 sequential admissions in 10 ICUs over 100 days in Scotland. Approximately 40% of patients were transfused, even with the application of evidence-based transfusion guidelines.²² The multicenter trials group of the American Burn Association studied patients with more than or equal to 20% total body surface burns at 21 burn centers in the United States and Canada. Overall, they found that nearly 75% of patients were transfused during their hospital stay, receiving a mean of 14 units. The number of units transfused correlated significantly with the number of infections and mortality.²³ In a prospective observational study by the North Thames Blood Interest Group, 53% of patients were transfused for a mean pretransfusion Hb level of 8.5 g/dL. About two-thirds were transfused for low Hb levels and only 25% for hemorrhage. ICU mortality in the transfused patients was significantly higher than that in the nontransfused patients (24.8% vs. 17.7%, respectively).²⁴

Anemia is not as poorly tolerated in critically ill patients as previously thought. Some clinical evidence comes from studies in Jehovah's Witness patients who refuse to accept PRBC transfusions on religious grounds. Mortality increases significantly at Hb values below 5 g/dL, more so in individuals older than 50 years.²⁵ In conscious healthy volunteers, isovolemic dilution can be tolerated until the Hb concentration decreases to 5 g/dL, without an increase in lactate concentration²⁶; however, significant cognitive changes were noted.²⁷

The risks of anemia must be balanced against the potentially deleterious effects of transfusion, especially since the efficacy of PRBC transfusions to augment oxygen delivery and the impact of this increase on tissue metabolism and clinical outcome remain unproven. Marik and Corwin analyzed outcomes in 272,596 patients as reported in 45 studies. Blood transfusion was associated with an increased risk of death, infectious complications, and development of acute respiratory distress syndrome (ARDS).²⁸

The only absolute indication for PRBC transfusion is in the therapy of hemorrhagic shock.²⁹ However, only 20% of transfusions are used for this indication.

Most transfusions in the ICU are performed for the treatment of anemia. In the CRIT trial, over 90% of transfusions were given for this reason.⁶ Perceived benefits of transfusion include increase in oxygen delivery to the tissues, increase in cell mass and blood volume, alleviation of symptoms of anemia including dyspnea, fatigue, and diminished exercise tolerance, and relief of cardiac effects. The optimal Hb concentration can be influenced by the premorbid health status, disease process, and other factors. The seminal Transfusion Requirements in Critical Care (TRICC) trial has been instrumental in changing transfusion practices over the past decade.³⁰ In this study, 838 euvoletic critically ill patients with Hb levels less than 9 g/dL were enrolled. Among these, 418 patients were randomly assigned to a restrictive transfusion strategy, where transfusion was provided if the Hb level fell below 7 g/dL, with a goal of maintaining circulating Hb concentration between 7 and 9 g/dL; the remaining 420 patients were assigned to the liberal transfusion group and received transfusions if the Hb levels were less than 10 g/dL, with transfusions provided to keep the Hb level between 10 and 12 g/dL. Overall the 30-day mortality was similar between the two groups (18.7% vs. 23.3%, $P = 0.11$). However, a significantly lower mortality was seen with a restrictive transfusion strategy in those less severely ill who had APACHE II scores of less than or equal to 20 (8.7% vs. 16.1%, $P = 0.03$) and in those younger than 55 years (5.7% vs. 13.0%, $P = 0.02$). No difference in mortality was observed in those with stable, clinically significant cardiac disease (20.5% vs. 22.9%, $P = 0.69$). This strategy resulted in a 54% decrease in the average number of units

transfused and avoidance of transfusion in 33% of patients. Lowering of the transfusion threshold, therefore, is a simple and inexpensive strategy for improving the outcome for critically ill patients. Caution must be used in applying this restrictive transfusion strategy to those patients with acute myocardial ischemia and unstable angina as this group was excluded from the TRICC trial. Compensatory cardiac mechanisms in anemic patients include increases in blood flow during rest and redistribution of blood away from the endocardium. In the presence of significant coronary artery disease, these adaptive changes are poorly tolerated, and anemic patients with myocardial infarction may have increased mortality.³¹

ADVERSE EFFECTS OF TRANSFUSION

A large proportion of ICU patients continue to receive PRBC transfusions for anemia, exposing them to serious risks, including transmission of infectious diseases, immune-mediated reactions (acute or delayed hemolytic reactions, febrile allergic reactions, anaphylaxis, and graft-versus-host disease), and non-immune-related complications (fluid overload, electrolyte toxicity, and iron overload). Transfusion-related complications are encountered in up to 4% of PRBC transfusions.⁶ The risk of adverse outcomes increases incrementally with each unit of PRBC transfused.^{32,33} In an observational cohort study of 5814 patients undergoing coronary artery bypass grafting, each unit of PRBC transfused resulted in more complications. Overall, there was a 73% increase in the odds of a major morbidity for each unit transfused (Table 20-2).³²

With advances in screening and improvements in blood banking technology, transmission of infectious agents is less common. Current estimates of the risk of infection per unit of blood are approximately 1 in 2 million for human immunodeficiency virus, 1 in 1 million for hepatitis C virus, and 1 in 100,000 for hepatitis B virus.³⁴ The most common transfusion-related infections are secondary to bacterial contamination, which has an incidence of 12.6 events per 1 million

TABLE 20-2

Potential Adverse Consequences Associated with Red Cell Transfusion⁸⁸

INFECTIOUS COMPLICATIONS

| | |
|---|---------------------------------|
| Human immunodeficiency virus infection | 1 in 2.3 million |
| Human T-lymphotropic virus infection | 1 in 2 million |
| Hepatitis C virus infection | 1 in 1.8 million |
| Hepatitis B virus infection | 1 in 350,000 |
| Parvovirus B19 virus infection | 1 in 10,000 |
| Bacterial infections (<i>Staphylococcus</i> , streptococci, <i>Yersinia enterocolitica</i> , etc.) | 1 in 250,000 |
| Parasitic infections (Chagas disease) | 1 in 29,000 donors seropositive |

NONINFECTIOUS COMPLICATIONS

| | |
|--|--|
| Hemolytic transfusion reactions | 1 in 10,000 to 1 in 50,000 |
| Delayed hemolytic transfusion reaction | 1 in 1500 |
| Febrile nonhemolytic transfusion reactions | 1 in 100 to 35 in 100 |
| Major allergic reactions | 1 in 20,000 to 1 in 50,000 |
| ABO mismatching | 1 in 14,000 to 1 in 38,000 |
| Transfusion-related acute lung injury (TRALI) | 1 in 5000 |
| Transfusion-related immunomodulation (TRIM) | 1 in 100 |
| Transfusion-associated circulatory overload (TACO) | Observed once two blood volumes replaced |
| Coagulopathy | Observed after transfusion of 10 to 15 units |
| Iron overload | |
| Hypothermia | |
| Hyperkalemia | |
| Thrombocytopenia | |
| Pulmonary hypertension | |

units of allogeneic blood components transfused.³⁵ The risk of bacterial contamination is higher for PRBCs than for whole blood. Transfusion-related bacterial infections are most often caused by gram-positive organisms (e.g., staphylococcal spp., streptococcal spp., 58%) but may also be caused by gram-negative organisms (e.g., *Yersinia enterocolitica*, 32%). About 10% of these infections will result in a fatal outcome.³⁵ Increasing global travel has led to the emergence of infectious diseases not usually seen in the United States. Chagas disease, caused by the parasitic protozoan *Trypanosoma cruzi*, is endemic in much of South and Central America. Immigrants from these endemic areas now form an increasing proportion of the blood donor pool. This issue is especially relevant in regions with high immigrant populations. In two such cities, Los Angeles and Miami, seropositive rates among donors were one in 7500 and one in 9000, respectively, and have been increasing.³⁶ Once acquired, the parasitemia persists long after acquisition of the infection.³⁷

Major ABO blood type mismatching is estimated to occur in 1 of 138,673 PRBC units transfused and results in 1 death per 2 million units transfused.³⁵ Incompatibility may also result from antigens not routinely detected by current antibody assays. As a consequence, fatal acute hemolytic reactions still occur in 1 of every 250,000 to 1 million transfusions, and 1 patient per 1000 demonstrates the clinical manifestations of a delayed hemolytic transfusion reaction.³⁸

Transfusion-related acute lung injury (TRALI) is a potentially serious pulmonary complication of transfusion. In severe cases, its clinical presentation is similar to that of ARDS.³⁹ Although initially described by Bernard in 1951⁴⁰ as noncardiogenic pulmonary edema related to transfusion, the term *TRALI* was coined by Papovsky et al.⁴¹ Transfusion-related acute lung injury (TRALI) presents with dyspnea and bilateral pulmonary edema during or within up to 6 hours of a transfusion, with no other risk factor to explain its development. It must be distinguished from pulmonary insufficiency due to circulatory overload. Hypoxemia, fever, hypotension, tachycardia, and cyanosis may also occur. Most often, symptoms appear within 1 or 2 hours following transfusion, but a delayed form with dyspnea appearing as late as 48 hours after transfusion has been reported. Chest X-ray shows bilateral infiltrates, which may progress and cause whiteout of the entire lung field. Differential diagnosis includes transfusion-associated circulatory overload, cardiac diseases, allergic and anaphylactic transfusion reactions, and bacterial contamination of the blood. Although the exact incidence is unknown, TRALI is estimated to occur in one of every 5000 transfusions.⁴² Current evidence suggests two forms of TRALI: immune and nonimmune. Potential mediators include antileukocytic antibodies, lipid peroxidation products, and other as yet unrecognized agents. Neutrophils are the key effector cells. Transfusions from multiparous female donors, owing to exposure to paternal leukocytes, are associated with the highest risk of the development of TRALI in the recipient.⁴³ Treatment is currently limited to supportive measures.

Transfusion-related immunomodulation (TRIM) results in an increased incidence of bacterial infections, cancer recurrence, and organ dysfunction.^{44,45} Opelz and colleagues first suggested clinical evidence of transfusion-associated immunomodulation in 1973, when improved renal allograft survival was observed in patients transfused prior to transplantation.⁴⁶ Current evidence implicates transfusions in the development of nosocomial infections including wound infections, pneumonia, and sepsis. In a prospective observational study, Taylor et al. found a significant association between transfusion and development of nosocomial infections (14.3% vs. 5.3%, $P < 0.0001$). In addition, mortality and length of stay were increased in the transfused group. The risk of infection increases 9.7% for each unit of PRBC transfused.⁴⁷ Development of these infectious complications results not only in increased length of stay but in increased in-hospital deaths and increased costs as well.⁴⁸ These effects may be reduced by the use of prestorage leukocyte depletion.⁴⁹ Other complications include transfusion-associated circulatory overload (TACO) with the development of fluid overload and pulmonary edema^{50,51} and pulmonary hypertension with a decreased right ventricular ejection fraction.⁵² Finally, the transfusion of PRBCs may not augment the oxygen-

carrying capacity of blood. This results from development of the "storage lesion" due to changes in red blood cells that occur during ex vivo storage. These changes are both structural and functional^{53,54} and include reduced deformability impeding microvascular flow,⁵⁵ altered adhesiveness and aggregation,⁵⁶ reduced intracellular levels of 2,3-diphosphoglycerate (which shifts the oxyhemoglobin dissociation curve to the left and reduces oxygen delivery to the tissues), reduced levels of nitric oxide and adenosine triphosphate,⁵⁷ and accumulated bioactive compounds with proinflammatory activity.⁵⁸ The risk of complications increases with the duration of storage.^{59,60} Koch and colleagues examined data from 6002 patients undergoing cardiac surgery. Patients given older blood had higher rates of in-hospital mortality and more complications.⁶¹ Other recent studies have not found such an effect of storage.

Role of Erythropoietin

Many factors contribute to the development of anemia in critically ill patients, but inappropriately low endogenous levels of erythropoietin in response to anemia represent a key pathophysiologic issue. Further, there is a failure of circulating erythropoietin to induce a response commensurate with the degree of anemia.⁶² Recognition of these considerations has prompted the use of pharmacologic doses of erythropoietin in an effort to reduce the need for and/or the amount of red cells transfused, but this approach has not been validated by scientific evidence. Corwin et al. conducted a prospective randomized, placebo-controlled trial (EPO3) on 1460 patients and found that epoetin alfa therapy did not decrease the number of PRBC units transfused and did not improve outcomes. Furthermore, a significant increase in thrombotic events was noted (hazard ratio, 1.41; 95% CI, 1.06-1.86).⁶³ Accordingly, routine use of erythropoietin cannot be recommended. At our institutions, erythropoietin use is limited to patients with chronic renal failure and Jehovah's Witnesses.

Current Recommendations

Transfusion of PRBCs should not be based on a transfusion trigger alone. The decision must be based instead on the patient's intravascular volume status, evidence of shock, duration and extent of anemia, and cardiopulmonary physiologic parameters.¹

Transfusion is indicated for patients with hemorrhagic shock. In this instance, the number of units transfused is based not on a particular Hb level but rather on the physiologic state of the patient. Transfusion is also indicated in the presence of evidence of acute hemorrhage with either hemodynamic instability or evidence of inadequate oxygen delivery as demonstrated by elevated blood lactate levels or base deficit. Serial assessment of these parameters can be used to determine the efficacy of resuscitation.⁶⁴

In hemodynamically stable patients with anemia, a restrictive strategy of transfusion can be employed. Transfusion with PRBCs should be instituted when the Hb level falls to less than 7 g/dL. For patients at risk of myocardial ischemia, a higher Hb concentration might be the appropriate transfusion trigger.

For patients with cardiac disease undergoing coronary artery bypass graft surgery, increased mortality is observed in patients with Hb levels below 8 g/dL on admission. Reduction in mortality can be achieved by transfusing to a hematocrit of 30% to 33%. No mortality benefit is seen with hematocrits above 33%, and increased mortality is observed when hematocrits above 36% are achieved.⁶⁵⁻⁶⁷

Use of transfusions to wean patients from mechanical ventilation is not indicated. No benefit in the weaning process or difference in duration of mechanical ventilation has been observed.⁶⁸

Transfusions should not be employed as the absolute method to improve tissue oxygen delivery in critically ill patients. In septic patients, PRBC transfusion increases oxygen delivery but not consumption.⁶⁹ Although increases in Hb levels are consistently seen following transfusion in septic patients, these increases do not necessarily translate to improvement in tissue oxygenation.⁷⁰ Transfusion may be

BOX 20-1**Summary of Current Recommendations¹**

1. Packed red blood cell (PRBC) transfusion is indicated in patients with hemorrhagic shock (level 1).⁸⁹
2. PRBC transfusion may be recommended for patients with acute hemorrhage after adequate fluid resuscitation if they have evidence of hemodynamic instability or evidence of inadequate systemic perfusion as demonstrated by elevated serum lactate or presence of a base deficit (level 1).⁶⁴
3. A restrictive strategy of transfusion for hemoglobin (Hb) levels <7 g/dL is recommended for hemodynamically stable critically ill patients, except for those with myocardial infarction or unstable angina.⁹⁰ This restrictive strategy is also recommended in critically ill trauma patients⁹¹ and in those with stable cardiac disease (level 1).⁹⁰
4. Transfuse patients with acute coronary syndromes who have admission Hb levels of <8 g/dL. Achieve posttransfusion hematocrit (Hct) of 30% to 33% (level 3).^{66,67,92}
5. Do not transfuse based on a transfusion trigger alone. Instead, individualize the decision based on the patient's intravascular volume status, evidence of shock, duration and extent of anemia, and cardiopulmonary status.
6. Transfuse as single units (level 5).¹
7. Do not use transfusion as a means to wean patients off mechanical ventilation (level 2).⁵
8. Do not use transfusion as a stand-alone strategy to improve tissue oxygen delivery (level 2).³³
9. In sepsis, transfusions can be recommended as part of a strategy of early goal-directed therapy during the initial resuscitation⁹⁴ (level 2).⁷⁰
10. Evidence for transfusion in patients with subarachnoid hemorrhage and traumatic brain injury should be individualized.^{95,96}

indicated for failure to achieve an adequate mixed venous saturation after adequate fluid resuscitation.⁷¹

TRICC data fail to show any difference in outcome with a restrictive strategy in patients with traumatic brain injury, but the study was underpowered to detect differences in this subgroup of patients.⁷² Others have shown transfusion-related improvement in brain tissue partial pressure of oxygen independent of cerebral perfusion pressure, arterial oxygen saturation, and fraction of inspired oxygen (FiO₂).⁷³ Similar improvements have been observed in patients with subarachnoid hemorrhage who had higher initial and mean Hb values.⁷⁴ Salim et al. retrospectively evaluated the effect of transfusion on outcomes in 1150 patients with traumatic brain injury. On logistic regression, when both anemia and transfusion were included in the model, transfusion resulted in an increased mortality while anemia did not. When transfusion was removed from the model, anemia was a significant risk factor for mortality and complications.⁷⁵ These confounding results preclude a definitive recommendation for patients with subarachnoid hemorrhage or brain trauma, and the decision to transfuse must be individualized. Recommendations are summarized in [Box 20-1](#).

Novel Strategies

It is evident that hemodynamically stable patients can tolerate marked degrees of anemia. Inasmuch as the transfusion of PRBCs is clearly deleterious, preventing the development and/or progression of anemia is of paramount importance. Strategies to achieve this include retrieving and reusing blood shed during surgery,⁷⁶ limiting transfusions, using low-volume adult or pediatric sampling tubes to reduce phlebotomy volumes, reducing the number of laboratory tests ordered, using point-of-care microanalysis for laboratory tests, and using closed blood conservation devices.⁷⁷

Other approaches may include the development of newer methods of blood storage,⁷⁸ use of advanced computing technologies to optimize the use of blood inventories,⁷⁹ and development of blood substitutes.

Blood substitutes are being developed largely in response to concerns regarding the potential transmission of infectious agents and the impending shortage of blood in the face of increasing demands.⁸⁰ Blood substitutes offer the distinct advantages of better shelf life

compared to banked blood, universal compatibility, clinically useful intravascular half-life (18-24 hours), and freedom from the risk of infectious disease transmission (possibly with the exception of prion-mediated diseases). Blood substitutes are also oncologically active and can increase blood volume by an amount in excess of the transfused volume.⁸¹ Furthermore, blood substitutes can improve microcirculatory flow by reducing blood viscosity.⁸² Most Hb-based oxygen carriers (HBOCs) scavenge nitric oxide and promote arteriolar vasoconstriction on this basis. Although nitric oxide scavenging was probably the cause of increased mortality in the trial of diaspirin cross-linked hemoglobin (DCLHb) for trauma victims,⁸³ nitric oxide scavenging might prove beneficial in septic patients. In septic patients, inducible nitric oxide synthase expression is increased, leading to overproduction of nitric oxide and hypotension on this basis. HBOCs might overcome this distributive shock and restore blood pressure,⁸⁴ but their use has also been disappointing.

McKenzie and colleagues recently described the outcome in 54 patients with severe life-threatening anemia (median Hb level, 4 g/dL) treated with the blood substitute HBOC-201; 23 (41.8%) of 54 patients survived to discharge. Survival was significantly more likely when the blood substitute was administered earlier (3.2 days in survivors vs. 4.4 days in nonsurvivors, $P = 0.027$).⁸⁵

Results were from small individual studies, and available data do not support the use of blood substitutes in their current form. In a meta-analysis of 16 trials involving five blood substitutes and over 3700 patients, Natanson and colleagues⁸⁶ found a significantly increased risk of myocardial infarction and death among HBOC-treated patients. Poorer outcome was not related to the type of blood substitute employed or the clinical indication for its use. In light of this evidence, future phase 3 trials of these products are not warranted.

KEY POINTS

1. Anemia is exceedingly common in patients admitted to the ICU. Over 60% are anemic on admission, and more than 80% become anemic by day 3 of their ICU stay.
2. Anemia in the critically ill patient is multifactorial in etiology. Iron-deficiency anemia and anemia of critical illness are the most frequent causes.
3. Anemia of critical illness is cytokine-mediated and results from decreased production of erythropoietin, reduced response to erythropoietin, and altered iron metabolism.
4. Transfusion is clearly indicated for hemorrhagic shock and hemodynamic instability associated with blood loss after adequate fluid resuscitation.
5. Transfusion of packed red blood cells is still employed by the majority of clinicians as the mainstay of therapy for anemia in critical illness. However, the optimal Hb concentration essential to maintain ideal tissue oxygen delivery remains unknown.
6. A restrictive transfusion strategy for critically ill, hemodynamically stable patients without evidence of cardiac ischemia. Transfusion in these patients can often be avoided when circulating Hb level is above 7 g/dL.
7. Treatment with recombinant human erythropoietin initially showed promise as a strategy for reducing exposure to allogeneic blood. More recent evidence, however, refutes these findings and points instead to an increase in thrombotic complications.
8. Novel strategies to avoid the need for blood transfusion include use of blood conservation techniques, improved blood storage techniques, advanced inventory control, and evaluation of the efficacy of blood substitutes.

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- Hébert PC, Wells G, Blajchman MA, et al. A multicenter randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;340(6):409–417.
- This Canadian study found no benefit of a liberal transfusion strategy when compared to a restrictive one when 838 anemic critically ill patients were compared for 30-day mortality or severity of organ dysfunction. This landmark trial demonstrated that a hemoglobin transfusion threshold of 7 g/dL was appropriate in critically ill patients without ongoing cardiac ischemia or GI bleeding.*
- Corwin HL, Gettinger A, Pearl RG, et al. The CRIT study: anemia and blood transfusion in the critically ill—current clinical practice in the United States. *Crit Care Med* 2004;32(1):39–52.
- This prospective, multicenter, observational study described the transfusion experiences of ICU patients at 284 ICUs over a short time period in the United States. Among subjects enrolled, 44% were transfused a mean of 4.6 ± 4.9 units; average ICU stay was 21 days. This study examined red blood cell transfusion practices in the critically ill in the United States.*
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- Corwin HL, Gettinger A, Fabian TC, et al. Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med* 2007;357(10):965–976.
- In this prospective, randomized, placebo-controlled trial, 1460 anemic ICU patients received weekly recombinant human erythropoietin or placebo without benefit regarding 140-day mortality or transfusion requirements. EPO was associated with a significant increase in the incidence of thrombotic events. The purported benefits of EPO in the critically ill were clearly dispelled by this large multicenter trial.*
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■ References for this chapter can be found at expertconsult.com.

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Thrombocytopenia is a common laboratory finding in critically ill patients. Up to 50% of patients develop platelet counts $<150 \times 10^9/L$, and severe thrombocytopenia ($<50 \times 10^9/L$) occurs in at least 5% to 20%.¹⁻³ Pronounced thrombocytopenia is associated with an increased bleeding risk⁴ but can also be the result of immune-mediated platelet activation that provokes a prothrombotic state. The treatment of thrombocytopenia differs depending upon the underlying causes.

PLATELET PHYSIOLOGY AND REGULATION OF PLATELET COUNT

Platelets are nucleus-free fragments of megakaryocytes. Their production is controlled by thrombopoietin (TPO), a growth factor that is primarily produced in the liver in a constant amount.⁵ Only circulating “free” TPO stimulates platelet production. TPO binds to specific receptors on circulating platelets and is thereby removed from the circulation. Therefore, higher platelet counts decrease free TPO levels and platelet production, while low platelet numbers result in higher plasma levels of free TPO and consequently enhanced platelet production.⁶ The two compartments of platelets are as follows: (1) the stationary compartment in the spleen, comprising about one-third of the whole platelet pool, and (2) circulating platelets, representing the remaining two-thirds. The two pools exchange freely. After a mean life span of about 10 days, platelets are eliminated by the reticuloendothelial system of the liver and spleen.

The platelet count is controlled by complex interactions between production, pooling, and elimination.^{6,7} Nevertheless, in healthy people, the platelet count usually remains quite constant.⁸ Thus, thrombocytopenia is a marker for an alteration of normal physiology. In intensive care unit (ICU) patients, thrombocytopenia is associated with increased mortality,⁹ **not because of increased bleeding but as a marker for severe morbidity.**

ETIOLOGY OF THROMBOCYTOPENIA

Thrombocytopenia occurs when platelet loss and/or consumption exceeds production. The following six underlying mechanisms can be distinguished, although more than one often contributes to thrombocytopenia in an individual patient: (1) pseudothrombocytopenia, (2) hemodilution following platelet loss as a result of bleeding, (3) platelet consumption (e.g., due to sepsis, bleeding, or extracorporeal circuits), (4) decreased platelet production (e.g., due to toxic bone marrow depression), (5) increased sequestration of platelets (e.g., due to hepatomegaly and/or splenomegaly), and (6) immune-mediated destruction of platelets.¹⁰ **Table 21-1** summarizes the most frequent differential diagnoses of thrombocytopenia in the ICU, their frequency, and some diagnostic clues.

DIAGNOSTIC APPROACH TO THROMBOCYTOPENIA

Confirmation of Thrombocytopenia

The first question when facing a patient with thrombocytopenia should be whether the low platelet count is actually pseudothrombocytopenia, an artifact caused by in vitro aggregation of platelets in the blood sample due to naturally occurring immunoglobulin M antibodies

directed against epitopes on platelet glycoprotein (GP) IIb/IIIa-receptors, which are expressed upon calcium chelation by ethylene diaminetetraacetic acid (EDTA).^{11,12} The diagnosis is made by repeating the platelet count measurement using a citrated blood sample and/or examining the blood smear for the presence of platelet aggregates. *Note:* During treatment with GPIIb/IIIa antagonists, pseudothrombocytopenia can occur in citrated blood.

Identification of the Underlying Cause of Thrombocytopenia

Clinical Context

Sepsis, disseminated intravascular coagulation (DIC), and nonimmune drug-induced thrombocytopenia (DTP) are the most common causes of thrombocytopenia in critically ill patients.¹³ Less frequent causes include thrombotic microangiopathies, heparin-induced thrombocytopenia (HIT), immune thrombocytopenia (ITP), drug-induced immune thrombocytopenias (DITP), and post-transfusion purpura (PTP). These special clinical conditions are discussed in more detail below.

History

A detailed history should include previous drugs (for DTP and DITP); dietary habits, including alcohol consumption; risk factors for HIV and infectious hepatitis; and previous transfusions (for PTP). Data regarding previous platelet count values is important for distinguishing between chronic or acutely acquired thrombocytopenia.

Physical Examination

Physical examination is necessary to quantify bleeding symptoms and to estimate the bleeding risk. New thrombosis manifesting shortly before or after the onset of thrombocytopenia should prompt suspicion for HIT, while hepatomegaly and palmar erythema suggest cirrhosis and its associated complex clotting disorder.

Laboratory Assessment

Initial laboratory tests comprise the following: a complete blood count to exclude other cytopenias; a differential blood smear to identify leukemia, nucleated red cells, or fragmented cells; measurements of prothrombin time, activated partial thromboplastin time (aPTT), and fibrinogen for the detection of DIC; liver function tests and liver enzymes for the diagnosis of hepatopathy; and the measurement of lactate dehydrogenase as a sign of possible hemolysis. Further specific laboratory tests should follow depending upon the results of these initial screening assays. For example, a test for platelet factor 4 (PF4)/heparin antibodies should be obtained when HIT is suspected.¹¹

Platelet Count Course

The platelet count course is typically biphasic in ICU patients. After an initial mild decrease reaching a platelet count nadir on days 2 to 4 after ICU admission, platelet counts increase to higher than prebaseline values, a phenomenon called reactive thrombocytosis (**Fig. 21-1**). Persistent thrombocytopenia after trauma/major surgery hints toward consumption, bleeding, or severe organ damage, while a slow decrease in the platelet count over several days is rather typical for infection or bone marrow toxicity. When the platelet count falls a second time within 2 to 3 days during the second week of treatment,

TABLE 21-1

Major Mechanisms of Thrombocytopenia, Typical Clinical Scenarios, and Relative Frequencies in the Intensive Care Unit

| MECHANISM AND DIFFERENTIAL DIAGNOSIS | CLINICAL SCENARIO/DIAGNOSTIC APPROACH | FREQUENCY IN THE CRITICALLY ILL |
|--|---|---------------------------------|
| PSEUDOTHROMBOCYTOPENIA | | |
| Platelet aggregates in EDTA-anticoagulated blood or therapy with GPIIb/IIIa-receptor antagonists | Unexpected thrombocytopenia in the absence of bleeding symptoms; therapy with GPIIb/IIIa-receptor antagonists. Repeat platelet count in citrated blood and control for aggregates in the blood smear. Note: GPIIb/IIIa antagonists often induce pseudothrombocytopenia in citrated blood also | <5% |
| HEMODILUTION | | |
| Infusion of fluids and/or plasma | Massive bleeding with consecutive massive infusion/transfusion | Common |
| PLATELET CONSUMPTION | | |
| Blood loss | Bleeding, anemia, and prolonged clotting times | Common |
| Massive blunt trauma | History and physical and radiologic examination | Common |
| Disseminated intravascular coagulation | Shock, infection or other typical underlying causes (see text), prolonged clotting times, and increased fibrin split products | Very common |
| Sepsis | Fever and further sepsis criteria, positive blood cultures | Very common |
| Extracorporeal circuit | Organ failure requiring extracorporeal circuit | Common |
| PLATELET SEQUESTRATION | | |
| Hepatosplenomegaly | History, sonography, or other diagnostic radiology | Common |
| DECREASED PLATELET PRODUCTION | | |
| Intoxication (alcohol and other drugs) | History of substance abuse or medication, typical laboratory findings for alcohol abuse | Common |
| Viral infection (HIV, HCV, EBV, CMV) | Diagnostic work-up of viral infections | Rare |
| Bone marrow infiltration (leukemia, tumors) | Bone marrow examination and nucleated red cells in the differential blood film | Rare |
| Radiation | History | Rare |
| Chemotherapy | History | Rare |
| PLATELET DESTRUCTION | | |
| Immune thrombocytopenia | Anti-platelet antibodies, normal or increased megakaryocytes in bone marrow, and normal or decreased thrombopoietin | Rare |
| Drug-induced immune thrombocytopenia | Medication history, platelet counts $< 10,000/\mu\text{L}$, specific antibodies, increase of platelet counts after cessation of suspected/laboratory confirmed drug | Rare |
| Heparin-induced thrombocytopenia | 50% decrease in platelet count (typical nadir $20\text{--}80,000/\mu\text{L}$) between day 5 and 14 of heparin treatment, w/o thromboembolic events with ongoing heparin therapy, platelet factor 4/heparin antibodies | 0.5-1% |
| Thrombotic microangiopathies (TTP, HUS, HELLP syndrome) | Hemolysis with negative direct Coombs test, fragmented red cells in blood smear, typical platelet count nadir $10\text{--}30 \times 10^9/\text{L}$, thrombotic events with neurologic (TTP) or renal (HUS) symptoms, pregnancy (HELLP syndrome) | Rare |
| Post-transfusion purpura | Transfusion history and history of pregnancy | Very rare |

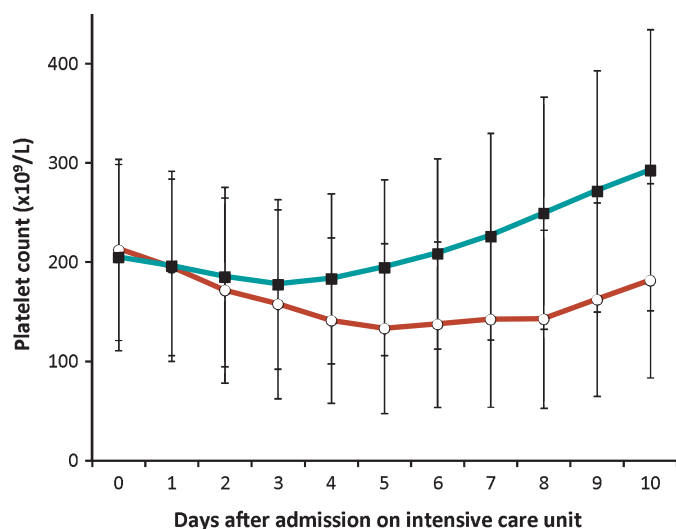


FIGURE 21-1 ■ Daily platelet counts in intensive care unit (ICU) survivors (filled squares) and nonsurvivors (unfilled circles) during 10 days in the ICU. Data are obtained from a prospective observational study in surgical/medical intensive care patients.²⁵

immune-mediated causes, such as HIT or PTP, should be considered. With HIT, the platelet count typically decreases by $>50\%$, but the nadir is 30 to $80 \times 10^9/\text{L}$. With PTP or DITP, the nadir is typically $<10 \times 10^9/\text{L}$.¹⁴ As a rule of thumb, platelet count nadir values of $>20 \times 10^9/\text{L}$ are more typical for nonimmune disorders (other than HIT), while platelet counts of $<10 \times 10^9/\text{L}$ should raise suspicion for an underlying immune-mediated process.

PLATELET TRANSFUSION

As many ICU patients also have a concomitant platelet function disorder caused by medications or platelet preactivation on extracorporeal circuits, the clinical symptoms are much more relevant than the absolute platelet count to decide on the indication for platelet transfusions. Bleeding \geq WHO grade 2 (i.e., more than mild blood loss like in epistaxis, hematuria, and hematemesis¹⁵) is a well-established trigger for platelet transfusion.¹⁶ Retinal bleeding and/or spontaneous bleeding of the oropharyngeal mucous membranes (wet purpura) indicate an increased risk for life-threatening bleeding into the central nervous system (CNS).

Patients with immune-mediated thrombocytopenia should only receive platelet transfusions in cases of serious or life-threatening hemorrhage.

Prophylactic platelet transfusions are given to prevent spontaneous serious bleeding or bleeding in the context of invasive procedures. The AABB¹⁵ recommends the transfusion of a single therapeutic unit (1 apheresis unit or 4-6 pooled platelet concentrates) in hospitalized adult

TABLE 21-2 Recommended Triggers for Platelet Transfusion (Data From¹⁵)

| TRANSFUSION INDICATION | THRESHOLD PLATELET COUNT ($\times 10^9/L$) | STRENGTH OF RECOMMENDATION | QUALITY OF EVIDENCE |
|--|--|----------------------------|---------------------|
| Prophylactic transfusion of adult patients | 10 | Strong | Moderate |
| Before central vein catheter placement | 20 | Weak | Low |
| Before elective diagnostic lumbar puncture | 50 | Weak | Very low |
| Before major elective surgery (excluding neurosurgery) | 50 | Weak | Very low |
| Prophylactic transfusion of nonthrombocytopenic patients before cardiopulmonary bypass surgery | No transfusion (only in case of bleeding) | Weak | Very low |
| Patients with intracranial hemorrhage and antiplatelet drugs | Independent of the platelet count | Uncertain | Very low |

patients with a platelet count of $\leq 10 \times 10^9/L$ to reduce the risk for spontaneous bleeding. A higher threshold of 20 to $30 \times 10^9/L$ should be considered in febrile and septic patients¹⁷ and even higher in patients with concomitant platelet dysfunction. These recommendations are supported by several randomized controlled trials in hematologic patients with radiation and/or chemotherapy-induced hypoproliferative thrombocytopenia; however, no data exist for ICU patients. It might be reasonable to restrict platelet transfusions to ICU patients with symptomatic bleeding, also because no study demonstrates that ICU patients benefit from platelet transfusions with regard to bleeding or mortality.¹⁸ The recommendations for platelet transfusion before invasive procedures¹⁵ (Table 21-2) are supported by observational studies. No data exist for patients at risk for bleeding in the CNS or those undergoing neurosurgery. For these patients, a transfusion threshold of $100 \times 10^9/L$ is often recommended.

Transfusion of a single therapeutic platelet unit should increase the platelet count by $\approx 15 \times 10^9/L$ in an ICU patient.¹⁸ Otherwise, persistence of the underlying cause of thrombocytopenia and/or immune-mediated etiologies must be considered.

THROMBOCYTOPENIA IN SPECIAL CLINICAL SCENARIOS

Sepsis

With a relative incidence of approximately 50%,^{9,19,20} sepsis is the most common reason for thrombocytopenia in ICU patients as a result of decreased platelet production and increased platelet consumption and destruction. Despite increased TPO levels in septic patients, platelet production is decreased, probably due to the active phagocytosis of megakaryocytes by monocytes and macrophages.¹⁹ The mechanisms of enhanced platelet consumption in sepsis include ongoing thrombin generation and increased adhesion of platelets to endothelial cells.¹⁹ Diagnosis and therapy should follow the current guidelines.¹⁷ Recommendations for platelet transfusion in these guidelines are derived from those for chemotherapy-induced thrombocytopenia and do not differ from those given in Table 21-2.

DIC

According to the definition of the International Society on Thrombosis and Hemostasis (ISTH), DIC is “an acquired syndrome characterized by the intravascular activation of coagulation with the loss of localization arising from different causes.”²¹ Sepsis, trauma, organ destruction (e.g., due to severe pancreatitis), tumors, and severe hepatic failure²¹ are conditions that are commonly associated with DIC. The consumption of coagulation factors and platelets manifests with typical laboratory findings that are used for a DIC score (Table 21-3). Clinically, patients often present with bleeding, although symptoms due to isolated microthrombi (e.g., digital ischemia) are also possible.

Therapy should be focused on managing the underlying cause of DIC. Patients with mild clotting abnormalities and no evidence of

TABLE 21-3 Diagnostic Scoring System for Disseminated Intravascular Coagulation

1. Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?
If yes, proceed with this algorithm
If no, do not use this algorithm
2. Order global coagulation tests (prothrombin time, platelet count, fibrinogen, fibrin-related marker)
3. Score results of global coagulation tests:

| PARAMETER | 0 POINTS | 1 POINT | 2 POINTS |
|-------------------------------|----------------------|-----------------------------------|---------------------|
| Platelets | $>100 \times 10^9/L$ | $<100 \times 10^9/L$ | $<50 \times 10^9/L$ |
| Fibrinogen | $>1.0 \text{ g/L}$ | $<1.0 \text{ g/L}$ | |
| Prothrombin time prolongation | $<3 \text{ s}$ | $\geq 3 \text{ to } <6 \text{ s}$ | $\geq 6 \text{ s}$ |
| D-dimer | $<1 \mu\text{g/mL}$ | $1\text{--}5 \mu\text{g/mL}$ | $>5 \mu\text{g/mL}$ |

4. Calculate score as follows:
 <5 points: suggestive of nonovert DIC, repeat scoring within next 1 to 2 days;
 ≥ 5 points: compatible with overt DIC, repeat scoring daily

Adapted from Toh CH, Hoots WK: SSC on Disseminated Intravascular Coagulation of the ISTH. The scoring system of the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview. *J Thromb Haemost*. 2007 Mar;5(3):604-6. Tab 1.

bleeding require no further treatment when thrombosis prophylaxis is part of the standard therapy. In cases of bleeding or a high bleeding risk, the substitution of coagulation factors and platelets may become necessary. A platelet transfusion trigger of $50 \times 10^9/L$ is recommended in DIC, although this recommendation is expert opinion based and not supported by valid studies.²²

DTP

DTP is the underlying cause in $\approx 10\%$ of thrombocytopenic ICU patients.^{9,19,20} Nonimmunological factors, such as bone marrow depression, are responsible for most cases of DTP. Table 21-4 summarizes the different mechanisms for DTP and the involved drugs.

DTP is rare and clinically manifests with an abrupt platelet count decrease to $<20 \times 10^9/L$. DTP is often accompanied by bleeding complications 5 to 14 days after starting a new drug. The suspected drug should be stopped immediately. Laboratory tests may be performed to support the diagnosis, but they are only provided by specialized laboratories and, with the exception of HIT, are not very sensitive. Thus, a negative test result does not exclude DTP. In contrast, platelet recovery, which usually begins 5 to 7 half-times after cessation of the causative drug, provides sufficient evidence for the diagnosis. Further therapy, which is sometimes necessary in severely bleeding patients, includes platelet transfusion, high doses of intravenous

TABLE 21-4 Mechanisms of the Development of Drug-Induced Thrombocytopenia (Data from^{23,33-35})

| MECHANISM | DESCRIPTION | DRUGS |
|-----------------------------------|--|--|
| Classic drug-dependent antibodies | Drug binds to platelet glycoproteins or antibodies, causes conformational changes thereby allowing antibody binding, resulting in increased platelet destruction by the reticuloendothelial system | Quinine, quinidine, antibiotics (sulfamethoxazole trimethoprim, vancomycin, rifampicin, cephalosporin), antiepileptics (valproate, carbamazepine, phenytoin), diuretics (furosemide, thiazides), ranitidine, nonsteroidal antiinflammatory drugs (diclofenac, ibuprofen) |
| Hapten-induced antibodies | Drug acts as a hapten that binds large molecules (e.g., proteins) on the platelet surface and stimulates antibody production | Penicillin and cephalosporin |
| Fiban-induced antibodies | Drug binds to epitopes on glycoprotein IIb/IIIa receptors on platelets and enhances affinity of preexisting anti-platelet antibodies | Tirofiban and eptifibatide |
| Drug-specific antibodies | Monoclonal antibodies bind to glycoprotein IIb/IIIa receptors on platelets and become targets of naturally occurring antibodies provoking increased platelet destruction | Abciximab |
| Autoantibodies | Platelet-specific autoantibodies are produced in the presence of a drug (exact mechanism unknown) | Procainamide, levodopa, and gold |
| Formation of immune complexes | Drug (e.g., heparin or protamine) binds to platelet factor 4 (PF4) in the circulation, creating complexes that provoke antibody formation. These antibodies bind with their Fab fragment to the drug/PF4 complex and with their Fc fragment to FcγRIIIa receptors on platelets causing platelet activation | Unfractionated heparin, low-molecular-weight heparin, and protamine |
| Bone marrow depression | Toxic bone marrow depression | Chemotherapeutics, linezolid, nonsteroidal anti-inflammatory drugs, and azathioprine |
| Thrombotic microangiopathy | Auto-antibodies against ADAMTS13 are produced in presence of the drug causing ADAMTS13 deficiency | Ticlopidine, clopidogrel, prasugrel, and cyclosporine |
| Unknown | The mechanism is unknown | Other antibiotics (daptomycin, nitrofurantoin), ganciclovir, fluconazole, digoxin, and haloperidol |

immunoglobulin (IVIG)—that is, 1 g/kg body weight on 2 consecutive days, and corticosteroids.²³ The responsible drug should be avoided in the future.

HIT

HIT usually occurs 5 to 10 days after starting treatment with unfractionated or low-molecular-weight heparin. HIT is caused by antibodies directed against a complex of PF4 and heparin (Table 21-4). HIT considerably differs from classic DITP: first, the platelet count is usually $\geq 20 \times 10^9/L$; second, thrombosis (often life-threatening) and not bleeding is the typical clinical manifestation; third, treatment consists not only of stopping heparin but also of starting an alternative anticoagulant—for example, a direct thrombin inhibitor (bivalirudin or argatroban) or the heparinoid danaparoid; fourth, in contrast to classic DITP, re-exposure to heparin can be safe under special circumstances (e.g., during cardiovascular surgery) when antibodies, which usually disappear 50 to 100 days after the acute episode of HIT, are no longer detectable.¹⁴

HIT occurs in 0.5 to 1% of ICU patients.²⁴ However, tests for anti-PF4/heparin antibodies are very sensitive for clinically irrelevant antibodies. Thus, PF4/heparin antibodies are found in up to 50% of ICU patients.²⁵ To reduce the risk of HIT overdiagnosis and to avoid the unnecessary and potentially harmful use of alternative anticoagulants, only patients with at least an intermediate pretest probability of HIT should be tested for anti-PF4/heparin antibodies (i.e., patients with ≥ 4 points on the 4Ts score)¹⁴ (Table 21-5). Although about 2 to 3% of patients with a low 4Ts score have HIT, a low 4Ts score plus a negative PF4/heparin test generally excludes HIT.

Trauma

Trauma is one of the common causes of thrombocytopenia in ICU patients, with a relative incidence of 7.5%.^{9,19,20} The mechanisms of

coagulopathy in trauma consist of the loss and consumption of coagulation factors and platelets, hyperfibrinolysis, and platelet dysfunction.²⁶ Therapy for volume deficiency may cause hemodilution and hypothermia and sometimes acidosis, all enhancing the bleeding risk.

In contrast to other coagulation factors (e.g., fibrinogen), blood loss must be massive before the platelet count falls below critical values. For example, in otherwise healthy patients undergoing elective surgery, the blood loss was 230% of the estimated blood volume before platelets decreased to $<50 \times 10^9/L$.²⁷ Therefore, platelet transfusion is probably only required in cases of severe bleeding and massive blood loss. The current European guideline recommends that platelets be given to maintain a platelet count of $>50 \times 10^9/L$ in all trauma patients and $>100 \times 10^9/L$ in patients with ongoing bleeding and/or traumatic brain injury.²⁸

ITP

ITP is “an autoimmune disorder characterized by immunologic destruction of otherwise normal platelets most commonly occurring in response to an unknown stimulus.”²⁹ Onset of ITP is extremely rare in adult ICU patients; however, it is possible that an ITP patient requires admission to the ICU because of bleeding. In this case, IVIG (≈ 1 g/kg body weight) together with corticosteroids should be administered.²⁹ Platelet transfusions can become necessary in cases of severe bleeding.

Thrombotic Microangiopathies (TMAs)

TMAs comprise a series of hereditary or acquired syndromes—namely, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), and the HELLP syndrome (characterized by hemolysis, elevated liver enzymes, and low platelets in pregnancy). All have microangiopathic hemolytic anemia, thrombocytopenia, and organ injury in common³⁰; however, their underlying mechanisms differ.³⁰ TTP is caused by hereditary or acquired ADAMTS13 deficiency.

TABLE 21-5 The 4Ts Score for Estimating the Pretest Probability of Heparin-Induced Thrombocytopenia¹⁴

| | POINTS (0, 1, OR 2 FOR EACH OF THE FOUR PARAMETERS; MAXIMUM POINTS = 8) | | |
|--|---|--|---|
| | 2 | 1 | 0 |
| Thrombocytopenia (acute) | >50% platelet count fall to nadir $\geq 20 \times 10^9/L$ | 30%-50% platelet count fall; or nadir $10-19 \times 10^9/L$ | <30% platelet count fall; or nadir $\leq 10 \times 10^9/L$ |
| Timing of fall in platelet count or other sequelae | Onset day 5-10 or <1 day (if heparin exposure within 30 days) | >Day 10, timing unclear, or <day 1 with recent heparin 31-100 days | Platelet count fall <day 4 (without recent heparin exposure) |
| Thrombosis or other sequelae | New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction | Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis—not confirmed | None |
| Other cause for thrombocytopenia | No other cause for platelet count fall is evident | Possible other cause is evident | Definite other cause is present |

Pretest probability score: 6–8 = High; 4–5 = Intermediate; 0–3 = Low

Hereditary TTP requires immediate plasma infusion (to replace ADAMTS13). In acquired TTP, plasma exchange (for the additional elimination of supposed anti-ADAMTS13 antibodies) combined with immunosuppressive therapy is essential to improve the patient's prognosis from $\approx 10\%$ survival to nearly 80%.³⁰ A special form of TTP in ICU patients is post-surgery TTP, which is typically nonimmune mediated and caused by the reduced activity of ADAMTS13 and concomitantly high von Willebrand factor levels.

Typical HUS is induced by bacteria (most often *Escherichia coli* strains producing Shiga toxin) and requires supportive therapy. Plasma exchange has not been shown to be effective. Atypical HUS is a hereditary disorder in patients with various mutations in proteins regulating the activity of the complement system.³¹ The inhibition of complement with eculizumab is the treatment of choice.

Thrombocytopenia in TMA is caused by increased platelet consumption resulting from excessive platelet activation and thrombus

formation in the microcirculation.³¹ Therefore, platelet transfusion is often avoided but remains justified in patients with clinically significant bleeding.

PTP

PTP presents very similarly to DITP—that is, with an abrupt fall in platelet count to $<20 \times 10^9/L$. PTP occurs 7 to 14 days after the transfusion of allogeneic blood products. Patients developing this rare complication are typically women older than 50 years, who were preimmunized during pregnancy against human platelet antigens (HPA; usually HPA1a). The transfusion of HPA1a-positive blood boosts the alloantibodies, which broaden their specificity by an immunologic phenomenon called antigen spreading, and also destroy autologous platelets. High-dose IVIG is the treatment of choice.

■ References for this chapter can be found at expertconsult.com.

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Disorders of clotting and hemostasis are common in the intensive care unit (ICU) setting, especially among patients with systemic inflammatory response syndrome (SIRS), sepsis, postoperative inflammatory states, and trauma.¹ Nearly all patients with a systemic inflammatory state fall somewhere on the broad spectrum of disordered hemostasis, ranging from minimally detectable dysfunction with no overt clinical manifestations to disseminated intravascular coagulation (DIC).^{2,3} Up to 28% of ICU patients have coagulation dysfunction, as evidenced by the prolongation of prothrombin time (PT) or the activated partial thromboplastin time (aPTT).¹ Detecting coagulopathy has important implications in the trauma population. In one study, 28% of patients presented with prolonged PT and 8% presented with prolonged aPTT; the presence of these findings increased the adjusted odds of mortality in these patients by 35% and 326%, respectively.⁴ In sepsis, mortality rates for patients with DIC range from 40% to 50%, and the presence of DIC confers a significantly higher risk of mortality.^{2,5}

In this chapter, we will focus on the cascade of soluble clotting factors and their associated natural anticoagulant proteins: the system of secondary hemostasis.⁶ Disorders of primary (cellular) hemostasis, including thrombocytopenia, are addressed in other chapters.⁷ We will utilize the SIRS/sepsis patient as a prototypical model for ICU coagulopathy, although there are certainly other populations warranting specific approaches, such as patients with trauma, cancer, or cirrhosis.

MECHANISMS OF HEMOSTASIS

Historically, students have been taught that coagulation comprises two cascading pathways of proteases that converge at the conversion of factor X to factor Xa: the intrinsic and extrinsic pathways (Fig. 22-1). Once active, factor Xa cleaves prothrombin (factor II) to thrombin, which performs the penultimate event of cleaving soluble fibrinogen to fibrin. Fibrin polymers are then further cross-linked by factor XIII, thereby generating a “stable clot.” The formation of fibrin serves not only to provide hemostasis but also aids in host defense by “walling off” pathogenic microbes.⁶ Counteracting these procoagulant mechanisms are several natural anticoagulants that minimize the unregulated generation of clots: antithrombin III, its co-factor heparan; protein C, its co-factor protein S; and tissue factor pathway inhibitor (TFPI). These factors act at various locations along the coagulation pathways to inhibit the coagulation process (Fig. 22-1). Clot formation is further regulated by fibrinolysis, a function of the enzyme plasmin, which breaks down polymerized fibrin into D-dimers. The overall control of hemostasis reflects a balance between pro- and anticoagulant elements.^{6,8}

Our contemporary perspective of the coagulation mechanism no longer equally weighs the extrinsic and intrinsic cascades in the generation of thrombus. Rather, the extrinsic pathway is now regarded as the main initiator of coagulation, whereas the intrinsic pathway serves to amplify the process via the mechanisms of intercommunication between the two pathways and feedback loops.⁸ Examples of this include the activated form of factor VII serving to activate both factor X and factor IX and the activation of factor XI and factor VIII by thrombin.⁸

INFLAMMATION AND THE DEVELOPMENT OF COAGULOPATHY

Immunity, inflammation, and coagulation are intimately intertwined, and although these systems historically have been considered in isolation, each possesses the capacity to augment or modulate the others. An inflammatory state, such as sepsis, tips the balance between anticoagulant forces and procoagulant forces in the direction of clot formation, predominantly by increasing the elaboration of tissue factor (TF) and its systemic exposure to the circulating blood.^{2,3} As most TF is produced by cells not normally in direct contact with the blood, the disruption of endothelial barriers due to trauma or inflammation increases the exposure of the blood to TF, thereby initiating coagulation. In sepsis, the release of proinflammatory cytokines, such as interleukin (IL)-6, causes monocytes, neutrophils, and endothelial cells that do not usually express TF to begin doing so.³

In states of systemic inflammation, decreased levels of natural anticoagulants (antithrombin, protein C, and TFPI) further exacerbate the imbalance and augment the expression of a procoagulant phenotype. Several biological mechanisms, including the consumption of existing factors, impaired production of new anticoagulant molecules, and degradation by neutrophil elastase of existing anticoagulant molecules, underlie the loss of anticoagulation.³ The summation of these events promotes excessive and unregulated clot formation and the further depletion of clotting factors.⁹ A vicious cycle now ensues. Compounding the issue of decreased natural anticoagulant levels is the loss of endothelial-bound thrombomodulin via endothelial shedding of thrombomodulin into the circulation,¹⁰ a process that interferes with the activation of protein C and thereby exacerbates the effects of protein C depletion.

The activation of fibrinolytic pathways occurs early and concomitant with the development of the septic procoagulant state, through the release of tissue plasminogen activator (tPA) and urokinase plasminogen activator from the endothelium in response to inflammatory cytokines, notably tumor necrosis factor (TNF)- α and IL-1 β .³ This increase in plasminogen activators is later accompanied by an increase in circulating plasminogen activator inhibitor type 1 (PAI-1), which blocks fibrinolysis and propagates microvascular thrombosis.³ Elevated levels of PAI-1 have been associated with worse outcomes in sepsis, but its overall role may be protective since mice deficient in PAI-1 show increased susceptibility to a variety of bacterial infections.¹¹

The coagulation and inflammatory cascades are linked by the activation of transmembrane cell receptors known as protease-activated receptors, which are found on vascular endothelial cells, mononuclear cells, platelets, fibroblasts, and smooth muscle cells.^{3,12} These receptors are cleaved and activated by coagulation cascade proteases, thrombin, and the TF-VIIa complex.^{3,12} Activation promotes inflammation by increasing the production of proinflammatory cytokines and cellular adhesion molecules.^{3,11} It is interesting to note that various components of the coagulation system, including TFPI, prothrombin, and factor X, have been found to have antimicrobial properties.¹¹ Coagulation, hemostasis, and the immune system are also linked by neutrophil extracellular traps (NETs).^{11,13} Responding to exposure to invading pathogens, neutrophils release a backbone of DNA stippled with

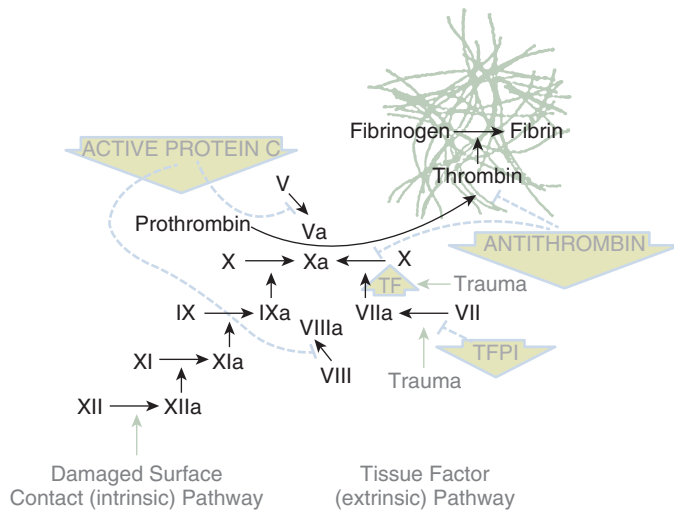


FIGURE 22-1 ■ Schematic of the Coagulation System. Further amplification of the intrinsic pathway occurs via thrombin-mediated activation of factor XI and factor VIII.

various bactericidal components, including histones, elastase, cathepsin G, and other components of azurophilic granules. NETs function by facilitating the extracellular trapping of bacteria.¹³ NET formation in sepsis has been implicated in the propagation of microvascular thrombosis, as the NETs can trap erythrocytes and platelets.^{11,13} Intravascular trapping of these blood cells can promote DIC by creating surfaces on which coagulation reactions can proceed.¹¹

DIAGNOSTIC METHODS AND CLINICAL MANIFESTATIONS

The clinical practice of assessing and monitoring coagulation status is achieved by testing the PT and activated partial thromboplastin time aPTT as measures of the extrinsic and intrinsic pathways, respectively (Table 22-1). Classically, PT measurements were used to monitor the effectiveness of warfarin for therapeutic anticoagulation, and aPTT measurements were used for monitoring heparin therapy. Use of the international normalized ratio (INR) has standardized testing of the extrinsic pathway, as unadjusted PT values may vary slightly among different clinical sites due to variations in reagents.¹⁴ Recent data have challenged the value of measuring aPTT and/or PT/INR for making the diagnosis and managing the treatment of coagulopathy. Critics highlight that the tests were designed for the management of warfarin and heparin therapy,^{14,15} and little evidence exists to support the use of PT, INR, or aPTT for guiding the treatment of coagulopathy.¹⁵

The development of newer anticoagulant therapeutics has necessitated the development of assays to assess their activity. Agents such as low-molecular-weight heparin (enoxaparin) and direct Xa inhibitors (e.g., fondaparinux) can be monitored using an anti-Xa activity assay. However, the favorable linear, and thus predictable, dose-response characteristics for these agents make laboratory monitoring less needed.¹⁴ Other less utilized tests include the Russell's viper venom assay (final common pathway) and the thrombin time and reptilase assays (sufficiency and functional status of fibrinogen).¹⁴

Fibrinogen levels can be measured directly, and this parameter may be a useful one to follow when there is a high suspicion of DIC. However, total fibrinogen levels may not be an optimal test; sufficient concentrations of fibrinogen, an acute phase reactant, can exist in the context of DIC and sepsis.¹⁶ Similarly, increased levels of D-dimer and/or fibrin/fibrinogen degradation are nonspecific findings in the ICU setting, as circulating levels of these proteins can be increased for a variety of reasons, especially in surgical or injured patients.^{14,16}

TABLE 22-1

Causes of Increased Prothrombin Time/International Normalized Ratio (PT/INR) and/or Activated Partial Thromboplastin Time (APTT)

INCREASED PT/INR—DEFECT IN EXTRINSIC PATHWAY

Deficiency or inhibitor of factor VII
Early warfarin (Coumadin) therapy
Early liver disease

INCREASED APTT—DEFECT IN INTRINSIC PATHWAY

Deficiency or inhibitor of factors XII, XI, IX, or VIII
Heparin (though usually affects PT as well)
Liver disease (though usually affects PT as well)
Lupus anticoagulant (may affect PT as well)

INCREASED PT/INR AND APTT—DEFECT IN COMMON PATHWAY OR COMBINED DEFECT IN EXTRINSIC AND INTRINSIC PATHWAYS

Heparin (all serine proteases affected, especially II and X)
Disseminated intravascular coagulation (all factors, including pro- and anticoagulants, affected)
Liver disease (all factors except VIII affected)
Warfarin (factors II, VII, IX, and X affected)
Vitamin K deficiency (factors II, VII, IX, and X affected)
Direct thrombin inhibitors
Lupus anticoagulant

Modified from: Rizoli S, Aird WC. Coagulopathy. In: Vincent JL, Abraham E, Moore FA, et al., editors. *Textbook of Critical Care*. 6th ed. Philadelphia: Elsevier; 2011.

DIC results in widespread activation of the coagulation system with the deposition of fibrin primarily in small-caliber vessels.¹⁷ Significant end-organ damage, including encephalopathy, acute lung injury, liver failure, and acute renal failure, can ensue.¹⁷ The diagnosis is difficult as the process may mimic other thrombotic microangiopathies (thrombotic thrombocytopenic purpura [TTP], hemolytic uremic syndrome [HUS], and *hemolysis, elevated liver enzymes, and low platelet count* [HELLP syndrome] associated with pregnancy), heparin-induced thrombocytopenia (HIT), and liver failure.^{17,18} No single laboratory test for DIC exists, but the syndrome is usually characterized by a low platelet count, prolonged PT and aPTT tests, increased fibrin degradation products, and decreased levels of natural anticoagulants.¹⁸ Two major scoring systems for the diagnosis of DIC have been created by the International Society on Thrombosis and Hemostasis (ISTH) and the Japanese Association for Acute Medicine (JAAM).¹⁹⁻²¹ The ISTH criteria take into account the platelet count, PT, fibrinogen level, and fibrin degradation product level, while the JAAM DIC scoring system awards points based upon the presence of SIRS criteria, prolonged PT, fibrin/fibrinogen degradation product level, and platelet count (Table 22-2).¹⁹⁻²¹

Less commonly tested pro- and anticoagulant laboratory values in septic patients that are currently not considered in available DIC scoring systems include the levels of protein C and protein S, antithrombin, TFPI, and PAI-1, as well as circulating plasma microparticle levels, and various other experimental markers.^{18,22} Markers like antithrombin and activated protein C are more readily testable than other more experimental markers but are nonspecific as they are decreased in SIRS, particularly sepsis.²³ Endothelial-derived procoagulant microparticles (lipid vesicles with proinflammatory and procoagulant properties released from stressed cells) have been shown to be associated with the development of DIC in septic patients and may represent a new biomarker or potential therapeutic target in sepsis-induced coagulopathy.^{11,13,22,24}

Finally, viscoelastic analysis of coagulation using thromboelastography (TEG) or rotational thromboelastometry (ROTEM) represents a relatively newer method of assessing coagulation status. These tests can identify both hyper- and hypocoagulable states.²⁵ Results from these studies can be visualized in real time, observing the clot

TABLE 22-2 Disseminated Intravascular Coagulation Scoring Systems**INTERNATIONAL SOCIETY ON THROMBOSIS AND HEMOSTASIS (ISTH) OVERT DIC SCORING SYSTEM**

Patient must have an underlying disorder known to be associated with overt DIC. Points assigned based on the following laboratory values:

- Platelet count ($>100 = 0$; $<100 = 1$; $<50 = 2$)
- Elevated fibrin-related marker (e.g., fibrin degradation products) (no increase = 0; moderate increase = 2; strong increase = 3)
- Prothrombin time (<3 seconds = 0; >3 seconds but <6 seconds = 1; >6 seconds = 2)
- Fibrinogen level (>1 g/L = 0; <1 g/L = 1)

Total score ≥ 5 compatible with overt DIC, repeat scoring daily

Score < 5 suggestive (but not affirmative) for nonovert DIC; repeat scoring next 1-2 days

JAPANESE ASSOCIATION FOR ACUTE MEDICINE DIC SCORING SYSTEM

Points assigned based on the following criteria:

- Systemic inflammatory response syndrome criteria ($\geq 3 = 1$; $0-2 = 0$)
- Platelet count (<80 or $>50\%$ decrease within 24 hours = 3; ≥ 80 and <120 or $>30\%$ decrease within 24 hours = 1; $\geq 120 = 0$)
- Prothrombin time (value of patient/normal value) ($\geq 1.2 = 1$; $<1.2 = 0$)
- Fibrin/fibrinogen degradation products (≥ 25 mg/L = 3; ≥ 10 and <25 mg/L = 1; <10 mg/L = 0)

Total score ≥ 4 compatible with a diagnosis of DIC

Sources: Taylor FB, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost* 2001;86(5):1327-30.

Gando S, Iba T, Eguchi Y, et al. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. *Crit Care Med* 2006;34(3):625-31.

formation/dissolution curve as the clot forms and then undergoes fibrinolysis. These methods assess whole clot formation and dissolution rather than analyzing only one component of the coagulation system. Furthermore, the transfusion of specific blood components can be directed based upon TEG or ROTEM parameters. The presence of a hypocoagulable TEG profile at the time of admission was predictive of mortality in patients with severe sepsis, and the degree of hypocoagulability was correlated with organ failure severity.^{18,25} TEG/ROTEM results are usually quickly available as point-of-care testing and are gaining popularity in the clinical assessment of coagulopathy.

TREATMENT OF COAGULOPATHY

The primary treatment for any form of coagulopathy is to correct the underlying cause. In the context of sepsis, treatment of the underlying cause involves the administration of antibiotics, source control, and supportive measures, as necessary. Transfusion of blood products are reserved for patients who are actively bleeding or undergoing a procedure with a high risk of bleeding. Abnormal laboratory parameters alone are not an indication for blood product administration in the absence of hemorrhage or anticipated procedures or surgery.¹⁸ If transfusion is deemed necessary, a variety of therapeutic options exist. Fresh frozen plasma (FFP) contains all of the circulating coagulation factors and remains the first-line treatment of hypocoagulability.¹⁶ The PROPPR trial examined the transfusion ratio of plasma to packed red blood cells (PRBC) in massively transfused trauma patients and found that transfusing platelets, FFP, and PRBC in a 1:1:1 ratio was superior for achieving hemostasis and preventing death due to exsanguination in the first 24 hours after trauma as compared to a 1:1:2 ratio (platelets:plasma:PRBC).²⁶ The study noted small improvements in 24-hour and 30-day mortality rates in patients receiving 1:1:1 transfusion ratios, but these differences were not statistically significant.

Cryoprecipitate contains fibrinogen, von Willebrand factor, factor VIII, and factor XIII in a concentrated solution for targeted factor replacement. Prothrombin complex concentrate (PCC) contains

TABLE 22-3 FDA-Approved Fractionated Plasma Products for Treatment of Coagulopathic Hemorrhage**FACTOR VIIA (RECOMBINANT), (NOVOSEVEN, NOVOSEVEN RT)**

Indicated for treatment or prevention of bleeding in patients with hemophilia A or B with inhibitors, acquired hemophilia, or congenital FVII deficiency.

FACTOR VIII (RECOMBINANT), (AKA ANTIHEMOPHILIC FACTOR, VARIOUS BRAND NAMES)

Indicated for patients with hemophilia A for prevention or control of bleeding episodes.

FACTOR VIII/VON WILLEBRAND COMPLEX (HUMAN), (HUMATE-P, ALPHANATE, WILATE)

For treatment of bleeding and perioperative prevention of bleeding in patients with von Willebrand disease.

FACTOR IX (RECOMBINANT), (ALPROLIX, BENEFIX, RIXUBIS)

For treatment of bleeding, prophylaxis, and perioperative prevention of bleeding in patients with hemophilia B.

FACTOR IX COMPLEX, (PROFILNINE SD)

Contains factor IX, factor II, factor X, and low levels of factor VII. For prevention and control of bleeding in patients with hemophilia B.

FACTOR XIII A-SUBUNIT (RECOMBINANT), (TRETTEIN)

Indicated for prophylaxis of bleeding in patients with congenital factor XIII A-Subunit deficiency.

FACTOR XIII CONCENTRATE (HUMAN), (CORIFACT)

Indicated for prophylaxis and perioperative management of bleeding in patients with congenital factor XIII deficiency.

FIBRINOGEN CONCENTRATE (HUMAN), (RIASTAP)

For treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency.

PROTHROMBIN COMPLEX CONCENTRATE (HUMAN), (KCENTRA)

Contains factor II, factor VII, factor IX, factor X, protein C, and protein S. For urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist therapy in adults with acute major bleeding.

ANTI-INHIBITOR COAGULANT COMPLEX (HUMAN), (FEIBA NF)

Contains factor II, factor IX, factor X, factor VIIa, and factor VIII coagulant antigen. Indicated for use in patients with hemophilia A and B with inhibitors for prophylaxis, perioperative management, and control of bleeding episodes.

Source: FDA Approved Fractionated Plasma Products. Available at: <http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/default.htm>. Accessed on 10/27/15.

factors II, VII, IX, and X and requires infusion of a smaller volume of fluid to effectively reverse warfarin-induced anticoagulation or replenish specific factor deficiencies. PCC may also be useful for reversing anticoagulation caused by treatment with direct factor Xa inhibitors like rivaroxaban and apixaban.^{27,28} The newer generation oral anticoagulants, including dabigatran, rivaroxaban, and apixaban, present a challenge for the reversal of coagulopathy, as no specific antidotes for any of these drugs are currently available. The reversal of rivaroxaban, but not dabigatran, was accomplished in a study of healthy volunteers using PCC.²⁸ Specific factor concentrates such as recombinant factor VIIa are sometimes used in an off-label fashion for various causes of coagulopathy, often as a last-ditch effort to control life-threatening hemorrhage (Table 22-3).¹⁶

Protamine is a specific reversal agent for unfractionated heparin, although multiple side effects have been reported, including hypotension, pulmonary vasoconstriction, and anaphylaxis.²⁷ The use of anti-fibrinolytic drugs, such as ϵ -aminocaproic acid or tranexamic acid (TXA), is warranted if hyperfibrinolysis is present. TXA has been

studied extensively in trauma victims.^{16,27,29} The CRASH-2 study analyzed data from over 20,000 patients presenting with significant hemorrhage within 8 hours of injury and found decreased mortality due to hemorrhage as well as decreased all-cause mortality when TXA was given within 3 hours of injury.²⁹

Anticoagulant therapy for the treatment of DIC has received a great deal of attention in the past two decades. Some experts advocate the use of heparin in low-grade DIC to treat and prevent further thrombosis.¹⁸ The infusion of recombinant human activated protein C (drotrecogin alfa) was studied in the PROWESS, ADDRESS, and PROWESS-SHOCK trials.^{23,30,31} Results from the most recent trial of drotrecogin alfa, the PROWESS-SHOCK trial, showed no improvement in overall mortality compared to the placebo, and the drug was withdrawn from the market in 2011. Other therapies that have been studied include human recombinant TFPI (tifacogin) and antithrombin.³²⁻³⁶ Thrombomodulin has yielded promising results in early clinical trials and is currently under further investigation.³⁷

■ References for this chapter can be found at expertconsult.com.

SUMMARY

- Coagulopathy is a common finding in the ICU with a wide range of severities at presentation.
- Increases in available tissue factor, decreases in natural anticoagulants, and impairment of fibrinolysis all contribute to the procoagulant state in sepsis.
- Inflammation, the immune system, and the coagulation system are intimately associated.
- No single laboratory test is diagnostic of DIC, but predictive scoring systems are available.
- TEG/ROTEM are good methods for point-of-care assessment of coagulation function.
- The mainstay for treatment of coagulopathy is treating the inciting condition (e.g., sepsis).
- Ongoing trials are investigating the role of anticoagulant therapy in the treatment of sepsis.

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Bilirubin is a byproduct of heme metabolism. Heme is largely derived from the hemoglobin in senescent red blood cells and is oxidized in the spleen, liver, and other organs by two isoforms of the enzyme heme oxygenase, in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) and molecular oxygen, to form biliverdin, carbon monoxide, and iron.¹ Subsequently, biliverdin is converted into bilirubin by the phosphoprotein, biliverdin reductase, which also uses NADPH as a cofactor.

Bilirubin is a lipophilic molecule. To be excreted, bilirubin that is produced in extrahepatic organs is bound to albumin and transported to the liver. The liver takes up the bilirubin-albumin complex through an albumin receptor. Bilirubin, but not albumin, is transferred across the hepatocyte membrane and transported through the cytoplasm to the smooth endoplasmic reticulum bound primarily to ligandin or Y protein, a member of the glutathione S-transferase gene family of proteins. Within hepatocytes, bilirubin is converted to water-soluble derivatives, bilirubin monoglucuronide and bilirubin diglucuronide, by the enzyme uridine diphosphate-glucuronosyl transferase. These conjugated forms of bilirubin are secreted across the canalicular membrane into the bile via an energy-dependent process. Conjugated bilirubin is excreted in the bile into the intestine, where it is broken down by the gut microflora into urobilinogen and stercobilin.

Total serum bilirubin consists of an unconjugated fraction and a conjugated fraction. The conjugated forms of bilirubin exist both freely in the serum and bound covalently to albumin. Conjugated bilirubin is water soluble and reacts directly to certain dyes added to the serum specimen. The unconjugated bilirubin does not react with the colorimetric reagents until a solvent is added. Accordingly, the conjugated and unconjugated forms of bilirubin are sometimes referred to as “direct” and “indirect” bilirubin. The sum of these two measurements is the “total” bilirubin. The normal total bilirubin concentration in adults is less than 18 $\mu\text{mol/L}$ (1.0 mg/dL). Although any total bilirubin concentration higher than the upper limit of normal constitutes hyperbilirubinemia, jaundice (i.e., yellow discoloration of the sclerae, mucous membranes, and skin) is usually not clinically apparent unless the serum total bilirubin level is greater than 50 $\mu\text{mol/L}$ (2.8 mg/dL). Unconjugated or indirect hyperbilirubinemia is present when the total serum bilirubin concentration is above the upper limit of normal and less than 15% of the total is in the direct or conjugated form.

■ DIFFERENTIAL DIAGNOSIS

The multitude of diagnoses depicted in [Box 23-1](#) divides the causes of hyperbilirubinemia into two large groups according to whether the predominant abnormality is an increase in the circulating concentration of unconjugated (indirect) bilirubin or an increase in the concentration of conjugated (direct) bilirubin. Although this classification scheme is useful under some circumstances, many of the diagnoses listed in [Box 23-1](#) are extremely rare and highly unlikely to be encountered by the intensivist caring for critically ill (adult) patients. A more useful classification scheme is depicted in [Box 23-2](#). In this scheme, the causes of jaundice are grouped into three primary categories: extrahepatic obstruction to bile flow, increased bilirubin production, and impaired excretion secondary to hepatocellular necrosis and/or intra-

hepatic cholestasis and hepatitis. It is common for multiple mechanisms to be involved simultaneously.

Hyperbilirubinemia occurs frequently in critically ill patients and is an independent risk factor for an unfavorable outcome.^{2,3} In a retrospective study of adult patients admitted to an intensive care unit (ICU) with severe sepsis or septic shock, the mortality rate was 12%, 24%, and 42% for individuals with a peak serum bilirubin concentration during the first 72 hours that was ≤ 1 , 1.1 to 2, or >2 mg/dL, respectively.⁴ In another retrospective study, hyperbilirubinemia was a significant risk factor for the development of the acute respiratory distress syndrome (ARDS) among patients admitted to an ICU with sepsis.⁵ In one widely cited study, hyperbilirubinemia occurred in 217 of 2857 trauma patients who had an Injury Severity Score greater than 14 and survived for longer than 48 hours after admission to the hospital.⁶ In this study, hyperbilirubinemia was significantly associated with an increased length of stay in the ICU and death. Hyperbilirubinemia is also common in ICU patients who are recovering from cardiac surgery.^{7,8} In this category of ICU patients, risk factors for the development of hyperbilirubinemia include prolonged cardiopulmonary bypass time, prolonged aortic cross-clamp time, and the use of an intraaortic balloon pump.⁸

Determining the cause of new-onset hyperbilirubinemia is important when managing ICU patients because some problems can be corrected. Exclusion of a mechanical cause for jaundice (e.g., obstruction of the common bile duct due to choledocholithiasis or stricture) assumes the highest priority because failure to correct this type of problem in a timely fashion can lead to serious morbidity or even mortality.

Iatrogenic injuries to the common bile duct are fortunately quite rare. Damage to the biliary tree, stricture of biliary anastomoses, and retained stones after cholecystectomy or common bile duct exploration present as hyperbilirubinemia and elevated circulating levels of alkaline phosphatase or gamma-glutamyl transpeptidase. Most often the diagnosis is made by detecting the dilation of intrahepatic and extrahepatic bile ducts using ultrasonography.

By exceeding the capacity of the liver to conjugate and excrete bilirubin into the bile, hemolysis can result in jaundice. However, the liver can excrete approximately 300 mg/day of bilirubin,⁹ and therefore, clinically significant hyperbilirubinemia is only apparent if the rate of hemolysis (i.e., the number of red blood cells lysed per unit time) is fairly rapid. Approximately 10% of the erythrocytes in an appropriately cross-matched unit of packed red blood cells undergo rapid hemolysis, yielding about 250 mg of bilirubin.¹⁰ Accordingly, transfusion of a single unit of packed red blood cells is not likely to increase the total serum bilirubin concentration. However, transfusion of multiple units of blood over a short period almost inevitably leads to some degree of hyperbilirubinemia, particularly if hepatic functionality is already impaired. Other common causes of acute hemolysis in ICU patients include sickle cell disease, immune-mediated hemolytic anemia, and disseminated intravascular coagulation.

Any condition that leads to extensive hepatocellular damage will increase the circulating total bilirubin concentration. Conditions in this category that are commonly encountered in ICU patients include viral hepatitis, “shock liver,” alcoholic hepatitis, and hepatocellular injury induced by drugs, especially acetaminophen.¹¹ In most forms of jaundice due to hepatic inflammation or hepatocellular damage,

[†]Deceased.

BOX 23-1**Differential Diagnosis of Hyperbilirubinemia**

- A. Unconjugated hyperbilirubinemia
 - 1. Overproduction of bilirubin
 - a. Hemolysis, intravascular: disseminated intravascular coagulation
 - b. Hemolysis, extravascular
 - i. Hemoglobinopathies
 - ii. Enzyme deficiencies (e.g., glucose-6-phosphate dehydrogenase deficiency)
 - iii. Autoimmune hemolytic anemias
 - c. Ineffective erythropoiesis
 - d. Resorption of hematoma
 - e. Massive transfusion
 - 2. Hereditary unconjugated hyperbilirubinemia
 - a. Gilbert's syndrome (autosomal dominant)
 - b. Crigler-Najjar syndrome type I (autosomal recessive)
 - c. Crigler-Najjar syndrome type II (autosomal dominant)
 - 3. Drugs
 - a. Chloramphenicol: neonatal hyperbilirubinemia
 - b. Vitamin K: neonatal hyperbilirubinemia
 - c. 5 β -Pregnane-3 α , 20 α -diol: cause of breast milk jaundice
- B. Conjugated hyperbilirubinemia
 - 1. Inherited disorders
 - a. Dubin-Johnson syndrome (autosomal recessive)
 - b. Rotor syndrome (autosomal recessive)
 - 2. Hepatocellular diseases and intrahepatic causes
 - a. Viral hepatitis
 - b. Alcoholic hepatitis
 - c. Drug-induced hepatitis (e.g., due to isoniazid, nonsteroidal antiinflammatory drugs, and zidovudine)
 - d. Cirrhosis
 - e. Drug-induced cholestasis (e.g., due to prochlorperazine, haloperidol [Haldol] and estrogens)
 - f. Sepsis
 - g. Postoperative jaundice
 - h. Infiltrative liver disease: tumors, abscesses (pyogenic, amebic), tuberculosis, parasites (e.g., *Toxoplasma*), *Pneumocystis jirovecii* pneumonia, *Echinococcus*
 - i. Primary biliary cirrhosis
 - j. Primary sclerosing cholangitis
 - 3. Extrahepatic causes
 - a. Gallstone disease
 - b. Pancreatitis-related stricture
 - c. Pancreatic head tumor
 - d. Cholangiocarcinoma
 - e. Primary sclerosing cholangitis

Adapted from Bernstein MD. Hyperbilirubinemia. In: Rakel RE, editor. Saunders Manual of Medical Practice. Philadelphia: Saunders; 1996. p. 371-3, with permission.

BOX 23-2**Classification for Acute Jaundice Associated with Critical Illness**

- I. Extrahepatic bile duct obstruction
 - A. Cholelithiasis
 - B. Common bile duct stricture
 - C. Traumatic or iatrogenic common bile duct injury
 - D. Acute pancreatitis
 - E. Malignancy (e.g., ampullary carcinoma)
- II. Increased bilirubin production
 - A. Massive transfusion
 - B. Resorption of blood collections (e.g., hematomas, hemoperitoneum)
 - C. Acute hemolysis
 - 1. Disseminated intravascular coagulation
 - 2. Immune-mediated
- III. Impaired excretion due to hepatocellular dysfunction, hepatitis, or intrahepatic cholestasis
 - A. Drug- or alcohol-induced hepatitis
 - B. Drug-induced intrahepatic cholestasis
 - C. Drug-induced hepatocellular necrosis
 - D. Gilbert's syndrome
 - E. Sepsis and other causes of systemic inflammation
 - F. Total parenteral nutrition
 - G. Viral hepatitis

circulating levels of transaminases are elevated to a greater extent than the total bilirubin concentration. Making a diagnosis of acetaminophen overdose early is extremely important because specific therapy using N-acetylcysteine can be lifesaving.¹¹

Efforts to understand the pathophysiological mechanisms responsible for cholestatic jaundice due to sepsis have largely focused on lipopolysaccharide (LPS)-induced alterations in the function and expression of various bile acid transporters.¹²⁻¹⁴ Nevertheless, another factor that likely contributes to the development of intrahepatic cholestasis is the back-leakage of bile from the canalicular spaces into the sinusoids.¹⁵

Total parenteral nutrition (TPN) is associated with the development of hyperbilirubinemia.¹⁶ The basis for TPN-induced cholestasis is thought to be multifactorial. Prolonged bowel rest and ileus may promote bacterial overgrowth and increased translocation of LPS into the portal vein on this basis. Phytosterols are present in the lipid emulsions used for TPN and have been associated with cholestasis, especially in premature infants.¹⁷ Results from two retrospective studies suggest that the administration of more than 1 g/kg/day of lipid emulsion is associated with an increased incidence of hepatocellular dysfunction.^{18,19} However, these data were derived from studying patients receiving TPN at home for prolonged periods and may not apply to ICU patients. In any case, TPN is associated with the development of jaundice and hepatocellular damage. Accordingly, except in rare cases, the majority of ICU patients are better served by receiving enteral rather than parenteral nutrition.

References for this chapter can be found at expertconsult.com.

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Gastrointestinal (GI) bleeding is a common reason for admission to the intensive care unit (ICU). Patients often present in various stages of hemodynamic instability and the location of the hemorrhage may not be certain at the time of initial presentation. Morbidity and mortality from GI bleeding have remained relatively stable even though management has improved. This is due to an aging population presenting with an increasing number of comorbidities and the use of newer anticoagulant medications that can complicate management. The most common causes of significant GI bleeding are peptic ulcer disease (PUD), esophageal varices, and diverticulosis.¹

Patients with significant active GI bleeding, hemodynamic instability, or significant comorbid conditions should be admitted to an ICU for monitoring. Critically ill patients presenting with GI bleeding benefit from having a multidisciplinary team of doctors, including an intensivist, a gastroenterologist, a radiologist, and a surgeon.

■ UPPER GI HEMORRHAGE

Epidemiology

Upper GI (UGI) bleeding is more common than lower GI (LGI) bleeding.¹ UGI bleeding in the United States results in more than 400,000 admissions per year, and a significant number of these cases are admitted to the ICU.² The risk of significant GI bleeding increases with age; accordingly, as the number of elderly people in the population increases, admissions for GI hemorrhage are expected to rise.^{3,4} Patients presenting with acute UGI bleeding have a high risk of mortality (4.5%-8.2%).⁵ Patients that develop UGI bleeding while in the hospital have an increased risk of mortality due to the presence of comorbid conditions.^{6,7,8} Approximately 80% of mortality in cases of GI hemorrhage is attributed to the exacerbation of other illnesses.⁹

Acute UGI bleeding is defined as blood loss that occurs proximal to the ligament of Treitz. UGI bleeding can present with coffee ground emesis, hematemesis, melena, or even hematochezia if bleeding is rapid.¹⁰ Factors predictive of a UGI bleeding source include a history of melena, the ratio of blood urea nitrogen (BUN) to serum creatinine concentration of >30 and coffee ground material on nasogastric (NG) tube lavage.⁵ UGI bleeding is classified as derived from a variceal or a nonvariceal source and about 80%-90% of episodes are nonvariceal. The most common causes of nonvariceal bleeding are PUD, esophagitis, and Mallory-Weiss tears. Common causes of PUD include nonsteroidal antiinflammatory drug (NSAID) use and *Helicobacter pylori* infection.¹¹ Variceal hemorrhage is seen in patients with cirrhosis. The presence of varices increases with worsening liver failure and varices are present in as many as 85% of patients with the advanced ("Child C") disease. The most important predictor of variceal hemorrhage is the size of the varix.¹²

Patient Approach

Key steps in the management of any patient with GI hemorrhage include the following: 1) resuscitation; 2) correction of coagulopathy, thrombocytopenia, and platelet dysfunction, if present; 3) diagnosis; 4) medical, endoscopic, or invasive radiologic or surgical intervention, if indicated (Fig. 24-1).

Resuscitation

The priority in the critically ill patient presenting with GI bleeding is establishing intravenous (IV) access and resuscitating the patient to

achieve hemodynamic stability. Large bore IV access catheters capable of supporting the rapid infusion of asanguinous fluids and blood products should be inserted. Infusion of a crystalloid solution should be started initially and followed by an infusion of packed red blood cells (PRBC) or other blood products, as indicated. Endotracheal intubation for airway protection should be considered early to reduce the risk of aspiration. The patient should be typed and crossed for blood transfusion. Laboratory studies should be obtained consisting of complete blood count (CBC), electrolytes, and coagulation profile. In acutely hemorrhaging patients, the initial blood hemoglobin concentration may not accurately reflect the extent of blood loss. Accordingly, blood hemoglobin concentration should be monitored frequently.

Transfusion should focus on maintaining a hemoglobin concentration greater than 7 g/dL. Studies have shown improved outcomes in patients with a threshold for transfusion of 7 g/dL rather than a transfusion trigger of 9 g/dL.¹³ In patients with brisk bleeding, a massive transfusion protocol should be performed by giving equal amounts of PRBC, fresh frozen plasma (FFP), and platelets to prevent development or worsening of coagulopathy due to dilution of clotting factors. The classification of anemia is also important as patients with acute GI bleeding have normocytic red blood cells whereas patients with chronic blood loss typically have microcytic red blood cells.

Correction of Coagulopathy

If the international normalized ratio (INR) is prolonged (due to treatment with warfarin or the presence of liver dysfunction), then FFP should be infused to restore normal coagulation. Endoscopy should not be delayed while waiting for normalization of the INR.^{14,15} For patients with GI hemorrhage who are being treated with a direct Factor Xa inhibitor (e.g., rivaroxaban), there are no FDA-approved antidotes. However, treatment with prothrombin complex concentrate (PCC) or activated Factor VIIa may be helpful.¹⁶ For patients with renal failure associated with possible uremic platelet dysfunction, desmopressin (DDAVP) should be administered to enhance platelet adhesion.^{17,18} For patients who are being treated with drugs, such as clopidogrel or aspirin (ASA), that inhibit the activation of platelets, platelet transfusion may be warranted. Platelet transfusion is also indicated for the treatment of thrombocytopenia (platelet count < 50,000/ μ L) in the setting of a GI hemorrhage. Treatment with tranexamic acid, a fibrinolysis inhibitor, should be considered in patients with a massive hemorrhage.¹⁹

Diagnosis and Treatment

These two steps need to be considered together because certain interventions, notably endoscopy and interventional radiology procedures, can serve both diagnostic and therapeutic goals.

Following the initial resuscitation, the diagnosis of the location of the hemorrhage becomes the priority. Initial assessment of the patient suspected of having UGI bleeding commences with a brief history and physical examination to establish potential sources of the bleeding and severity. Patients with a history of a previous GI hemorrhage episode are usually bleeding from the same location. The patient's medication history should be obtained, focusing on the use of NSAIDs or ASA, as well as anticoagulant drugs, such as warfarin or Factor Xa inhibitors. A nasogastric tube (NGT) should be placed early and lavage performed to help identify the source and possibly the severity of the hemorrhage.¹⁰ Even with blood in the rectum, NGT placement should be considered, as a UGI lesion could be the source of bleeding. If the NGT returns bilious material without any blood, then a distal source is more likely.²⁰

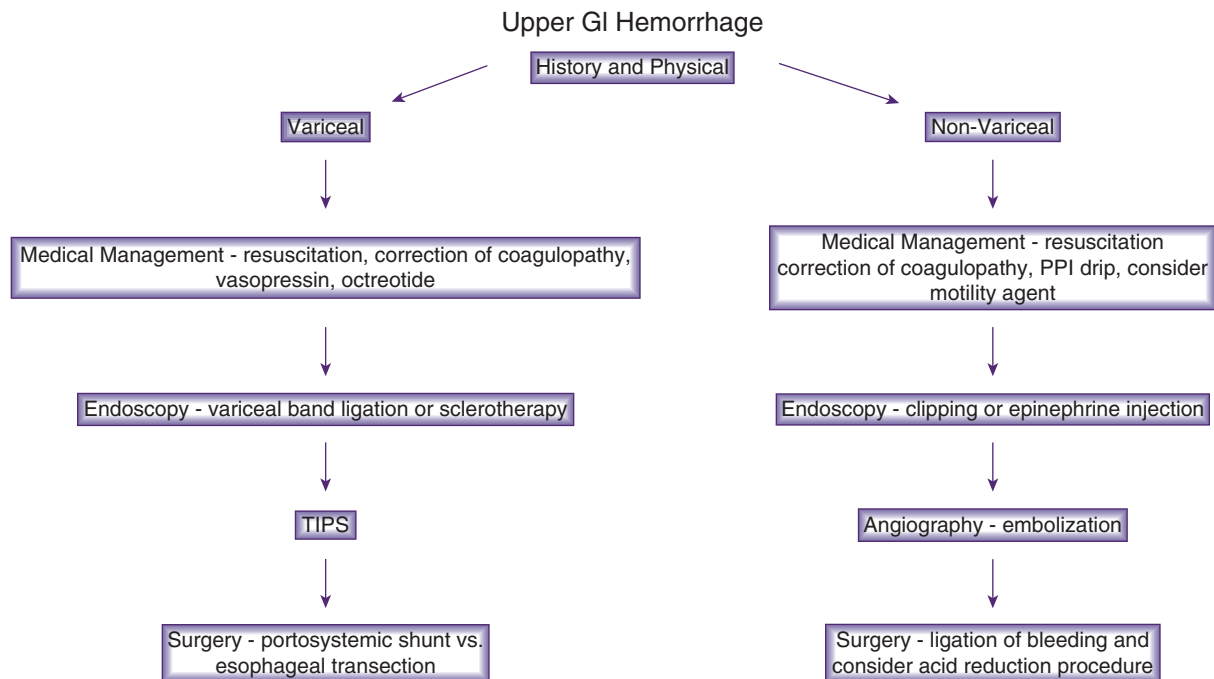


FIGURE 24-1 ■ Algorithm for Management of Upper GI Hemorrhage.

Fiber optic esophagogastroduodenoscopy is the next step in the diagnosis and treatment of patients with significant UGI bleeding. Endoscopy should ideally be performed when the patient is clinically stabilized and able to tolerate the procedure. Early endoscopy within 24 hours of admission can lower transfusion requirements, length of stay, and risk of mortality.²

If the patient experiences continued hemodynamic instability after the intervention, there is a risk that the patient may be experiencing rebleeding or a complication of endoscopy. Complications, such as perforation of the bowel, are surgical emergencies. Rebleeding occurs in about 20% of patients and increases the risk of mortality.^{21,22} With rebleeding, repeated endoscopy is typically warranted.

High-dose proton pump inhibitor (PPI) therapy to decrease gastric output should be initiated early when UGI bleeding is suspected. Treatment with a PPI can reduce the rate of rebleeding, decrease the length of hospital stay, and decrease the need for blood transfusion.²³ PPI therapy should be started before making a firm diagnosis, since the therapy can be stopped after endoscopy if it is no longer warranted. Pantoprazole should be administered as a bolus (80 mg IV) followed by a continuous infusion of 8 mg/h for 72 hours after significant bleeding has stopped, to lower the risk of rebleeding and mortality.^{24,25,26,27}

Prokinetic drug therapy prior to endoscopy has also been studied. The use of erythromycin or metoclopramide to stimulate gastric contractions and push the clot out of the stomach has been shown to clear the stomach of the clot burden and reduce the need for a repeat endoscopy to diagnose the source of the bleeding.^{28,29,30}

PUD

Patients presenting with bleeding secondary to PUD have a 90% rate of spontaneous resolution without intervention.^{24,21} Endoscopy should be performed and endoscopic treatment attempted to achieve hemostasis. A PPI should be infused and prokinetic therapy considered prior to endoscopy. Location of the bleeding is important and significant bleeding can occur from posterior ulceration of the proximal duodenum due to erosion into the gastroduodenal artery.

The Forrest classification system is used to identify ulcers with an increased likelihood of rebleeding. An actively bleeding vessel has a 90%-100% risk of rebleeding. A nonbleeding vessel has a 40%-50% risk of rebleeding. The presence of a visible clot carries a 20%-30% risk of rebleeding.

Endoscopic therapy should be attempted to stop the bleeding with coagulation, injection, and clipping as options. Endoscopy is successful at stopping acute bleeding in 90% of cases.³¹ Testing should be carried out to diagnose infection with *H. pylori* and if present, treated appropriately as likelihood of recurrent ulceration and bleeding is increased with persistence of *H. pylori* infection.³²

With continued bleeding or rebleeding, repeated endoscopic intervention should be attempted.²⁴ Repeat endoscopy was able to control bleeding in 73% of cases and was associated with less morbidity than surgical intervention even though mortality was similar. When endoscopy fails to control bleeding, angiography with embolization can be attempted prior to proceeding with surgical intervention. Embolization has a 90% success rate and is less invasive than surgical intervention. Superselective embolization is preferred as it carries a lower complication rate than embolization of larger vessels.³³ Superselective embolization may be associated with a higher risk of rebleeding. Early rebleeding rates are higher when angiography identifies significant active bleeding or is performed in patients with coagulopathy.³⁴ If a source of bleeding is identified during endoscopy and no extravasation is seen via angiography then relatively blind embolization can be performed with success.^{35,36} Common complications of embolization include bleeding from the site of arterial puncture and ischemia of the segment of bowel being embolized.

Surgical intervention is usually reserved for cases in which other interventions have failed to control the bleeding due to PUD. Patients requiring surgery are typically critically ill and other methods have failed and are therefore associated with a higher rate of mortality. Occasionally, a patient may present with separate bleeding and a perforated ulcer simultaneously. These are referred to as “kissing ulcers” and represent a unique surgical challenge. These patients are usually both hypovolemic from blood loss, septic from the perforated viscus, and are severely hemodynamically compromised.

Variceal Hemorrhage

Variceal disease secondary to cirrhosis and portal hypertension is another common cause of UGI bleeding. In patients with cirrhosis, varices form at a rate of 5%-15% per year and about 50% of people with cirrhosis have varices. One-third of patients with varices will develop a variceal hemorrhage.³⁷ The likelihood of developing a hemorrhage increases with the size of the varices and worsening portal hypertension.^{38,39} Particular attention needs to be paid to the correction of coagulopathy in patients with liver dysfunction. Mortality secondary to variceal hemorrhage is approximately 20%^{40,41} and rebleeding within the first six weeks occurs in 30%-40% of cases and is associated with an increased mortality rate.⁴²

Most bleeding varices are located in the lower third of the esophagus. Bleeding from gastric varices is often more severe than bleeding from esophageal varices and is more difficult to treat endoscopically.

When variceal bleeding is suspected, medical therapy should be initiated immediately and not delayed pending confirmation of a variceal source. The goal of pharmacologic therapy is to reduce portal venous blood flow and thus pressure. Useful medications include vasopressin, terlipressin, octreotide, and somatostatin. These agents are successful at controlling variceal hemorrhage in up to 80% of cases.⁴³ Administration of one or more of these agents prior to endoscopy can aid in visualization during the endoscopic intervention.^{41,44} Vasopressin promotes splanchnic arteriolar constriction, leading to decreased portal venous pressure. Terlipressin is a synthetic analog of vasopressin that has a longer duration of action but similar physiologic effects. Somatostatin and its longer acting analog, octreotide, inhibit the release of vasodilator hormones, such as glucagon and indirectly cause splanchnic vasoconstriction.⁴⁵ Somatostatin is administered as a 250 µg IV bolus followed by an infusion of 250 µg/h for up to 5 days to prevent rebleeding.⁴⁶ Octreotide has a longer half-life than somatostatin and is administered as a 100 µg IV bolus followed by infusion at 50-100 µg/h. Octreotide and somatostatin alone have not been proven to reduce mortality.^{47,48} Terlipressin is the only single agent that has been shown to reduce mortality however, it is not available in the United States.^{49,50} Vasoactive medications, in general, have been shown to decrease mortality, decrease hospital stay, improve hemostasis, and decrease blood transfusion requirements.⁵¹ Prophylactic broad spectrum antibiotics should be started early in patients with variceal hemorrhage as they have a risk of developing spontaneous bacterial peritonitis.^{52,53}

When variceal hemorrhage is suspected, endoscopy can be diagnostic and the therapeutic procedure of choice. Even when bleeding is short lived, endoscopy should be pursued as the rate of significant rebleeding is high. Options for endoscopic treatment include band ligation or sclerotherapy. Band ligation involves placing a small elastic band around the varices. Sclerotherapy involves injecting a sclerosant into the vein to cause thrombosis. Band ligation and sclerotherapy are both effective at stopping bleeding about 90% of the time, but the risk of rebleeding may be higher with sclerotherapy.⁵⁴

Another option for the management of bleeding from esophageal varices is the placement of a Sengstaken-Blakemore (SB) tube. The patient should first be intubated for airway protection. The tube is introduced through the mouth and into the stomach. Radiographic confirmation should be used to confirm that the gastric balloon is in the stomach before inflation, as inflation in the esophagus can cause rupture of the esophagus. The gastric balloon is then inflated with saline and placed on gentle traction to compress the gastroesophageal junction against the diaphragm and thereby tamponade hemorrhage. If bleeding stops, then the tube is secured without inflation of the esophageal balloon. If bleeding continues, the esophageal balloon is inflated until the bleeding stops. The pressure in the esophageal balloon cannot be allowed to exceed 45 mm Hg as doing so can lead to esophageal perforation. Inflation and traction are maintained for 24 hours. The SB tube is useful as a temporizing measure to control bleeding until other therapeutic options can be employed.

Transjugular intrahepatic portosystemic shunting (TIPS) should be considered in patients with refractory variceal bleeding despite medical

management. TIPS is performed via jugular cannulation. A catheter is advanced into a hepatic vein and then a needle is introduced through the hepatic parenchyma into the portal vein. This tract is then dilated and stented open to create a portosystemic shunt. Following TIPS, 90%-100% of patients will achieve hemostasis.^{42,55} Absolute contraindications to TIPS placement are heart failure, severe pulmonary hypertension, systemic infection, and severe tricuspid regurgitation. A relative contraindication is portal vein thrombosis. The patient should be monitored for the development of hepatic encephalopathy after the TIPS procedure.

Surgical interventions for the management of variceal hemorrhages, such as the creation of a side-to-side portocaval anastomosis or the Sigura procedure are rarely indicated or used. Mortality from these procedures approaches 50%.

Other Causes of UGI Bleeding

Stress ulceration can occur in critically ill patients, although this problem is relatively rare because of the routine use of drugs to inhibit gastric acid production in high-risk patients. When it occurs, GI hemorrhage secondary to stress ulceration is associated with a high mortality rate, since patients with this problem typically have significant comorbid conditions.

Mallory-Weiss tears are longitudinal disruptions of the mucosa of the distal esophagus or proximal stomach that result in submucosal bleeding.⁵⁶ These tears stop bleeding spontaneously in 90% of cases. The endoscopic intervention will control the bleeding in the remainder of cases.

Dieulafoy's lesion is a large anomalous submucosal artery that is most commonly located along the lesser curvature near the cardia of the stomach.^{57,58} Dieulafoy's lesion is responsible for about 2% of UGI bleeding episodes. Bleeding can be controlled endoscopically, with angiography and embolization, or surgically. Morbidity and mortality of bleeding due to Dieulafoy's lesion are high as patients with this problem typically have other comorbid conditions.⁵⁹

Other causes of significant UGI bleeding are hemobilia and aortoenteric fistula. Hemobilia should be part of the differential diagnosis when patients with UGI hemorrhage have a history of the recent hepatic instrumentation of any sort. Hemobilia is caused by hepatic arterial damage, leading to the formation of a fistula between the hepatic arterial tree and the biliary ductal system. Hemobilia usually presents with hematemesis. Endoscopy demonstrates blood coming from the bile duct. Hemobilia is most effectively treated with angiographic embolization of branches of the hepatic artery.

Aortoenteric fistula should be considered in patients with a history of abdominal aortic aneurysm repair. This problem commonly presents with a herald bleed and computed tomographic (CT) scanning of the abdomen usually shows signs of inflammation between the duodenum and the aorta. Aortoenteric fistula is a surgical emergency and patients suspected of having this diagnosis should be evaluated by a surgeon immediately.

LGI HEMORRHAGE

LGI bleeding is about half as common as UGI bleeding. The incidence of LGI bleeding is about 36/100,000 population. The mortality rate of acute LGI bleeding is 2%-4%.⁶⁰ Clinical factors predictive of severe colonic bleeding include anticoagulant use, comorbidities, tachycardia, hypotension, prior history of bleeding, and hospitalization for a different reason.⁶¹ Common causes of colonic bleeding include diverticulosis, cancer, and angiodysplasia. LGI bleeding presents with hematochezia. Melena can be a presenting sign if the rate of bleeding is relatively slow and the source is in the ascending colon. Even when hematochezia is the presenting sign, a UGI source of bleeding should still be ruled out with NGT lavage as UGI bleeding can present with hematochezia 10%-15% of the time.⁶⁰ Risk factors for complications include hemodynamic instability, advanced age, comorbidities, anticoagulation use, current hospitalization, and persistent signs of

Lower GI Hemorrhage

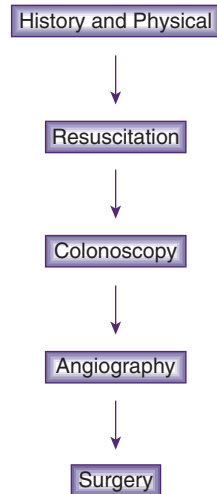


FIGURE 24-2 ■ Algorithm for Management of Lower GI Hemorrhage.

bleeding.^{62,63,64,65} In 80%-85% of patients, the bleeding will stop before the colonoscopy is performed.

Approach to the Patient

In general, the initial management of patients with significant LGI bleeding is similar to that already described above regarding the UGI hemorrhage (Fig. 24-2). Intravenous access and resuscitation should be initiated and coagulopathy (if present) corrected while diagnostic studies are being conducted to identify the source of the bleeding.

Localization

Colonoscopy should be the initial diagnostic study for locating the source of bleeding. However, performing a colonoscopy can be difficult in acutely bleeding patients. Bowel preparation is desirable but may not be possible if the patient is too unstable. Without bowel preparation, it is difficult to maneuver the scope all the way to the cecum and to locate the source of bleeding. In a randomized trial, urgent colonoscopy improved the localization of the source of bleeding compared with expectant management but did not reduce hospital stay, transfusion requirements, need for surgery, or mortality.⁶⁶

Localization also can be attempted with a radiolabeled red blood cell (RBC) scan. However, this approach is purely diagnostic and has no therapeutic potential. The overall rate of a positive scan is approximately 50%. However, 25% of tagged RBC scans suggest a location of bleeding that turns out to be incorrect. Angiography can localize the source of LGI bleeding. When a source is identified, the relevant vessel can be embolized at the time of the procedure. For patients with multiple repeat episodes of LGI bleeding with the inability to find the source of the bleeding, an infusion of heparin or tissue plasminogen activator (TPA) before and during angiography can be used to promote bleeding so it can be seen angiographically. If patients stabilize without the identification of a source of bleeding, they should be monitored for 24 to 48 hours before discharge. In unstable patients, if no LGI source of bleeding is found, UGI endoscopy should be performed as a UGI source is identified in up to 15% of patients.

Treatment

Colonoscopic interventions can control LGI bleeding in many cases. Embolization is another effective way of controlling hemorrhage. Embolization is feasible in 80% of patients with active bleeding

identified with angiography. When embolization is attempted, bleeding is successfully controlled in 97% of cases.⁶⁷ However, complications from embolization can be serious. There is a 20% risk of intestinal infarction, as well as risks of other complications, such as arterial thrombus formation or renal failure from the use of IV contrast.^{68,69}

In unstable patients with LGI bleeding and no acutely identifiable source, a subtotal colectomy may be necessary. This procedure is associated with significant morbidity and increased risk of complications. There is also the possibility that an occult lesion in the small intestine is responsible for the bleeding.

Diverticulosis is a common problem with more than 65% of people over the age of 80 having colonic diverticula. Diverticulae are predominantly located in the descending colon but bleeding is more common from diverticula in the ascending colon. Diverticular bleeding stops spontaneously in 75% of all cases and 99% of patients transfused with <4 units of PRBC, although there is a 38% risk of rebleeding.⁷⁰ Bleeding diverticula can usually be controlled with colonoscopic thermocoagulation, epinephrine injection, or hemoclip application.⁷¹

Postpolypectomy bleeding should be considered in patients with serious LGI bleeding after a polypectomy. This bleeding is usually from an arterial source. It can generally be treated with repeat colonoscopy and thermocoagulation, epinephrine injection, or hemoclipping.⁷²

Inflammatory bowel disease accounts for 1%-5% of all LGI bleeds.^{73,74,75,76} Severe bleeding is the reason for 10% of colectomies performed for ulcerative colitis.⁷⁷

Rectal bleeding is responsible for approximately 2% of LGI bleeding. It can be significant in patients with portal hypertension and bleeding hemorrhoids. Bleeding can be controlled with hemorrhoidal banding. Medical therapy to reduce portal venous pressure is important for long-term control in these patients.

Small Intestinal Bleeding

Between 1%-7% of patients with blood per rectum have a source located in the small intestine.^{78,79,80} The outcome for patients with a small bowel source of bleeding tends to be worse than for patients with GI hemorrhage from other sources. This is because bleeding from the small intestine continues without localization for a longer period. If there is continued significant bleeding without a visualized source on the upper or lower endoscopy, a small bowel source should be considered. Common reasons for small bowel bleeding are angiodysplasia, tumors, Crohns disease, or Dieulafoy's lesions.⁸¹ Angiodysplasia is common in the elderly with renal failure.⁸² Small bowel bleeding is intermittent in nature and is, therefore, difficult to identify with tagged RBC scan or angiography. Confirmatory diagnosis is often accomplished by capsule endoscopy, push enteroscopy, or double-balloon enteroscopy. Provocative angiography with heparin or TPA may be necessary to identify a source. Once the source of bleeding is identified, angiography with embolization or surgical resection is the treatment of choice.

KEY POINTS

1. Resuscitation, correction of coagulopathy, diagnosis, and treatment are the order of priorities when taking care of an acute GI bleed.
2. UGI bleeding is most commonly PUD or variceal in nature and patient history is key in making the diagnosis.
3. Medical management (PPI, octreotide) should be initiated when bleeding is suspected and not delayed until a diagnosis is made.
4. LGI bleeding is most commonly from diverticula and colonoscopy is the initial diagnostic and therapeutic procedure of choice.

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■ DEFINITION AND DIAGNOSIS

While a normal peritoneal cavity contains only 25 mL of fluid, the peritoneum has the capacity to absorb 900 mL/day.¹ Ascites is the pathologic accumulation of peritoneal fluid, occurring most commonly in decompensated liver cirrhosis (85%), with malignancy, tuberculosis, heart failure, and pancreatitis accounting for the remainder.^{2,3} The International Club of Ascites classifies ascites severity, with fluid detectable only on imaging (<100 mL) as grade 1, moderate symmetric abdominal distention with up to 1 L of fluid as grade 2, and tense distention associated with a large volume of fluid as grade 3.⁴ Cirrhotic ascites can be uncomplicated or complicated, the latter involving concomitant development of spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, or hepatic hydrothorax. Refractory ascites (5%-10% of cases) is persistent or rapidly recurring ascites despite maximal medical therapy.⁴

Symptoms of ascites include weight gain, abdominal pain, fullness, early satiety, and shortness of breath. History and physical exam looking for signs of liver disease or other underlying cause form the foundation of diagnostic evaluation. Detecting ascites on exam can prove difficult if <1500 mL is present. If flank dullness on percussion is not appreciated, there is a 90% chance no ascites is present.⁵ While CT will identify ascites, ultrasound is the preferred imaging modality. It is a highly sensitive, low-cost, non-radiation-producing method that simultaneously allows evaluation of the liver and hepatic vasculature.

Patients with new-onset ascites should undergo diagnostic paracentesis, with removal of 20 to 30 mL for evaluation of fluid color, turbidity, and total protein and for calculation of the serum-ascites albumin gradient (SAAG).^{6,7} An SAAG > 1.1 g/dL is 97% accurate in identifying ascites due to portal hypertension (Table 25-1).⁸ Infected ascites is a life-threatening complication, requiring timely assessment of the ascitic cell count and differential. A recent study of hospitalized patients with cirrhosis and SBP demonstrated a 3% increase in mortality for every hour that diagnostic paracentesis was delayed.⁹ Fluid can be sent for triglyceride levels if chylous ascites is suspected, amylase for pancreatitis, cytology for malignancy, or mycobacterium culture for tuberculosis.

■ PATHOPHYSIOLOGY

Portal hypertension from either increased hepatic resistance or increased portal blood flow is the key pathophysiologic event in the formation of ascites and is described in detail in Chapter 92. Normal portal venous pressure is <5 mm Hg. Once it is over 10 mm Hg, fluid from hepatic sinusoids and splanchnic capillaries overwhelms the peritoneal lymph drainage.^{3,10,11} However, increased pressure is only one aspect of the pathophysiology, as fluid dysregulation and development of ascites results from a complex interplay of hemodynamic and hormonal responses.^{7,12} In liver cirrhosis, hepatic sinusoidal congestion with progressive fibrotic transformation leads to endothelial cell dysfunction, causing nitric oxide-mediated vasodilation of splanchnic and peripheral arterial vascular beds. Initially, a hyperdynamic circulatory response compensates for the vasodilation to maintain adequate perfusion pressure. As vasodilation worsens and effective circulating volume decreases, however, compensatory activation of the sympathetic nervous and renin-angiotensin-aldosterone systems results in renal sodium and water retention, leading to fluid overload and hyponatremia (Fig. 25-1).¹²⁻¹⁸ This process is hastened when infection from bacterial translocation causes endotoxin release, compounding

vasodilation. Ultimately, tissue perfusion is compromised, leading to life-threatening organ dysfunction, the most salient being hepatorenal syndrome with a decreasing glomerular filtration rate and severe renal vasoconstriction, as detailed in Chapter 93. In contrast to the mechanisms in cirrhosis, ascites in infection and malignancy is due to inflammation and leakage of high-protein lymph.³

■ MANAGEMENT

Initial treatment of cirrhotic ascites is salt restriction (no more than 2000 mg/day) and oral diuretics to promote natriuresis. Although the aldosterone antagonist spironolactone can be used alone, addition of the loop diuretic furosemide, particularly in patients with a moderate to large volume of ascites, has proven efficacy and is recommended.^{19,20} Starting daily doses of 100 mg of spironolactone and 40 mg of furosemide achieve natriuresis without significant hypokalemia. Doses can be increased while maintaining the same ratio over 3 to 5 days to maximum daily doses of 400 mg of spironolactone and 160 mg of furosemide.^{6,21} Initial goals of diuretic therapy are weight loss of 0.5 kg/day (or up to 1 kg/day in edematous patients) and a measured 24-hour sodium excretion of 78 mmol/day.^{11,22} Side effects include intravascular volume depletion, renal insufficiency, and electrolyte abnormalities. If creatinine increases by more than 50% or more than 1.5 g/dL or if sodium falls by more than 10 mEq/L, therapy should be adjusted.²² Nonsteroidal antiinflammatory drugs (NSAIDs) should be avoided, not only because of the risk of renal injury but also because they impede diuretic-mediated sodium excretion.²³ Along with standard diuretic therapy, midodrine at a dose of 7.5 mg orally three times a day can increase urine volume, urinary sodium excretion, and mean arterial pressure, resulting in significantly decreased mortality.²⁴

Paracentesis

Diuretics are started for initial control, but therapeutic paracentesis may also be indicated in settings of tense ascites to relieve abdominal pressure. The procedure is relatively safe when done under ultrasound guidance. Complications (<1%) include leakage of ascitic fluid, bleeding, infection, and bowel perforation.²⁵ Routine correction of thrombocytopenia or prolongation in the prothrombin time is not recommended, as paracentesis has been performed safely in patients with platelets < 50,000/uL and INR > 2. In a retrospective study of 4729 procedures, the incidence of significant bleeding was relatively low (0.19%) despite coagulopathy in many patients.²⁶ The only real contraindication to paracentesis is disseminated intravascular coagulopathy.

Following removal of a large volume, paracentesis-induced circulatory dysfunction can result from effective hypovolemia with activation of the renin-angiotensin system, resulting in hyponatremia and renal impairment. When fluid removal exceeds 5 L, intravenous replacement of albumin is recommended (8 g/L of ascites removed), which is supported by data demonstrating improved survival.²⁷ While large-volume paracentesis is time consuming and costly, benefits include improved patient comfort, shortened hospitalization, preserved hemodynamics, and a decreased risk of SBP and hepatic encephalopathy.²⁸

■ PROGNOSIS AND COMPLICATIONS

Ascites signifies progression from compensated to decompensated liver failure and carries a 20% 1-year mortality.²⁹ Within the first

TABLE 25-1

Causes of Ascites in the Normal or Diseased Peritoneum by Serum-to-Ascites Albumin Gradient (SAAG)

NORMAL PERITONEUM

PORTAL HYPERTENSION (SAAG > 1.1 g/dL)

Hepatic congestion
Congestive heart failure
Constrictive pericarditis
Tricuspid insufficiency
Budd-Chiari syndrome

HYPOALBUMINEMIA (SAAG < 1.1 g/dL)

Nephrotic syndrome
Protein-losing enteropathy
Severe malnutrition with anasarca

LIVER DISEASE

Cirrhosis
Alcoholic hepatitis
Fulminant hepatic failure
Massive hepatic metastases

MISCELLANEOUS CONDITIONS (SAAG < 1.1 g/dL)

Chylous ascites
Pancreatic ascites
Bile ascites
Nephrogenic ascites
Urine ascites
Ovarian disease

DISEASED PERITONEUM (SAAG < 1.1 g/dL)

INFECTIONS

Bacterial peritonitis
Tuberculous peritonitis
Fungal peritonitis
HIV-associated peritonitis

OTHER RARE CONDITIONS

Familial Mediterranean fever
Vasculitis
Granulomatous peritonitis
Eosinophilic peritonitis

MALIGNANT CONDITIONS

Peritoneal carcinomatosis
Primary mesothelioma
Pseudomyxoma peritonei
Hepatocellular carcinoma

decade of diagnosis, 50% of patients with cirrhosis will develop ascites.³⁰ Once complications such as refractory ascites or hepatorenal syndrome develop, yearly mortality increases to 75%.^{31,32} Ascites features in a validated scoring system for liver failure, serving as one of five components of the Child-Turcotte-Pugh (CTP) score that also factors in encephalopathy, albumin, INR, and total bilirubin to predict mortality.³³ Given the poor prognosis, once ascites develops, patients should begin evaluation for liver transplantation.

Spontaneous Bacterial Peritonitis

SBP occurs in 30% of patients with ascites, carries a 20% mortality rate, and is defined by³⁴:

1. Positive bacterial culture (single organism)
2. Ascitic fluid polymorphonuclear cell count $\geq 250/\text{mm}^3$
3. Absence of surgically treatable source of infection

SBP arises from translocation of intestinal bacteria, predominantly *Escherichia coli* and *Klebsiella*.³⁵ Common symptoms include fever, abdominal pain, nausea and vomiting, increasing encephalopathy, and decreased renal function. Prompt diagnostic paracentesis is indicated, with ascitic fluid sent for cell count, total protein, glucose, amylase, lactate dehydrogenase, Gram stain, and anaerobic and aerobic cultures. Cultures of ascitic fluid should be inoculated in blood culture bottles at the bedside to maximize chances of identifying a causative organism.^{7,21} Patients with a low ascitic protein content ($<1.5 \text{ g/L}$) are particularly at risk of developing SBP.³⁶ Treatment should start as soon as infection is suspected with a third-generation cephalosporin, such as ceftriaxone or cefotaxime, for a 5- to 7-day course.^{6,21}

SBP should be differentiated from secondary bacterial peritonitis due to abscess or perforated viscus, as treatment is substantially different. Secondary bacterial peritonitis should be suspected if ascitic fluid analysis has a glucose $<50 \text{ mg/dL}$, elevated lactate dehydrogenase, or polymicrobial culture results.³⁷ Further workup includes upright plain films, CT with water-soluble contrast, and surgery consultation.

TABLE 25-2

Management of Refractory Ascites

Definitions

Ascites that is not eliminated even with maximum diuretic therapy
Ascites that is not eliminated because maximum dosages of diuretics cannot be attained, given the development of diuretic-induced complications

Recommended therapy

Total paracentesis + IV albumin (6-8 g/L of ascites removed)
If $<5 \text{ L}$ of ascites is removed, a synthetic plasma volume expander may be used instead of albumin.
Continue with salt restriction and diuretic therapy as tolerated.

Alternative therapy

TIPS for patients who require frequent paracenteses (every 1-2 weeks) and whose CTP score is ≤ 11
Peritoneovenous shunt for patients who are not candidates for TIPS or transplant

CTP, Child-Turcotte-Pugh; IV, intravenous; TIPS, transjugular intrahepatic portosystemic shunt. Data from Garcia-Tsao G, Lim JK; Members of the Veterans Affairs Hepatitis C Resource Center Program. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program. *Am J Gastroenterol*. 2009;104:1802-1829.

After an initial SBP event, the chance of a repeat infection is 70%.³⁸ A meta-analysis of eight studies of 647 patients investigating antibiotic prophylaxis to prevent recurrent SBP demonstrated an overall mortality of 16% in the antibiotic group versus 25% for the control. Statistically significant improvements were seen in rates of re-infection as well as a 3-month survival benefit.³⁹ Oral prophylaxis with norfloxacin or trimethoprim/sulfamethoxazole is recommended for patients following one SBP episode and, for those with active gastrointestinal bleeding, a low-protein ascitic fluid ($<1.5 \text{ g/dL}$), impaired renal function ($\text{Cr} \geq 1.2$), or liver failure (CTP score ≥ 9 and bilirubin ≥ 3).⁶

Refractory Ascites

Refractory ascites is diagnosed when maximal medical management for at least 1 week or repeated large volume paracenteses within 4 weeks are insufficient to remove ascites.¹⁵ Diuretic failure results from resistance to or complications from therapy, including renal impairment or electrolyte perturbations (hypo- or hyperkalemia, hyponatremia). Refractory ascites carries a mortality of 21% at 6 months and 70% at 2 years, so expedited evaluation for liver transplantation is indicated.⁴⁰ Treatment consists of serial therapeutic paracentesis, transjugular intrahepatic portosystemic shunt (TIPS), or liver transplantation (Table 25-2).

TIPS involves percutaneous placement of an expanding metal stent within an artificially created channel that diverts portal blood flow into the hepatic veins, thus decreasing portal hypertension and ascites. Consideration for TIPS occurs once patients require more than two large volume paracentesis in a month. Complications include stent occlusion, worsened liver failure, heart failure, infection, renal failure, and increased hepatic encephalopathy. In the most recent meta-analysis of TIPS versus repeated paracentesis aggregating six randomized controlled trials with a total of 390 patients, TIPS was shown to significantly improve liver transplant free survival ($\text{HR} = 0.61$, 96% CI 0.46-0.82, $P < 0.001$).^{40a} This is different from a previous Cochrane review of five randomized control trials dating from 1996 to 2004 comparing 162 patients who showed no difference in 30-day or 2-year mortality. However, patients who underwent TIPS showed a significant increase in hepatic encephalopathy (OR 2.24, 95% CI 1.39, $P < 0.01$).⁴¹ Selection of patients for TIPS is key. It is not recommended if bilirubin is $>5 \text{ mg/dL}$, age > 70 years old, model for end-stage liver disease score > 18 , or CTP score > 11 .^{42,43}

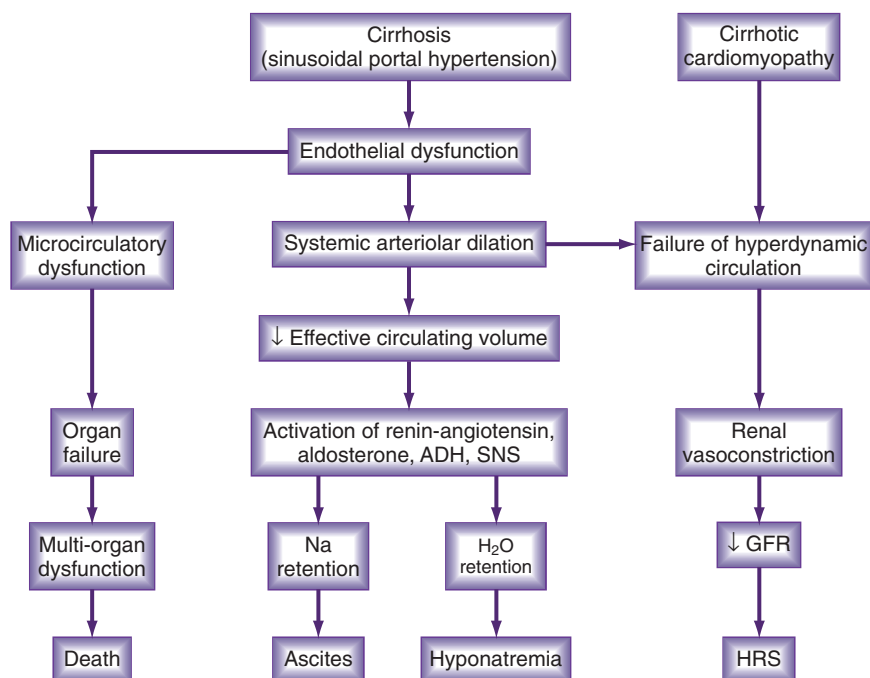


FIGURE 25-1 ■ Pathophysiology of cirrhosis and ascites. Cirrhosis is associated with splanchnic arterial vasodilation, leading to a decrease in effective circulating volume and a hyperdynamic circulation. The decrease in effective circulating volume causes the activation of renal sodium and water retentive pathways (e.g., RAAS, renal SNS, and ADH). Resulting sodium and water retention leads to ascites due to the spillage of excess sodium and water from hepatic lymph into the peritoneal cavity. As the disease progresses, a progressive decrease in effective circulating volume develops, causing severe renal vasoconstriction and a decrease in glomerular filtration rate. The onset of cirrhotic cardiomyopathy accentuates this problem and tips the patient over into hepatorenal syndrome. The accompanying circulatory disturbance leads to organ failure and death. Sepsis is frequently associated with this process. ADH, antidiuretic hormone; RAAS, renin-angiotensin system; SNS, sympathetic nervous system. (From Salerno F, Camma C, Enea M, Rossle M, Wong F. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. *Gastroenterology*. 2007;133:825-834.)

KEY POINTS

1. Ascites is most commonly due to liver disease and has a 20% yearly mortality.
2. Diagnostic paracentesis should be performed in all patients with new ascites to differentiate between ascites secondary to portal hypertension (SAAG > 1.1 g/dL) from other conditions.
3. Medical management includes sodium restriction and oral diuretics, usually starting with spironolactone 100 mg and furosemide 40 mg daily.
4. SBP is a life-threatening complication, and treatment should begin promptly with a third-generation cephalosporin as soon as infection is suspected.
5. Treatment options for refractory ascites include serial paracentesis or TIPS, but expedited evaluation for liver transplantation should also begin for appropriate candidates.

ANNOTATED REFERENCES

Garcia-Tsao G, Lim JK, Members of Veterans Affairs Hepatitis C Resource Center Program. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program. *Am J Gastroenterol*. 2009;104:1802-1829.

This comprehensive review provides evidence-based recommendations for management of the patient with either compensated or decompensated cirrhosis, including management of ascites, refractory ascites, SBP, and other complications, including hepatorenal syndrome.

Bai M, Qi X-S, Yang Z-P, Yang M, Fan D-M, Han G-H. TIPS improves liver transplantations-free survival in cirrhotic patients with refractory ascites: an updated meta-analysis. *World Journal of Gastroenterology*. 2014;20(10):2704-2714.

This updated meta-analysis of six randomized controlled trials with 390 patients showed a significant improvement of transplant-free survival of cirrhotic patients with refractory ascites, decreased ascites recurrence, and improved hepatorenal syndrome despite a significantly higher number of hepatic encephalopathy episodes in the TIPS group.

Wong CL, Holroyd-Leduc J, Thorpe KE, Straus SE. Does this patient have bacterial peritonitis or portal hypertension? How do I perform a paracentesis and analyze the results? *JAMA*. 2008;299:1166-1178.

This publication includes a systematic review of nine randomized controlled trials (n = 806 procedures) that examined the use of plasma expanders for therapeutic paracentesis. No significant differences

were identified between therapeutic paracentesis with and without volume expansion with albumin, nor with nonalbumin plasma expanders compared with albumin in terms of hyponatremia, renal impairment, encephalopathy, or death. However, these studies did not specifically examine prevention of paracentesis-induced circulatory dysfunction (defined by an increase in plasma renin activity or aldosterone concentration), and some studies determined that albumin prevented this condition more effectively than synthetic plasma expanders.

Saab S, Hernandez JC, Chi AC, Tong MJ. Oral antibiotic prophylaxis reduces spontaneous bacterial peritonitis occurrence and improves short-term survival in cirrhosis: a meta-analysis. *Am J Gastroenterol*. 2009;104:993-1001.

This meta-analysis of eight prospective clinical trials with a total of 647 patients randomized to oral antibiotic prophylaxis for SBP compared with placebo or no intervention documented an overall mortality benefit (RR = 0.65; 95% CI 0.48-0.88) for antibiotic treatment groups. The overall mortality rate was 16% for treated patients and 25% for the control cohort. Groups treated with prophylactic antibiotics also demonstrated a lower incidence of all infections (including SBP) of 6.2% compared with the control group rate of 22.2% (RR = 0.32; 95% CI 0.20-0.51).

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Acute abdominal pain in the critically ill has a differential that is expansive and a diagnosis that can be difficult. The differential encompasses the same disease states as for noncritically ill patients but additionally includes causes specific to special cohorts including those who have been hospitalized for prolonged periods, the elderly, the immunosuppressed, the injured, and postsurgical patients. Because of this diversity, the diagnosis and management of acute abdominal pain require critical care practitioners to have a thorough understanding of the mechanisms and pathophysiology of different causes of acute abdominal pain and the ability to recognize more than classic patterns and presentations. Understanding abdominal pain begins with understanding the neurologic reception of pain in the abdomen, which is dependent on both mechanical and chemical stimuli. Pain elicited by mechanical stimuli is primarily driven by the stretch of visceral receptors located on serosal surfaces, in the mesentery, and between the muscularis mucosa and submucosa of hollow visceral organs. Additionally, pain elicited by chemical stimuli is primarily driven by mucosal reception of substances that include substance P, bradykinin, serotonin, histamine, and prostaglandin in response to inflammatory or ischemic signals.¹⁻³ The localization of pain is dependent on the type, distribution, and number of visceral nociceptors; therefore, the processing of these signals varies between individuals and pathologies.⁴ Because of these complexities, pain that is perceived in the abdomen may actually arise from other nonvisceral locations including myocardial ischemia, pneumonia, and herpes zoster, among others.

INITIAL APPROACH

Underlying disease or chemically induced depression in consciousness level in intensive care unit (ICU) patients inhibits their ability to communicate and the physician's ability to perform an adequate physical exam. At times, patients are so critically ill that they may not be able to travel for adjunct studies, further compromising traditional diagnostics.

Patient History

Despite limitations, trying to glean an adequate history, including the presence of symptoms associated with pain such as fever, chills, nausea, vomiting, diarrhea, constipation, obstipation, and bloating, can be critical. Events before and during the patient's hospitalization are important to the history, including arrhythmic events, hypotensive episodes, and medications administered (including vasopressors and antibiotics). The events before the patient's hospitalization hold the same importance given that the nidus for their abdominal pathology may have existed before their critical illness.

Physical Exam

The physical exam is centered on the standard abdominal exam but must additionally include examination of all tubes (nasal- and orogastric, rectal, urinary drainage catheters, and surgical drains) for both quantity and quality of output. Assessment of all surgical scars and their stage of healing is critical. Additionally, an assessment of the patient's vital signs and any hemodynamic-altering medications remains important.

Diagnostic Adjuncts

Laboratory adjuncts include complete blood counts with leukocyte differentials, comprehensive metabolic panels including liver function tests with conjugated bilirubin, coagulation studies, arterial or venous blood gases, and lactic acid measurements. If concern for infection exists, complete infectious workups, including chest plain radiography to evaluate for intrathoracic processes, urine analysis and culture, blood cultures from central and peripheral lines, stool cultures, and *Clostridium difficile* toxin assays, should be considered. Radiographic adjuncts include plain films, ultrasound to evaluate for biliary tract and renal disease, and computed tomography (CT) to evaluate for other intraabdominal sources of pain.

This chapter will focus on the broad differentials based on location of abdominal pain with spotlights on certain diagnoses that have noteworthy importance in critically ill patients.

DIFFERENTIAL DIAGNOSES BASED ON LOCATION

The differential diagnosis of abdominal pain in critically ill patients is expansive (Fig. 26-1). Upper abdominal pain can have cardiac and respiratory causes, whereas lower abdominal pain can have urologic and gynecologic causes.

Upper Abdominal Pain

Upper abdominal pain may have an origin in the upper digestive tract, including gastritis and peptic ulcer pathology. Alternatively, pain may come from the biliary tract, including calculous and acalculous cholecystitis, cholangitis, pancreatitis, splenic infarction, or abscess. Organ systems and disease processes outside the abdomen, including ischemic heart disease and pneumonia, should always be entertained as causes of upper abdominal pain in the appropriate patient.

Of particular importance in critically ill patients are biliary and gastric or peptic sources of abdominal pain. Right upper quadrant and epigastric pain coupled with fever, leukocytosis, and alterations in liver functions tests can distinguish biliary pathologies. Ultrasonography is the most sensitive imaging modality. In addition, the use of ultrasound in the ICU is practical and can distinguish among different types of biliary diseases.

Acalculous cholecystitis is associated with prolonged enteral fasting states. The mortality of acalculous cholecystitis is high; therefore, prompt diagnosis and treatment are critical.^{5,6} For all cholecystitis, drainage via cholecystostomy tube is a lifesaving intervention in someone critically ill and unfit for surgery.⁵

Gastric and peptic sources of abdominal pain can occur secondary to physiologic stress-related mucosal damage of the gastroduodenum. One primary driver of this condition is prolonged mechanical ventilation. The presenting symptoms of gastritis and peptic ulceration can range from painless gastrointestinal bleeding to epigastric pain to peritonitis due to perforation. If upper abdominal pain is thought to be secondary to gastroduodenal ulceration, upper endoscopy is diagnostic. Suitable treatment includes the administration of proton pump inhibitors and removal of offending agents, including nonsteroidal antiinflammatory medications. If the patient's acute abdominal pain is due to perforated gastroduodenal ulcer, surgical repair is required.

| Upper | Lower | Generalized |
|---|--|--|
| Gastritis Peptic ulcer disease Biliary tract disease Pancreatitis Hepatitis Pulmonary embolism Pneumonia Myocardial infarction | Gastroenteritis Ischemic or infectious colitis Acute mesenteric ischemia Appendicitis Diverticulitis Inflammatory bowel disease Sigmoid/cecal volvulus Ovarian cyst/torsion Testicular torsion Cystitis/pyelonephritis Ectopic pregnancy Prostatitis Salpingitis | Perforated viscus Ruptured aortic aneurysm Nephrolithiasis Intraabdominal abscess |

FIGURE 26-1 ■ Differential diagnosis of acute abdominal pain by location in critically ill patients.

New data highlighting an increased incidence of infectious complications including hospital-acquired pneumonia and *C. difficile* enteritis with the administration of stress ulcer prophylaxis has led to the questioning of the routine use of stress-ulcer prophylaxis.⁷ Modern meta-analyses suggest that critically ill patients who are enterally fed do not require stress-ulcer prophylaxis.

Similar to biliary sources of abdominal pain, the acute inflammation of pancreatitis can produce characteristic upper abdominal pain in the epigastrium with radiation to the back. In acute pancreatitis, approximately 15% of patients can develop sepsis and multiorgan failure with an overall mortality of 13%.^{8,9} Laboratory findings include elevated serum lipase and metabolic abnormalities including hemoconcentration, hypocalcemia, and hyperglycemia. CT findings may include focal or diffuse enlargement of the pancreas, with peripancreatic fluid and fat stranding and abnormal enhancement in areas of necrosis. When CT is performed 3 or more days after the onset of pain, it can reliably predict the severity of disease, the extent of necrosis, and the presence of local complications.¹⁰ Management of acute pancreatitis has changed over the years in regard to fluid resuscitation, prophylactic antibiotics, and surgical débridement.¹¹ Recent studies have shown that less aggressive resuscitative measures have led to improved outcomes.¹²⁻¹⁴ The incidence of abdominal compartment syndrome in patients with acute pancreatitis is as high as 85%;¹⁵ however, more restrictive resuscitative measures are found to be associated with a lower incidence.¹⁶

Two large randomized controlled trials confirmed that antibiotics should be given only with demonstrated infected pancreatic necrosis.^{17,18} The surgical treatment of pancreatic necrosis has also evolved, and less invasive approaches are associated with better outcomes.¹⁹ Algorithms now include first-line percutaneous drainage procedures followed by endoscopic and minimally invasive surgeries and avoidance of early surgery if possible.^{20,21} Finally, evidence supports early (within 24 hours) enteral nutrition in acute pancreatitis to prevent bacterial translocation. Nasogastric feeds may be comparable to nasojejunal feeds in efficacy and complications.²²⁻²⁴

Lower Abdominal Pain

Lower abdominal pain usually has an origin in the lower digestive tract and can be due to colitis (infectious, ischemic), acute colonic pseudo-obstruction, sigmoid or cecal volvulus, diverticulitis, or appendicitis. Additionally, one must entertain abdominal or pelvic sepsis due to intraabdominal abscess in certain populations of patients, including those who have had previous abdominal surgery or have a known perforation of a hollow viscus organ (including perforated diverticulitis and appendicitis). Neutropenic patients are at risk of developing neutropenic enterocolitis, which can manifest with lower abdominal pain, fevers, leukocytosis, diarrhea, and imaging consistent with colitis.

Organ systems outside the abdomen, including gynecologic and urologic (urinary tract infection, kidney stones, bladder distention, pelvic inflammatory disease, adnexal pathology, endometriosis, and pregnancy), should be taken into consideration.

Abdominal pain from infectious or ischemic colitis can be from local inflammation, necrosis, or perforation. Lower abdominal pain coupled with fever, leukocytosis, acidosis, elevated lactate and bloody or nonbloody diarrhea should prompt immediate evaluation. Ischemic colitis may be caused by vascular occlusion or may be nonocclusive. Acute arterial occlusion (embolic or thrombotic), venous thrombosis, and nonocclusive hypoperfusion can all lead to intestinal ischemia. Certain patient populations, particularly those who have undergone ligation of the inferior mesenteric artery in aortic repairs, are at increased risk, and the presence of postoperative diarrhea, abdominal pain, or acidosis should prompt immediate colonoscopic evaluation. Although there are multiple causes of ischemic colitis, all lead to mucosal injury.²⁵

Nongangrenous colitis is the most common colonic ischemia and is usually seen in “watershed” areas including the splenic flexure and rectosigmoid junction of the colon. This condition can be treated with resuscitation and has a low mortality rate. However, gangrenous colitis requires early recognition and surgical treatment and has a mortality rate between 50% and 75% for those surgically treated and 100% for those who are too ill to undergo surgical intervention.²⁶ CT scan findings are nonspecific; the gold standard for diagnosis is colonoscopic evaluation. Broad-spectrum antibiotics should be started in cases where ischemia is suspected.²⁷ If ischemia is secondary to mesenteric venous thrombosis or has an embolic source, anticoagulation is then indicated. Life-saving surgery is reserved for full thickness ischemia or perforation, which is needed in approximately 20% of cases.²⁸

Critically ill patients are at an increased risk of infectious causes of colitis as well. The gastrointestinal tract is colonized with pathogenic organisms, the most intrusive of which is *C. difficile*, a spore-forming anaerobic and gram-positive bacillus bacterium. This bacterium colonizes healthy individuals but can become an invasive organism leading to cytotoxic bowel inflammation, pseudomembrane formation, toxic megacolon, and perforation in patients exposed to antibiotic treatment; it has a high morbidity and mortality rate in hospitalized patients. Lower abdominal pain, fever, bloody or nonbloody diarrhea, and leukocytosis should prompt evaluation for *C. difficile* infection in any such patient who has had exposure to antibiotics. An unexplained leukocytosis in a critically ill patient without other symptoms may be *C. difficile* infection.²⁹ Diagnosis is made with identification of *C. difficile* toxins or toxigenic *C. difficile* in stool.³⁰ Additionally, *C. difficile* can be diagnosed by colonoscopic and histopathologic findings of pseudomembranes, which are virtually pathognomonic. Fulminant colitis can progress to toxic megacolon and perforation. Additionally,

manifestations of symptoms of ileus without diarrhea can be present because of a dilated and nonfunctional colon.^{31,32} Toxic megacolon is a clinical diagnosis based on colonic distention up to >7 cm at the greatest diameter with associated severe shock. Prompt surgical evaluation and intervention are essential.

Finally, acute colonic pseudo-obstruction (Ogilvie's syndrome) characteristically has significant dilation of the cecum and right colon without any anatomic obstruction and is associated with underlying disease in 95% of patients; it has a strong association with opiate administration.³³ Lower abdominal pain coupled with constipation, distention, nausea, vomiting, and paradoxical diarrhea are common. Most patients have metabolic derangements that may be reflected in electrolyte abnormalities.³³ Plain supine imaging reveals a distended colon (most often right-sided), and CT confirms the diagnosis by excluding evidence of mechanical obstruction or toxic megacolon due to colitis. Treatment includes relieving distention and discomfort and avoiding complications such as perforation. Treat the underlying cause, correct electrolyte abnormalities, provide gastric and rectal decompression, and avoid opiates, sedatives, and anticholinergics. The anticholinesterase inhibitor neostigmine may be effective for colonic decompression but requires cardiac monitoring and should be used with caution in patients with asthma or cardiac abnormalities and the elderly.³⁴ Colonoscopic decompression can be attempted when supportive measures fail.

Generalized Abdominal Pain

Generalized abdominal pain may represent severe and life-threatening diseases such as mesenteric ischemia, peritonitis, intestinal obstruc-

tion, ruptured abdominal aortic aneurysm, or an alternatively benign disease, including constipation. Peritonitis is nonspecific inflammation of the peritoneum that has multiple causes. Pain is usually in the region of the source but becomes generalized as the inflammation progresses. Other findings of peritoneal inflammation include fever, tachycardia, hypotension, significant tenderness on exam with rebound tenderness, involuntary guarding, and rigidity due to the activation of the afferent visceral and cutaneous pain receptors. Laboratory evaluations including complete blood count, comprehensive metabolic panel, and lactate, as well as imaging with upright plain abdominal films to evaluate for intraperitoneal air and CT of the abdomen are cornerstones of identifying the cause of peritonitis. Patients with generalized peritonitis often require surgical exploration without imaging in many cases.

Intestinal obstruction may present with acute crampy diffuse abdominal pain coupled with nausea and vomiting, obstipation, distention, and tenderness on exam. Obstruction can be partial or complete and can involve the small or large bowel. Obtaining an adequate history of previous surgeries and colonoscopies is important. Additional findings including fever, tachycardia, leukocytosis, and lactic acidosis are concerning for intestinal ischemia due to obstruction. Plain imaging will demonstrate air-fluid levels and dilated bowel (large or small). CT with oral contrast can often identify a transition point or other causes of obstruction like volvulus or intussusception. Decreased intestinal wall enhancement on CT, peritoneal signs, and leukocytosis are predictive of intestinal ischemia in patients with small bowel obstructions.³⁵ Nonoperative management may be appropriate with nasogastric decompression and bowel rest. However, in bowel obstructions that do not resolve or have signs of ischemia present, surgical management is imperative.

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Ileus is defined as the disruption of normal coordinated propulsive motor activity of the gastrointestinal (GI) tract due to a nonmechanical cause.¹ Ileus most frequently occurs in the postoperative setting and may be viewed as a normal physiologic response to abdominal surgery.² However, when ileus is prolonged, it must be differentiated from mechanical bowel obstruction or other postoperative complications.

■ PATHOPHYSIOLOGY

Physiologic bowel motility is a complex process that results from the interaction of various neural networks and neurohormonal mediators. During the fasting state, the coordinated contractions of the GI tract are referred to as *migrating motor complexes* (MMC). The contractions occur in three phases: the resting phase, intermittent contractions of moderate amplitude, and high-pressure waves. When a food bolus is introduced into the intestine, the MMCs terminate, and the digested food, or chyme, is propelled through the GI tract via coordinated contractions (peristalsis) of the smooth muscle layers in the intestinal wall. This process is regulated primarily by the enteric nervous system (ENS), which is comprised of myenteric and submucosal sensory and motor nerve plexi and the interstitial cells of Cajal. The ENS transmits sensory information from the intestinal wall to the central nervous system (CNS) via a network of visceral sensory afferents in the vagus, splanchnic, and pelvic nerves. The ENS also connects the visceral motor efferents in these same nerves with the intestinal smooth muscle cells. The ENS and intestinal smooth muscle activity are inhibited by sympathetic signaling and stimulated by parasympathetic cholinergic signaling. Alternatively, the ENS can function independently of CNS control via the autonomic nervous system through secreted mediators that include substance P, vasoactive intestinal peptide, and nitric oxide.

Ileus can develop when physiologic neural signaling and neurohormonal networks are disrupted. Ileus can result from the presence of inhibitory neuroenteric signaling through increased sympathetic activity, inflammation of surrounding organs or the bowel wall itself, paracrine and endocrine activity of inhibitory gastrointestinal peptides or endogenous opioids, and the use of exogenous opioids for analgesia.³

Ileus is common following abdominal operations. Traditionally, it has been taught that small-bowel motility returns within the first 24 hours after the procedure, gastric motility returns within 24 to 48 hours, and colonic motility within 48 to 72 hours.⁴ However, recent studies demonstrate that the duration of postoperative intestinal dysmotility may be shorter than previously thought; gastric and small intestinal motility return within hours of surgery, and colonic activity may return by postoperative day 2 or 3.⁵⁻⁷ When the expected period of time extends beyond what is viewed as acceptable in common practice, which is 5 days for open abdominal operations and 3 days for laparoscopic procedures, the patient has a pathologic postoperative ileus and a cause for ileus should be sought.⁸

■ CLINICAL FEATURES

Symptoms of ileus can include abdominal distention, bloating, diffuse abdominal pain, nausea, vomiting, inability to tolerate an oral diet, and inability to pass flatus or stool. Physical examination generally reveals

abdominal distention, tympany, and decreased or absent bowel sounds. There are no diagnostic laboratory tests for ileus, but workup may reveal associated pathologic conditions such as electrolyte abnormalities, or leukocytosis secondary to an intraabdominal infection.

Distinguishing ileus from a mechanical bowel obstruction is often difficult as these conditions share many of the same signs and symptoms. For this reason, imaging studies may be necessary to make the correct diagnosis. Plain abdominal films are often the first imaging modality obtained and will show dilated loops of bowel with air in the colon and rectum without a transition zone to suggest obstruction (Fig. 27-1). If plain films are not helpful or there is suspicion of a secondary cause of ileus (such as an intraabdominal abscess), abdominal CT should be obtained (Fig. 27-2). CT has a sensitivity and specificity of 90% to 100% in distinguishing ileus from complete mechanical bowel obstruction.⁹

■ TREATMENT

There are no data to support specific therapy for ileus, and treatment is largely supportive care. The first step is identification and remediation of any inciting factors, which may include medications, electrolyte abnormalities, or other underlying intraabdominal processes. Medications known to be associated with bowel dysmotility include narcotics, phenothiazines, diltiazem, anticholinergics, and clozapine. These medications should be discontinued if possible, and opioids should be used sparingly for pain control. Electrolyte abnormalities including hypokalemia, hyponatremia, hypo- and hypermagnesemia, and hypo- and hypercalcemia have all been shown to contribute to the development of ileus.

While awaiting recovery of bowel function, patients should be made nil per os (NPO) and given adequate intravenous fluids to maintain normovolemia. For patients with moderate to severe abdominal distention, nausea, or vomiting, a nasogastric (NG) tube should be placed for decompression. In the absence of these findings, NG insertion is not recommended, as it does not speed recovery from ileus and may in fact contribute to other complications including atelectasis and pneumonia.¹⁰

Studies on the administration of pharmacologic promotility agents for resolution of ileus have been disappointing, and there are no data to support use of metoclopramide or erythromycin.¹¹ More recently, the peripherally acting mu-opioid receptor antagonists, alvimopan and methylnaltrexone, have been evaluated as treatments for acute postoperative ileus. There are six randomized controlled trials supporting the use of alvimopan; however, the trials do not meet reporting guidelines, and meaningful clinical benefit remains uncertain.¹¹ Methylnaltrexone is currently under investigation for treatment of opioid-induced gut dysmotility, though two phase III trials evaluating its use for postoperative ileus found no benefit.¹²

■ PREVENTION

Opioid use should be limited in favor of alternative agents such as nonsteroidal antiinflammatory drugs (NSAIDs) and intravenous acetaminophen. NSAIDs have been shown to reduce postoperative nausea and vomiting as well as improve GI transit in several studies.¹³ Acetaminophen may also be useful in limiting narcotic use, particularly

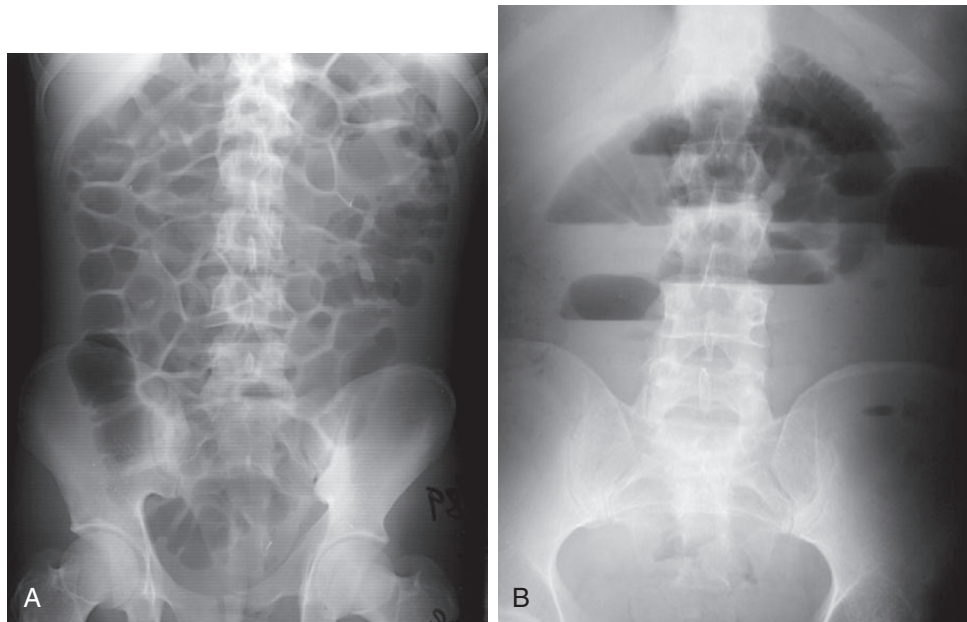


FIGURE 27-1 ■ (A) Ileus. Abdominal radiograph shows multiple air-filled dilated loops of small bowel as well as an air-filled colon and rectum. (B) Small bowel obstruction. Abdominal radiograph shows dilated loops of small bowel and multiple air/fluid levels. Small bowel has a paucity of gas and no evidence of air within the colon.

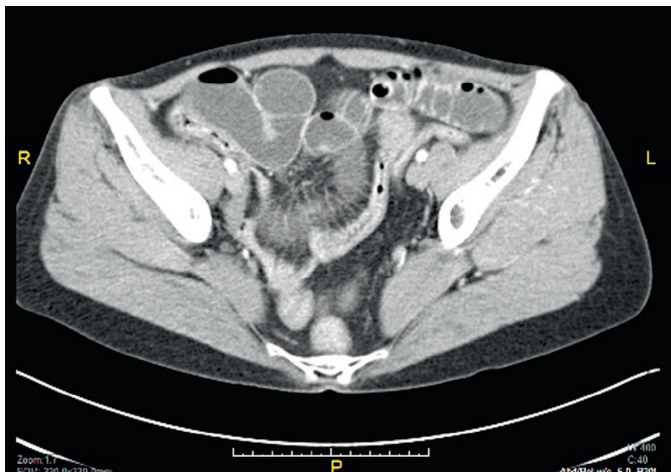


FIGURE 27-2 ■ **Small bowel obstruction.** Abdominal computed tomography scan demonstrates a clear transition point between the dilated and decompressed small bowel.

when NSAIDs are contraindicated.¹⁴ Epidural analgesia may be the best choice for postoperative pain control after abdominal operations as this modality can shorten the period of GI dysmotility.¹⁵ To be most effective, epidural catheters should be placed at the midthoracic level, and epidural agents should be administered intraoperatively and continued for at least 48 hours postoperatively.

Chewing gum may hasten postoperative bowel recovery as demonstrated by multiple trials in patients who have undergone abdominal surgeries.¹⁶ A large systematic review demonstrated decreased time to passage of flatus and bowel movement, as well as decreased length of stay. Although the review was somewhat limited by the quality of studies included, there are no known adverse consequences associated with chewing gum, and it should therefore be considered.

KEY POINTS

1. Ileus is defined as the disruption of normal coordinated propulsive motor activity of the gastrointestinal tract due to a nonmechanical cause and is common in the postoperative period.
2. Symptoms of ileus include abdominal distention, bloating, diffuse abdominal pain, nausea, vomiting, inability to tolerate an oral diet, and inability to pass flatus or stool.
3. If ileus is prolonged, it must be distinguished from a mechanical bowel obstruction, and an underlying pathologic cause must be sought.
4. Treatment is largely supportive, along with the identification and remediation of any inciting factors.
5. Limiting postoperative opioid use and utilizing a thoracic epidural for pain control help prevent ileus following abdominal operations.

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Delaney CP, Senagore AJ, Viscusi ER et al. Postoperative upper and lower gastrointestinal recovery and gastrointestinal morbidity in patients undergoing bowel resection: pooled analysis of placebo data from 3 randomized controlled trials. *Am J Surg* 2006;191(3):315–319.

This study pools data from three randomized, double-blind multicenter controlled trials in order to analyze gastrointestinal recovery in patients undergoing bowel resection. The analysis provides valuable clinical insight into GI recovery in a large patient population.

Jørgensen H, Wetterslev J, Møiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database Syst Rev* 2000(4):CD001893.

This large meta-analysis of 22 randomized controlled trials involving a total of 1023 patients undergoing abdominal surgery demonstrated that patients receiving epidural local anesthesia had reduced time to return of gastrointestinal function when compared to those receiving systemic opioids.

Li S, Liu Y, Peng Q, Xie L, Wang J, Qin X. Chewing gum reduces postoperative ileus following abdominal surgery: a meta-analysis of 17 randomized controlled trials. *J Gastroenterol Hepatol* 2013;28(7):1122–1132.

This meta-analysis of 17 randomized controlled trials involving 1374 participants undergoing abdominal surgery demonstrated that overall time for patients to pass flatus, time to bowel movement, and overall length of stay were significantly reduced in patients randomized to chewing gum.

Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. *Cochrane Database Syst Rev* 2007(3):CD004929.

This large meta-analysis of 33 randomized controlled trials encompassing 5240 patients showed that the routine use of nasogastric decompression did not reduce the incidence of postoperative complications, including return of bowel function.

Traut U, Brügger L, Kunz R, Pauli-Magnus C, Haug K, Bucher HC et al. Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults. *Cochrane Database Syst Rev* 2008(1):CD004930.

This meta-analysis of 39 randomized controlled trials and 4615 patients showed that alvimopan may shorten the duration of postoperative ileus, whereas erythromycin showed a consistent absence of an effect.

Vather R, Trivedi S, Bissett I. Defining postoperative ileus: results of a systematic review and global survey. *J Gastrointest Surg* 2013;17(5):962–972.

In this manuscript, the authors discuss the lack of standardization in defining postoperative ileus and propose a set of concise clinically quantifiable definitions.

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Diarrhea is one of the most common abnormal manifestations of gastrointestinal (GI) dysfunction in the intensive care unit (ICU); the reported incidence is between 2% and 63%.¹ Diarrhea is best defined as bowel movements that, owing to increased frequency, abnormal consistency, or increased volume, cause discomfort to the patient or the caregiver. This definition demonstrates the subjectivity in diagnosing diarrhea, a fact that complicates interpretation of the literature and limits applicability of guidelines. The impact of diarrhea on patient care in the ICU, including its cost in morbidity and mortality, is unknown. However, it is undeniable that diarrhea remains a persistent problem in many ICUs.

CRITERIA

Several criteria are used to diagnose diarrhea:

1. Abnormal frequency. Normal frequency is described as one or two bowel movements per day and is in part determined by the amount of fiber in the diet. Three or more bowel movements per day are considered abnormal.¹
2. Abnormal consistency. Abnormal consistency is described as either nonformed stool or stool having excessive fluid content that causes "inconvenience" to the patient, nursing staff, or caregiver. Normal stool water content is 60% to 85% of the total weight.¹
3. Abnormal amount. Stool amount and volume vary significantly with the amount and type of enteral intake. Insoluble fiber adds a significant amount of bulk volume. A "normal" amount is considered to be approximately 200 grams per day (g/d).¹ Abnormal amounts are considered to be greater than 300 g/d, or volumes greater than 250 mL/d.^{1,2}

To date, clinicians are lacking a consistent scale or index that allows a reliable and practical way of measuring stool volume, consistency, and frequency. In its absence, the bedside nurse remains the most reliable person to diagnose the presence of diarrhea.

PATHOPHYSIOLOGY

Bowel movements with normal physiologic volume, consistency, and frequency are the result of a GI tract that integrates motility, secretion, and absorption of fluids and adapts to the quality of the food bolus given. The result is a fecal bolus that is produced once or twice every 24 hours and has consistency and fluidity within the boundaries of normal.

Diarrhea results when there is a disorder of GI physiology or when GI tract function is incapable of handling the food bolus. There are several classifications of diarrhea, suggesting that no classification is ideal at helping the clinician plan for patient care. Perhaps the most useful approach is to classify diarrhea according to alterations of physiologic events:

1. Increased fluid secretion that overwhelms absorption. On average, up to 9 L of fluid is secreted into the GI lumen in addition to the normal oral intake. Less than 1% of that fluid is contained in stool, owing to the amazingly large absorptive capacity of the small and large bowel. Within the intestinal mucosa, passive and active transport of sodium determines the amount of water that is absorbed. Stimulation of the active secretion of fluids into the GI lumen occurs when intracellular levels of the second messenger,

cyclic adenosine monophosphate (cAMP), increases within enterocytes. Increased intracellular cAMP concentration promotes chloride secretion.³ Thus, diarrhea caused by excessive secretion of fluids is called *secretory diarrhea*. Secretory diarrhea characteristically contains large amounts of fluid and is described as watery. Secretory diarrhea is observed in certain infectious diseases such as cholera or infections with rotavirus. Secretory diarrhea also can be observed in endocrine disturbances associated with carcinoid syndrome or vasoactive intestinal peptide (VIP)-secreting tumors.

2. Increased mucous secretion from the large bowel. Overproduction of mucus by the large bowel can lead to development of diarrhea. Excessive mucus secretion is observed in colonic infections such as *Clostridium difficile* colitis and amebiasis.⁴ The incidence of infectious diarrhea in the ICU is unknown.
3. Contaminated food products. Of particular concern is the contamination of the food being given in the ICU. Contamination of enteral formulas can occur at multiple levels, including preparation of the enteral product, use of "open units," addition of modular dietary components, and contamination of the enteral access port (i.e., feeding tube, gastrostomy tube). The incidence of diarrhea due to contaminated feeding tubes is unknown.
4. Diarrhea due to increased osmotic load. Many substances that are taken orally and are not fully absorbed can exert a significant osmotic force, overwhelming the physiologic absorptive capacity of the GI tract. A significant number of patients with diarrhea in the ICU fall into this category.
 - a. Osmotic diarrhea caused by medications. Sorbitol is frequently and inadvertently given to patients in the ICU as a means of preparing many medications for delivery via feeding tubes and is an often overlooked culprit causing diarrhea.⁵ Other osmotic agents include Golytely and magnesium-containing medications.
 - b. Incomplete digestion and malabsorption. The incidence of malabsorption in the ICU is unknown. However, there are many instances where malabsorption should be considered as a cause of diarrhea in the critically ill patient. These include:
 - i. Incomplete protein digestion (azotorrhea). Protein digestion occurs mainly in the stomach by pepsin (only activated at low pH) and hydrochloric acid. In the ICU, virtually all patients receive medications to raise intragastric pH, such as histamine receptor type 2 (H₂) blockers or proton pump inhibitors.^{6,7} In addition, feeding tubes frequently "bypass" the stomach, eliminating both gastric acid and gastric proteolytic digestion.
 - ii. Undigested carbohydrates. In addition to sorbitol (see earlier discussion), excessive glucose, lactose, or fructose in tube-feeding formulas can overwhelm the absorptive capacity of the small bowel, causing an osmotic influx into the gut lumen.⁸
 - iii. Undigested fats. Steatorrhea (diarrhea caused by undigested fats) is characteristically observed in patients with pancreatic insufficiency. Inadvertent lack of mixing pancreatic enzymes with the food bolus can occur in patients with intestinal bypass or pancreatic fistulas or in patients who have undergone pancreatectomy. It is also observed in patients with

incomplete bile production, such as patients who have a biliary diversion.

- iv. Excessive dietary load. Diarrhea due to excessive load (overfeeding) of any of the main dietary components (protein, carbohydrate, or fat) can be observed in the ICU. Iatrogenic overfeeding occurs in up to 33% of patients in the ICU and is a result of inappropriate estimations of caloric and protein needs or inadequate metabolic surveillance.⁹ Excessive loads of protein, carbohydrate, or fat also occur with “specialized” formulas that contain altered amounts of one or more of these components. For example, certain diets may contain high amounts of fat, overwhelming digestive and absorptive processes.
- v. Atrophy of the GI tract. Atrophy of the intestinal brush border is associated with decreased capacity of digestion and absorption. Atrophy is observed in malnourished patients; thus, diarrhea is observed commonly in patients with hypoalbuminemia. Atrophy also occurs when enteral intake is interrupted for more than a few days. This is a particular problem in surgical patients when prolonged “bowel rest” is ordered.
5. Abnormal motility. Intestinal dysmotility is a frequent problem in the ICU. The use of promotility agents (e.g., erythromycin) can inadvertently cause diarrhea in these patients.
6. Abnormal gut flora. Colonic flora is essential for normal absorption and function of the large bowel. Antibiotics create massive disruptions in colonic flora and can sometimes lead to nosocomial infections with resultant diarrhea. Currently, *C. difficile* is the leading cause of nosocomial diarrhea and accounts for 30% of patients with antibiotic-associated diarrhea.¹⁰ The gut microflora can be modulated through the use of probiotic agents, but this topic is under intense investigation, and no current guidelines exist regarding their use to treat or prevent diarrhea in ICU patients.¹¹

CLINICAL CONSEQUENCES OF DIARRHEA

Untreated, diarrhea can lead to multiple problems. These include:

1. Wound breakdown and secondary soft-tissue infection. Diarrhea can cause a moist, contaminated environment; if left untreated, this can lead to skin breakdown and eventual soft-tissue infection. Particularly concerning are the presence of decubitus ulcers; diarrhea can be either a causative factor or can worsen or complicate management.
2. Fluid and electrolyte disturbances are particularly frequent in patients with secretory diarrhea. In these patients, clinicians need to pay attention to fluid replacement and correct metabolic acidosis and/or hypokalemia.
3. Malnutrition. Inadequate nutrient absorption can lead to poor nutrient utilization.
4. Increased workload for nurses and caregivers. Diarrhea imposes a substantial burden on nurses and other caregivers. In addition, the presence of a soiled patient evokes a sense of poor quality of care. Maintaining a clean patient with diarrhea requires additional ICU personnel time and resources that could be better used.

DIAGNOSIS

Careful and complete evaluation of diarrhea is necessary for good patient care. Unfortunately, diarrhea is often ignored or hastily “treated” while clinicians pay more attention to other organ systems. Diagnostic laboratory tests often do not exist, making it ever more difficult to identify and treat the patient. We propose the following approach:

1. Does the patient really have diarrhea? Clinicians rarely will question the diagnosis of diarrhea. Most diagnoses are probably made without a clear understanding of the definition of diarrhea. A concerted effort to diagnose diarrhea by all members of the ICU staff

is essential. The creation of scales or indices could become particularly useful as a means of communication. These could also aid in following the effectiveness of treatment.

2. Can an iatrogenic cause explain the presence of diarrhea?
 - a. Is the patient on prokinetic agents or stool softeners?
 - b. Is the patient receiving medications with high concentrations of sorbitol?
 - c. Is the patient being overfed?
 - d. Is the patient intolerant to any of the components of the diet?
 - e. Is a specialized diet providing an excessive amount of a substance (e.g., fat) that the patient is having difficulty digesting?
 - f. Is bypassing the stomach or inhibiting acid secretion affecting the digestion of protein?
 - g. Is the patient on any other medication that can cause diarrhea?
3. Assessing the patient's absorptive or digestive capacity.
 - a. Does the patient have gut atrophy, as seen with prolonged bowel rest? Would this patient benefit from an intestinal rehabilitation strategy?
 - b. Is the patient malnourished?
 - c. Does the patient have a condition (e.g., pancreatitis) that alters the secretion of digestive enzymes?
 - d. Does the patient have a chronic disease process (e.g., short gut syndrome) that alters absorption?
4. Does the patient have an infection?
 - a. Is there any evidence of contamination of feeding tubes? Are you using a closed system? How often is it being changed?
 - b. Is there cause for nosocomial bowel infection? Is the patient's *C. difficile* toxin negative?
 - c. Has colonic flora been altered significantly with antibiotics?

TREATMENT

Treatment is dependent on identification of the underlying cause. One or several reasons for the presence of diarrhea generally can be identified. Once identified, the causes of diarrhea should be eliminated, modified, or treated. In particular, iatrogenic causes of diarrhea should be identified and corrected whenever feasible. For example, prolonged courses of prophylactic antibiotics are no better than short courses for the prevention of surgical site infections; therefore, adherence to current guidelines to limit antibiotics is important.^{12,13}

Modification of the diet may be important if the GI tract is being overwhelmed with high quantities of a particular nutrient. This is particularly important for patients receiving formulas that deliver excessive fat loads.

Digestive enzymes such as pancreatic enzymes or bile substitutes should be supplemented when the disease process (or treatment) is associated with decreased production of these enzymes.

Agents that inhibit GI motility, such as loperamide, should be used with caution. These drugs are often ordered empirically and may worsen underlying pathology, especially when the causative agent is infectious.

Bulk-forming agents are sometimes given to patients to improve the consistency of the fecal bolus. These agents have to be used in the appropriate amount, since they can also be a cause of diarrhea.¹⁴

Antibiotics to treat infectious diarrhea also should be used with caution. If the diarrhea is causing minimal discomfort and is of no physiologic consequence, waiting for the arrival of results of tests for *C. difficile* may be advised.¹⁵

Restoring normal colonic flora has become an increasingly frequent practice in the ICU. Provision of prebiotics and probiotics in different presentations is now being suggested, but the implications of such therapies are not clear and require further investigation.^{11,16} Soluble fiber may have a role in restoring normal colonic function and flora.

Stopping or decreasing the rate of enteral nutrition is often done; however, this is only advocated if the patient is being overfed or exhibits intolerance to the diet. Only under exceptional circumstances should stopping oral intake and giving total parenteral nutrition be advocated as a treatment for diarrhea.

CONCLUSION

Diarrhea is a poorly studied clinical manifestation of GI dysfunction in the ICU. The true incidence of diarrhea in ICU patients is unknown

because of the lack of a universally accepted definition or a concerted effort to study the problem. Despite these limitations, when discovered, diarrhea can be effectively treated with careful clinical evaluation of the patient and easily implemented therapeutic measures.

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The clinical diagnostic approach to rash and fever in the intensive care unit (ICU) depends on whether the rash and fever were community or nosocomially acquired. Community-acquired rash and fever are best approached by considering the distribution and characteristics of the rash.¹⁻⁵ Rashes are visible clues to infectious or noninfectious disorders. In addition to the rash and fever, often the associated findings, such as history, physical examination, and laboratory abnormalities, are keys to the correct diagnosis.^{1,4,6-8}

Nosocomially acquired rashes have more limited differential diagnostic possibilities.⁶ The clinician should determine whether the rash and fever represents the primary clinical problem or is a superimposed finding unrelated to another process. For example, ICU patients admitted for acute myocardial infarction can develop a drug rash from an antiarrhythmic medication, beta-blockers, diuretics, or sulfa-containing stool softener (Colace).^{1,3}

Acutely ill patients with a rash and fever in the ICU should have the benefit of an infectious disease consultation by an experienced infectious disease clinician.^{1,3} Both community and nosocomially acquired rash and fever are best diagnosed using the clinical syndromic approach in which associated clinical findings, not the appearance of the rash alone, are the main determinants of arriving at the correct diagnosis.^{5,7}

COMMUNITY-ACQUIRED RASH AND FEVER

Patients admitted to the ICU from the community with rash and fever are best approached by the type and distribution of the rash.² The degree of fever relative to the pulse rate and fever pattern are also important diagnostic considerations.^{3,9}

Petechial/Purpuric Rash and Fever

While petechial and purpuric rashes are common causes of community-acquired rash and fever, petechiae can accompany a variety of systemic infections, as well as a variety of noninfectious disorders.¹⁰⁻¹² Rash and fever is often potentially life-threatening (e.g., meningococcemia [MC] with or without meningitis, Rocky Mountain spotted fever [RMSF], dengue fever [DF], and arboviral hemorrhagic fevers), and patients should have the benefit of a diagnostic evaluation by an experienced infectious disease consultant.^{1,4,10,11}

The two most common infectious diseases presenting with a petechial/purpuric rash are MC and RMSF. RMSF should be suspected with a history of recent tick exposure and a characteristic location and distribution of the rash. Importantly, RMSF is the only infectious exanthema that begins on the wrists and/or ankles.¹³⁻¹⁵ In contrast, the rash of MC is asymmetrical with irregularly shaped painful petechial or purpuric lesions.^{1,8,11}

Post-splenectomy sepsis (PSS) can resemble meningococcemia but only occurs in patients with impaired or absent splenic function.^{1,4,11}

Clinicians should be familiar with the disorders associated with the diminished splenic function. A key clinical clue to impaired splenic function is the presence of Howell-Jolly bodies or “pocked/pitted” red blood cells in the peripheral smear. The number of Howell-Jolly bodies is inversely proportional to splenic function.^{1,8}

High-grade and continuous *Staphylococcus aureus* bacteremia (methicillin-sensitive/methicillin-resistant [MSSA/MRSA]) from abscesses or acute bacterial endocarditis (ABE) is often accompanied by splinter hemorrhages and petechial or purpuric rashes on the distal extremities.^{1,10,11}

Maculopapular Rashes and Fever

The most common maculopapular rashes and fever associated with serious systemic diseases are toxic shock syndrome (TSS) and systemic lupus erythematosus (SLE). SLE flares can mimic infectious diseases.^{1,4,11} Thus, SLE pneumonitis can mimic community-acquired pneumonia (CAP), and SLE cerebritis can mimic acute bacterial meningitis (ABM). Laboratory studies can differentiate an SLE flare in the absence of infection from an SLE flare with an infection. Typically, SLE flares without infection are accompanied by leukopenia, decreased complement levels, and elevated α_1/α_2 globulins on serum protein electrophoresis (SPEP).^{1,8}

TSS can occur in any patient colonized or infected with a TSS-1-producing strain of *S. aureus*. However, TSS may not be considered when there are no overt signs of clinical infection (e.g., staphylococcal colonization of the nares). TSS also may be due to group A streptococci or *Clostridium sordelli*.^{2,4,11}

Vesicular/Bullous Rashes and Fever

Vesicular eruptions limit the diagnostic possibilities to chickenpox or herpes zoster (shingles) due to varicella zoster virus (VZV). Herpes zoster may be localized (dermatomal) or disseminated.⁵⁻⁷ Prior to the appearance of the vesicular rash and fever, dermatomal herpes zoster can be a difficult diagnostic problem, mimicking many disorders.⁶ Herpes zoster involving the head and neck may be associated with VZV meningitis or encephalitis. Disseminated shingles can resemble chickenpox, but patients with herpes zoster have a prior history of chickenpox.^{1,4,11}

Community-acquired bullous lesions in the ICU may be due to *S. aureus* soft-tissue abscess, *Vibrio vulnificus*, or gas gangrene (clostridial myonecrosis). Except when due to *S. aureus*, all the causes of bullae/fever are painful and tense and accompanied by diarrhea. Clostridial myonecrosis (i.e., gas gangrene) may be present after a crush injury or trauma. The most common cause of bullae and fever is *S. aureus* abscess or pyoderma.¹⁰⁻¹²

The differential diagnostic features of community-acquired rash and fever are presented in tabular form in [Tables 29-1 to 29-10](#).¹⁻¹⁹

TABLE 29-1 Community-Acquired Rash and Fever in the ICU

PETECHIAL/PURPURIC RASHES

| DISORDER | CENTRAL > PERIPHERAL | | PALMS AND SOLES | RASH | RASH DETAILS | CLINICAL FEATURES | OTHER FEATURES | DIFFERENTIAL DIAGNOSIS (KEY DDx POINTS) |
|----------------------|----------------------|----------------------|-----------------|------|--|---|---|---|
| | CENTRAL > PERIPHERAL | PERIPHERAL > CENTRAL | | | | | | |
| Meningococcemia (MC) | + | ± | | | <p>Rash appears 1-2 hours after fever</p> <p><i>Irregular/painful</i></p> <p>petechial lesions</p> <p>Early, spares palms/soles/face</p> <p>Late, may involve palms/soles</p> <p>Often appear in "crops," especially near pressure points</p> <p>Many petechial/purpuric lesions (vs. RMSF)</p> <p>Prognosis ~ number of petechiae</p> | <p>Clinical Findings:</p> <p>Headache, myalgias</p> <p><i>Hypotension</i> (if Waterhouse-Friderichsen syndrome)</p> <p>Rapidly fatal ("well at 1 pm, dead at 3 pm")</p> <p>Laboratory Findings:</p> <p><i>Leukocytosis</i></p> <p><i>Thrombocytopenia</i></p> <p>AST(SGOT)/ALT(SGPT); WNL</p> <p>Early complement components ↓ (C₁₋₃)</p> <p>DIC (schistocytes and thrombocytopenia) common</p> <p>Diagnosis:</p> <p>Clinical appearance/presentation</p> <p>Blood cultures <i>positive</i> for <i>Neisseria meningitidis</i></p> <p>Petechiae/purpura</p> <p>Gram stain/culture <i>positive</i> for <i>N. meningitidis</i></p> | <p>History of recent upper respiratory tract infection</p> <p>Common in late winter-early spring</p> <p>May present alone or with meningococcal meningitis</p> <p>Digital gangrene (late)</p> | <p>RMSF:</p> <p><i>Tick exposure</i></p> <p>Common in early/late summer</p> <p><i>Relative bradycardia</i></p> <p>Conjunctival suffusion</p> <p>Bilateral periorbital edema</p> <p>Petechial rash on wrists/ankles</p> <p><i>Edema of dorsum of hands/feet</i></p> <p>WBC count: WNL</p> <p>Elevated AST(SGOT)/ALT(SGPT)</p> <p>Blood cultures negative for <i>N. meningitidis</i></p> <p>Digital gangrene (late)</p> <p>Enteroviruses:</p> <p><i>Rash prominent on face/trunk</i></p> <p>Petechiae <i>small/regularly shaped on face/extremities > trunk</i></p> <p><i>Loose stools/diarrhea common</i></p> <p>WBC/platelet counts: WNL</p> <p>Elevated enterovirus titers</p> <p>Staphylococcus aureus bacteremia/SBE:</p> <p><i>New/changing heart murmur</i></p> <p>PMH positive for valvular disease or recent intra-cardiac procedure/device</p> <p>High-grade bacteremia: blood cultures <i>positive</i> for (4/4-4/4) <i>S. aureus</i> (MSSA/MRSA)</p> <p>If ABE, TTE <i>positive</i> vegetations</p> <p>Post-splenectomy sepsis (PSS):</p> <p><i>Underlying disorder associated with hyposplenic function</i> (see PSS)</p> <p>No Howell-Jolly bodies and/or "pocked/pitted" RBCs</p> <p>No target cells or Pappenheimer bodies</p> <p>Blood cultures <i>positive</i> for <i>Staphylococcus pneumoniae</i>, <i>Haemophilus influenzae</i>, or <i>Capnophagia canimorsus</i>; (<i>N. meningitidis</i>) less likely</p> <p>Henoch-Schönlein purpura (HSP):</p> <p><i>Small-vessel vasculitis</i> (more common in children)</p> <p>Often preceded by an upper respiratory viral infection, drugs, or immunizations</p> <p><i>Only extensive purpuric rash limited to below the waist</i></p> <p>Fevers < 102°F without chills</p> <p>Abdominal pain prominent</p> <p>± Peritarticular tenderness</p> <p><i>Palpable purpura below the waist</i> with arthralgias, abdominal pain, or GMN should suggest HSP</p> <p>Urinalysis shows hematuria/RBC casts</p> <p><i>Blood cultures negative</i></p> <p>Skin biopsy shows leukoclastic vasculitis with IgA deposition in small vessel walls</p> <p>Kidney biopsy shows focal/segmental GMN</p> |

ALT, alanine aminotransferase/SGPT; serum glutamic-pyruvic transaminase; AST, aspartate aminotransferase/SGOT; serum glutamic-oxaloacetic transaminase; DIC, disseminated intravascular coagulation; GMN, glomerulonephritis.

TABLE 29-2 Community-Acquired Rash and Fever in the ICU

PETECHIAL/PURPURIC RASHES

| DISORDER | CENTRAL > PERIPHERAL | PERIPHERAL > CENTRAL | PALMS AND SOLES RASH | RASH DETAILS | CLINICAL FEATURES | OTHER FEATURES | DIFFERENTIAL DIAGNOSIS (KEY DDx POINTS) |
|-------------------------------------|----------------------|----------------------|----------------------|--|--|--|--|
| Rocky Mountain spotted fever (RMSF) | | + | + | Rash appears 3-5 days after fever Begins on wrists/ankles Painless macular rash early Relatively few petechial/purpuric lesions (vs. meningococcemia) | Clinical Findings: Relative bradycardia Conjunctival suffusion Severe frontal headache Bilateral periorbital edema ± Splenomegaly ± Abdominal pain Edema of dorsum of hands/feet Hypotension late (due to excessive fluids/myocarditis) | Usually occurs in late spring/early fall History of recent tick exposure No infiltrates on CXR unless CHF (late) | Meningococcemia (MC): Not toxemic in appearance No relative bradycardia No periorbital edema No edema of the dorsum of hands/feet Doesn't start on wrists/ankles Leukocytosis Blood cultures/lesions positive for <i>Neisseria meningitidis</i> Typhus: Recent louse exposure (epidemic typhus) or flea exposure (murine typhus) Rash truncal (sparing palms/soles) CNS symptoms (delirium, vertigo, tinnitus) common GI symptoms (nausea/vomiting) common Elevated <i>Rickettsia prowazekii</i> or <i>Rickettsia typhi</i> titers Atypical measles: Received killed measles vaccine (1963-1968) Nodular infiltrates on CXR with pleural effusions BHA on CXR Pneumonia predominant clinical finding (unlike RMSF) Maculopapular rash not petechial and does not begin on ankles/wrists Rash spreads centrally to trunk but does not spread above nipple line Dry cough frequent Myalgias and abdominal pain common Edema of hands/feet common Hepatosplenomegaly in some Leukopenia in some No thrombocytopenia Eosinophilia (late) Highly elevated measles IgM titers Enteroviruses: Rash prominent on face/trunk Petechiae small/regularly shaped and relatively sparse Loose stools/diarrhea common WBC/platelet counts: WNL Elevated enteroviral titer Henoch-Schönlein Purpura (HSP): Small vessel vasculitis (more common in children) Often preceded by an upper respiratory viral infection, drugs, or immunizations Only extensive purpuric rash limited to below the waist Fever < 102°F without chills Abdominal pain prominent ± Periarthral tenderness Urinalysis shows hematuria/RBC casts Palpable purpura below the waist with arthralgias, abdominal pain, or GMN should suggest HSP Skin biopsy shows leukoclastic vasculitis with IgA deposition in small vessel walls Kidney biopsy shows focal/segmental GMN Blood cultures negative |

ALT, alanine aminotransferase/SGPT, serum glutamic-pyruvic transaminase; AST, aspartate aminotransferase/SGOT, serum glutamic-oxaloacetic transaminase; BHA, bilateral hilar adenopathy; CHF, congestive heart failure; CXR, chest x-ray; ESR, erythrocyte sedimentation rate.

TABLE 29-3 Community-Acquired Rash and Fever in the ICU

PETECHIAL/PURPURIC RASHES

| DISORDER | CENTRAL > PERIPHERAL | PERIPHERAL > CENTRAL | PALMS AND SOLES RASH | RASH DETAILS | CLINICAL FEATURES | OTHER FEATURES | DIFFERENTIAL DIAGNOSIS (KEY DDx POINTS) |
|---|----------------------|----------------------|----------------------|--|---|---|--|
| <i>Staphylococcus aureus</i> high-grade continuous bacteremia/ABE | + | + | + | Rash appears <i>days after fever</i> <i>Irregular, painful petechial/gangrenous lesions on distal extremities</i> | Clinical Findings: Fever > 102°F Shaking <i>chills</i> New/changing heart murmur if ABE Clinical focus/source of bacteremia (e.g., abscess) usually apparent Laboratory Findings: Leukocytosis ± Thrombocytopenia Increased ESR/CRP AST(SGOT)/ALT(SGPT): WNL Diagnosis: Clinical appearance/presentation Petechial/purpuric lesions Gram stain/culture <i>positive</i> for <i>S. aureus</i> (MSSA/MRSA) Continuous/high-grade (3/4-4/4) MSSA/MRSA bacteremia TTE: if ABE, <i>positive</i> for vegetation | Recent history of <i>S. aureus</i> (MSSA/MRSA) skin/soft-tissue infections Recent <i>S. aureus</i> (MRSA/MSSA) abscesses | RMSF: Tick exposure Common in <i>early/late summer</i> Relative bradycardia Conjunctival suffusion Bilateral periorbital edema Petechial rash on wrists/ankles Edema of dorsum of hands/feet WBC count: WNL Elevated AST(SGOT)/ALT(SGPT) Blood cultures <i>negative</i> for <i>S. aureus</i> (MSSA/MRSA) Digital gangrene (late) Vasculitis: No heart murmur No <i>chills</i> Blood cultures <i>negative</i> for MSSA/MRSA TTE: no cardiac vegetations ANA, p-ANCA/c-ANCA <i>positive</i> |

ALT, alanine aminotransferase/SGPT, serum glutamic-pyruvic transaminase; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic autoantibody; AST, aspartate aminotransferase/SGOT, serum glutamic-oxaloacetic transaminase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TTE, transthoracic echocardiography.

TABLE 29-4 Community-Acquired Rash and Fever in the ICU

PETECHIAL/PURPURIC RASHES

| DISORDER | CENTRAL > PERIPHERAL | PERIPHERAL > CENTRAL | PALMS AND SOLES RASH | RASH DETAILS | CLINICAL FEATURES | OTHER FEATURES | DIFFERENTIAL DIAGNOSIS (KEY DDx POINTS) |
|------------------------------|----------------------|----------------------|----------------------|-----------------------------------|--|--|---|
| Postsplenectomy sepsis (PSS) | + | — | — | Rash appears 1–2 days after fever | <p>Clinical Findings: Diffuse asymmetrical purpuric lesions Fulminant hypotension/shock</p> <p>Laboratory Findings: Leukopenia Thrombocytopenia Howell-Jolly bodies “packed/pitted” RBCs Pappenheimer bodies and/or target cells</p> <p>Diagnosis: Clinical appearance/presentation in patients with splenectomy scar or disorders associated with hyposplenism* Blood cultures positive for <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i>, <i>Neisseria meningitidis</i>, or <i>Campylobacter jejuni</i> (DF-2)</p> | No seasonal incidence Occurs in asplenic (e.g., trauma, staging procedures for lymphoma, congenital asplenia) Also occurs in patients with disorders that impair splenic function* | <p>Meningococcemia (MC): Not toxic in appearance No relative bradycardia No periorbital edema No edema of hands/feet Doesn't start on wrists/ankles Blood cultures/lesions positive for <i>Neisseria meningitidis</i></p> <p>Toxic shock syndrome (TSS) <i>Staphylococcus aureus</i>: Hypotension common Scarlatiniform rash Conjunctival suffusion Bilateral periorbital edema Mucosal hyperemia Edema dorsum of hands/feet Elevated AST(SGOT)/ALT(SGPT) Elevated CPK Colonization/infection with <i>S. aureus</i> TSS-I producing strain</p> <p>Henoch-Schönlein Purpura (HSP): Small vessel vasculitis (more common in children) Often preceded by an upper respiratory viral infection, drugs, or immunizations Only extensive purpuric rash limited to below the waist Fever < 102°F without chills Abdominal pain prominent ± Peritardular tenderness Palpable purpura below the waist with arthralgias, abdominal pain, or GMN should suggest HSP Urinalysis shows hematuria/RBC casts Skin biopsy shows leukoclastic vasculitis with IgA deposition in small vessel walls Kidney biopsy shows focal/segmental GMN Blood cultures negative</p> |

*Sickle cell trait/disease, cirrhosis, rheumatoid arthritis, SLE, systemic necrotizing vasculitis, amyloidosis, celiac disease, chronic active hepatitis, Fanconi's syndrome, IgA deficiency, intestinal lymphangiectasia, intravenous gamma-globulin therapy, myeloproliferative disorders, non-Hodgkin's lymphoma, regional enteritis, ulcerative colitis, Sézary syndrome, splenic infarcts/malignancies, steroid therapy, systemic mastocytosis, thyroiditis, infiltrative diseases of spleen, mechanical compression of splenic artery/spleen, Waldenström's macroglobulinemia, hyposplenism of old age, congenital absence of spleen.

ALT, alanine aminotransferase/SGPT, serum glutamic-pyruvic transaminase; AST, aspartate aminotransferase/SGOT, serum glutamic-oxaloacetic transaminase; CPK, creatine phosphokinase; DIC, disseminated intravascular coagulation; TSS, toxic shock syndrome.

TABLE 29-5 Community-Acquired Rash and Fever in the ICU**PETECHIAL/PURPURIC RASHES**

| DISORDER | CENTRAL > PERIPHERAL | PERIPHERAL > CENTRAL | PALMS AND SOLES RASH | RASH DETAILS | CLINICAL FEATURES | OTHER FEATURES | DIFFERENTIAL DIAGNOSIS (KEY DDx POINTS) |
|--|----------------------|----------------------|----------------------|--|---|---|--|
| Dengue fever (DF), dengue shock syndrome (DSS), dengue hemorrhagic fever (DHF) | + | | — | Rash appears 2–6 days after fever Rash begins on thorax Scarlatiniform truncal rash with palpable “pinpoint petechiae” (feels like sandpaper) Facial flushing | Clinical Findings: Fever < 103°F and are continuous, not spiking “Camelback” fever pattern Severe frontal headache and myalgias Retro-ocular pain Pain on eye movement Conjunctival suffusion Generalized lymphadenopathy DSS → same as DF plus hypotension DHF → same as DF plus hemorrhagic manifestations Laboratory Findings: Leukopenia Relative lymphocytosis late Hemoconcentration (increased Hct > 20%) Increased AST(SGOT)/ALT(SGPT) Diagnosis: Clinical presentation/appearance Increased IgM Dengue virus titers | Recent travel history to Caribbean, Latin America, or Asia Recurrent mosquito exposure | Chikungunya fever (CHIK): Not endemic in Caribbean, Latin America Relative bradycardia Polyarthralgias prominent Arthralgias > myalgias Rash pruritic No pinpoint palpable petechiae Meningoencephalitis uncommon Conjunctival suffusion Generalized adenopathy uncommon Leukocytosis (not leukopenia) No hemoconcentration Elevated AST(SGOT)/ALT(SGPT) Elevated Chikungunya IgM titers |

ALT, alanine aminotransferase/SGPT, serum glutamic-pyruvic transaminase; AST, aspartate aminotransferase/SGOT, serum glutamic-oxaloacetic transaminase; DHF, Dengue hemorrhagic fever; DSS, dengue shock syndrome; Hct, hematocrit.

TABLE 29-6 Community-Acquired Rash and Fever in the ICU

PETECHIAL/PURPURIC RASHES

| DISORDER | CENTRAL > PERIPHERAL | PERIPHERAL > CENTRAL | PALMS AND SOLES RASH | RASH DETAILS | CLINICAL FEATURES | OTHER FEATURES | DIFFERENTIAL DIAGNOSIS (KEY DDX POINTS) |
|--|----------------------|----------------------|----------------------|---|---|---|---|
| Arboviral hemorrhagic fevers (yellow fever, Lassa fever, Ebola fever, Omsk hemorrhagic fever, Marburg virus) | + | | ± | Rash appears 5-7 hours after fever Maculopapular rash day # 5 (early) Hemorrhagic manifestations prominent (epistaxis late) Jaundice early with yellow fever | Clinical Findings: Hyperacute onset Severe prostration Relative bradycardia Severe headache Conjunctival suffusion Facial flushing/edema Dry cough Profuse watery diarrhea Sore throat Severe myalgias/back pain ±Encephalopathy ±Generalized adenopathy ±Cervical adenopathy (Lassa fever) | History of recent travels to Africa, Latin America, Asia Rapidly fatal | RMSF: Subacute onset Tick exposure Common in early/late summer Relative bradycardia Conjunctival suffusion Bilateral periorbital edema Petechial rash on wrists/ankles Edema of dorsum of hands/feet WBC count: WNL Elevated AST(SGOT)/ALT(SGPT) Blood cultures negative Digital gangrene (late) |
| | | | | | Meningococcemia (MC): Not toxic in appearance No relative bradycardia No periorbital edema No edema of hands/feet Doesn't start on wrists/ankles Blood cultures/lesions positive for <i>Neisseria meningitidis</i> | | |
| | | | | | Laboratory Findings: Leukopenia Thrombocytopenia Hematuria Elevated AST(SGOT)/ALT(SGPT) | | |
| | | | | | Diagnosis: Clinical appearance/presentation CDC ELISA RT-PCR (CDC) positive for arboviruses | | Smallpox (hemorrhagic): Petechial/purpuric rash in "swimming trunks" distribution Toxicemic appearance Delirium common No dry cough Rapidly fatal early, before vesicles appear Myalgias not prominent |

ALT, alanine aminotransferase/SGPT, serum glutamic-pyruvic transaminase; AST, aspartate aminotransferase/SGOT, serum glutamic-oxalobacetic transaminase; CDC, Centers for Disease Control and Prevention; DIC, disseminated intravascular coagulation.

TABLE 29-7 Community-Acquired Rash and Fever in the ICU

PETECHIAL/PURPURIC RASHES

| DISORDER | CENTRAL > PERIPHERAL | PERIPHERAL > CENTRAL | PALMS AND SOLES RASH | RASH DETAILS | CLINICAL FEATURES | OTHER FEATURES | DIFFERENTIAL DIAGNOSIS (KEY DDx POINTS) |
|---|----------------------|----------------------|----------------------|---|---|--|--|
| Smallpox (hemorrhagic/toxic)* Types: Hemorrhages before rash ("purpura variolosa") Hemorrhages after rash ("variola pustulosa hemorrhagica") | + | | + | Rash appears with the fever Petechial/hemorrhagic rash in a "swimming trunk" distribution Petechiae appear early on inner thighs (Simon's crural triangle) and groin Petechia in lateral line from thorax along rib margins to navel Generalized erythroderma ("scarlatiniform" rash) by 2nd day in some Those with "scarlatiniform" rash develop dark purple velvet skin color by 4th day | Clinical Findings:* Severe headache and backache precede rash Profound toxemia and restlessness Profound prostration Conjunctival hemorrhages early Epistaxis Fetid breath Chest heaviness/pain common Hematuria Laboratory Findings: Leukopenia Relative lymphocytosis Monocytosis Normoblasts with basophilic stippling Thrombocytopenia AST(SGOT)/ALT(SGPT): WNL Diagnosis: Clinical appearance/presentation | Patients may expire before vesicular lesions develop Sudden death on 6th-day fever from pulmonary edema not hemorrhages Suspect bioterrorism | Toxic shock syndrome (TSS) Staphylococcus aureus: Hypotension common Scarlatiniform rash Conjunctival suffusion Bilateral periorbital edema Mucosal hyperemia Edema dorsum of hands/feet Elevated AST(SGOT)/ALT(SGPT) Elevated CPK Colonization/infection with <i>S. aureus</i> TSS-1 producing strain Typhus: Recent louse exposure (epidemic typhus) or flea exposure (murine typhus) Rash truncal (spares palms/soles) CNS symptoms (delirium, vertigo, tinnitus) common GI symptom (nausea/vomiting) common Elevated Rickettsia prowazekii or Rickettsia typhi titers Postsplenectomy sepsis (PSS): Underlying disorder associated with hyposplenic function (see PSS) No Howell-Jolly bodies and "pocked/pitted" RBCs No target cells or Pappenheimer bodies Blood cultures positive for <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , or <i>Capnophagia caninorus</i> (<i>N. meningitidis</i>) less likely Meningococcemia (MC): Not toxic in appearance No relative bradycardia No periorbital edema Diffuse (irregularly shaped) painful petechiae Petechiae not in a "swimming trunks" distribution No edema of hands/feet Doesn't start on wrists/ankles Leukocytosis (not leukopenia) Blood cultures/lesions positive for <i>Neisseria meningitidis</i> |

*Refers to early hemorrhagic smallpox.

ALT, alanine aminotransferase/SGPT, serum glutamic-pyruvic transaminase; AST, aspartate aminotransferase/SGOT, serum glutamic-oxaloacetic transaminase; DIC, disseminated intravascular coagulation.

TABLE 29-8 Community-Acquired Rash and Fever in the ICU

MACULOPAPULAR RASHES

PALMS AND SOLES

| DISORDER | CENTRAL > PERIPHERAL | | RASH | RASH DETAILS | CLINICAL FEATURES | OTHER FEATURES | DIFFERENTIAL DIAGNOSIS (KEY DDx POINTS) |
|----------|----------------------|---------|------|---|--|---|---|
| | PERIPHERAL | CENTRAL | | | | | |
| Measles | + | - | - | Rash appears 4 days after fever Rash begins at hairline and behind ears on head/face Rash blanches on pressure Rash blotchy/mottled on trunk Rash rapidly becomes confluent first on face Rash spreads from head to feet in 3 days | Clinical Findings: <i>Dry cough, runny nose, and sore throat</i> prominent Laryngitis common <i>Conjunctivitis</i> <i>Tender anterior cervical adenopathy</i> common Laboratory Findings: <i>Leukopenia</i> <i>Relative lymphopenia</i> ± Thrombocytopenia Diagnosis: Clinical appearance/presentation <i>Elevated</i> IgM measles titers Warthin-Finley cells in stained smears of nasal mucosa diagnostic | Mild upper respiratory tract infection precedes rash Common in <i>spring</i> <i>Toxicemic early, but toxicemic appearance fades as rash reaches feet</i> <i>Koplik's spots</i> ("grains of salt" appearance) on dark red buccal mucosa <i>opposite lower 2nd molar appear 1-2 days before rash</i> (not Fordyce aphthae on pale buccal mucosa) May later develop "giant cell" measles pneumonia or later bacterial pneumonia (rare) In some, abdominal pain (<i>pseudo-appendicitis</i>) Fever peaks day 2 or 3 of rash then falls Encephalitis (rare) Hemorrhagic measles (mucosal/skin); measles with hemorrhages rare but often fatal | Rubella: Also occurs in spring Fever < 102°F (short duration) Patient <i>not</i> toxicemic <i>No URI</i> symptoms <i>No conjunctivitis</i> <i>No enanthem</i> Bilateral <i>posterior cervical adenopathy</i> <i>Forchheimer's spots</i> (petechiae) on soft palate Rash transient and not confluent Rash spreads in 1 day and rapidly fades Rash doesn't spread from head → feet WBC count usually WNL (mild leukopenia in some) Elevated rubella titers Adult Kawasaki's disease: <i>High fevers</i> (>102°F) >5 days <i>No relative bradycardia</i> <i>Conjunctival suffusion</i> Mild anterior uveitis (in most) <i>Nonexudative pharyngitis</i> <i>Mucosal hyperemia</i> Bilateral <i>cervical adenopathy</i> Scarlatiniform rash Erythema multiforme-like rash (in some) Diarrhea/abdominal pain common <i>Carditis</i> (nonspecific (ST/T wave abnormalities) ± Splenomegaly <i>Perianal hyperemia</i> <i>Edema of dorsum of hands/feet</i> <i>Leukocytosis</i> <i>Thrombocytopenia</i> (1st week) <i>Thrombocytosis</i> (2nd-3rd week) <i>Highly/persistently elevated ESR</i> <i>Mildly elevated</i> AST(SGOT)/ALT(SGPT) <i>Highly elevated ferritin levels</i> <i>Sterile pyuria</i> Epstein-Barr virus (EBV) infectious mononucleosis: High fevers with <i>prominent fatigue</i> Rash has "sprinkled paprika" appearance <i>Bilateral upper eyelid edema</i> early (Hoagland's sign) Exudative/nonexudative <i>pharyngitis</i> <i>Palatal petechiae</i> <i>Bilateral posterior cervical adenopathy</i> Splenomegaly (<i>late</i>) <i>Leukopenia</i> ± thrombocytopenia Lymphocytosis/atypical lymphocytes (2nd week) Highly elevated ESR 30% have <i>positive group A streptococci throat cultures</i> <i>Mildly elevated</i> AST(SGOT)/ALT(SGPT) <i>Elevated</i> EBV VCA IgM titers |

ALT, alanine aminotransferase/SGPT, serum glutamic-pyruvic transaminase; AST, aspartate aminotransferase/SGOT, serum glutamic-oxaloacetic transaminase; IgM, immunoglobulin M; URI, upper respiratory infection; VCA, viral capsid antigen.

TABLE 29-9 Community-Acquired Rash and Fever in the ICU

VESICULAR RASHES

| DISORDER | CENTRAL > PERIPHERAL | PERIPHERAL > CENTRAL | PALMS AND SOLES RASH | RASH DETAILS | CLINICAL FINDINGS: | OTHER FEATURES | DIFFERENTIAL DIAGNOSIS (KEY DDx POINTS) |
|---|----------------------|----------------------|----------------------|--|---|--|--|
| | | | | | | | |
| Smallpox (ordinary) Subtypes: Confluent Semi-confluent Discrete | | + | ± | Rash appears 2-4 days after fever decreases Macular lesions ("herald spots") appear at hairline followed by papules) Exanthem on hard palate, soft palate, and tongue early when macules appear On 3rd day of rash, papules become vesicular Vesicles/pustules rapidly cover the face and upper extremities Relative sparing of the trunk Rash on palms/soles appear last Umbilication of pustules begins on 5th day. All vesicles become pustules by the 6th day Umbilicated pustules are deep in the dermis Rash is pruritic Usually, skin lesions are in the same stage of development in each anatomic region, but stage of rash differs from region to region All pustules are in the same stage of development by 7th day Rarely, lesions may appear as a "single crop" and then present with all lesions in the same stage Lesions on extremities (distal > proximal, extensor surfaces > flexor surfaces, convexities > concavities) Apex of axilla free of lesions (Rickett's sign) On 9th day, pustules reach maximum size and begin to flatten Pustular scabbing begins on 13th day | Prodrôme: 10-14 days Patient appears toxicemic Patient feels better when fever decreases on 3rd day and rash begins Abdominal pain common (pseudo-appendicitis if in RLQ) Severe headache/backache before rash Dry cough common Nausea, vomiting or diarrhea in some Delirium in some Fever reappears on 7th or 8th day Laboratory Findings: Leukocytosis Relative lymphocytosis ±Basophil Platelet count: WNL AST(SGOT)/ALT(SGPT): WNL Diagnosis: Clinical appearance/presentation Tzanck test negative | Suspect bioterrorism Exanthem source of airborne viral spread during coughing | Chickenpox: Patients not toxicemic Vesicles primarily on trunk > extremities/face (hands/feet relatively spared) Vesicles appear in "successive crops" from day 1 to day 3 Vesicles in different stages of development Vesicles superficial not deep in dermis ("dewdrop on rose petal" appearance) ±Basophil Tzanck test positive Vesicle fluid DFA positive for VZV Monkeypox: Endemic in West Africa Exposure to cats, prairie dogs, or West African rodents Patients not toxicemic Usually fewer lesions than smallpox Painful regional adenopathy |

ALT, alanine aminotransferase/SGPT, serum glutamic-pyruvic transaminase; AST, aspartate aminotransferase/SGOT, serum glutamic-oxaloacetic transaminase; DFA, direct fluorescent antibody; RLQ, right lower quadrant.

TABLE 29-10 Community-Acquired Rash and Fever in the ICU

BULLOUS RASHES

| DISORDER | CENTRAL > PERIPHERAL | PERIPHERAL > CENTRAL | PALMS AND SOLES RASH | RASH DETAILS | CLINICAL FEATURES | OTHER FEATURES | DIFFERENTIAL DIAGNOSIS (KEY DDx POINTS) |
|--------------------------|----------------------|----------------------|----------------------|---|---|---|--|
| <i>Vibrio vulnificus</i> | + | — | — | Rash appears <i>hours-days</i> after fever Painful bullous lesions usually on buttocks | Clinical Findings: Fever/chills Watery diarrhea prominent ± abdominal pain Laboratory Findings: Leukocytosis AST(SGOT)/ALT(SGPT): WNL Diagnosis: Clinical appearance/presentation Blood/stool/wound cultures positive for <i>V. vulnificus</i> | Ingestion of water contaminated with “halophilic vibrios” Recent exposure of wound with water contaminated with “halophilic vibrios” | Gas gangrene: No recent colon/pelvic surgery No exposure to “halophilic vibrios” No fever/chills No muscle involvement (myonecrosis) Culture of bullae negative for <i>Vibrio vulnificus</i> Diabetic cSSSIs: Diabetes may develop bullae (without infection) but are not toxemic Diabetes with mixed aerobic/anaerobic infections are febrile but have no muscle involvement (myonecrosis) Diabetes with mixed aerobic/anaerobic with cSSSIs have crepitus/abundant gas on soft-tissue x-rays No acute hemolytic anemia No watery diarrhea Bullous fluid foul smelling Bullous fluid/soft-tissue cultures positive for aerobes/anaerobes (not Clostridium) |

ALT, alanine aminotransferase/SGPT, serum glutamic-pyruvic transaminase; AST, aspartate aminotransferase/SGOT, serum glutamic-oxaloacetic transaminase.

NOSOCOMIAL-ACQUIRED RASH AND FEVER

Petechial/Purpuric Rash and Fever

Staphylococcal bacteremia (high-grade and continuous) is usually related to an intravascular or interventional procedure or device.^{1,3} Staphylococcal bacteremia or ABE presents initially with petechial or purpuric lesions that later can become hemorrhagic and/or gangrenous. The diagnosis is suggested by the peripheral location of these irregular, painful lesions in the setting of high-grade and continuous staphylococcal bacteremia.^{1,4,11}

An underrecognized but important cause of nosocomial rash and fever is cholesterol emboli syndrome (CES).²⁰ Cholesterol emboli may be released into the systemic circulation during or following cardiovascular procedures. CES presents as a petechial or purpuric rash with a livedo reticularis-like appearance.^{1,8} The rash occurs on the trunk and extremities and may be accompanied by signs of cholesterol emboli to other organs such as the heart (myocardial infarction), pancreas (acute pancreatitis), kidneys (acute renal failure), or central nervous system (stroke). Excluding drug rash and fever, cholesterol emboli syndrome is the only acute rash in the ICU associated with peripheral eosinophilia.^{8,20}

Drug rashes are drug hypersensitivity reactions presenting with a rash and fever. Most patients who develop drug rashes do so after receiving new medications in the hospital, but some develop drug rash and fever years after taking sensitizing chronic medications. Drug rashes are generalized, maculopapular or petechial, and may be pruritic. Fever is usually present and may be high (>102°F), regularly accompanied by relative bradycardia.^{8,9} Mild increases in serum transaminase levels and eosinophils in the blood smear are common findings.⁸ The clinical difficulty with drug rash and fever is distinguishing it from underlying medical disorders. Even after discontinuing the sensitizing drug, the rash and fever may take days or weeks to resolve.^{1,3,4,9}

Maculopapular Rashes and Fever

Maculopapular rash due to surgical TSS is uncommon. Typical surgical TSS occurs from wound infection several days after surgery. A key clinical clue is that drainage from the wound is serosanguineous rather than purulent.^{5,7,11,12}

Vesicular/Bullous Rashes and Fever

Particularly following distant extremity trauma or distal abdominal surgery, gas gangrene should be considered in the differential diagnosis.^{3,6} In patients with gas gangrene (i.e., clostridial myonecrosis), the vesicular or bullous eruptions spread rapidly (over minutes to hours). The skin near the bullous lesions is tense and extremely tender, and the fluid in the lesions is not foul smelling. Patients with gas gangrene are afebrile or have only a low-grade fever, but these patients often have watery diarrhea.^{1,3} A key clinical clue to gas gangrene is rapidly progressive hemolytic anemia due to lysis of red blood cells by clostridial lethicinases.^{1,4,11} On physical examination, gas in tissues is not clinically detectable or obvious and is not a feature of gas gangrene. On a computed tomography (CT) scan, small gas bubbles may be visible along the muscle planes.^{1,3} Large collections of gas in the soft tissues on imaging studies should suggest a mixed aerobic-anaerobic infection by nonclostridial gas-producing organisms. Mixed aerobic-anaerobic soft-tissue infections are most common in diabetics and do not involve muscle (myonecrosis).^{1,3,10}

Fever is usually prominent with mixed aerobic or anaerobic soft-tissue infections, but clostridial gas gangrene characteristically is associated with little or no fever. The differential diagnosis of nosocomial rash and fever is presented in [Tables 29-11 to 29-14](#).^{1,4,10,11}

The diagnostic approach to rash and fever depends on correctly correlating the location and characteristics of the rash with associated nondermatologic features, such as physical examination, laboratory findings, or both to arrive at a clinical syndromic diagnosis ([Table 29-15](#)).¹⁻²⁰

TABLE 29-11 Hospital-Acquired Rash and Fever in the ICU

PETECHIAL/PURPURIC RASHES

| DISORDER | CENTRAL > PERIPHERAL | PERIPHERAL > CENTRAL | PALMS AND SOLES RASH | RASH DETAILS | CLINICAL FEATURES | OTHER FEATURES | DIFFERENTIAL DIAGNOSIS (KEY DDx POINTS) |
|--|----------------------|----------------------|----------------------|--|--|--|--|
| <i>Staphylococcus aureus</i> high-grade continuous bacteremia/ABE | + | + | | Rash appears 3-5 hours after fever Irregular, painful petechial/gangrenous lesions on distal extremities | <p>Clinical Findings: Fever > 102°F Shaking chills New/changing heart murmur if ABE Source of bacteremia (abscess, CVC, etc.) usually clinically apparent</p> <p>Laboratory Findings: Leukocytosis ± Thrombocytopenia Increased ESR/CRP AST(SGOT)/ALT(SGPT): WNL</p> <p>Diagnosis: Clinical appearance/ presentation Petechial/purpuric lesions Gram stain/culture positive for <i>S. aureus</i> (MSSA/MRSA) Continuous/high-grade bacteremia 3/4-4/4 blood cultures positive for MSSA/MRSA TTE: if ABE, positive for vegetation</p> | Recent history of intracardiac procedure, CVC, pacemaker/defibrillator, vascular grafts/shunts Recent post-op MSSA/MRSA skin/soft-tissue infection or abscesses | <p>Drug Rash: Often atopic PMH Cause of drug fever usually not an antibiotic Patient looks "relatively well" (not "septic" for degree of fever 102°F-106°F) Relative bradycardia (if temperature >102°F and not on β-blockers, diltiazem, or verapamil) Pruritus common Rash usually due to chronic drugs, not new drugs Rash always generalized, not localized Leukocytosis common (with left shift) Eosinophils common (eosinophilia less frequent) Elevated ESR Mildly elevated AST(SGOT)/ALT(SGPT) After sensitizing medication stopped, fevers may persist for days or weeks</p> <p>Cholesterol emboli syndrome: History of recent carotid surgery, cardiac catheterization, coronary angioplasty, anticoagulation, or open heart surgery day before rash Leg pain prominent Otherwise unexplained, acute renal failure typical GI bleed common Normal peripheral pulses Toes often purple and painful</p> <p>Vasculitis: No heart murmur No chills Blood cultures negative for MSSA/MRSA TTE: No cardiac vegetations ANA, p-ANCA/c-ANCA positive</p> |

ABE, acute bacterial endocarditis; ALT, alanine aminotransferase/SGPT, serum glutamic-pyruvic transaminase; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic autoantibody; AST, aspartate aminotransferase/SGOT, serum glutamic-oxaloacetic transaminase; CRP, C-reactive protein; CVC, central venous catheter; ESR, erythrocyte sedimentation rate; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*; TTE, transthoracic echocardiography.

TABLE 29-12 Hospital-Acquired Rash and Fever in the ICU

MACULOPAPULAR RASHES

| DISORDER | CENTRAL > PERIPHERAL | | PALMS AND SOLES | | RASH DETAILS | CLINICAL FEATURES | OTHER FEATURES | DIFFERENTIAL DIAGNOSIS (KEY DDx POINTS) |
|-------------------------------------|----------------------|----------------------|----------------------|------|--|---|---|---|
| | CENTRAL > PERIPHERAL | PERIPHERAL > CENTRAL | PERIPHERAL > CENTRAL | RASH | | | | |
| Surgical toxic shock syndrome (TSS) | + | | | ± | Diffuse erythroderma Erythema intense around wound Generalized erythroderma (in some) Severe back pain Wound pain disproportionate to appearance of wound Diffuse erythroderma Local wound edema | <p>Staphylococcus aureus: Clinical Findings: Abrupt-onset fever, rash, and hypotension Mucosal hyperemia Edema of dorsum of hands/feet Leukocytosis but not eosinophilia Wound discharge serosanguineous (not purulent)</p> <p>Diagnosis: Blood cultures for <i>S. aureus</i> negative Wound cultures for <i>S. aureus</i> positive</p> <p>Group A streptococci: Clinical Findings: Often associated with necrotizing fasciitis Purple bullae/edema at site (necrotizing fasciitis) Acute-onset hypotension and renal failure in most</p> <p>Laboratory Findings: WBC count: WNL/leukocytosis (but left shift)</p> <p>Platelet count: WNL Increased AST(SGOT)/ALT(SGPT)</p> <p>Diagnosis: Blood cultures positive for group A streptococci Wound culture positive for group A streptococci</p> <p>Clostridium sordellii: Clinical Findings: Acute onset of hypotension, fever and weakness Nausea/vomiting common</p> <p>Laboratory Findings: ↑↑ WBC count: (leukemoid reactions common with WBC counts >50 K/mm³) Thrombocytopenia Increased AST(SGOT)/ALT(SGPT)</p> <p>Diagnosis: Cultures negative for all other pathogens Culture of blood/wound positive for <i>C. sordellii</i></p> | <p>Often nausea, vomiting, or diarrhea Delirium common History of recent surgery Some on NSAIDs Cellulitis Varicella (VZV) infection Recent childbirth Burn wounds Associated with necrotizing soft-tissue infections Associated with trauma or cadaveric musculoskeletal grafts Associated with recent childbirth or abortion Associated with black tar heroin use</p> | <p>Drug rash: Often atopic PMH Cause of drug fever usually not an antibiotic Patient looks "relatively well" (not "septic" for degree of fever 102°F-106°F) Relative bradycardia (if temperature >102°F and not on β-blockers, diltiazem, or verapamil) Pruritus common Rash usually due to chronic drugs, not new drugs Rash always generalized, not localized Leukocytosis common (with left shift) Eosinophils common (eosinophilia less frequent) Elevated ESR Mildly elevated AST(SGOT)/ALT(SGPT) After sensitizing medication stopped, fevers may persist for days or weeks</p> |

ALT, alanine aminotransferase/SGPT, serum glutamic-pyruvic transaminase; AST, aspartate aminotransferase/SGOT, serum glutamic-oxaloacetic transaminase; VZV, varicella zoster virus.

TABLE 29-13 Hospital-Acquired Rash and Fever in the ICU

MACULOPAPULAR RASHES

| DISORDER | CENTRAL > PERIPHERAL | PERIPHERAL > CENTRAL | PALMS AND SOLES RASH | RASH DETAILS | CLINICAL FEATURES | OTHER FEATURES | DIFFERENTIAL DIAGNOSIS (KEY DDx POINTS) |
|---|----------------------|----------------------|----------------------|---|--|---------------------------|---|
| Surgical scarlet fever (group A streptococci) | + | | ± | Rash appears 1-3 days after fever Scarlatiniform rash (not pruritic) Circumoral pallor Mucosal hyperemia Pastia's lines in antecubital fossae | Clinical Findings: Not critically ill Not hypotensive Conjunctival suffusion Wound discharge serosanguineous (not purulent) Laboratory Findings: Leukocytosis Eosinophilia Platelet count: WNL AST(SGOT)/ALT(SGPT): WNL Diagnosis: Clinical appearance/ presentation Blood/wound cultures positive for group A streptococci | History of recent surgery | Surgical TSS: Staphylococcus aureus: Abrupt-onset fever, rash, and hypotension Diffuse erythrodema Mucosal hyperemia Nausea, vomiting, or diarrhea common Delirium common Edema of dorsum of hands/feet Erythema intense around wound Wound discharge serosanguineous (not purulent) Leukocytosis but not eosinophilia Blood cultures for <i>S. aureus</i> negative Wound cultures positive for <i>S. aureus</i> Surgical TSS: Group A streptococci: History of recent surgery Associated with NSAIDs Associated with cellulitis Associated with varicella (VZV) infection Associated with recent childbirth Associated with burn wounds Generalized erythrodema in some Severe local pain disproportionate to appearance of wound Often associated with necrotizing fasciitis Purple bullae/edema at site (necrotizing fasciitis) Acute onset of hypotension and renal failure in most Blood cultures positive for group A streptococci Wound culture positive for group A streptococci |

ALT, alanine aminotransferase/SGPT, serum glutamic-pyruvic transaminase; AST, aspartate aminotransferase/SGOT, serum glutamic-oxaloacetic transaminase; NSAIDs, nonsteroidal antiinflammatory drugs; VZV, varicella zoster virus.

TABLE 29-14 Hospital-Acquired Rash and Fever in the ICU**BULLOUS RASHES**

| DISORDER | CENTRAL > PERIPHERAL | PERIPHERAL > CENTRAL | PALMS AND SOLES RASH | RASH DETAILS | CLINICAL FEATURES | OTHER FEATURES | DIFFERENTIAL DIAGNOSIS (KEY DDx POINTS) |
|--|----------------------|----------------------|----------------------|---|---|---|--|
| Gas gangrene (clostridial myonecrosis) | + | — | — | Initial rash appears suddenly and advances in minutes to hours Extremely painful bullae (fluid not foul smelling) Skin discolored (orange/black) painful and tense | Clinical Findings: Low grade/no fevers Relative tachycardia No crepitus! Odor of bullous fluid sweetish (not foul) Laboratory Findings: Leukocytosis Acute/profound hemolytic anemia ↑↑↑ LDH Little/no gas on soft-tissue x-rays Diagnosis: Clinical appearance/presentation Wound Gram stain positive for gram-positive bacilli (with few PMNs) Blood or wound cultures positive for <i>Clostridia</i> sp. | Recent trauma Recent colon/pelvic surgery Patient appears extremely toxic Rapidly fatal without prompt, adequate débridement Watery diarrhea common | Diabetic cSSSIs: Diabetes may develop bullae (without infection) but are <i>not</i> toxicemic Diabetes with mixed aerobic/anaerobic infections are febrile but have no muscle involvement (myonecrosis) Diabetes with mixed aerobic/anaerobic cSSSIs have crepitus/abundant gas on soft-tissue x-rays No acute hemolytic anemia No watery diarrhea Bullous fluid foul smelling Bullous fluid/soft-tissue culture positive for aerobes/anaerobes (not <i>Clostridia</i>) |

cSSSI, complicated skin/skin structures infection; LDH, lactate dehydrogenase.

TABLE 29-15 Differential Diagnostic Laboratory Features of Fever and Rash in the ICU

| | INFECTIOUS CAUSES | NONINFECTIOUS CAUSES |
|--|--|--|
| Rash with elevated AST(SGOT)/ALT(SGPT) | EBV HIV RMSF PSS Arboviral hemorrhagic fevers TSS Dengue fever | Drug rash Adult Kawasaki's disease |
| Rash with relative lymphopenia | HIV RMSF Chikungunya fever Dengue fever | SLE Adult Kawasaki's disease |
| Rash with leukocytosis | RMSF ABE (<i>Staphylococcus aureus</i>) MC Chikungunya fever | Drug rash |
| Rash with eosinophilia | Scarlet fever | Cholesterol emboli syndrome Drug rash |
| Rash with leukopenia | TSS PSS Dengue fever Smallpox Arboviral hemorrhagic fevers | SLE Atypical measles |
| Rash with generalized adenopathy | Arboviral hemorrhagic fevers EBV Dengue fever Scarlet fever Measles Rubella | SLE Adult Still's disease |

ABE, acute bacterial endocarditis; ALT, alanine aminotransferase/SGPT, serum glutamic-pyruvic transaminase; AST, aspartate aminotransferase/SGOT, serum glutamic-oxaloacetic transaminase; DF, dengue fever; MC, meningococcemia; RMSF, Rocky Mountain spotted fever; SLE, systemic lupus erythematosus; TSS, toxic shock syndrome.

Adapted from: Cunha CB. Differential diagnosis of infectious diseases. In: Cunha BA, editor. Antibiotic Essentials. 15th ed. New Delhi: JayPee Medical Publishers; 2016. p. 474-506.

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■ References for this chapter can be found at expertconsult.com.

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Chest pain in the intensive care unit (ICU) is a somewhat different entity from chest pain seen in the office, inpatient ward, or emergency department. The keys to management of chest pain in the ICU are rapid assessment and treatment of immediately life-threatening conditions, careful consideration of the differential diagnosis, a logical evaluation plan, and empiric treatment while pursuing a definitive diagnosis.

INITIAL APPROACH

Several life-threatening conditions can cause chest pain in the critically ill, and the initial approach should focus on prompt evaluation and resuscitation of the airway, breathing, and circulation. Assess the patient's level of consciousness, palpate the pulse, and listen to the breath sounds and heart. Obtain vital signs, including oxygen saturation by pulse oximetry, and ensure that the patient is on a cardiac monitor and has adequate intravenous (IV) access. Adhering to this algorithmic approach (Fig. 30-1) in patients with chest pain will ensure that critical conditions such as hypoxemia, hypotension, tension pneumothorax, and unstable ventricular arrhythmias are quickly identified and treated. These conditions, as well as the life-threatening causes of chest pain discussed below, are covered in greater detail in other chapters in this textbook.

HISTORY

After the initial evaluation and stabilization, obtain a more detailed history. If the patient can communicate, start with an open-ended question like "What's going on, Mr. Jones?" Physicians typically interrupt patients within 23 seconds, but one should resist this temptation and allow the patient to describe his or her symptoms.¹ Physicians often neglect to ask even basic questions about the quality of chest pain, as was shown in a study of patients with aortic dissection, and this omission is associated with a delay in diagnosis.² The mnemonic OLDCAAR can help avoid this mistake (Table 30-1). Ask the bedside nurse about recent changes in the patient's condition (e.g., changes in mental status, respiratory pattern, or recent medications). Last, a quick "chart dissection" should be performed, focusing on the findings noted on initial presentation, reason for ICU admission, past history, and recent progress notes.

PHYSICAL EXAMINATION

Inspect the chest for asymmetric excursions, rashes, or obvious sources of pain, such as chest tubes. Palpate the chest and neck for crepitus, which can result from a pneumothorax or pneumomediastinum. Check for pulsus paradoxus and jugular venous distention. Assess for asymmetry in the carotid, femoral, or radial pulses, which can be a sign of aortic dissection. If the breath sounds are asymmetrical, hyperresonance to percussion may confirm a pneumothorax. Cardiac auscultation may reveal a friction rub from pericarditis, "crunching" sounds from mediastinal emphysema (Hamman's sign), a systolic murmur of aortic stenosis, or an aortic insufficiency murmur from a proximal aortic dissection. A focused examination also should include the abdomen to avoid missing an abdominal catastrophe masquerading as chest pain. Unfortunately, the physical examination has its limitations, and further diagnostic testing is often necessary.

DIAGNOSTIC ADJUNCTS

In the absence of an obvious cause of chest pain (e.g., shingles), a portable chest x-ray (CXR) and electrocardiogram (ECG) should be obtained. Serial cardiac enzymes should be strongly considered to exclude a myocardial infarction (MI). The ECG is often nonspecific but occasionally will show evidence of acute coronary syndrome (ACS), pericarditis, or pulmonary embolism (PE). The CXR is a useful screening tool for life-threatening causes of chest pain, including aortic dissection, pneumothorax, and esophageal rupture. Both the ECG and CXR should be compared with those performed prior to the onset of pain. Although the ECG or CXR may be suggestive of a diagnosis, other confirmatory studies may be necessary.

IV contrast-enhanced computed tomography (CT) can help diagnose a number of causes of chest pain, including PE, aortic dissection, esophageal rupture, pneumothorax, and pneumonia. The benefits of CT scanning, however, must be weighed against the risks of transporting a critically ill patient out of the ICU, as well as the potential for causing contrast nephropathy. Ultrasound (including echocardiography) can be rapidly performed with minimal risk to the patient and does not require transport out of the ICU. Pericarditis with associated effusion, wall motion abnormality from MI, aortic stenosis, aortic dissection, and pneumothorax are all within the diagnostic realm of ultrasound. Ultrasound has the added benefit of providing information about cardiac function.

DIFFERENTIAL DIAGNOSES

Two rules to live by:

1. Do not assume the admission diagnosis is correct or all inclusive. Premature closure, that is, failing to consider alternative possibilities after a diagnosis has come to mind, is a common cause of medical error.³ Premature closure likely contributes to the delay in diagnosis described in hospitalized patients with aortic dissection.⁴
2. Do not be biased by the type of ICU to which the patient is admitted. Aortic dissection can present as a stroke, prompting admission to a neurologic ICU, or an acute abdomen can develop in a medical ICU patient. Indeed, a review of abdominal catastrophes concluded that "delays in surgical evaluation and intervention are critical contributions to mortality rate in patients who develop acute abdominal complications in a medical ICU."⁵

Potentially Life-Threatening Causes of Chest Pain

Acute Coronary Syndrome

ACS includes unstable angina and MI with or without ST-segment elevation MI. The classic symptoms of ACS include chest pressure radiating to the left arm, nausea, and diaphoresis, but this history has several limitations with regard to the diagnosis of ACS. Although certain features (pain radiating down the right arm or both arms) are associated with a higher likelihood of ACS, and other characteristics (pleuritic, positional, or sharp pain) with a lesser likelihood, none of these can reliably confirm or exclude the diagnosis.^{6,7} Further complicating matters, the conventional cardiovascular risk factors, including diabetes, smoking, dyslipidemia, hypertension, and a family history,

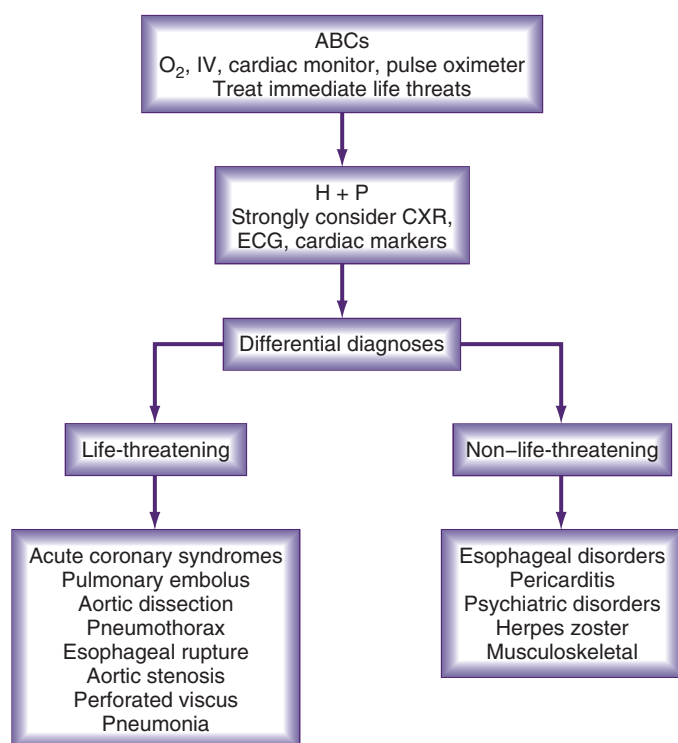


FIGURE 30-1 ■ Approach to chest pain in the ICU. ABC, airway, breathing, circulation; CXR, chest x-ray; ECG, electrocardiogram; H + P, history and physical examination; ICU, intensive care unit; IV, intravenous access.

TABLE 30-1 OLDCAAR Mnemonic for Evaluating Pain

| DOMAIN | SUGGESTED QUESTIONS |
|--------------------------------|---|
| Onset | Sudden or gradual? Maximal pain at onset? |
| Location | Generalized or localized? Can you point with one finger to where it hurts? |
| Duration | When did it start? Just now, or did the pain occur earlier, but you didn't want to bother anyone? Is it constant or intermittent? If intermittent, is there a trigger, or is it random? |
| Character | Sharp? Dull? Ache? Indigestion? Pressure? Tearing? Ripping? |
| Associated symptoms | "Dizzy" (vertiginous or presyncopal)? Diaphoresis? Palpitations? Dyspnea? Nausea or vomiting? |
| Alleviating/aggravating | Position? Belching? Exertion? Deep breathing? Coughing? |
| Radiation | To the back? Jaw? Throat? Arm? Neck? Abdomen? |

predict the development of heart disease over years in asymptomatic patients but may be less useful in predicting ACS in patients with acute chest pain.⁸ Reduction in pain after the administration of nitroglycerin is also not a reliable indicator of cardiac chest pain.⁹ Thus, ACS should almost never be excluded as a cause of chest pain based on the symptoms alone.

Physical examination findings in patients with ACS may include signs of left ventricular dysfunction, such as hypotension, jugular venous distention (JVD), and an S₃ or S₄ heart sound. The ECG should be examined for ST segment elevation or depression, Q waves, and

T-wave inversions. The ECG has a low sensitivity for diagnosing MI, but yield increases with serial ECGs. Given the limitations of the ECG and history and examination findings, cardiac enzymes should be measured in most ICU patients with chest pain.

All patients suspected of having ACS should be placed on oxygen and, if not contraindicated, treated with aspirin (clopidogrel or ticagrelor if there is aspirin allergy). Sublingual nitroglycerin and IV morphine should be used to relieve pain if the systolic pressure is above 90 mm Hg. Further treatment of ACS is primarily dictated by ECG findings and the patient's clinical status. It may include emergency percutaneous coronary intervention (the preferred strategy) or fibrinolysis in the setting of ST segment elevation when on-site cardiac catheterization is not available and the bleeding risk is acceptable. Adjunct therapies, depending on cardiac findings and the treatment administered may include dual antiplatelet therapy (aspirin plus clopidogrel, prasugrel, or ticagrelor), a beta-blocker, statin, angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist, and aldosterone receptor antagonist.

Pulmonary Embolism

Approximately 1% to 2% of ICU patients develop deep vein thrombosis (DVT) or PE, but the true incidence is probably higher.¹⁰ Unrecognized PE carries a high mortality, but survival improves dramatically with prompt diagnosis and treatment. Chest pain due to PE is usually pleuritic and often associated with dyspnea, hemoptysis, cough, or syncope.¹¹ ICU patients often have one or more risk factors for PE, including immobility, advanced age, recent surgery or trauma, malignancy, and central venous catheterization. Do not be deterred from evaluating for PE in patients receiving subcutaneous heparin, as in one study of patients in intensive care, two-thirds diagnosed with DVT and PE were receiving prophylaxis at the time of diagnosis.¹⁰

Physical examination findings are generally nonspecific in PE. Unexplained tachypnea or tachycardia may be the only diagnostic clues. Hypoxia is often present but is not a universal finding, and its absence cannot exclude PE. A large PE may present with hypotension or cardiovascular collapse. Signs of pulmonary hypertension and right heart failure, such as a loud second heart sound (P₂), JVD, or a right-sided S₄ heart sound may be present. Lung examination may reveal crackles, decreased breath sounds, wheezing, rhonchi, or a pleural friction rub.

An elevated arterial-alveolar gradient may be noted on blood gas analysis, but this is a nonspecific finding in the critically ill. The ECG is often normal, but it may show sinus tachycardia, right axis deviation, nonspecific ST segment and T-wave changes, or a right bundle branch block.¹² The CXR can be normal but more commonly reveals nonspecific findings such as pleural effusion, infiltrates, or atelectasis.¹³ Although D-dimer testing has been used to rule out venothromboembolic disease in outpatients with a low likelihood of this diagnosis, the D-dimer assay does not appear to be a particularly useful diagnostic tool in the ICU setting.¹⁴ The sensitivity of transthoracic echocardiography (TTE) for PE varies considerably, but the test can be useful in patients who have large clots that are of hemodynamic significance. In such cases, TTE can be performed rapidly at the bedside when it is unsafe to transport patients out of the ICU. TTE has the added benefit of assessing the response to thrombolytics by evaluating right heart function and changes in pulmonary artery pressure.¹⁵ A ventilation/perfusion scan can be time consuming and difficult to perform in mechanically ventilated patients, and interpreting it may be challenging in the presence of other lung pathology.¹⁶ An IV contrast-enhanced CT of the chest can be performed rapidly, and newer scanners have high sensitivity and specificity, making this the diagnostic study of choice in most ICU patients.

Initial treatment of patients with confirmed PE involves anticoagulation with subcutaneous low-molecular-weight heparin or fondaparinux, IV unfractionated heparin, or the newer oral factor Xa inhibitors rivaroxaban or apixaban. Patients with hemodynamic instability due to PE may require thrombolysis or surgical- or catheter-mediated embolectomy.¹⁷

Thoracic Aortic Dissection

Aortic dissection results from a tear in the aortic intima, allowing blood to dissect between the intima and adventitia. The Stanford system classifies dissections as type A (involving the ascending aorta) or type B (not involving the ascending aorta). Risk factors include hypertension, male sex, pregnancy, advanced age, atherosclerosis, cocaine use, intraaortic catheterization, Ehlers-Danlos syndrome, Turner syndrome, high-intensity weight lifting, chest trauma, and giant cell arteritis.¹⁸ Patients younger than 40 years are more likely to have Marfan syndrome, Loeys-Dietz syndrome, bicuspid aortic valve, prior aortic surgery, or aortic aneurysm.¹⁹ The mortality rate is as high as 1% to 2% per hour from symptom onset, and the history remains critical to early diagnosis.²⁰ Clinicians correctly suspect aortic dissection in more than 90% of cases when questions about quality, radiation, and intensity of the pain are asked. If one or more of these questions is omitted, the correct diagnosis is missed in over half of cases.² Many patients complain of sudden onset of chest pain that radiates to the back or abdomen. Contrary to popular belief, patients more commonly describe their pain as sharp, rather than tearing.¹⁹ Dissection can extend into any of the major aortic branches, causing a multitude of clinical presentations owing to ischemia of the brain, heart, kidney, spinal cord, or gut.

Certain physical examination findings should raise the suspicion of aortic dissection. About one-third of patients have pulse deficits in the carotid, radial, or femoral arteries, and some have focal neurologic deficits related to cerebral or spinal cord ischemia.¹⁸ Hypotension often occurs with type A dissection, whereas hypertension is more commonly seen in type B dissection.²⁰ A significant difference in systolic blood pressure (>20 mm Hg) between the upper extremities may be seen with dissection, but this is not a pathognomonic finding. A diastolic murmur of aortic insufficiency can result from retrograde dissection into the aortic valve.

The ECG may be normal or show nonspecific ST segment or T-wave changes or left ventricular hypertrophy secondary to hypertension. Rarely, the ECG reveals evidence of an MI from retrograde dissection into a coronary artery. Over 90% of patients will have some abnormality on CXR, such as widening of the mediastinum, an abnormal aortic contour, pleural effusion, or displacement of intimal aortic calcification from the outer border of the aortic knob.²¹ Therefore, it behooves the clinician to scour the CXR for these findings when considering aortic dissection as a cause of chest pain. The diagnosis can be confirmed with CT, magnetic resonance imaging (MRI), or transesophageal echocardiography, all of which have high sensitivity and specificity. The choice of diagnostic study will depend on physician preference and the risks involved. Initial management should focus on blood pressure control, usually with beta-blockers and a potent vasodilator such as nitroprusside²⁰ and emergent cardiothoracic surgical consultation.

Pneumothorax

Pneumothorax is caused by air from the alveoli or the atmosphere entering the potential space between the parietal and visceral pleura. Pneumothorax in the ICU is often iatrogenic, resulting from mechanical ventilation (particularly with acute respiratory distress syndrome), attempts at central venous catheterization, thoracentesis, tracheostomy, or bronchoscopy.²² Virtually any lung pathology can contribute to a pneumothorax, but a ruptured bleb from chronic obstructive pulmonary disease is the most common culprit. Patients with pneumothorax typically complain of the sudden onset of ipsilateral pleuritic chest pain with associated dyspnea.

Chest examination may reveal palpable crepitus, decreased breath sounds, decreased chest wall excursion, or hyperresonance to percussion on the affected side. Vital signs may be significant for tachycardia, hypoxia, or tachypnea. Patients with a tension pneumothorax classically have tracheal deviation, JVD, and hypotension. Patients on mechanical ventilation can have increased peak inspiratory airway pressures. The signs of pneumothorax are nonspecific, and any signifi-

cant deterioration in a patient on a ventilator should prompt a diagnostic evaluation for pneumothorax.

CXRs are often performed in the semiupright or supine position in the ICU, whereas the classic finding in pneumothorax of a visceral pleural line is often seen only on upright CXR. In supine patients, a deep sulcus sign may be seen where the costophrenic angle extends more inferiorly than normal as air collects in this space. Alternatively, a sharp delineation of the cardiac silhouette from the lucency of an anteromedial pneumothorax may be seen. In an experienced operator's hands, ultrasound can effectively rule out a pneumothorax in seconds.²³

Because of a high rate of conversion to tension pneumothorax in patients on mechanical ventilation, prompt diagnosis and treatment are critical. Treatment involves evacuation of air from the pleural space, usually through tube thoracostomy. In patients with hemodynamic compromise from a suspected tension pneumothorax, treatment with immediate needle thoracostomy, followed by tube thoracostomy, should not be delayed while waiting for a CXR.

Esophageal Rupture

A full-thickness tear of the esophagus carries high mortality owing to the intense inflammatory response to gastric contents in the mediastinum, secondary bacterial infection, and subsequent sepsis and multi-system organ failure. Most cases of esophageal perforation are caused by upper gastrointestinal tract endoscopy.²⁴ The risk of esophageal injury from a diagnostic endoscopy is low but increases dramatically when interventions such as dilation or stent placement are performed. Esophageal rupture may be caused by other procedures commonly performed in the ICU, including nasogastric or tracheal intubation. Spontaneous rupture of the esophagus (Boerhaave syndrome) occurs from a sudden increase in intraluminal pressure, usually from vomiting or retching. Patients with esophageal disease such as cancer, Barrett's esophagus, strictures, prior radiation, and varices are particularly vulnerable to rupture. With thoracic perforations, the pain localizes to the substernal or epigastric area, but it may occur in the neck with cervical perforations. Other associated symptoms include dysphagia, odynophagia, and dyspnea.

The patient is often febrile. Crepitus can be felt in the neck with perforation of the cervical esophagus. Mediastinal emphysema can sometimes be detected by a crunching sound on cardiac auscultation (Hamman's sign). A CXR often reveals subcutaneous emphysema, pneumomediastinum, pneumothorax, or pleural effusion. The CXR is abnormal in almost 90% of cases but may be normal early after the perforation occurs.²⁴ A water-soluble contrast study of the esophagus or a CT scan of the chest can be performed in cases where there is a high clinical suspicion and the CXR is nondiagnostic.

Treatment may involve operative repair, endoscopic therapy, or conservative management with broad-spectrum antibiotics and close observation.

Aortic Stenosis

Aortic stenosis causes left ventricular outflow obstruction, which leads to left ventricular hypertrophy. Aortic stenosis may result from a congenitally abnormal (bicuspid) valve, rheumatic heart disease in young adults, or from valvular calcification in the elderly. Clinical manifestations of aortic stenosis, including angina, congestive heart failure, and syncope, occur when the hypertrophied left ventricle can no longer overcome the valvular stenosis or when the hypertrophy itself causes diastolic dysfunction or excessive myocardial oxygen demand leading to ischemia.

Physical examination features of aortic stenosis include narrow pulse pressure, a delayed and slow rise of the carotid pulse (pulsus tardus et parvus), a systolic murmur at the right second intercostal space often radiating to the carotid arteries, and an S₄ heart sound (if patients are in sinus rhythm). CXR and ECG may show signs of left ventricular hypertrophy, but the diagnostic study of choice is a Doppler echocardiogram.

Definitive therapy involves valve replacement, either surgical or in select cases via transcatheter aortic valve replacement. Temporizing

management focuses on cautiously decreasing afterload with vasodilators. Close hemodynamic monitoring is essential when using vasodilators because of the risk of hypotension. Angina and congestive heart failure are treated with oxygen and the careful administration of nitrates, morphine, and diuretics. Occasionally, balloon aortic valvuloplasty may be used to bridge patients until they can undergo surgical or transcatheter valve replacement.²⁵

Miscellaneous

Other causes of potentially life-threatening chest pain in the ICU include pneumonia and acute abdominal processes. Pneumonia is often accompanied by pleuritic chest pain or shoulder pain referred from diaphragmatic irritation. A perforated ulcer can sometimes present with chest pain, and the diagnosis is often made when free air is incidentally discovered under the diaphragm on an upright CXR.

Non-Life-Threatening Causes of Chest Pain

The following causes of chest pain should be considered only after life-threatening causes have been excluded.

Esophageal Disorders

In patients with noncardiac chest pain, gastroesophageal reflux disorder and esophageal motility disorders (e.g., esophageal spasm) are common. Esophageal disease is associated with pain precipitated by lying flat, postprandial pain, heartburn, or dysphagia. Owing to the shared innervation of the heart and esophagus, visceral pain originating from these two organs can be similar in character. Relief of symptoms after a "GI cocktail" cannot be relied upon to identify chest pain as noncardiac in origin.²⁶ Confirmatory testing with esophageal manometry and esophageal pH monitoring can be performed, but a trial of a proton pump inhibitor may be a more practical diagnostic approach.²⁷ Last, a nasogastric tube with the distal tip in the esophagus can produce chest pain; this is easily remedied by advancing the tube distally into the stomach.

Musculoskeletal Disorders

The chest wall is a common source of pain in patients without a cardiorespiratory etiology of their symptoms. Pain from costochondritis is often reproduced with palpation or with arm movement. Up to 15% of patients with MI also have chest wall tenderness, so this finding does not exclude ACS.²⁸ Most cases of costochondritis are self-limiting and treated with nonsteroidal antiinflammatory drugs (NSAIDs). ICU patients may have other causes of chest wall pain, including rib fractures, chest tubes, postoperative pain after cardiothoracic surgery, or an intercostal muscle strain from coughing.

Pericarditis

Pericarditis is a relatively rare cause of chest pain in the inpatient setting.²⁹ The condition most commonly results from viral or idiopathic causes, but other etiologies include bacterial infections, malignancy, tuberculosis, uremia, autoimmune diseases, transmural MI (Dressler's syndrome), and cardiac surgery (postpericardiotomy syndrome). Chest pain from pericarditis is typically pleuritic, sharp, and retrosternal and radiates to the back, neck, or arms. The pain is often relieved by sitting forward and exacerbated by lying flat. Although uncomplicated pericarditis is not generally life threatening, pericardial inflammation can lead to pericardial effusion and cardiac tamponade if the effusion is large or acute.

A pericardial friction rub is highly specific for pericarditis and is present in the majority of cases. A classic pericardial rub with systolic and diastolic component sounds similar to hair being rubbed together

and is best heard with the diaphragm of the stethoscope over the left sternal border, with the patient sitting forward. Beck's triad (JVD, hypotension, muffled heart tones) is the classic description of pericardial tamponade, but unexplained tachycardia and tachypnea may be early signs. Pulsus paradoxus, or a fall in systolic blood pressure by more than 10 mm Hg with inspiration, is often seen in tamponade but is nonspecific.

ECG findings can clinch the diagnosis of pericarditis. Both MI and pericarditis may result in ST segment elevation, but with pericarditis, ST segment depression is typically absent in the reciprocal leads. Absence of Q waves, diffuse concave ST segment elevation, and PR depression strongly favor pericarditis.²⁹ Careful ECG review, auscultation, and history are key to distinguishing ACS from pericarditis and avoiding the potentially fatal complication of administering thrombolytics to a patient with pericarditis and precipitating hemotamponade. Electrical alternans and low voltage on the ECG, coupled with cardiomegaly on CXR, strongly favor pericardial effusion. Although the ECG and CXR findings of pericardial effusion can be useful, echocardiography should be performed to confirm the diagnosis.

Treatment is aimed at the underlying etiology. NSAIDs relieve pain and inflammation in cases of viral or idiopathic pericarditis. Colchicine may be used as an adjunct to NSAIDs in reducing bouts of recurrent pericarditis.³⁰ Pericardiocentesis is performed for therapeutic purposes in the case of tamponade and for diagnostic purposes if tuberculosis, bacterial infection, or malignancy is suspected. An IV fluid challenge may be a helpful temporizing measure in hypovolemic patients with tamponade.

Psychiatric Disorders

A significant number of patients with noncardiac chest pain suffer from panic disorder.³¹ In addition to chest pain, panic attacks can cause other symptoms that mimic MI, including diaphoresis, dyspnea, palpitations, and a sense of impending doom. A self-report of anxiety is a clue to the diagnosis of underlying panic disorder. Severe illness and its treatment with invasive procedures in the ICU can provoke profound psychological distress. The development of posttraumatic stress disorder is well described in ICU survivors, particularly in patients who experience episodes of extreme fear.³² Thus, while chest pain due to panic attack may not be acutely life threatening, this condition should not be considered benign and must be treated. Benzodiazepines are helpful in this regard. Psychiatric patients with cardiac or pulmonary disease can be especially challenging to diagnose, and a thorough, empathetic history is essential.

Herpes Zoster

Reactivation of the varicella-zoster virus from thoracic sensory ganglia causes a painful, dermatomal rash on the chest. The pain of shingles may precede the rash by several days, which can delay the diagnosis. The rash is characterized by vesicles that crust over after approximately 1 week. Oral acyclovir, valaciclovir, or famciclovir reduces the duration of herpetic neuralgia. Immunocompromised hosts are at high risk of complications from zoster infections and often require more aggressive treatment with IV acyclovir.

CONCLUSION

Attention to immediate life-threatening conditions and a thorough history and physical examination after initial stabilization are fundamental to managing chest pain in the ICU. A CXR, ECG, and serial cardiac enzymes should be ordered liberally but intelligently. A high index of suspicion for occult disease is necessary for complex ICU patients.

ANNOTATED REFERENCES

Gajic O, Urrutia LE, Sewani H, Schroeder DR, Cullinane DC, Peters SG. Acute abdomen in the medical intensive care unit. *Crit Care Med*. 2002;30(6):1187-1190.

In this retrospective study, delays in surgical evaluation and intervention were independent correlates of mortality. Risk factors for surgical delay included opioid use, mechanical ventilation, no peritoneal

signs, antibiotics, and altered mental state. A heightened index of suspicion for an acute abdomen is necessary in ICU patients with these risk factors.

Graber ML, Franklin N, Gordon R. Diagnostic error in internal medicine. *Arch Intern Med*. 2005; 165(13):1493-1499.

An analysis of 100 cases identified premature closure, that is, failing to consider alternatives once an initial diagnosis was made, as the most common cause of diagnostic error by internists. This study underscores the importance of not assuming that the admission diagnosis is necessarily correct or the only problem.

Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAAD): new insights into an old disease. *JAMA*. 2000;283(7):897-903.

The IRAAD is composed of 12 international referral centers, from which 3 years of data and 464 patients were analyzed. A key finding was that what are considered classic presentations of aortic dissection such as tearing or ripping chest pain (50.6%), aortic regurgitation (31.6%), and pulse deficit (15.1%) were frequently absent, leading the authors to urge clinicians to maintain a high index of suspicion.

Han JH, Lindsell CJ, Storrow AB, et al. The role of cardiac risk factor burden in diagnosing acute coronary syndromes in the emergency department setting. *Ann Emerg Med*. 2007;49(2):145-152.

This post hoc analysis of more than 10,000 emergency department patients suspected of having ACS suggests that clinicians should not use cardiac risk factor burden to determine whether or not chest pain is cardiac in nature in patients older than 40. Interestingly, for patients younger than 40, the odds of ACS increased dramatically as the total number of cardiac risk factors increased.

Marvel MK, Epstein RM, Flowers K, Beckman HB. Soliciting the patient's agenda: have we improved? *JAMA*. 1999;281(3):283-287.

Although this study was conducted in primary care offices and not in an ICU, it emphasizes the importance of the basic history-taking process and listening to patients. It found that physicians interrupted their patients after a mean of only 23.1 seconds and that late-arising patient concerns were more common when physicians did not solicit questions during the interview.

■ References for this chapter can be found at expertconsult.com.

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The identification of myocardial injury is an important problem in the critical care setting. Biomarkers have been used to detect myocardial injury since 1954,¹ and since then, the sensitivity of serologic techniques has increased dramatically. While increased sensitivity has allowed clinicians to detect smaller amounts of myocardial necrosis, this has also posed several interpretive challenges. What constitutes significant myocardial damage? How should evidence of myocardial necrosis be interpreted in the absence of classical clinical criteria for myocardial infarction? In response to some of these challenges, a task force was formed to formulate a universal definition of myocardial infarction.² The task force developed a clinical classification of different types of myocardial infarctions (MIs), which was recently updated in 2012 (see Table 31-1).³ Of the five types, the most pertinent in the critical care setting are Type I (plaque rupture) and Type II (demand ischemia leading to infarction). These definitions rely on both electrocardiographic and biochemical information and stress that, in addition to biochemical findings, the diagnosis of MI requires symptoms or characteristic electrocardiogram (ECG) changes or findings from imaging, angiography, or autopsy.

ELECTROCARDIOGRAPHIC EVIDENCE

The acute coronary syndromes are classified by initial ECG findings, biochemical data, and clinical data. Patients are divided into three groups: those with ST elevation (STEMI); those without ST elevation but with enzyme evidence of myocardial damage (non-ST elevation MI or NSTEMI); and those with unstable angina (UA). Collectively, NSTEMI and UA are referred to as non-ST elevation acute coronary syndrome (non-STE-ACS). Classification according to a presenting ECG coincides with current treatment strategies since patients presenting with ST elevation benefit from immediate reperfusion.⁴ Accordingly, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that patients with suspected ACS have an ECG obtained and interpreted within 10 minutes of presentation.⁵

Criteria for the diagnosis of STEMI include^{3,6}:

- New ST elevation at the J-point in at least two contiguous leads with the cut points
- 0.1 mV in all leads except V_{2-3} (for those leads cut points are as follows: ≥ 0.15 mV in V_{2-3} in women, ≥ 0.2 mV in V_{2-3} in men ≥ 40 , and ≥ 0.25 mV in V_{2-3} in men <40)
- New left bundle branch block
- New multilead ST depression with coexistent ST elevation in aVR
- New ST depression in ≥ 2 precordial leads (V_{1-4}) suggestive of a posterior MI

Many conditions can mimic STEMI and lead to false positives.³ An early repolarization pattern with up to 3-mm ST elevation in leads V_{1-3} can be seen in healthy individuals, typically in young men. Pre-excitation, bundle branch block, pericarditis, pulmonary embolism, subarachnoid hemorrhage, metabolic disturbances (e.g., hyperkalemia and hypothermia), and a left ventricular aneurysm can be associated with ST elevation in the absence of acute myocardial ischemia. On the other hand, some conditions can lead to false negatives, including prior myocardial infarction, paced rhythm, and LBBB when acute ischemia is not recognized. These pitfalls are common in the real world and large

clinical trials. When ECGs from the GUSTO IIB trial were reviewed by expert readers at a core lab, 15% of patients with STEMI were found to have been misclassified as NSTEMI, and these patients had a 21% higher mortality.⁷

“Nondiagnostic” ECGs are common in the setting of acute MI (AMI). In one study, 8% of patients who were subsequently determined to have ACS had a normal ECG, and an additional 35% had nonspecific changes.⁸ These nondiagnostic ECG findings may be due to an occlusion of only small vessels or an insensitivity of the 12-lead ECG to ischemia in the lateral or posterior left ventricular territory. Supplemental leads, such as V_{3-4R} and V_{7-9} , can be used to improve the detection of an MI of the free wall of the right ventricle and the inferior wall, respectively, increasing the sensitivity without decreasing specificity.⁹ An 80-lead body surface mapping system has also been shown to increase the sensitivity and specificity of ECG diagnosis of ischemia, but challenges with rapid application at the bedside remain.¹⁰ If ischemia is strongly suspected without ECG changes, serial ECGs or ECGs with additional leads should be performed.⁵ Serial ECGs have been shown to increase the sensitivity of MI detection from 55% to 68% compared to single ECGs.¹¹

ST segment depression on an ECG identifies patients with ACS at a high risk. In the Thrombolysis in Myocardial Infarction (TIMI) Risk Score, which has been shown to predict the likelihood of death and ischemic events, ST segment changes, along with advanced age and prior coronary artery disease, show the strongest association with severe coronary artery disease.¹²

T wave changes can also be prognostic, but the pretest probability of coronary artery disease must be taken into account. Large studies in asymptomatic patients demonstrate that most T wave changes are nonspecific. However, in the intensive care unit (ICU), some patterns are strongly associated with myocardial ischemia. Marked symmetric precordial T wave inversions (≥ 2 mm) suggest acute ischemia, usually due to a critical stenosis of the left anterior descending artery.¹³ In patients presenting to the emergency department with ACS, those with isolated T wave changes have a lower risk than those with ST depression but a higher risk than those with a normal ECG.¹⁴

CK-MB AND TROPONIN

With cardiac cell death, proteins are released into the blood, and detection of these proteins has played a key role in establishing the diagnosis of ACS, predicting its outcome, and directing treatment. Beginning early in the 1970s, creatine kinase (CK) and its isoenzyme MB (CK-MB) became the biomarkers of choice to establish myocardial injury and infarction. However, these biomarkers have been superseded by troponin T and I, parts of the troponin-tropomyosin complex in cardiac myocytes due to their increased sensitivity and specificity. Indeed, the current guidelines suggest that there is no benefit to checking CK-MB if contemporary troponin assays are available.⁵ Troponin elevations are highly specific for myocardial cellular injury, except for infrequent false positives due to fibrin interference or cross-reacting antibodies.¹⁵ Troponin is also much more sensitive than CK-MB as a result of its higher concentration in cardiac muscle and can detect even minor cardiac injury.¹⁵ Even minor increases in circulating troponin values correlate with adverse short-term and long-term outcomes.¹⁵ In non-STE-ACS, elevated troponins not only

TABLE 31-1

Clinical Classification of Different Types of Myocardial Infarctions

Type 1

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis

Type 2

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH

Type 3

Cardiac death with symptoms is suggestive of myocardial ischemia and presumed new ischemic ECG changes or new left bundle branch block. However, death occurring before blood samples could be obtained or before cardiac biomarkers could rise, or in rare cases cardiac biomarkers were not collected

Type 4a

Myocardial infarction associated with percutaneous coronary intervention

Type 4b

Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

Type 5

Myocardial infarction associated with coronary artery bypass grafting

Thygesene K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation* 2012;126:2020-35.

predict increased risk but also identify the patients most likely to benefit from more aggressive antiplatelet strategies and an early invasive strategy with coronary angiography and revascularization when appropriate.⁵

The challenge for the clinician and particularly for the intensivist is that while the elevation of serum troponin is highly specific for myocardial cell damage, not all of the damage is a consequence of the rupture of an atherosclerotic plaque. Demand ischemia (Type II MI) can also lead to troponin release. Other causes of elevated troponin, many of which are common in the ICU, are listed in Table 31-2.³

This highlights the fact that MI should only be diagnosed in the appropriate clinical setting.³ Troponin release in critically ill patients may not always represent myocardial cell death. Endotoxin, cytokines, and other inflammatory mediators, along with catecholamines and conditions such as hypotension, inotropes, or hypoxia may cause the breakdown of cytoplasmic troponin into smaller fragments that can pass through endothelial monolayers and subsequently be detected by sensitive troponin assays.¹⁶ Although detectable troponin levels usually emanate from myocardial cells, they may not always represent either irreversible cell death or myocardial ischemia. Renal dysfunction is another factor associated with elevated troponin levels and both the sensitivity and specificity of this biomarker is decreased in this population.

Regardless of the cause, it is clear that the elevation of serum troponin levels is associated with a worsened outcome both in and out of the ICU, even after adjustment for severity of the disease.¹⁷ What is less clear is whether myocardial dysfunction represents the proximate cause of the worsened prognosis. It is often difficult to exclude ischemia in critically ill patients, but in a study of patients with septic shock, troponin predicted mortality even in patients in whom flow-limiting lesions were excluded either by stress echocardiography or at autopsy.¹⁸

These challenges are likely to be compounded by the greater use of high-sensitivity troponin (hs-cTn) assays. Compared to conventional

TABLE 31-2

Elevations of Cardiac Troponin Values Because of Myocardial Injury Not Due to Myocardial Ischemia

INJURY NOT RELATED TO MYOCARDIAL ISCHEMIA

Cardiac contusion, surgery, ablation, pacing, or defibrillator shocks

Rhabdomyolysis with cardiac involvement

Myocarditis

Cardiotoxic agents (e.g., anthracyclines and Herceptin)

MULTIFACTORIAL OR INDETERMINATE MYOCARDIAL INJURY

Heart failure

Stress (Takotsubo) cardiomyopathy

Severe pulmonary embolism or pulmonary hypertension

Sepsis and critically ill patients

Renal failure

Severe acute neurologic diseases (e.g., stroke or subarachnoid hemorrhage)

Infiltrative diseases (e.g., amyloidosis or sarcoidosis)

Strenuous exercise

Thygesene K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation* 2012;126:2020-35.

assays, these assays have greater sensitivity (0.88 versus 0.75) and negative predictive value (0.96 versus 0.94).¹⁹ In one study, 62% of hospitalized internal medicine patients had an elevated level of hs-cTn, although only 6% of patients had a diagnosis of ACS. Accordingly, there is no consensus on how to use and interpret hs-cTn. Another challenge is that these assays are not yet standardized.²⁰

A further difficulty in the ICU is that patients may not experience classic symptoms of ischemia or may be unable to report them. Despite this potentially confounding factor, it is useful to the clinician to recall that an MI is diagnosed when sensitive and specific biomarkers are elevated in the right clinical setting.³ A characteristic rise and fall should be seen, as an initially elevated troponin may not result from ischemia.²¹ Troponin levels should be repeated to define the clinical course.

OTHER BIOMARKERS

While no biomarker has been shown to provide sensitivity or specificity for the diagnosis of MI superior to troponin, some biomarkers have been shown to provide information regarding prognosis.

Brain natriuretic peptide (BNP), and N-terminal pro-BNP (NT-proBNP) that is more stable are produced by the cleavage of the prohormone proBNP. ProBNP is released by the heart in response to stretching of the wall. The ischemic myocardium also releases BNP. Higher BNP levels in ACS patients correlate with an increased risk of subsequent death, and BNP appears to confer information independent of other clinical markers. Thus, in a study of 449 acute coronary syndrome patients, those with a high Global Registry of Acute Coronary Events (GRACE) Risk Score and high BNP were more likely to die than those with a high GRACE Risk Score and low BNP.²² Since women and older individuals have higher BNP levels, age- and gender-specific cutoffs may be needed.²³ Obese individuals have lower values, but renal dysfunction increases BNP levels, sometimes dramatically.²⁴⁻²⁵ BNP levels can also be increased in the setting of right ventricular strain, including patients with pulmonary embolism, in whom both elevated BNP and elevated troponin levels predict a worsened prognosis.²⁶ BNP remains a good indicator of ventricular dysfunction and myocardial wall stress, but what cutoff levels should be used in the ICU and what the clinician should do when the BNP exceeds those levels remains unclear.

C-reactive protein (CRP), an acute-phase reactant protein produced by hepatocytes, is a marker of inflammation shown to provide prognostic information in the setting of ACS. In GUSTO IV, CRP quartile correlated with a 30-day mortality in patients with ACS not undergoing revascularization, independent of troponin T.²⁷ Measuring CRP may be useful in the setting of ACS, but its value in a critical care setting may be limited to levels that can be elevated for reasons other than ACS.

MicroRNAs (mi-RNAs), short, noncoding RNAs that regulate gene expression at the post-transcriptional level, are novel markers that may prove clinically useful. In a recent meta-analysis, three mi-RNAs: 1) miR-133a; 2) miR-208b; and 3) miR-499 demonstrated high sensitivity and specificity for the ability to detect AMI.²⁸ However, the lack of a strong correlation among troponin-I, troponin-T, and high-sensitivity troponin-T and miR-499 in this study was concerning, as was significant heterogeneity among the patient groups.

■ References for this chapter can be found at expertconsult.com.

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Recent advances in ultrasound technology have allowed these devices to become smaller, more portable, and less expensive, so that this powerful imaging tool can be readily brought to the patient's bedside.¹ The concept of point-of-care (POC) ultrasound refers to the use of portable ultrasonography at the patient's bedside for diagnostic and therapeutic purposes.² POC ultrasound has rapidly proven to serve a vital role in the rapid assessment of cardiac, pulmonary, hemodynamic, vascular, neurologic, and gastrointestinal status. This chapter seeks to review the current use of POC ultrasound in the critical care setting. Specifically this chapter will discuss the following areas: (1) ultrasound physics and probe selection, (2) assessment of pulmonary status, (3) vascular access, and (4) additional topics. Chapter 33 provides a thorough discussion of echocardiography, including the echocardiographic assessment of intravascular volume status (preload responsiveness) and the use of echocardiography to diagnose shock and monitor the response to treatment. Training on these topics using a model-simulation-based educational curriculum has been shown to be effective and to positively impact patient care.³

ULTRASOUND PHYSICS AND PROBE SELECTION

Clinical ultrasound systems use transducers that emit and detect sound waves with a frequency between 2 and 27 MHz. Image production depends on the strength of the returning ultrasound signal and is directly related to the angle at which the beam strikes the acoustic interface. The ultrasound signal is described by its frequency and wavelength. A shorter wavelength (i.e., a higher frequency) provides better resolution but less penetration into tissues. Therefore, higher frequency probes (5 to 10 MHz) provide better resolution but are useful only for imaging superficial structures. Lower frequency probes (2 to 5 MHz) provide better penetration but have a lower resolution. Probe selection is based on matching the properties of the ultrasound probe with the particular structure that one is trying to image. Besides frequency, additional properties of the probe include the footprint (area emitting the ultrasound) and shape. Typical phased array probes emit at 3 to 5 MHz, have a small footprint, and produce a wide ultrasound image by sending out packets of ultrasound that are stitched together. Curved linear probes emit at 4 to 7 MHz, have a large footprint, and are ideal for imaging of abdominal structures. These probes generate a wide image because of the way the ultrasound waves are emitted. Linear probes emit at 10 to 27 MHz and are used for imaging superficial structures (Fig. 32-1).

Acoustic gel is used to minimize the difference in acoustic impedance from the probe to the skin. Standard 2D image creation is called B-mode (brightness mode). In this mode, there is a change in spot brightness for each ultrasound signal that is received by the transducer. M-mode (motion mode) is a graphic B-mode pattern that is a single screen line of ultrasound signal displayed over time and is used to assess the motion of structures along the ultrasound beam. Doppler ultrasound is a modality that is used to assess direction and intensity of flow by assessing the change in velocities secondary to the motion of the structure of interest (usually red blood cells). It is important to remember that Doppler signals are more accurate when the ultrasound signal is *parallel* to the direction of flow. With color Doppler, the Doppler echoes are displayed with colors corresponding to the direction of flow. With continuous wave Doppler, one assesses

the summation of velocities of flow along a line of the ultrasound signal. With pulse wave Doppler, one is able to assess flow velocity in an exact location but with the limitation of only being able to assess a range of velocities. From each transducer position, the target structure is focused on by three major movements: (1) *Tilt* refers to scanning left-to-right and is used to position structures in the middle of the screen, (2) *angle* refers to scanning superior-to-inferior, and (3) *rotation* refers to moving the probe in a clockwise or counterclockwise direction.

ASSESSMENT OF PULMONARY DISORDERS

Ultrasound assessment of pulmonary disorders offers tremendous value to the critical care physician. Ultrasound provides noninvasive, immediate bedside diagnosis, unlike a CT scan, which requires moving the patient. Ultrasound is especially useful in pregnant and pediatric patients where minimizing radiation exposure is important.

Performing an ultrasound for detection of pneumothorax is a simple, easily learned technique. Studies showed that inexperienced, recently trained personnel produced high detection rates for pneumothorax.^{4,5} Ultrasound of the lung relies on the physical principle that fluid collects in dependent areas, whereas gases collect superiorly. Therefore, positioning the patient appropriately for the exam is critical. In reporting the findings, the physician should specify both the patient's position (e.g., sitting, supine, right side down, or left side down) and the location of the probe. Probe placement should be posterior and inferior for detection of fluid but anterior and superior for detection of air. Although the probe can be placed transversely between two ribs, longitudinal placement with a view of the ribs is recommended because of the enhanced orientation provided by the rib shadows.

The curvilinear probe provides the best visualization of the pleural cavity. Although the lower frequency of 4 to 5 MHz does not allow the distinction of visceral from parietal pleura, it does yield visualization of lung sliding and air artifacts.

One of the initial steps in performing ultrasound of the lung is to visualize the diaphragm, which is a concave hyperechoic structure that descends with every breath. The liver on the right and the spleen on the left serve as landmarks during this initial visualization.

A subcostal or transdiaphragmatic abdominal approach can also be used to visualize the pleural cavity, but a potential difficulty of this view is that concave organs, such as the spleen, may reverberate, producing artifacts that appear to be dense lesions in the pleural cavity.

A normal ultrasound image of the lung will have the following features:

1. **Lung sliding:** As the lung inflates or deflates, the visceral pleura moves against the parietal pleura. The ultrasound images show this to and fro pleural movement, called lung sliding. Lung sliding is more prominent at the lung bases than the apex. It is absent in the presence of air (pneumothorax) or fluid (pleural effusion) in the pleural cavity. Inflammation leading to adherence of the two pleural membranes will also lead to absence of lung sliding. In the M-mode, lung sliding can be best seen with the muscle and parietal pleura represented as static horizontal lines above the to-and-fro movement of the visceral pleura and lung, which appears granular. This appearance on M-mode is called the *seashore sign* (Fig. 32-2).

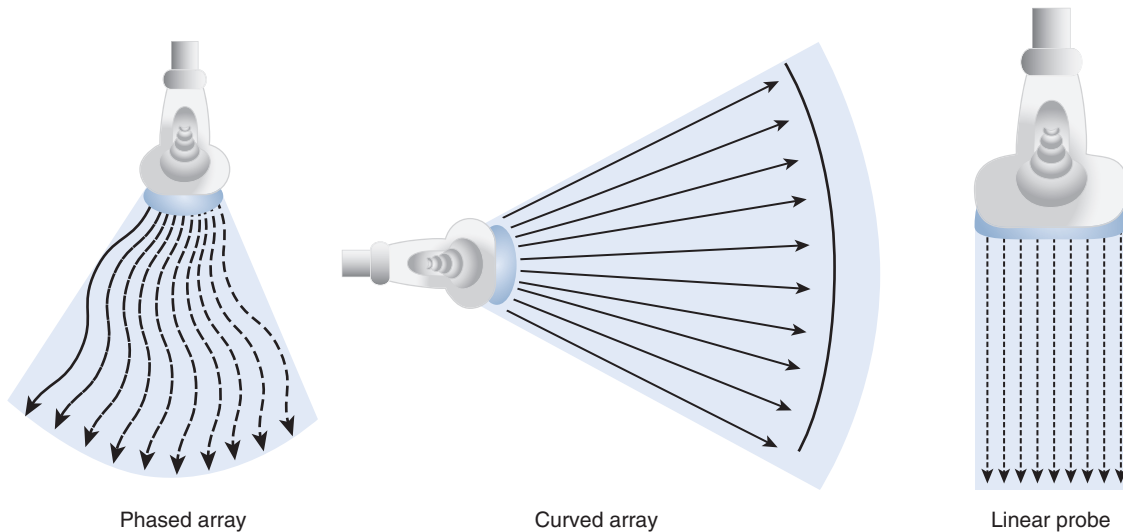


FIGURE 32-1 ■ Ultrasound probe types.

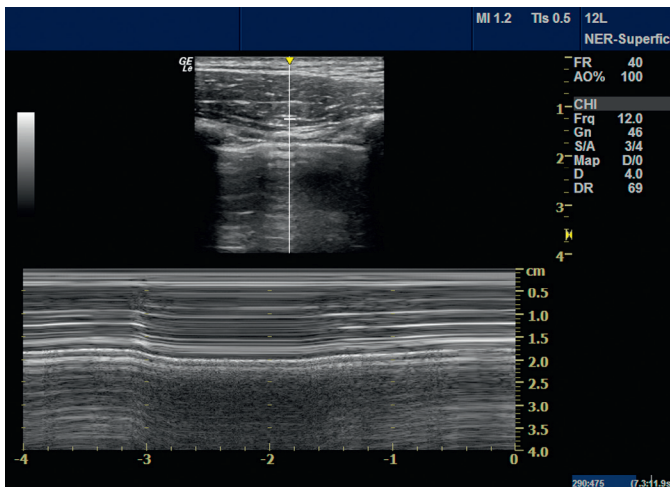


FIGURE 32-2 ■ Seashore sign. M-mode ultrasound of normal lung.

2. A-Lines: These are motionless horizontal reverberations of the pleural lining that give a regularly spaced, hyperechoic artifact on the ultrasound image.
3. B-Lines: Also called *ultrasound lung comets*, B-lines probably represent the ultrasonic equivalent of radiologic Kerley B-lines. These artifacts have seven features: (1) a hydroaeric comet tail, (2) a hyperechoic signal, (3) well-defined on ultrasound, (4) arise from the pleural lining, (5) associated with disappearance of A-lines, (6) move with lung sliding when present, and (7) a pattern of indefinite spreading in a cephalad direction.⁶ B-lines are artifacts of water-thickened interlobular septa and indicate increasing amounts of extravascular pulmonary edema, such as occurs in congestive heart failure (Fig. 32-3).

Pleural Effusion

The pleural cavity is quite accessible to ultrasound visualization. Pleural effusions are best seen in dependent areas of the chest, that is, posterior or inferior areas. The fluid is bounded inferiorly by the diaphragm and peripherally by the visceral and parietal pleura. With respiration, the visceral pleural should move toward the parietal pleura, producing a sinusoid sign with M-mode, which is highly specific (97%) for the

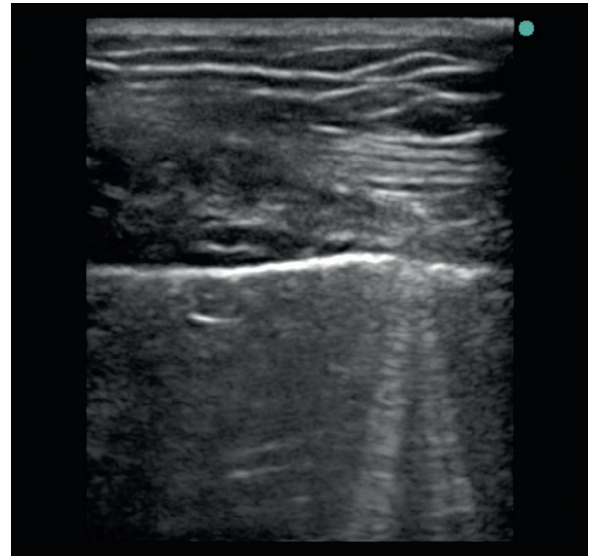


FIGURE 32-3 ■ B-Line.

presence of a pleural effusion⁷ (Fig. 32-4). At times, the lung may appear to be floating in the pleural fluid. A positive sinusoid sign can detect the presence of a low-viscosity pleural effusion, but it may be falsely negative if the pleural fluid is very viscous.

Ultrasound is more sensitive and specific than either auscultation or chest x-ray and is therefore the method of choice to detect pleural effusions.^{8,9} Effusions over 1 cm thick are easily detected with an accuracy greater than 90%.⁹ Anterior presentation of an effusion suggests that it is abundant. When large effusions are present, deeper structures can be visualized, such as a consolidated lung or the mediastinal contents. A large effusion may reveal air artifacts in the lung and allow the examiner to differentiate consolidated from aerated lung.

With experience, the examiner can estimate the amount of effusion as mild, moderate, or large. The echogenicity of an exudate allows the examiner to make an educated guess as to whether it is a transudate or an exudate; all transudates are anechoic, whereas exudative effusions are usually echogenic.

Hemothorax and purulent pleurisy present similar ultrasound patterns. Hemothorax produces an echogenic signal, indicating numerous particles floating within the effusion. In rare cases, the entire pleural

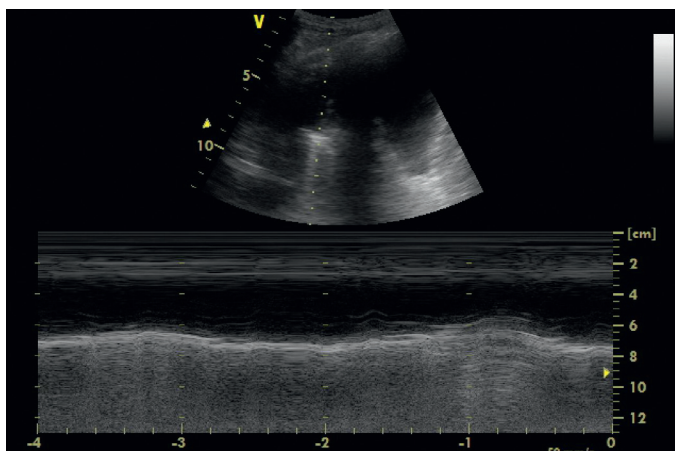


FIGURE 32-4 ■ Sinusoid sign. The visceral pleura moves toward the parietal pleura with lung expansion, giving a sinusoidal sign on M-mode.

cavity might be hypoechoic, mirroring a whiteout seen on chest x-ray. CT will be helpful in these cases.

Ultrasound can facilitate thoracocentesis. The patient should be positioned in a sitting or lateral decubitus position. It is important that the patient remain in the same position throughout the localization of the lesion and the subsequent procedure. Before performing thoracocentesis, the operator should verify that the effusion is at least 1.5 cm thick and is visible over at least three intercostal spaces.⁷ The operator should identify the most dependent part of the pleural cavity and carefully insert the needle under direct (real-time) ultrasound visualization, making every effort to avoid accidental puncture of other structures during the process. Ultrasound-guided thoracocentesis is safe in mechanically ventilated patients.⁷ Following aspiration or biopsy, small pigtail catheters can be inserted and left in place for continuous drainage of the effusion.

Pulmonary Edema

Common practice in POC ultrasound of the lung parenchyma is the evaluation of B-lines. The number of B-lines correlates with the amount of extracellular lung water and the pulmonary wedge pressure ($P < 0.001$).⁶ Three or more B-lines in a single view are called B+ lines and represent interstitial edema.¹⁰ The presence of B-lines in a patient with acute dyspnea, evaluated together with measurement of circulating N-terminal pro b-type natriuretic peptide and the Framingham criteria, helps distinguish between cardiogenic and noncardiogenic pulmonary edema ($P < 0.001$).¹¹ The presence of 9 or more B-lines was found to be 100% specific for cardiogenic dyspnea.¹¹ Ultrasound can provide more than 90% sensitivity and specificity for the detection of acute cardiogenic pulmonary edema. Therefore, when combined with bedside echocardiography to evaluate cardiac function, the diagnosis of congestive heart failure can be confirmed before administering a diuretic.

Lung Consolidation

Lung consolidation is associated with air bronchograms and is visualized on ultrasound as lenticular air pockets within hypodense areas of consolidated lung.

Lung ultrasound has been found to be comparable to chest x-ray in making a diagnosis of pneumonia.^{12,13} The signal changes seen on ultrasound depend on the stage of the infection. Subpleural consolidation with a tree-like vascular pattern on Doppler might be present in the initial hepatization phase of lobar pneumonia. Lung sliding may be absent in the involved lobe secondary to inflammatory exudates. Later, during the resolution phase, ultrasound can detect

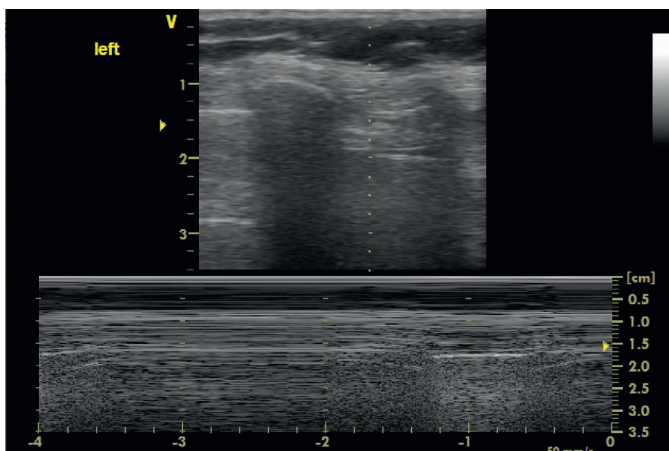


FIGURE 32-5 ■ Lung point in M-mode. Both the bar code and sea-shore signs are seen as the lung point moves across the image.

the appearance of B-lines, which appear secondary to increased aeration of the lung. Lung ultrasound can therefore be used to monitor the progression of pneumonia. There is a close correlation between the results of lung CT and ultrasound for evaluating re-aeration of the lungs.¹⁴

Pneumothorax

Ultrasound is highly accurate at detecting pneumothorax. The primary ultrasound feature is abolition of lung sliding, occasionally associated with A-lines and the absence of B-lines. In M-mode, this would give the appearance of multiple horizontal lines similar to a bar code. This nonspecific finding is seen in a number of other conditions, such as malignancy, chronic obstructive pulmonary disease (COPD), and pneumonia. More specific is the visualization of a lung point, that is, a point at which the lung and air can easily be visualized in the same M-mode image (Fig. 32-5). Moving the probe along the anterior, lateral, and posterior intercostal spaces and observation during an entire respiratory cycle at each point can help locate the lung point.

Chronic Obstructive Pulmonary Disease

Lung ultrasound in patients with COPD shows predominant A-lines with or without lung sliding but without a lung point. Ultrasound has an 89% sensitivity and 97% specificity for COPD.⁶

When using ultrasound to evaluate patients with dyspnea, first check for lung sliding and then for a lung point. The absence of lung sliding in association with the presence of a lung point indicates a diagnosis of pneumothorax. The presence of lung sliding with prominent B-lines ($>3/\text{field}$) indicates a diagnosis of pulmonary edema or pneumonia. The next steps are to check for the presence or absence of a dependent pleural effusion and evaluate for the presence or absence of lung consolidation. An exudative effusion, indicated by absence of a sinusoidal sign in association with lung consolidation, favors the diagnosis of pneumonia. Absence of prominent B-lines and predominance of A-lines indicate either a pulmonary embolism, worsening COPD, or pneumonia. Deep vein thrombosis (DVT) can be ruled out at this time by doing a venous exam of the lower and upper extremities. Absence of DVT and absence of any lung consolidation or pleural effusion favor the diagnosis of an exacerbation of COPD to explain the dyspnea. In patients with unclear or equivocal findings, further imaging modalities such as CT should be used.⁶

Lung ultrasound has some limitations. Central lung pathologies and areas under the ribs or scapula cannot be visualized. Examination of obese patients is difficult. Examination of trauma patients with subcutaneous emphysema is difficult or impossible.

Advanced Vascular Access

The use of ultrasound to aid in vascular access has advanced beyond its now widespread use for central venous access. Specifically, ultrasound has proven to reliably aid in the placement of difficult intravenous^{15,16} and intraarterial catheters.^{17,18} Use of ultrasound for peripheral venous access has been shown to significantly increase success rates as well.¹⁹ A recent meta-analysis was conducted to compare an ultrasound guidance technique for central venous access with an anatomic landmark technique and showed decreased risk of cannulation failure, arterial puncture, hematoma, and hemothorax with ultrasound.²⁰ However, it is important to emphasize that good anatomic knowledge and dynamic hand-eye-probe coordination to follow the needle tip are vital for success and avoidance of inadvertent arterial puncture.²¹ Use of ultrasound has resulted in complications related to injury of deeper structures (subclavian or vertebral artery) while inserting internal jugular central lines.²¹ This underlines the importance of formal training in ultrasound and simulated practice of central line placement, as supported by recently published guidelines.²¹

■ ADDITIONAL AREAS OF ASSESSMENT

POC ultrasonography is useful in assessing several other areas relevant to the issues faced by the critical care physician.

Deep Venous Thrombosis and Pulmonary Embolus

The current standard for evaluation of patients suspected to have DVT or pulmonary embolus involves CT pulmonary angiography and lower extremity compression ultrasonography. These tests are often performed despite a low pretest probability, and obtaining them potentially delays diagnosis.²² A recent study in patients with a moderate to high probability of pulmonary embolus evaluated multiorgan ultrasound, performed by intensivists, involving lung ultrasonography to search for subpleural infarcts, transthoracic echocardiography to detect right ventricular dilatation, and leg vein ultrasonography to detect DVT. The study showed that multiorgan ultrasound had a high sensitivity (90%) and specificity (86.2%) for detection of pulmonary embolus.²⁴

Airway Management

1. Endotracheal tube placement

A recent study has shown the utility of ultrasound for verification of successful endotracheal intubation, reporting a sensitivity and

specificity of 100% for the detection of successful endotracheal intubation versus esophageal intubation.²⁵ A recent evaluation of POC ultrasound examination, which included assessment for tracheal dilation with endotracheal tube cuff inflation and bilateral pleural lung sliding, demonstrated a high degree of sensitivity (93%) and specificity (96%) to detect endobronchial versus tracheal intubation.²⁶

2. Emergency cricothyroidotomy

Surface landmarks for identification are often not reliable for the identification of the cricothyroid membrane, especially in obese and female patients.^{27,28} Bedside ultrasound is a reliable modality for rapid identification of the anatomy for emergency cricothyrotomy (Fig. 32-6).²⁹

3. Percutaneous tracheostomy placement

Ultrasound improved success in accessing the trachea with more than 90% correct placement with the first-pass attempt in a cadaveric study.³⁰ Real-time ultrasound has been used for percutaneous tracheostomies with improved accuracy for midline placement of the needle.^{31,32}

Gastric Volume Assessment

POC ultrasound has also been used to assess gastric content and volume.^{33,34} A grading system has been proposed based exclusively on qualitative sonographic assessment of the gastric antrum and has shown a strong correlation with predicted gastric volume (Fig. 32-7).³⁴ The presence of fluid in the antrum identified by ultrasound in both the supine and right lateral decubitus positions correlates with a large, clinically significant amount of gastric contents. This ability to detect gastric volume by POC ultrasonography may be useful in assessing aspiration risk.

Intracranial Pressure Estimation

POC ultrasonography has been shown to provide rapid assessment of elevated intracranial pressures (ICP) based on the measurement of the optic nerve sheath diameter. The optic nerve sheath is contiguous with the dura mater and has a trabeculated subarachnoid space through which cerebrospinal fluid circulates. The relationship between the optic nerve sheath diameter and ICP has been well established.^{35,36} The sensitivity of ultrasonography in detecting elevated ICP was 100% (95% confidence interval [CI] 68% to 100%), and specificity was 63% (95% CI 50% to 76%).³⁵ An optic nerve sheath diameter of greater than 5 mm at a point approximately 2 mm from the retina suggests elevated ICP (Fig. 32-8).

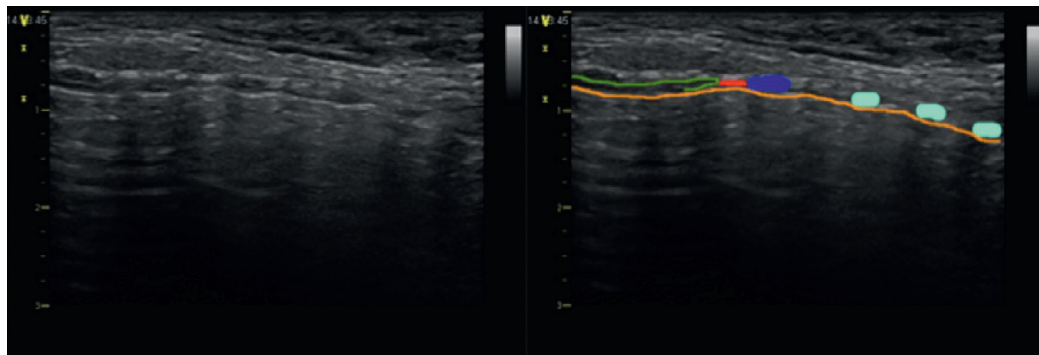


FIGURE 32-6 ■ Longitudinal ultrasound view of the trachea. Longitudinal midline-scan view of the neck shows the cricothyroid membrane in red. Green and dark blue represent the thyroid and the cricoid cartilages, respectively. The orange lining shows the air-tissue border between the trachea and air. The light blue represent the tracheal cartilages.

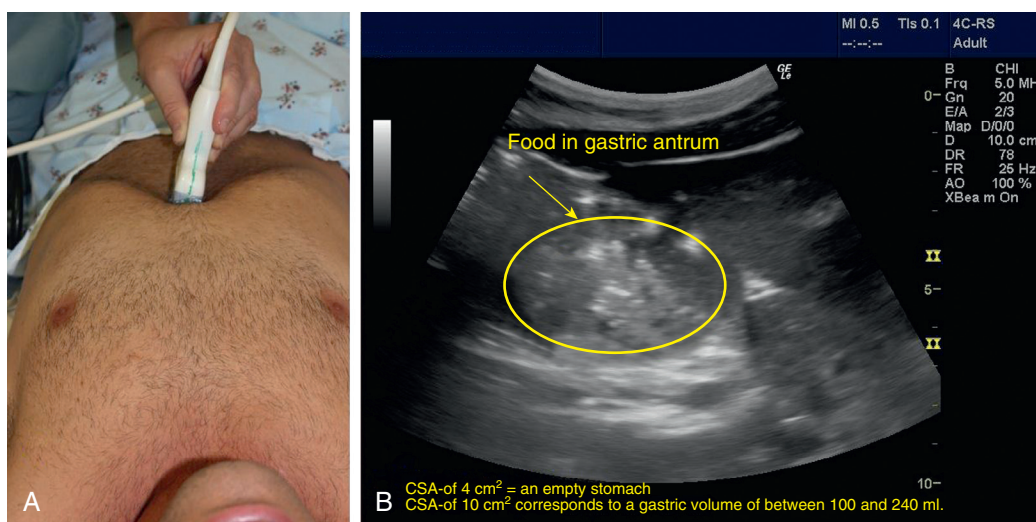


FIGURE 32-7 ■ Ultrasound of gastric antrum to assess gastric volume. **A**, Probe (curved linear) position for gastric antrum acquisition. **B**, Ultrasound image.

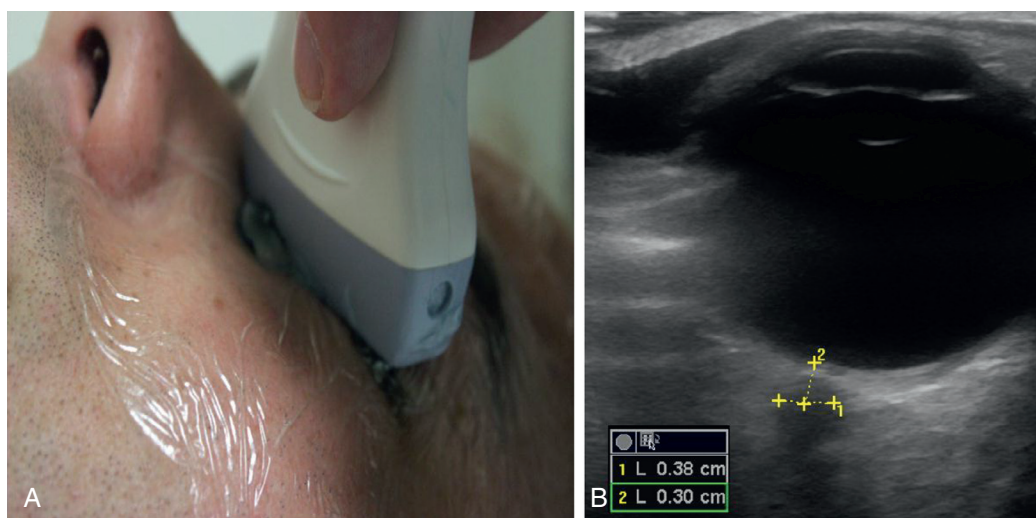


FIGURE 32-8 ■ Ultrasound of optic nerve sheath diameter. **A**, Probe (linear) position. **B**, Ultrasound image.

KEY POINTS

1. Ultrasound machines are becoming less expensive and more portable, resulting in wider bedside application during physical examination to aid in clinical decision making. For this reason POC ultrasound use and knowledge is becoming a basic clinical skill for the critical care physician.
2. Probe selection depends upon the organ to be examined. Deeper structures need a lower frequency probe, which allows better penetration.
3. Doppler signals are more accurate when ultrasound signals are parallel to the direction of flow. Pulse wave Doppler can assess the flow velocity in an exact location whereas continuous Doppler assesses for a summation of velocities along the line of ultrasound signal.
4. Lungs ultrasound allows comprehensive assessment of the pulmonary system, especially with detection of pneumothorax and pleural effusion with high sensitivities and specificity. Bedside

KEY POINTS—cont'd

- ultrasound-guided thoracocentesis is safe even in mechanically ventilated patients.
5. Successful and safe POC ultrasound use for vascular access involves excellent anatomic knowledge and dynamic hand-eye-probe coordination to follow the needle tip at all times to prevent inadvertent arterial punctures and other complications.
 6. Evaluation for pulmonary embolus by POC ultrasound involves a multiorgan examination including lung ultrasonography, echocardiography, and lower extremity assessment to detect DVT.
 7. POC ultrasound has high sensitivity and specificity for the detection of successful endotracheal intubation as well as identification of anatomical structures and landmarks for cricothyroidotomy and percutaneous bedside tracheostomy.
 8. Lately, POC ultrasound is increasingly being used for assessment of gastric volume and content, especially prior to intubation for assessing aspiration risk.

■ References for this chapter can be found at expertconsult.com.

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Over the past 60 years, echocardiography has undergone substantial developments to become one of the most common modalities in the field of cardiovascular imaging. Starting in the 1980s, technologic advancements and the recognition of its potential moved echocardiographic imaging quickly into the operating room, emergency room, and intensive care unit (ICU). Today, it is fully integrated into medical subspecialties, such as anesthesiology, emergency medicine, critical care, and others.¹⁻³

Several aspects differentiate critical care echocardiography from the comprehensive cardiology echocardiographic examination. Critical care echocardiography is focused on the immediate integration of diagnostic information into clinical management. In ICU patients, the interaction of heart and lung function and the presence of multiple medical interventions can make the interpretation of findings more complex. The ability to obtain adequate images can be limited. The hemodynamic profiles of patients tend to change continuously. Therefore, 24-hour access to echocardiography is important.

Indications, Contraindications, and Safety

Indications for echocardiography, including the critical care and perioperative settings, are well established in the literature.⁴⁻⁷ While applications for echocardiography in the ICU continue to expand, the main indication remains the evaluation of hemodynamic instability and guidance of its clinical management (Table 33-1). Transthoracic echocardiography (TTE) represents the standard modality in the ICU, as it is noninvasive, readily available, and easy to use. While TTE presents minimal risk to patients, acquiring satisfactory images is often problematic. In particular, surgical dressings, obesity, chronic obstructive pulmonary disease (COPD), and the requirement for mechanical ventilation can make imaging difficult. Problems associated with obtaining satisfactory images using TTE are the most common indication for transesophageal echocardiography (TEE) in the critical care setting, especially when patients are already intubated and sedated. Other less frequent indications are the need to diagnose cardiac valvular pathologies, endocarditis, or intracardiac thrombi, or shunts. TEE requires advanced expertise and is an invasive procedure. As it carries increased risks of complications, absolute and relative contraindications are defined (Table 33-2), and risks and benefits must be considered prior to performing TEE.

Impact of Echocardiography in the ICU

Echocardiography is a valuable tool to identify the etiology of hemodynamic instability and to guide clinical management in a critical care setting.^{8,9} Although some results support the view that echocardiography can impact the management of ICU patients,¹⁰⁻¹² data regarding the impact of echocardiography on clinical outcomes remain sparse.^{13,14} One small study showed that using TEE to diagnose nonventricular pathologies as the etiology of hypotension was associated with improved ICU survival.¹⁵ In a study of 220 ICU patients, Kanji et al. showed that therapy in subacute shock guided by limited TTE was associated with an improved 28-day survival and reduced the

incidence of acute kidney injury (AKI) requiring renal replacement therapy (RRT).¹⁶

Training and Accreditation

While guidelines for training and accreditation for comprehensive echocardiography by cardiologists are well defined, similar guidelines are still evolving concerning the use of focused echocardiography by noncardiologists. Since about 2005, professional societies all over the world have been developing specific pathways and recommendations for training and accreditation requirements for focused critical care ultrasound. The first document on training and accreditation of echocardiography in intensive care developed by an international group of experts was published by the World Interactive Network Focused on Critical Ultrasound (WINFOCUS) in 2008.¹⁷ In 2009, a working group formed by the American College of Chest Physicians and La Société de Réanimation de Langue Française published a consensus statement about competency for performing critical care ultrasonography.¹⁸ Subsequently, an international expert group led by the European Society of Intensive Care Medicine proposed training guidelines and standardization of competency assessment for critical care ultrasonography including echocardiography.¹⁹ The same group published a consensus statement on the standards for advanced echocardiography in the ICU in 2014.²⁰

Billing

With the growing use of point-of-care (POC) echocardiography in the ICU, the question of reimbursement has been a topic of ongoing discussion. Several components of the focused critical care echocardiographic examination differ from the classic comprehensive echocardiographic examination. Physicians not fully accredited in echocardiography often perform the focused echocardiographic exam in critically ill patients, and the liability of interpretation only extends to the specific focus of the assessment. Images commonly are not stored for further clinical use. In the United States, Medicare uses the Current Procedural Terminology (CPT) code for the reimbursement of medical, surgical, and diagnostic services. Currently, the CPT coding does not incorporate an individual code for focused critical care ultrasound examinations, and its components do not fulfill the requirements of the standard diagnostic TTE exams or the limited/follow-up exam, as described in their coding system. TEE requires specific competence and is performed by physicians with advanced training. When performed in the ICU, these exams are commonly accepted using existing CPT codes for TEE examinations.

POC echocardiography has the potential to reduce overall ICU costs considerably. By adding a noninvasive, less expensive diagnostic and monitoring technology, it can expedite and focus clinical management and decrease the risk to patients significantly. With standardization of critical care echocardiography training, its differentiation from the classic comprehensive training, and the increasing evidence of the benefits of POC echocardiography, a specific billing code for the focused exam is warranted.²¹⁻²³

TABLE 33-1 Indications for Echocardiography in the ICU

- Circulatory failure (hypotension, shock)
- Sepsis
- Low cardiac output state
- Cardiac arrest
- ACS
- Pulmonary embolism
- Suspected cardiac etiology of respiratory failure
- Aortic dissection
- Cardiac trauma
- Endocarditis
- Suspected cardiac etiology of systemic embolism
- Cardiac evaluation for potential organ donation
- Guidance and assessment of circulatory assist devices (TVPM, IABP, ECMO, VAD)

ACS, acute coronary syndrome; ECMO, extracorporeal membrane oxygenator; IABP, intraaortic balloon pump; TVPM, transvenous pacemaker; VAD, ventricular assist device.

TABLE 33-2 Indications and Contraindications for TEE in the ICU

| INDICATIONS | CONTRAINDICATIONS |
|--|---|
| <ul style="list-style-type: none"> • Poor image quality in acute hemodynamic instability • Poor image quality second to severe obesity, emphysema, surgical drains/dressing • Comprehensive assessment of aortic dissection, endocarditis, valvular pathologies, prosthetic valves, intracardiac thrombus • Assessment of circulatory assist devices • Assessment of intracardiac shunt | <p>ABSOLUTE:</p> <ul style="list-style-type: none"> • Perforated viscus • Esophageal pathology (stricture, tumor, trauma, diverticulum, varices) • Recent esophageal or gastric surgery, s/p esophagectomy or esophagogastrostomy • Active upper GIB • Cervical spine injury <p>RELATIVE:</p> <ul style="list-style-type: none"> • Recent upper GIB • PUD • Coagulopathy, thrombocytopenia • Hiatal hernia |

TEE is mandatory for the comprehensive assessment of certain cardiac pathologies. In hemodynamic instability, when TTE imaging results in insufficient image quality, the intensivist has to weigh risk and benefits of performing invasive TEE exam. GIB, gastrointestinal bleed; PUD, peptic ulcer disease.

BASICS

Equipment

Typically, echocardiography equipment used in echocardiography laboratories and cardiac operating rooms features the newest and most advanced technologies. The most advanced equipment is not needed for use in a critical care setting. Several companies now offer machines with specific features geared toward use in emergency departments, trauma bays, or ICUs. These machines are used for the broad spectrum of critical care applications, including lung, vascular, and abdominal ultrasonography. The machines can be equipped with multiple software programs, including those useful for TTE and TEE. The ideal ICU ultrasound system is compact, portable, and durable. It requires minimal start-up time and has an easy-to-use operator interface. For routine daily use, it should have an extended battery life and internal storage capacity.

The transducers used for TTE and TEE examinations are typically phased-array transducers. They provide a frequency ranging from 1-10 MHz, which offers the optimal balance of penetration and resolution required to image the heart.

Knobology

Echocardiography machines have a collection of knobs and buttons to adjust image quality, utilize different modalities, and store images. As each manufacturer has a set arrangement of knobs and sliders and buttons, it is essential for each operator to become familiar with the layout of the machine that he or she will use on a regular basis. The most important controls and their function are as follows:

GAIN: Adjusts overall image brightness

TIME-GAIN-COMPENSATION (TGC): Selectively adjusts sector image brightness

DEPTH: Adjusts depth of view

ZOOM: Selects specific image sector

FOCUS: Adjusts focal zone

DYNAMIC RANGE: Adjusts grey-scale to filter out background noise

Ultrasound Modalities

More so than during the examination of anatomic structures other than the heart, the use of multiple ultrasound modalities is essential for echocardiography. The most commonly used modalities in the ICU are two-dimensional (2D) imaging, motion mode (M-mode), color flow Doppler (CFD), pulsed wave Doppler (PWD), and continuous wave Doppler (CWD). 2D remains the initial and most commonly used mode of anatomic imaging and qualitative assessment of gross pathologies in the ICU. A modality less frequently used is M-mode. M-Mode represents a one-dimensional image against time and has the advantage of excellent temporal resolution, which is useful for the imaging of fast moving structures like valvular leaflets.

When assessing hemodynamic profiles, the use of Doppler echocardiography, in addition to classic 2D imaging, provides the information needed for quantitative measurements. CFD displays blood flow velocity and direction of flow by color mapping. It combines qualitative 2D imaging with semiquantitative information about blood flow. CFD is useful for diagnosing intracardiac shunts or valvular pathologies, as well as seeking evidence of obstructions to blood flow. When a quantitative assessment is needed for the calculation of stroke volume (SV), cardiac output (CO), and pulmonary artery pressures (PAP), PWD and CWD are the modalities of choice. Both modes provide information about blood flow direction and numeric estimates of blood flow velocity at the interrogated anatomic site. Whereas PWD measures blood flow velocity at the specific site of the sample volume and is limited by a certain velocity threshold called the Nyquist limit, CWD displays the maximum velocity along the whole interrogation beam without a velocity threshold. Both modalities require alignment of the interrogation beam with the direction of blood flow to minimize the underestimation of velocity due to a suboptimal incidence angle. As with 2D imaging, several interventions can be applied to enhance Doppler quality and prevent artifacts due to the Nyquist limit. Most importantly, adjustment of the transducer location and frequency, sample volume depth, and movement of the baseline can maximize peak velocities with PWD.^{24,25}

STANDARD VIEWS AND ANATOMY

When performing echocardiographic examinations, the position of the transducer in relationship to the body is called the *acoustic window*, and the image plane is defined as the *view*. Image planes are in reference to the point of focus, which most commonly is the left ventricle (LV).

Image Acquisition and Optimization

Following a consistent order of image acquisition minimizes the risk of missing images and pathologies, and facilitates learning. Clockwise positioning and rotation of the transducer provides a simple and logical approach to the focused exam (Fig. 33-1).

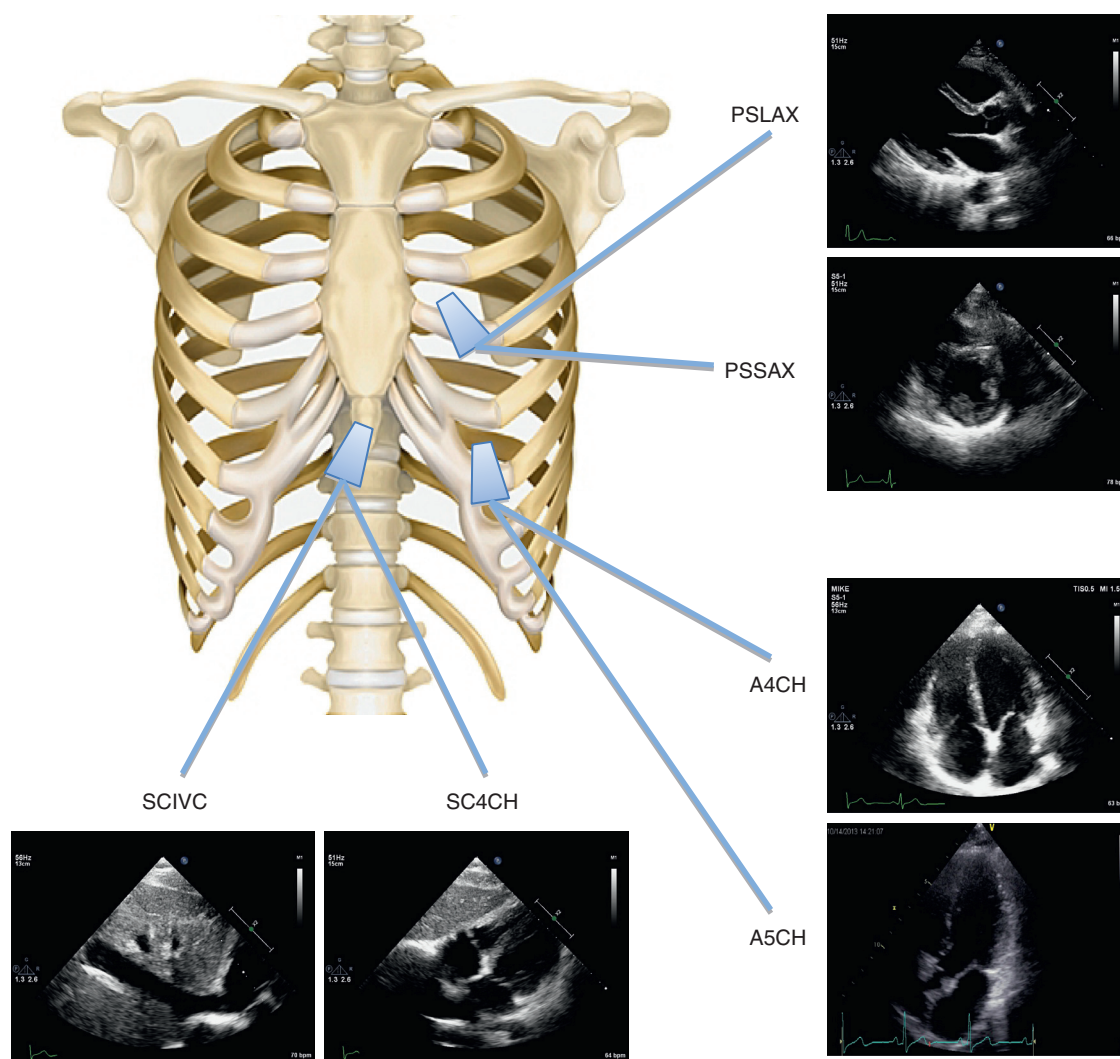


FIGURE 33-1 ■ TTE transducer position and imaging windows. Starting with the PSLAX and the probe marker toward 11 o'clock, the clockwise movement and rotation of the transducer will provide a systematic approach to obtaining acoustic windows and imaging views. Rotation of the transducer from the PSLAX view by 90 degrees clockwise will show the PSSAX view. In the PSSAX view, tilting the transducer cephalad or caudad will visualize the short axis of the AV, LV midpapillary, and LV apical. Further rotation of the transducer from 1 o'clock to 3 o'clock and movement to the apical position visualizes the A4CH view. Flattening of the transducer will show the LVOT and A5CH views. Counterclockwise rotation in the apical view will show the A2CH and A3CH views. Maintaining the probe marker in the 3 o'clock position visualizes the SC4CH view in the SC position. The slight rightward angle of the transducer provides the LAX of the IVC. A2CH, apical two chamber; A3CH, apical three chamber; A4CH, apical four chamber; A5CH, apical five chamber; AV, aortic valve; IVC, inferior vena cava; LAX, long axis; LV, left ventricle; LVOT, left ventricular outflow tract; PSLAX, parasternal long axis; PSSAX, parasternal short axis.

Whether with TTE or TEE, standardized views are based on anatomic landmarks, which can be obtained at defined acoustic windows with specific transducer positions and angles. To avoid inadequate imaging and the risk of misinterpretation, knowledge of the specific anatomic landmarks defining each view is pertinent. In addition, the following techniques should always be used to optimize imaging. *Body position:* Extension of the left arm opens up the parasternal windows while a slight left-side tilt can bring the cardiac apex closer to the chest wall. Flexing the legs at the hip facilitates the acquisition of subcostal windows. *Image acquisition:* Small changes in transducer position and angle, a change in intercostal space above or below, and

the use of TEE can provide improved imaging. *Machine setting:* Aside from adjusting gain, TGC, and dynamic range, precisely adjusting the focus and depth to the region of interest (ROI) is critical. In addition, using the zoom feature can also be helpful. Especially in Doppler modes, these adjustments can improve measurements and avoid Doppler aliasing. Another option for improving image quality is contrasted echocardiography.²⁶ Even though not commonly utilized by intensivists when performing focused ICU exams, injection of contrast media can significantly enhance opacification of the right and left ventricular chambers and enhanced the definition of the endocardial border.

Transthoracic Echocardiography

In TTE, three standard acoustic windows are used: the parasternal, apical, and subcostal positions (Fig. 33-1). A fourth position called suprasternal is additionally used during comprehensive exams and in the pediatric population.

Standard Transthoracic Views

The focused echocardiographic exam in the ICU commonly includes five major views: (1) the parasternal long-axis (PS LAX); (2) the parasternal short-axis (PS SAX); (3) the apical four-chamber (A4CH); (4) apical five-chamber (A5CH); and (5) the subcostal long-axis (SC LAX) (Table 33-3).^{17,20}

PS LAX is obtained by positioning the transducer in the left third or fourth intercostal space (ICS), along the anterior midclavicular line, with the transducer marker directed toward the right shoulder (Fig. 33-1). This view is primarily used to evaluate LV and right ventricle (RV) size and systolic function, as well as to obtain quantitative measurements of ventricular size and wall thickness by the M-mode. The mitral valve (MV) and aortic valve (AV), including the left-ventricular outflow tract (LVOT) and aortic root, can be assessed with 2D and CFD for regurgitation, stenosis, or dynamic outflow obstruction. Additionally, this view can be used for the visualization of pericardial pathologies.

PARASTERNAL SHORT-AXIS VIEWS are obtained in the same transducer position as the parasternal long-axis view, with the transducer rotated 90° clockwise and the marker directed toward the left shoulder (Fig. 33-1). Within this view, multiple planes of the heart can be imaged depending on the tilt of the transducer. When tilting the probe from superiorly to inferiorly, visualization starting with the short axis of the AV over the basal and mid-SAX of the LV down to the apical segment of the LV is possible. This view is best used for the evaluation of LV size and systolic function. It is optimal for describing regional wall motion abnormalities, as all territories of coronary perfusion can be visualized simultaneously. In addition, the basal AV SAX view can provide information about the tricuspid valve (TV), including measurements of right ventricular systolic pressure (RVSP) by CWD.

APICAL VIEWS provide images of all four chambers (Fig. 33-1). Most commonly used in the ICU are the A4CH and A5CH views. With the transducer positioned at the apex of the heart, commonly in the 6th or 7th ICS along the anterior axillary line, the probe marker is directed toward the left axilla. With tilting of the probe superiorly, the 4CH and 5CH views are obtained.

The 4CH view is utilized for the assessment of atrial and ventricular chamber sizes, biventricular systolic function, and regional wall motion abnormalities. Due to the optimal incidence angle and visualization of the TV, MV, and AV in the 4CH and 5CH views, quantitative measures by M-mode, CFD, CWD, and PWD are best obtained from the apical position. These views are mostly used by intensivists for quantitative evaluation of RV function and RVSP, LV cardiac output and diastolic function, as well as the evaluation of valvular pathologies by spectral-Doppler echocardiography.

From the 4CH position, a counterclockwise rotation of the transducer by 90° and 110° will visualize the apical two-chamber (A2CH) and three-chamber views (A3CH), which completes the visualization of all left-ventricular wall segments when combined with the 4CH view.

SUBCOSTAL VIEWS are obtained by positioning the transducer in the subxiphoid or subcostal position while maintaining the marker directed toward the left lateral side of the patient. Aiming the probe toward the left shoulder and maintaining it flat on the abdomen, the heart is cut in a horizontal plane, showing all four chambers and particularly the RV free wall (Fig. 33-1). A 90° rotation of the transducer counterclockwise while slightly aiming the probe toward the right shoulder will visualize the inferior vena cava (IVC) and its junction into the RA. These views can provide information about pericardial pathologies, such as pericardial effusion and tamponade. When angled slightly toward the right and caudad, global volume status can be assessed by measuring IVC diameter and dynamic collapse with respiratory variation (Fig. 33-1).

Transesophageal Echocardiography

In the past, the use of TEE in a critical care setting was restricted by availability, technical issues, and need the for operator expertise. With improvements in equipment and growing expertise among intensivists, the use of this modality is increasing. Superior image quality and the ability to evaluate for certain pathologies remain the advantages of TEE over TTE.

Safety of Transesophageal Echocardiography

TEE in ambulatory and nonoperative settings has an incidence of adverse events of between 0.2% and 0.5% and a mortality rate of <0.01%.²⁷ TEE in the ICU has slightly higher morbidity and mortality. Multiple studies show that the incidence of adverse events ranges from 1.6% to 5%.^{15,28-30} In a recent review of 20 studies, Huettemann

TABLE 33-3 Standard TTE Views, Anatomic Structures Seen, and Their Common Use

| STANDARD TTE VIEWS | STRUCTURES | COMMON ASSESSMENT |
|--------------------|-----------------------------------|--|
| PS LAX | LA, LV, RV, MV, AV, LVOT, Desc Ao | LV and RV size, LV and RV systolic function, RWMA, AV and MV pathologies, LVOT obstructions (SAM), pericardial effusion/clot/tamponade, pleural effusion, LVOT diameter for SV calculation, aortic dissection and aneurysm |
| PS SAX AV | LA, RA, RV, PA, AV, TV, PV | AV pathologies, RV size and systolic function, TV pathologies, RVSP, intracardiac shunts, catheters/PM leads/cannulas |
| *PS SAX MID-PAP | LV, RV | LV size and systolic function, RWMA, pericardial effusion/clot/tamponade |
| *A4CH | LA, RA, LV, RV, MV, TV | LV and RV size, LV and RV systolic function, RWMA, LA and RA size, MV and TV pathologies, RVSP, TAPSE |
| A5CH | LA, RA, LV, RV, LVOT, AV, MV | LVOT obstructions (SAM), VTI LVOT and AV, AV pathologies |
| A2CH | LA, LV, MV | RWMA, MV pathologies |
| *SC SAX | RA, LA, RV, LV, diaphragm | Pericardial effusion/clot/tamponade, RV size and systolic function, RA size, catheters/PM-leads/cannulas |
| *SC IVC LAX | IVC | Volume status, pericardial effusion/clot/tamponade |
| SC IVC SAX | IVC, Desc Ao | Volume status, pericardial effusion/clot/tamponade, aortic dissection and aneurysm, IABP |

As seen, the PS SAX, A4CH, and SC SAX in combination provide most information needed in the acute situation. Additional views for hemodynamic assessment are added to show the most common views used in the ICU. 2CH, two chamber; 4CH, four chamber; 5CH, five chamber; A, apical; AV, aortic valve; Desc Ao, descending aorta; IABP, intraaortic balloon pump; IVC, inferior vena cava; LA, left atrium; LAX, long axis; LV, left ventricle; LVOT, left ventricular outflow tract; MV, mitral valve; PM, pacemaker; PS, parasternal; RA, right atrium; RV, right ventricle; RWMA, regional wall motion abnormalities; SAM, systolic anterior mitral valve leaflet motion; SAX, short axis; SC, subcostal; TV, tricuspid valve; VTI, velocity-time interval.

et al. reported that the incidence of TEE-related complications in the ICU was 2.6%; there were no TEE-related deaths.^{27,31} The main complications associated with TEE are arrhythmias, hypotension, airway compromise, and bleeding. These complications are more likely to occur in critically ill patients as compared to relatively healthier subjects because ICU patients often are hemodynamically unstable or already prone to hemorrhage. Nevertheless, if the operator is cognizant of the potential complications and takes pains to weigh the risks versus the benefits carefully, TEE can be performed safely in the ICU. Preparation of the patient before TEE is important. First, the indications for and specific questions to be answered by the exam have to be defined. Second, potential contraindications to TEE, such as recent esophageal or gastric surgery or active upper gastrointestinal bleeding, must be ruled out. Third, coagulation status must be assessed, and abnormalities corrected, if possible. Fourth, nil per os (NPO) status must be assured. Fifth, the mode of sedation, the need for administration of paralytic agents, and airway protection have to be addressed. When performing the exam, insertion and manipulation of the probe should be tailored to the patient's condition and coexisting risk factors.

Standard Transesophageal Views

The TEE exam in the perioperative setting includes twenty standard views.³² TEE in the ICU rarely requires a comprehensive exam. Several different protocols have been proposed for the focused TEE exam in critically ill patients, emergency room patients, or acute intraoperative emergencies.^{33,34} The goal of the focused exam remains the same as with TTE, and unless prohibited by the severity of situation, acquisition of standardized views should be obtained.

Although a comprehensive TEE exam utilizes views at four levels of the esophagogastric tract, the two main depths used during the focused exam are the midesophageal and transgastric planes. The midesophageal level provides optimal views for specific anatomic evaluation of cardiac structures, as the transducer is near the heart. Transgastric views are mainly used for quick evaluations of LV size, systolic function, and wall motion abnormalities. In addition, spectral-Doppler of the AV is performed in the deep transgastric view, as the incidence alignment angle is best in this location. The transgastric view can also show loculated or dependent pericardial effusions, which may be difficult to see in the midesophageal views.

HEMODYNAMIC ASSESSMENT

Echocardiography represents a method for the immediate diagnosis, management, and monitoring of hemodynamic profiles in critically ill patients. With an examination that rarely takes more than a few minutes to complete, echocardiography can provide the intensivist with anatomic information about the critically ill patient's intravascular volume status, the presence or absence of various forms of cardiac pathologies (e.g., pericardial effusion and tamponade; regional wall motion abnormalities), myocardial contractility, and ventricular dimensions. For the subsequent interpretation and use of this information, it is pertinent to incorporate the influence of concurrent pathologies and medical treatments on echocardiography findings. Especially common factors, such as arrhythmias, vasopressor or inotropic support, and mechanical ventilation, need to be considered during the qualitative and quantitative hemodynamic assessment.

Cardiac Preload and Volume Responsiveness

As the management of the critically ill patient has evolved, the question of volume (i.e., preload) responsiveness has taken priority over static parameters like central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP).⁹ Many experts are skeptical about the clinical utility of static pressures for guiding the hemodynamic management of critically ill patients. Neither CVP nor PAOP is a good predictor of preload responsiveness (i.e., an increase in cardiac output

or stroke volume after bolus administration of intravenous crystalloid or colloid solutions). With the validation of echocardiography, bedside examination is increasingly replacing invasive monitoring in the contemporary evaluation of cardiac preload and prediction of volume responsiveness.^{9,35} Assessment of IVC diameter and the collapsibility, cardiac chamber size, and ventricular outflow tract stroke volume (LVOT SV) measurements are the most common methods used for qualitative and quantitative evaluation of these parameters.³⁶

Assessment of IVC size and its dynamic variation during changes in intrathoracic pressure with mechanical ventilation is the most common way for using echocardiography to evaluate cardiac preload and volume responsiveness in ICU patients. The average diameter of the IVC is 17 mm. The absolute IVC diameter by itself, unless <10 mm or >20 mm, does not correlate well with right atrial pressure (RAP) or preload responsiveness.³⁷ However, dynamic changes in the IVC diameter due to respiration can provide information about preload responsiveness.^{36,38} Barbier et al. showed that dynamic changes in IVC diameter of >18% predict fluid responsiveness with a sensitivity and specificity of 90% to 93%.³⁹ Feissel et al. confirmed these findings with a slightly different index of IVC collapsibility, showing a sensitivity and specificity of 90% to 92%, respectively.³⁷ At the subcostal acoustic window, optimal measurements of the IVC diameter are made using the M-mode in the short-axis view. When interpreting information derived from IVC diameter measurements, it is important to incorporate the effects of atrial arrhythmias, significant tricuspid regurgitation, atrial shunting, or increased intraabdominal pressure on the appearance of the IVC.

Imaging of cardiac chamber size is routinely used in conjunction with other measurements to assess qualitatively intravascular volume status. Most common measurements are LV end-diastolic diameter (LVEDD) and the left ventricular end-diastolic area (LVEDA) utilizing the SAX view of the LV (Fig. 33-2). Attention should be paid to poor image quality and foreshortening of the chamber, as these worsen endocardial border definition and lead to false calculations. Although the measurement of LVEDA provides a reliable estimation of left-ventricular volume in most patients,⁴⁰ low LVEDA does not necessarily indicate systemic hypovolemia; other causes of low LV preload must be considered. Other potential causes of impaired LV diastolic filling include loss of atrial contraction due to arrhythmias, right ventricular dysfunction, and mitral valve dysfunction. Apart from situations of severe hypovolemia,^{41,42} quantitative measurements of left or right ventricular chamber size have not been shown to correlate reliably with cardiac preload and volume responsiveness.⁴³ Dynamic changes in LVEDA, however, correlate with volume responsiveness.⁴⁴

Stroke Volume and Cardiac Output

Left-ventricular stroke volume (LV SV) and cardiac output (CO) can be calculated using echocardiography.^{45,46} Whereas CO measured by thermodilution is a reflection of right-sided CO, measurements with echocardiography utilize left-sided inflow and outflow at the level of the mitral valve (MV), LVOT, and aortic valve (AV). In addition, newer noninvasive modalities are based on PWD of aortic blood flow to assess cardiac output.³¹ While all of these anatomic locations have been validated in the literature, calculations using LVOT and AV are the most accurate when compared to the thermodilution method.^{45,47} The continuity equation is used to calculate LV stroke volume by measuring LVOT diameter and LVOT VTI. Moreover, measurements by TTE are best obtained in the PS-LAX and A5CH views. Once LV SV is calculated, multiplication by the HR provides CO (Fig. 33-3). As LV SV is dependent on the LV preload, limitations affecting LV filling, as mentioned above, have to be considered when calculating SV and CO.⁴⁸

Right- and Left-Ventricular Afterload

With the ability to determine pressure gradients and flow in the heart by echocardiography, pulmonary vascular resistance (PVR) and

$$FS = [(EDD - ESD) / EDD] \times 100$$

$$FAC = [(EDA - ESA) / EDA] \times 100$$

Example:

$$FS_{LV} = [(6.0 - 4.5) / 6.0] \times 100$$

$$= 25 \%$$

$$FAC_{LV} = [(18.5 - 7.3) / 18.5] \times 100$$

$$= 60 \%$$

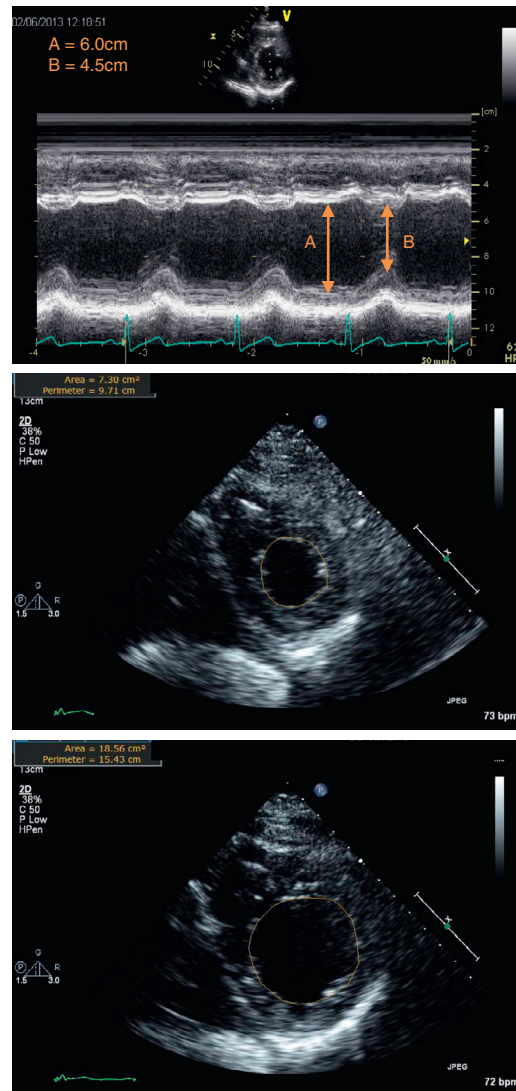


FIGURE 33-2 ■ Chamber size and semiquantitative calculation of left ventricular function.

Fractional shortening methods utilized LV end-diastolic and end-systolic diameter from PSLAX or PSSAX midpapillary to calculate percentage value. Normal FS values are 25%-45%, correlating to normal EF. Fractional-area-change values correlate directly with EF. Measurements of area are taken from PSSAX midpapillary view. EDA, end-diastolic area; EDD, end-diastolic diameter; ESA, end-systolic area; ESD, end-systolic diameter; FAC, fractional area change; FS, fractional shortening; PSLAX, parasternal long axis; PSSAX, parasternal short axis.

systemic vascular resistance (SVR) can be indirectly calculated using the following equation:

$$\text{Resistance} = \Delta P / CO$$

Based on this concept, several small studies have shown an adequate correlation using transvalvular gradients at the tricuspid valve (TV) and MV to calculate pulmonary and systemic vascular resistance. Clinically cumbersome and without broad validation in the literature, these methods are not used on a routine basis in the ICU. In clinical practice, qualitative aspects seen on echocardiography are used to assess SVR. Best seen in the LV SAX view, a hyperdynamic ventricle in the setting of normovolemia suggests a low SVR. From this view, measurement of LVEDD and visual estimation of LV contractility can be used for fast and easy qualitative SVR estimation.⁴⁹

For the assessment of PVR at the bedside, indirect calculation of PAP by TR jet when present is commonly achieved using the modified Bernoulli equation (Fig. 33-4). Measurement of peak TR_{vel} , when added to RAP, provides an estimate of RV systolic pressure (RVSP) that correlates well with SPAP in the absence of tricuspid or pulmonary valve pathology.

Left-Ventricular Systolic Function

Assessment of LV systolic function is one of the key elements of the ICU echocardiographic exam. Not only can an assessment of LV systolic function provide information about the etiology of circulatory or respiratory failure, but it also can be used to guide and monitor ensuing medical management. Multiple methods are available for the echocardiographic evaluation of LV function (Table 33-4). In an acute setting, the fastest and easiest assessment of myocardial function and

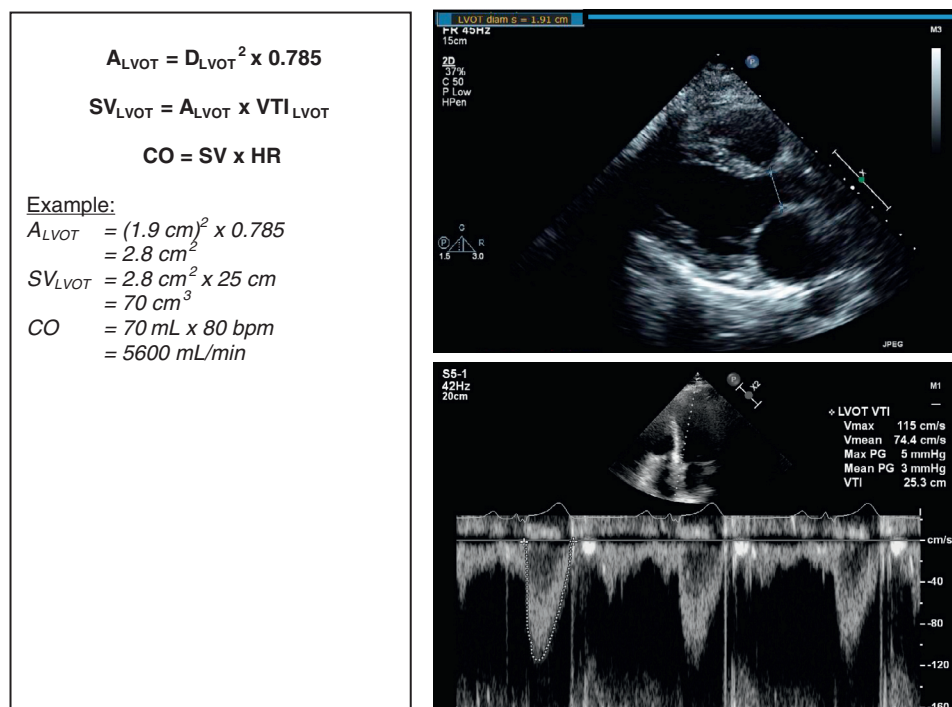


FIGURE 33-3 ■ LV SV and CO calculation. When LVOT diameter is measured in the PSLAX view, the LVOT area can be calculated. LVOT VTI is measured using PWD in the A5CH view. As seen above, in this example the LV SV is 70 mL. When multiplying with an HR of 80 bpm, a CO of 5.6L/min is estimated. A_{LVOT} , LVOT area; CO, cardiac output; D_{LVOT} , LVOT diameter; HR, heart rate; LVOT, left ventricular outflow tract; SV, stroke volume; VTI, velocity-time-integral.

$$RVSP = (TR_{PEAK})^2 + RAP$$

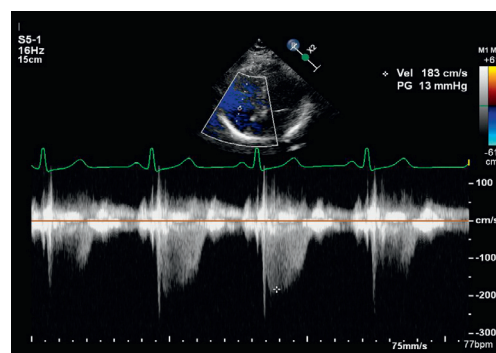


FIGURE 33-4 ■ RVSP measurement using the TR jet. After optimal alignment of the Doppler beam with the TR jet in the A4CH view, RVSP can be calculated by adding the square of the TR peak velocity in m/s to the RAP. When estimating an RAP of 10 mm Hg, RVSP in this example would be 23 mm Hg. RAP, right atrial pressure; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation; TR_{PEAK} , peak velocity of TR jet.

ejection fraction (EF) uses qualitative or semiquantitative methods. For the qualitative assessment, thickening of the myocardium and endocardial inward motion in the LV SAX view is used to estimate systolic function. Caution must be taken when the LV is small, or there is significant LV hypertrophy (LVH), as LV function appears different depending on the intracavitary size. A simplified classification scheme for LV function (i.e., hyperdynamic, normal, moderately depressed, or severely depressed) is usually sufficient in a critical care setting, and several authors have shown that little training is required to make this assessment reliably.^{50,51} When performed by an experienced

echocardiographer, estimates of LVEF correlate well with quantitative measurements.^{52,53}

Semiquantitative measurements can be obtained utilizing the LV SAX view by calculating fractional shortening (FS) or fractional area change (FAC) (Fig. 33-2). Since this view only visualizes one plane of the myocardium, additional qualitative assessments of the complete LV should be performed to avoid errors due to coexisting regional wall motion abnormalities (RWMA).

A more accurate (but more time-consuming) assessment of LV systolic function can be made by volumetric measurements.

Both the area-length formula and Simpson's method reliably estimate LVEF.⁵⁴

Right-Ventricular Systolic Function

Compared to the assessment of LV function, assessment of RV function is more complex as ventricular compliance, wall thickness, systolic function, and TV function are more closely linked.^{55,56} Significant RV systolic dysfunction often presents with RV dilation and TV regurgitation. Simultaneously, normal RV function can be observed with RV dilation and significant TV regurgitation when the RV has time to adjust to chronically increased afterload by wall hypertrophy. Additionally, the RV has a complex geometric structure, making volumetric measurements and imaging more difficult. For these reasons, an assessment of right ventricular function is currently done using a combination of qualitative and semiquantitative measures (Table 33-5). Image acquisition is best via utilizing the PS LAX and apical 4CH views. Semiquantitative measures only assess certain regions of the ventricle,

and caution must be taken not to extrapolate these findings. FAC is currently recommended for semiquantitative calculation of RVEF, as traditional 2D methods assume symmetry of the ventricular structure,^{57,58} and 3D methods are still being validated. Tricuspid annular plane systolic excursion (TAPSE) is easily obtained by TTE and is commonly used in combination with other methods (Fig. 33-5). RVSP, as described above, can reflect the ability of the RV to generate pressure and indirectly provides information about RV function. It is important to correlate measurements with factors that affect RV preload, pulmonary vascular resistance, and valvular function before making clinical judgments. Conditions that are commonly encountered in the ICU, such as adult respiratory distress syndrome (ARDS), pulmonary edema, volume overload, and arrhythmias, influence measured RVSP and often render them uninterpretable.

CIRCULATORY FAILURE

Systematic Approach to Circulatory Failure

Circulatory failure is one of the most common indications for echocardiography in the ICU.^{5,59} Several algorithms for hemodynamic assessment and management of circulatory failure by echocardiography have been described.⁶⁰⁻⁶² The algorithm should include the following steps: (1) seek to identify gross pathologies, such as cardiac tamponade, abnormal myocardial function, or marked hypo- or hypervolemia; (2) determine volume responsiveness and signs of low SVR; and (3) look for more subtle etiologies for hemodynamic instability like valvular pathologies (Fig. 33-6). Even though the clinical

TABLE 33-4 Methods for Assessment of the LV and RV

| LV ASSESSMENT | NORMAL VALUES | |
|------------------------------------|--------------------------------|--------------------------------|
| Assessment of LV size | male | female |
| *LV size (midpapillary diameter) | EDD: 40-60 mm ESD: 25-40 mm | EDD: 35-55 mm ESD: 20-35 mm |
| Assessment of LV systolic function | | |
| Qualitative | | |
| Semi-quantitative | | |
| *FS | 25%-45% | |
| *FAC | 35%-65% | |
| Quantitative | | |
| 2D volumetric EF | >55% | |
| 3D volumetric EF | >55% | |
| *LV wall thickness | <10 mm | |
| dP/dt | >1200 mm Hg/sec | |
| Assessment of MR | | |
| *Extent/quality of MR | | |

| RV ASSESSMENT | NORMAL VALUES |
|------------------------------------|---------------|
| Assessment of RV size | |
| *RV size (RV basal EDD) | >4.2 cm |
| *RV to LV ratio | >0.8 |
| Assessment of RV systolic function | |
| *Qualitative | |
| *FAC | 35%-65% |
| *TAPSE | >20 mm |
| *RV wall thickness | <5 mm |
| RV MPI | <0.40 |
| RV S' | >10 cm/s |
| dP/dt | |
| 3D RV EF | |
| Assessment of TR | |
| *Extent of TR | |
| *RVSP | |

Most commonly used methods in the ICU are marked with asterisks. EDD, end-diastolic diameter; EF, ejection fraction; ESD, end-systolic diameter; FAC, fractional area change; LV, left ventricle; MPI, myocardial performance index; MR, mitral regurgitation; S', velocity of RV free wall or TV annulus by PWD; TAPSE, tricuspid annular plane excursion.

TABLE 33-5 Echocardiographic Signs Suggestive of Pericardial Tamponade

PERICARDIAL TAMPONADE

- Effusion/clot on echo
- Dynamic collapse of RA +/- RV
- IVC plethora
- Exaggerated transvalvular flow patterns of tricuspid and mitral valve >25% with respiration
- Increase in interventricular dependence with respiration

Respiratory-induced pulsus paradoxus with exaggerated changes in flow >25% is seen in mitral or tricuspid valve Doppler flow. IVC, inferior vena cava; RA, right atrium; RV, right ventricle.

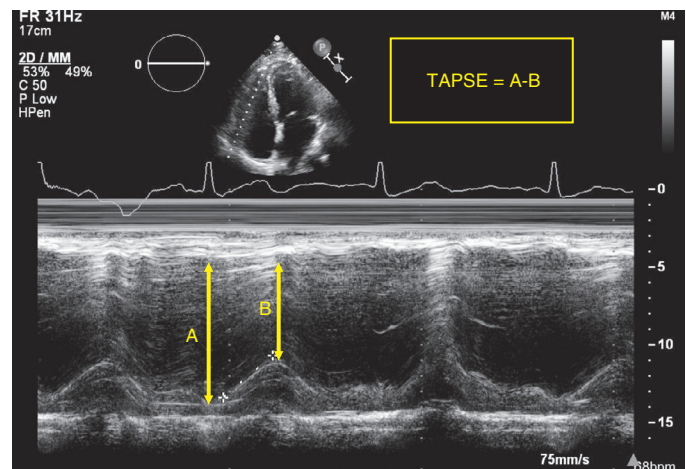


FIGURE 33-5 ■ Tricuspid Annular Plane Systolic Excursion (TAPSE). The distance of the tricuspid annulus from the apex is measured in the A4CH view. Subtraction of systolic from diastolic distance results in the TAPSE value. Normal values are greater than 20 mm.

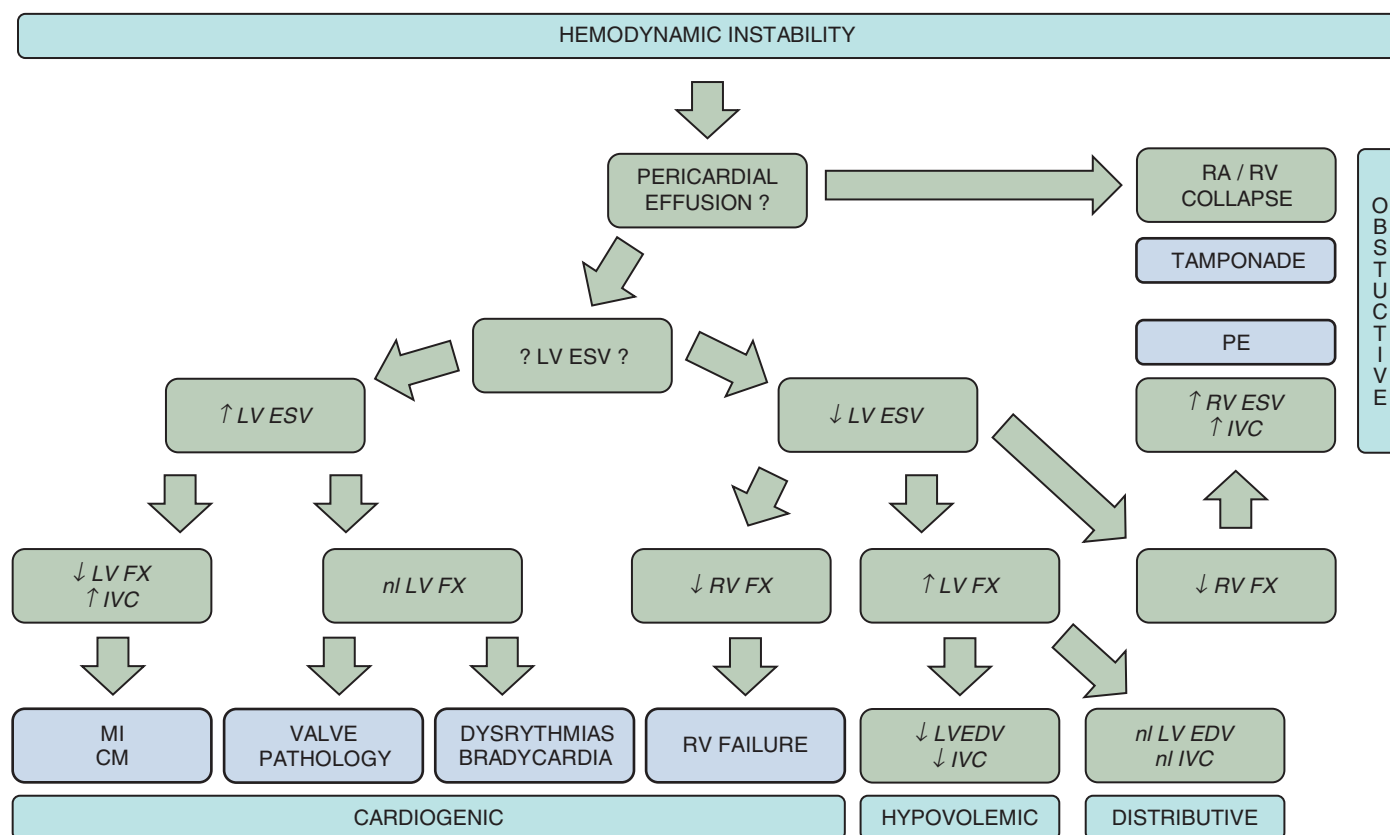


FIGURE 33-6 ■ Algorithm for the echocardiographic assessment of hemodynamic instability.

After initial 2D assessment for hemodynamic-compromising pericardial effusion, evaluation of LV and RV size in systole and diastole and LV and RV systolic function is performed. Differentiation in cardiogenic, distributive, hypovolemic, or obstructive etiology of shock is often possible by following this algorithm. CM, cardiomyopathy; EDV, end-diastolic volume; ESV, end-systolic volume; FX, systolic function; IVC, inferior vena cava; LV, left ventricle; MI, myocardial ischemia; nl, normal; RA, right atrium; RV, right ventricle; ↑, increased/hyperdynamic; ↓, decreased/depressed.

context will initially prompt evaluation for specific pathologies, it is important to perform a systematic assessment to avoid overlooking coexisting or complicating pathologies that need to be addressed or managed. When patients are being treated with inotropic agents or vasopressors, the echocardiographic findings must be interpreted in this context. The concurrent presence of different types of shock can complicate the hemodynamic assessment and the interpretation of echocardiographic findings. As myocardial function and SVR are pharmacologically altered, the underlying etiology for hemodynamic dysfunction may be obscured. Apparently normal ventricular function in the setting of sepsis can be observed with concomitant myocardial depression. Moreover, hyperdynamic ventricular function can be seen in both sepsis and hypovolemia. Therefore, it is essential to correlate echocardiographic findings with the overall clinical picture. Table 33-6 shows the integration of echocardiographic findings and invasively measured values in different states of shock.

When monitoring clinical management, serial imaging must be performed and findings compared with previous ones. Additionally, management should be correlated to the overall picture as not every patient with a certain hemodynamic disorder benefits from the same specific treatment.

Hypovolemic Shock

Hypovolemic shock is the result of an absolute or relative decrease in circulating volume secondary to volume loss or maldistribution.

Echocardiography can identify intravascular hypovolemia and volume responsiveness using several approaches.⁹ As described above, the most commonly used modalities are the evaluation of the IVC, LV EDD or EDA, and variation in LV SV (Fig. 33-7). An IVC diameter of <10 mm and significant changes in the IVC diameter with positive pressure ventilation reflect systemic hypovolemia and suggest volume responsiveness.^{37,39} If the EDD is <25 mm with hyperdynamic LV systolic function, and kissing papillary muscles are seen during systole, then significant LV hypovolemia is present (Video 33-1).⁴¹ Variations in LV SV reflected by changes in LVOT velocity predict the volume responsiveness. A change in LVOT V_{MAX} of >12% and a change in VTI_{LVOT} of >20% is seen in fluid responders.⁶³

Cardiogenic Shock

Left heart failure due to systolic dysfunction is associated with low LVEF, low CO, commonly systemic volume overload, and signs of pulmonary and hepatic congestion. Echocardiography can evaluate pathognomonic findings for heart failure and cardiogenic shock, as well as possibly provide insights regarding etiology. Global myocardial dysfunction causing cardiogenic shock can be recognized when combining qualitative with supporting echocardiographic and clinical findings. Strong indicators for cardiogenic etiology of shock include enlarged LV size, qualitatively depressed LV function, FS <25%, low EF by FAC, and low CO by LVOT Doppler measurements.⁶⁴

TABLE 33-6 Echocardiographic and Hemodynamic Profiles in Different Shock States

| TYPE OF SHOCK | ECHO | | | | | INVASIVE MONITORING | | | |
|-----------------------|------------------|-------|--------|--------|---------------------------------|---------------------|-----|---------|------------------|
| | CARDIAC FUNCTION | LVESA | LVEDA | IVC | 2D | PULSE PRESSURE | PAP | RAP CVP | SVO ₂ |
| DISTRIBUTIVE | ↑ | ↓ | ↓ / nl | ↓ / nl | | wide | nl | ↓ / nl | ↑ |
| HYPOVOLEMIC | nl / ↑ | ↓ | ↓ | ↓ | | narrow | ↓ | ↓ | ↓ |
| CARDIOGENIC | ↓ | ↑ | ↑ | ↑ | | narrow | ↑ | ↑ | ↓ |
| OBSTRUCTIVE TAMPONADE | nl / ↑ | ↓ | ↓ | ↑ | Effusion/clot RA/RV collapse | narrow | nl | ↑ | ↓ |
| OBSTRUCTIVE PE | LV ↑ RV ↓ | LV ↓ | LV ↓ | ↑ | RA/RV dilation RV failure | narrow | ↑ | ↑ | ↓ |

Different types of shock present with specific echocardiographic and hemodynamic findings. CVP, central venous pressure; IVC, inferior vena cava; LVEDA, left ventricular end-diastolic area; LVESA, left ventricular end-systolic area; nl, normal; PAP, pulmonary artery pressures; PE, pulmonary embolus; RAP, right atrial pressures; SVO₂, mixed venous oxygenation; ↑, increased; ↓, decreased.

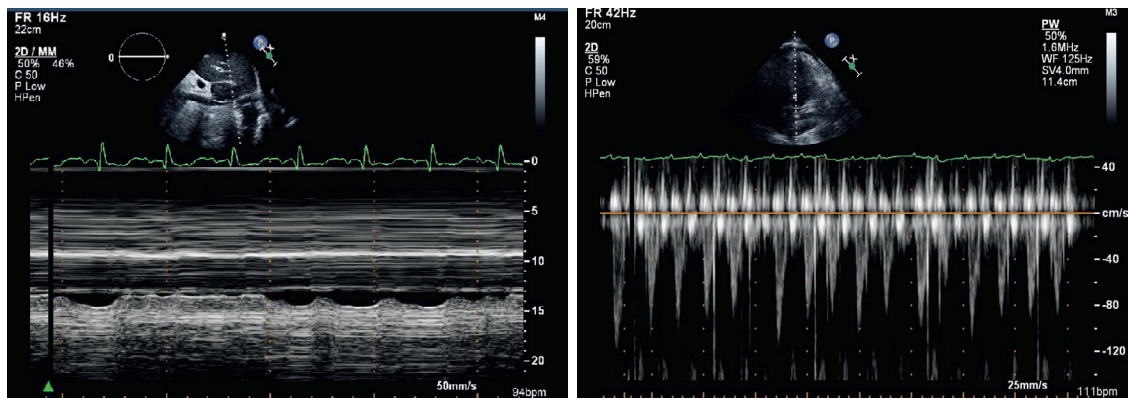


FIGURE 33-7 ■ IVC and LVOT velocities in hypovolemia. An IVC <1.5 cm with >50% respiratory collapse suggests intravascular hypovolemia. PWD of the LVOT shows respiratory variation in velocities. IVC, inferior vena cava; LVOT, left ventricular outflow tract; PWD, pulse wave Doppler.

When assessing specific etiologies of cardiogenic shock, significant new RWMA, and new or worsening mitral regurgitation can suggest acute myocardial ischemia (Video 33-2). Valvular pathologies, dynamic LVOT obstruction, and cardiac tamponade can cause hemodynamic instability, and these problems can be diagnosed using echocardiography. Another important etiology of cardiogenic shock in the ICU is stress-induced cardiomyopathy (SCM). The incidence of this problem in ICU patients could be as high as 28%, and early diagnosis is facilitated using echocardiography.⁶⁵ Typical echocardiographic findings are apical ballooning with global LV dysfunction and compensatory hyperdynamic function of the basal segments (Video 33-3).

Right-sided heart failure, isolated or in the setting of biventricular failure, presents with slightly different echocardiographic findings. Mainly qualitative findings are depressed RV contractility, decreased EF by FAC, a TAPSE <16 mm in combination with RV dilation, RV/LV ratio of >0.8, and severe TV regurgitation (Video 33-4).⁵⁷ In this setting, low RVSP in conjunction with increased RAP, suggested by an IVC diameter >20 mm, can be due to the inability of the myocardium to create adequate pressure. Evaluation of the LV often shows signs of hypovolemia with isolated RV failure due to decreased LV preload.

The most common pathologies causing RV failure leading to acute cardiogenic shock are acute volume or pressure overload, new valvular pathologies, or acute ischemia. Chronic RV dysfunction predisposes patients to RV failure during critical illness due to noncardiogenic causes. RV dilation, TV regurgitation, ventricular septal shifts, abnormal RVSP, and IVC dilation all help to inform the clinician about the

etiology of acute RV failure. In particular, ventricular septal shifts have to be interpreted in this context, as they are commonly present in chronic valvular or pulmonary disease states, and do not necessarily indicate the presence of acute RV failure (Fig. 33-8).

Distributive Shock

Septic shock can present with a highly variable clinical picture, and dynamic changes in the appearance of shock can occur within hours with or without intervention. The clinical picture of septic shock can range from aspects of a pure distributive shock to combinations of hypovolemic, cardiogenic, and distributive shock.^{66,67} For this reason, echocardiography aids in the assessment and management of septic patients, and serial reevaluation is imperative to adapt to the dynamic evolution of the disease. Bedside echocardiography in the septic patient is focused on the systematic evaluation of volume status and fluid responsiveness, SVR, and ventricular function. Early echocardiographic signs supporting the diagnosis of septic shock are hyperdynamic LV systolic function and high CO levels in conjunction with small or normal LV EDA (Video 33-5). However, the findings will depend on intravascular volume status and RV function. It is important to differentiate between hypovolemia and low SVR in this situation, as the only distinction may be the difference in LVEDA (Video 33-1 vs. 33-5).

There are some caveats specific to the evaluation and monitoring of distributive shock. Fluid resuscitation often eliminates signs of

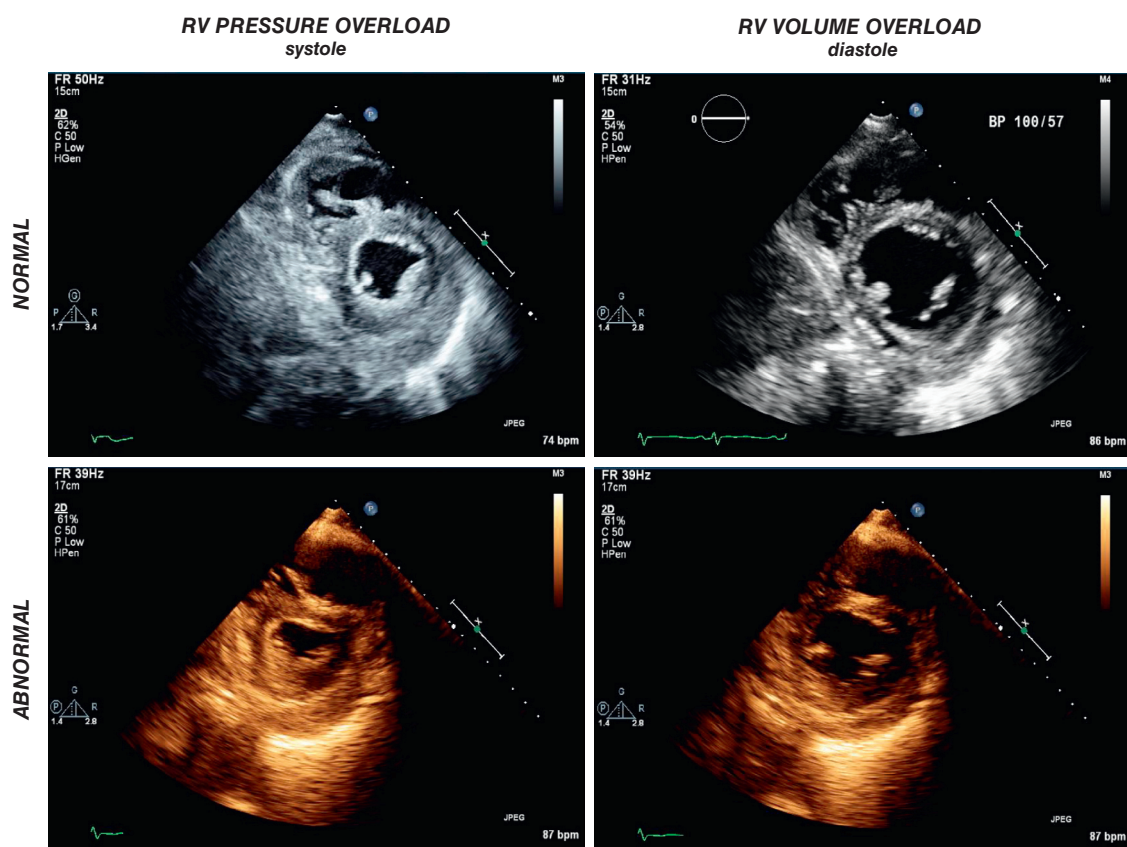


FIGURE 33-8 ■ Paradoxical interventricular septal shift. Pathologies causing RV pressure overload such as pulmonary hypertension will result in septal flattening during systole. With RV volume overload, a septal shift occurs in diastole. In acute RV failure, commonly both pathognomonic findings are seen. RV, right ventricle.

hypovolemia, and vasopressors may depress the hyperdynamic appearance of the LV. If myocardial dysfunction is present, the ventricular function may appear normal or hyperdynamic on initial or follow-up imaging as opposed to the classic hyperdynamic shock picture. Inotropic support can alter echocardiographic findings even further.⁶⁸⁻⁷⁰

Obstructive Shock

Circulatory collapse due to mechanical interference with ventricular filling or emptying is classified as an obstructive shock.⁷¹ Potential causes of obstructive shock include pericardial effusion and tamponade, tension pneumothorax, and pulmonary embolism, as well as less common entities, such as intracardiac tumors or vena cava compression. As these mechanisms are mechanical, echocardiography has the potential of visualizing the source of shock pathology directly aside from identifying the hemodynamic profile.

Pericardial effusion and cardiac tamponade are dynamic diseases closely linked to changes in intravascular volume status, intrathoracic pressures, and patient position. Although the etiology of an effusion cannot be defined by echo, certain findings such as clot formation or stranding can hint toward hemorrhagic or purulent effusions of serous fluid (Fig. 33-9). When evaluating cardiac tamponade, echocardiography can exhibit signs suggestive of hemodynamically significant pericardial effusion or clot^{72,73} (Table and Video 33-6). In postcardiac surgery patients, tamponade may not always be present with the classic circumferential effusion, and echocardiographic imaging should include an assessment for the localized clot or fluid collections in uncommon locations, such as the IVC-RA junction or posterior to the LA.

A pulmonary embolism causes the obstruction of blood flow from the right side of the heart to the left. It commonly presents with signs of right-sided pressure overload and RV failure, in conjunction with a hypovolemic and hyperdynamic LV (Table and Video 33-7).⁷⁴ The McConnell sign with akinesis of the RV free wall and normal function of the RV apex is pathognomonic but not always observed (Video 33-7).⁷⁵ Occasionally, the obstructing embolism can be seen in the very proximal pulmonary vasculature. Additionally, it is pertinent to evaluate patients for intracardiac shunts, as these present a risk for paradoxical embolism and hypoxia and have a worse short-term prognosis.^{76,77}

Tension pneumothorax can cause decreased cardiac preload, and echocardiographic findings show hypovolemia and possible mechanical cardiac compression or shift. Further imaging via chest ultrasound or radiography is necessary for the diagnosis. Other pathologies, such as extra- or intracardiac masses causing obstruction to ventricular filling, are uncommon. However, when these problems are present, echocardiography can be helpful for making the diagnosis and evaluating the hemodynamic significance.

Echocardiography during Cardiopulmonary Resuscitation

Echocardiography is part of the global use of ultrasound in cardiac arrest. It focuses on identifying the immediate causes of cardiac arrest, such as cardiac tamponade, pulmonary embolism, hypovolemia, or myocardial failure, and can guide and follow resuscitation efforts.^{78,79} Additionally, Salen et al. and Blyth et al. showed that the echocardiographic identification of cardiac activity can predict

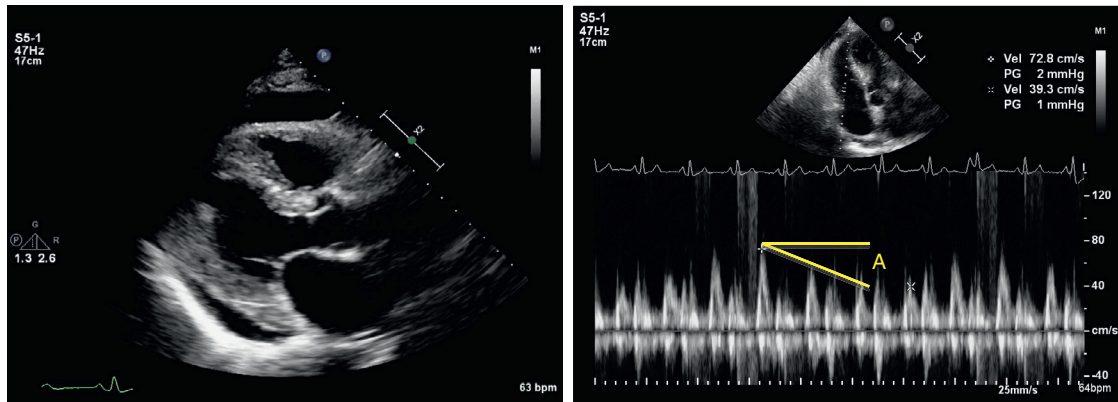


FIGURE 33-9 ■ Hemodynamic is compromising pericardial effusion/tamponade. Respiratory variation in TV inflow of >25% is suggestive of hemodynamic-compromising pericardial effusion and tamponade. It is important to differentiate a pericardial from a pleural effusion. The arrow marks the descending thoracic aorta. A pericardial effusion does not extend superiorly (leftward) past the descending thoracic aorta, whereas a pleural effusion projects more distal to the aorta with extension past the vessel toward the left of the image. Circumferential effusion, the diastolic collapse of RA or RV, and IVC plethora are additional signs suggestive of tamponade physiology, as seen in Video 33-6.

TABLE 33-7

Echocardiographic Signs Were Seen with a Significant Pulmonary Embolism

PULMONARY EMBOLISM

- Clot in proximal pulmonary vasculature
- Depressed RV systolic function +/- hypovolemic and hyperdynamic LV
- Interventricular septum shifts consistent with RV pressure overload
- McConnell sign
- TR
- IVC plethora
- Intraatrial shunt

Dependent on the extent of RV compromise the LV will exhibit signs of hypovolemia. Classic sign of RV pressure overload shows a systolic shift of Interventricular septum. Evaluation for intraarterial communication with R to L shunting is pertinent in patients with significantly increased right-sided pressures due to PE. IVC, inferior vena cava; LV, left ventricle; RV, right ventricle; TR, tricuspid valve.

recovery of spontaneous circulation.^{80,81} The best view for immediate evaluation in cardiac arrest is the LV SAX view. This is because it can provide information about extreme changes in volume status, myocardial function, and pericardial tamponade simultaneously. Additionally, it is easy to obtain and interpret. In the acute setting, TEE can often provide better continuous imaging when chest compressions are ongoing, but it may interfere initially with intubation attempts.

■ SPECIFIC EVALUATION

Valvular Pathologies

A detailed assessment of valvular pathologies requires comprehensive echocardiographic skills and is performed by cardiologists or cardiothoracic anesthesiologists with advanced echocardiographic training. During limited ICU echocardiographic exams, the operator should seek to identify gross valvular pathologies, as their presence can alter management. Aside from the immediate adjustment in hemodynamic management, any valvular pathology found on the basic bedside exam warrants further subsequent evaluation by a comprehensive examination.

Basic components of valve assessment include gross anatomic evaluation for obvious pathologies, such as calcifications or ruptured leaflets and papillary muscles (Table 33-8). CFD is used to recognize significant transvalvular flow acceleration suggestive of stenotic lesions or patterns of valvular regurgitation of hemodynamic significance. Basic quantitative measurements of transvalvular gradients by CWD can be obtained through AV and MV for grading of stenotic lesions and calculation of valve area, but this is part of the in-depth exam.^{82,83} The five most common valvular pathologies are seen in Video 33-8 to 33-12.

Cardiomyopathies and Dynamic Outflow Obstruction

Primary disease of the heart muscle plays a significant part in the overall morbidity and mortality of cardiovascular disease. Echocardiography provides information about the magnitude of systolic and diastolic heart failure, as well as the etiology of cardiomyopathy. Echocardiography permits the assessment of immediate and long-term prognosis. As cardiomyopathies can alter the hemodynamic response to acute illnesses and their management in the ICU, it is important for the intensivist to know the echocardiographic patterns that are characteristic of these chronic disorders.⁸⁴

Cardiomyopathies (CM) are commonly differentiated into three main types: (1) dilated CM; (2) hypertrophic CM; and (3) restrictive CM.⁸⁵ Dilated CM presents with echocardiographic findings of dilated ventricles and reduced ventricular systolic function (Video 33-13). Hypertrophic CM is characterized by symmetric or asymmetric concentric hypertrophy of the myocardium (Video 33-14). It is important to recognize a dynamic obstruction of the LVOT in hypertrophic obstructive cardiomyopathy (HOCM). This is because the presence of this problem alters the usual management of cardiogenic shock management since the administration of inotropic agents can be detrimental in patients with HOCM. Dynamic outflow obstruction in these cases is caused by the systolic anterior motion of the mitral valve leaflet (SAM) (Video 33-15).⁸⁶ As in HOCM, SAM can also be present after mitral valve surgery.⁸⁷

Restrictive CM is more difficult to diagnose as it presents with diastolic dysfunction of the ventricles, and echocardiographic findings require an evaluation of diastolic function. For the intensivist, if evaluation for diastolic dysfunction is difficult, findings of atrial

TABLE 33-8 Common Valvular Pathologies and Their Echocardiographic Findings

| VALVE PATHOLOGIES | | FINDINGS |
|------------------------------|-----|---|
| Aortic stenosis (AS) | 2D | Calcification of leaflet and annulus, restrictive leaflet motion, LVH |
| | CFD | Transvalvular flow acceleration, AI |
| | CWD | Transvalvular flow acceleration, increased peak mean, and peak gradient rounded Doppler profile |
| Aortic insufficiency (AI) | 2D | Leaflet disruption, LV enlargement |
| | CFD | Regurgitant diastolic flow, turbulent flow, regurgitant jet direction |
| | CWD | Regurgitant diastolic flow, Doppler profile density, diastolic flow reversal in proximal thoracic aorta |
| Mitral stenosis (MS) | 2D | Calcification of leaflet and annulus, restrictive leaflet motion, dilated LA |
| | CFD | Transvalvular flow acceleration, PISA, MR |
| | CWD | Transvalvular flow acceleration increased peak mean and peak gradient |
| Mitral insufficiency (MR) | 2D | Leaflet pathology, chordal tethering, dilated annulus, LA enlargement, LV enlargement |
| | CFD | Regurgitant systolic flow, turbulent flow, regurgitant jet severity and direction |
| | CWD | Regurgitant diastolic flow, Doppler profile density, diastolic flow reversal in proximal thoracic aorta |
| | PWD | Pulmonary vein flows blunting/reversal |
| Tricuspid regurgitation (TR) | 2D | Dilated annulus, leaflet pathology, RA enlargement, RV enlargement |
| | CFD | Regurgitant systolic flow, turbulent flow, regurgitant jet severity and direction |
| | CWD | Regurgitant diastolic flow, Doppler profile density |
| | PWD | Hepatic vein flows blunting/reversal |

LA, left atrium; LVH, left ventricular hypertrophy; PISA, proximal isovolumetric flow acceleration.

enlargement with small ventricles and subjective restricted ventricular function are often the best supportive indicators for restrictive cardiomyopathies.⁸⁴

Infectious Pathologies and Embolic Sources

TEE is utilized in the evaluation of infectious and embolic sources in patients with unexplained sepsis or embolic strokes. In an acute setting, transthoracic findings of new regurgitant valvular lesions in the setting of bacteremia can be suggestive of infectious endocarditis. However, TEE is warranted for the optimal assessment when vegetations are anticipated (Video 33-16). As differentiation can be difficult and an evaluation for coexisting involvement of the valvular structures is pertinent for possible surgical management, comprehensive TEE is commonly performed by cardiologists.⁸⁸ When the etiology of a stroke in the absence of an infection is unclear, or in the event of planned cardioversion for prolonged supraventricular tachyarrhythmias in patients with a high risk of thrombus formation, TEE is performed to evaluate for the presence of left atrial appendage clot.^{89,90} Additionally, when evaluating for cardiac sources of thromboembolic events, the presence of intracardiac shunts as the source for paradoxical events should be ruled out. As these are not always detected by simple CFD interrogation, a bubble study during a Valsalva maneuver is performed to aid in the detection of right to left shunting.

Aortic Pathologies

Echocardiographic assessment of aortic disease in acute hemodynamic instability in critically ill patients mainly focuses on the evaluation of aortic dissection. As TTE is of limited utility for evaluation of the thoracic and abdominal aorta, TEE is the modality of choice.⁹¹ TEE has been shown to be equally accurate when compared to CT or MRI in the diagnosis and confirmation of thoracic aortic dissection.⁹² The evaluation includes the visualization of the dissection flap, identification of the true and false lumens, estimation of blood flow, and determination of active extravasation. When the aortic root is involved, assessment includes evaluation for subsequent complications, including

aortic insufficiency (AI), pericardial effusion, and acute ischemia secondary to coronary involvement.

Trauma

Echocardiography in critically ill patients after trauma can evaluate the hemodynamic status, as well as anatomic pathologies following forceful injuries.⁹³ After blunt chest trauma, echocardiography is a useful tool in the initial evaluation.⁹⁴ Catastrophic structural injuries, such as cardiac tamponade, cardiac rupture, coronary artery thrombus, disruption of valvular structures, and traumatic aortic injury, can be identified quickly.⁶¹ More commonly, patients only present with signs of cardiac contusion, and echocardiography can assist with identification of myocardial dysfunction in the acute setting. Specific TTE views are part of the standard algorithms for an emergency ultrasound, such as the FAST or FOCUS exams.^{95,96} When available and no contraindications are present, TEE is the modality of choice as it provides superior image quality and can diagnose aortic injury.⁹⁷

Interventional Use of Echocardiography

Interventional procedures involving cardiac structures are common in the ICU, and basic ultrasound and echocardiography play important roles in the conduct of these interventions. TTE or TEE performed at the bedside alleviate the need for transporting patients to the cardiac catheterization lab or procedure room for fluoroscopic guidance. This eliminates the risks that are associated with moving critically ill patients. Use of echocardiography can also decrease exposure to radiation.⁹⁸ While the basic US can assist significantly in multiple types of procedures, including venous and arterial vascular access and drainage of pleural effusions or other fluid collections, echocardiography can assist in more advanced procedures. TTE can assist with pericardiocentesis and with gross localization of a transvenous pacemaker lead.⁹⁹⁻¹⁰¹ TEE provides optimal image quality for specific cardiovascular interventions, such as an intraaortic balloon pump (IABP) placement and positioning of extracorporeal membrane oxygenation (ECMO or ventricular assist device (VAD) cannulas.^{61,102-104} TEE

best evaluates mechanical assist devices. Thromboembolic events, overt hemolysis, or fluctuation in device power or flow warrant the evaluation for thrombus formation, cannula position, and device function.^{105,106}

Hypoxemia

Echocardiography can assist in the diagnosis and management of acute respiratory failure. In pulmonary edema, differentiation between cardiogenic and noncardiogenic etiology aids in medical management. Either by invasive measurements or echocardiographic evaluation, estimation of LA and LV filling pressures is pertinent for the diagnosis of hydrostatic pulmonary edema. When a regular rhythm is present, LV filling pressures can be estimated by transmitral and pulmonary venous Doppler studies and is the most commonly used parameter for an easy, reproducible assessment in the ICU.¹⁰⁷ Common cardiac causes for pulmonary congestion are volume overload, acute mitral or aortic valve regurgitation, mitral stenosis, and severe LV systolic and diastolic dysfunction. All these problems can be assessed using 2D, CFD, and spectral Doppler echocardiographic modalities. In noncardiogenic ARDS, echocardiography can allow the clinician to assess changes in RV function with adjustments of mechanical ventilation.¹⁰⁸ Severe ARDS with increased pulmonary resistance and the use of high levels of positive end-expiratory pressure (PEEP) may lead to acute or pulmonary issues with sudden RV failure and subsequent hemodynamic and respiratory decompensation.¹⁰⁹ Similarly, acute increases in pulmonary vascular resistance due to pulmonary embolus (PE) can cause RV failure.¹¹⁰ In these cases, echocardiography is often used as a supportive tool for the diagnosis and assessment of hemodynamic significance.

Another common cause of hypoxemia in mechanically ventilated patients is the presence of intracardiac shunts. With a prevalence of >25% in the general population, intraatrial communications, such as patent foramen ovale (PFO) and atrial septum defects (ASD), are frequently clinically silent.^{111,112} In healthy patients with PFO or ASD, shunting typically is either absent or directed from left to right. During critical illness, however, increased right-sided pressure due to pulmonary hypertension, RV failure, volume overload, or TV regurgitation, is common and can lead to right to left shunting, resulting in hypoxemia due to the admixture of nonoxygenated with oxygenated blood.⁶¹ Echocardiographic evaluation focuses on detection of intracardiac shunting and directional flow of the shunt by 2D echo and CFD.

FUTURE DIRECTIONS

Many miniaturized and TTE and TEE devices have been introduced recently into the critical care environment for the use by noncardiologists for goal-directed therapy of the hemodynamically unstable patient. Handheld TTE devices demonstrate usefulness in the clinical setting when used by intensivists after undergoing brief training.¹¹³⁻¹¹⁶ Miniaturized, disposable TEE probes that provide monoplane images have been introduced for the continuous use up to 72 hours. The initial experience has demonstrated good utility in the management of hemodynamically unstable patients.^{117,118} These novel monitoring devices for continuous echocardiographic imaging have great potential for

providing many features of a regular TEE while minimizing the risks and allowing for use over a period of time.^{119,120} Advanced echocardiographic modalities, such as contrast echocardiography and endocardial border-tracking, can be valuable when available.¹²¹⁻¹²³

On the operator side, more intensivists are becoming skilled in echocardiography, and ICU fellowship programs increasingly teach focused echocardiography. With the growing importance of critical care echocardiography, critical care societies across the world propose the further integration of formal echocardiographic training into ICU fellowship training. Specific criteria are being defined for the future trainees while courses in focused ICU echocardiography are offered for the practicing intensivist.¹⁷⁻¹⁹

Despite significant advancements in the field over the past decade, a broader validation of echocardiographic use in the ICU is needed. Outcome-based studies looking at the use of focused echocardiography as a monitoring tool and integration into goal-directed therapy will be helpful in strengthening the broad use of this valuable tool.

KEY POINTS

1. TTE and TEE are valuable diagnostic and monitoring tools in the critical care setting and can have a significant impact on management and outcome of critically ill patients.
2. Training, accreditation and maintenance of expertise in focused echocardiography are essential, and further development of these areas by national societies is needed.
3. An understanding of ultrasound physiology, the echo machine, anatomy, and normal echocardiographic findings is essential for the appropriate use echocardiography in the ICU.
4. The most common use of bedside echocardiography is the evaluation of acute circulatory and respiratory failure.
5. An algorithmic approach to the hemodynamically unstable patient is warranted, and repeated echocardiographic assessment to confirm and adjust medical management needs to ensue until the patient stabilizes.
6. Interpretation of echocardiographic findings should take into account the patient's history, pathophysiology, and current medical interventions.
7. Management based on echocardiographic information needs to follow the complete clinical picture of the critically ill patient.
8. With rapid advancement in ultrasound technology, pocket-sized handheld TTE devices, and miniaturized TEE probes for continuous monitoring are being developed and will further promote the integration of focused echocardiography in the daily critical care practice.

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Shock is among the most common indications for admission to the intensive care unit (ICU). As with any complex physiologic derangement, monitoring of the shock state requires constant vigilance. The ultimate goal of treating the patient with shock centers on normalizing cellular respiration and reducing the sequelae of end organ dysfunction.¹ Specific end organ tissue perfusion and oxygen utilization are difficult to measure; surrogate systemic cardiovascular metrics are used in their place. Awareness of hemodynamic trends is necessary to ensure adequate perfusion to end organs and generate a meaningful clinical response. Postoperative complications, length of hospital stay, and mortality from elective surgical procedures can be reduced by targeting therapy to meet preselected cardiovascular goals.²

Knowledge of a patient's overall volume status is profoundly important, as the goal of shock resuscitation is to normalize tissue metabolism. This usually requires optimization of end organ perfusion.³ Classically, variables such as central venous pressure, pulmonary capillary wedge pressure (PCWP), and ventricular end-diastolic volume have been used in an effort to identify the patient who will increase end organ perfusion in response to a fluid bolus. These static parameters indirectly attempt to identify a patient who is on the steep portion of the Frank-Starling end-diastolic pressure-stroke volume curve at any given point in time. These parameters are easily measured but have proven unable to identify the fluid-responsive patient. In response, modern approaches to cardiac output (CO) optimization have focused on dynamic indicators of fluid responsiveness, which identify changing conditions over time. These dynamic parameters include pulse pressure variation, stroke volume variation, change in right atrial pressure, change in aortic blood velocity, and change in vena cava diameter. All of these metrics relate to the change in stroke volume throughout the respiratory cycle, with the assumption that alterations in intrathoracic pressure, such as those that occur with ventilation, create transient physiologic swings in cardiac preload and output. They have proven to be significantly more useful in identifying the fluid-responsive patient and may lead to an improvement in clinical outcome when coupled with appropriate intervention.^{4,5}

Measurement of these dynamic parameters is complex. A variety of monitoring systems are available to follow the trend of the CO. Some devices are more effective than others, but all have advantages and limitations. They are discussed here, stratified by level of invasiveness and underlying technology. Particular attention is paid to their ability to accurately estimate CO, improvement of which is the intended outcome when treating shock. Fig. 34-1 outlines one possible approach to monitoring the patient with shock.

■ NONINVASIVE MONITORS

For the purpose of this chapter, a noninvasive cardiovascular monitoring device is defined as one that does not require arterial or central venous cannulation. While more invasive devices are certainly associated with increased potential for complications, this should not imply that noninvasive devices are not without risk of injury.^{6,7} Furthermore, by their nature, noninvasive devices indirectly measure hemodynamic parameters and thus may be prone to variability and inaccuracy.⁸

Standard Monitoring

At its most basic, noninvasive cardiovascular monitoring includes routine use of pulse oximetry, noninvasive blood pressure manometry,

and electrocardiography. Aside from physical examination, these are among the simplest and most ubiquitous tools for objective assessment of a patient's hemodynamic status. Despite their prevalence, very few prospective trials have been conducted to evaluate the independent (or grouped) impact of these monitors on clinical outcome. However, as formal hemodynamic monitoring became more accessible and widespread, anesthetic-related morbidity and mortality rate, for example, declined significantly from the 1950s to 1980s worldwide. It is impossible to know if this improvement is attributable solely to advances in monitoring. Changes in surgical populations, advances in perioperative science, secular trends, or a combination of factors may have provided additional benefit.⁹ Regardless, these basic devices are now recommended by governing societies as essential monitors during perioperative care^{10,11} and are thus unlikely to be subject to future randomized trials.

Despite lack of documented mortality benefit from routine use, basic noninvasive devices are invaluable for identifying the patient who may need advanced monitoring. Indeed, hypotension, arrhythmia and/or myocardial infarction, and hypoxemia often accompany (or precipitate) shock and can be recognized by sphygmomanometry, electrocardiography, and pulse oximetry, respectively.^{1,12,13}

Photoplethysmography

Since widespread adoption of the pulse oximeter in the 1980s, there has been a slow increase in adaptations of the underlying engineering principles of this device. Clearly, the plethysmographic signal is very similar to the arterial pressure waveform. Many investigators have attempted to extrapolate from this observation with hopes of using the waveform to estimate arterial blood pressure, systemic vascular resistance, stroke volume, and continuous CO.¹⁴⁻¹⁶ These ventures have largely been unsuccessful. Determination of volume status using respiratory variation in oximeter waveform amplitude has been especially vigorously investigated. However, these investigations have had conflicting results, and this is not considered an accurate dynamic indicator of fluid responsiveness in most settings.¹⁷

Several commercial photoplethysmographic devices are designed for continuous estimation of arterial blood pressure and are worthy of further discussion. Namely, the CNAP (CNSystems, Graz, Austria), ClearSight (formerly called NexFin; Edwards Lifesciences, Irvine, CA), and Finometer (Finapres Medical Systems, Amsterdam, Netherlands) monitoring systems take advantage of a volume-clamp technique to deliver a constant visual display of arterial pressure. The volume-clamp technique uses a very rapid feedback loop between an oximeter and inflatable finger cuffs (akin to traditional blood pressure cuffs). By rapidly increasing or decreasing the pressure in one or two cuffs to a point at which photoplethysmographic waveform oscillations are greatest, the finger's inflow artery can be held in a constant, unstretched position. At this position, the pressure in the cuffs will equal the inflow arterial pressure. Many studies have explored the accuracy of these devices compared to direct pressure transduction, but a meta-analysis concluded these devices produced imprecise and potentially inaccurate measurement of arterial pressures, larger than what was deemed acceptable.¹⁸ However, these devices are still useful to identify rapidly changing hemodynamics, such as occurs with induction of general anesthesia. More recent research has focused on the use of these systems to estimate CO, which have had some success.¹⁹ However, use of these devices for accurate continuous

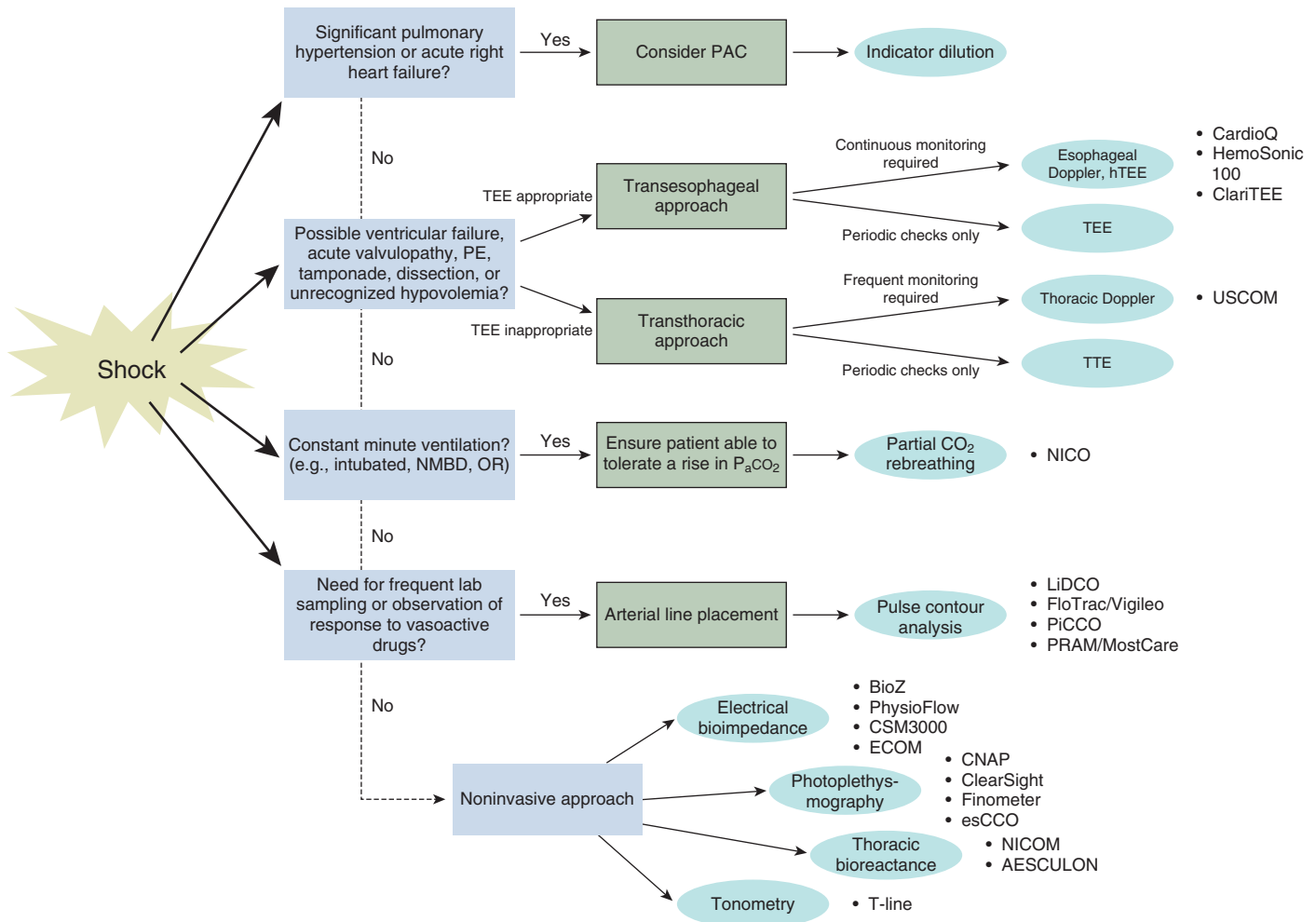


FIGURE 34-1 ■ Approach to cardiovascular monitoring strategy in the patient with shock. Detection of hemodynamic deterioration must be coupled to an appropriate intervention in order to change patient outcome. Common devices are listed, which are discussed in detail in the text. hTEE, hemodynamic transesophageal echocardiography; NMBD, neuromuscular blocking drugs; OR, operating room; PAC, pulmonary artery catheter; P_aCO_2 , partial pressure of arterial CO_2 ; PE, pulmonary embolism; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

assessment of CO (rather than at a single time point) has not been validated.

When combined with electrocardiography to estimate pulse transit time (i.e., the time from a ventricular beat until blood is delivered to the oximetry site), photoplethysmography has been successfully used to estimate short-term changes in blood pressure in patients following induction of anesthesia.^{20,21} This information can be indirectly calculated using traditional approaches or, alternatively, can be measured with the esCCO monitor (Nihon Kohden, Tokyo, Japan), which also incorporates patient-specific demographics to generate a continuous estimation of CO. Unfortunately, the esCCO device has been found to be relatively inaccurate (when not calibrated using additional data obtained invasively) compared to thermodilution approaches for estimation of CO.¹⁶

Much of the limitation in applied photoplethysmography stems from the need for significant processing to remove noise from the oximeter signal. Some of this noise reflects the influence of autonomic nervous control of vascular tone in venous or tissue oximetry; the influence of anesthesia, surgery, or critical illness on these modifiers is unpredictable and complicates interpretation. Furthermore, many of the studies evaluating the efficacy of photoplethysmography initially

show high correlation when compared with gold standard methods in healthy controls but lose fidelity when applied to critically ill patients.¹⁷ Nevertheless, photoplethysmography remains an interesting approach to hemodynamic monitoring with the potential for future clinical application.

Tonometry

Applanation tonometers electromechanically measure pressure in the radial artery, akin to estimating pressure by palpating pulse amplitude. The T-line device (Tensys Medical Inc., San Diego, CA) displays continuous radial artery pressure and also continuously calculates CO. The T-line device requires a high-quality arterial waveform signal (i.e., the tonometer needs to be optimally positioned over the radial artery), which may be challenging in a spontaneously moving patient. Of note, a 2014 meta-analysis concluded this device was too imprecise to reliably predict arterial pressure. However, this analysis focused on several commercially available noninvasive devices, including the previously discussed CNAP and ClearSight systems, and it did not stratify results by individual device. The results thus may represent unfavorable performance of other devices rather than poor T-line performance.¹⁸

When compared to transpulmonary thermodilution, the T-line system is acceptably accurate for measurement of CO in critically ill patients.²²

Electrical Bioimpedance

Originally developed in the 1960s, electrical bioimpedance systems operate on the principle that impedance varies as the total volume of fluid in the thorax changes throughout the cardiac cycle. After application of voltage-generating sensors to the thorax, bioimpedance devices measure the change between applied and detected voltage and mathematically extrapolate stroke volume from this difference. A number of bioimpedance monitors are currently marketed, including the BioZ (CardioDynamics, San Diego, CA), PhysioFlow (NeuMedX, Inc., Bristol, PA), NICOMON (Larsen and Toubro Ltd., Mumbai, India), NICCOMO (Medis, Ilmenau, Germany), and CSM3000 (Cheers Sails Medical, Shenzhen, China) devices.²³ Advantages of the bioimpedance devices include relatively low cost and ease of application. However, they are significantly confounded by the presence of extravascular lung water, improper electrode placement, presence of arrhythmia, concurrent electrical interference, and atypical systemic vascular resistance values.²⁴ In a recent meta-analysis, bioimpedance devices were found to have poor concurrence with CO measurements obtained via thermodilution techniques.²⁵ Thus, these devices are generally not recommended for long-term monitoring in a critically ill individual, but they may provide insight into CO at an isolated point in time.

A relatively newer device, the ECOM system (ConMed Corp., Utica, NY), attempts to overcome some of the limitations of traditional bioimpedance sensing by measuring intrathoracic, rather than external, impedance. This system incorporates electrodes within a specially designed endotracheal tube. Measuring impedance from within the trachea, which lies in close proximity to the aorta, may help increase accuracy by avoiding some of the noise captured with electrode placement on a patient's chest. Unfortunately, when calculating cardiac index, this approach is relatively inaccurate, though is useful for identifying fluid responsiveness. Furthermore, the ECOM system requires the presence of an arterial catheter and is therefore more appropriately considered minimally invasive.²⁶

Thoracic Bioreactance

In response to limitations of bioimpedance, thoracic bioreactance devices have been developed that process the impedance signal differently. These devices operate in similar fashion but use an expanded algorithm to detect the phase shift in transthoracic voltage (dependent on thoracic resistance and capacitance, which changes only with significant acute change in thoracic fluid volume). They detect pulsatile flow alone and are less likely to be aberrantly influenced by the presence of lung water.²⁴ Marketed bioreactance systems include NICOM (Cheetah Medical, Portland, OR) and AESCULON (Osypka Medical Services, Berlin, Germany). Despite avoiding confounding by minimizing the influence of lung water, these devices have many of the same limitations as bioimpedance devices.²³ Nevertheless, the NICOM system in particular has been found to be highly accurate in measuring CO when compared to transthoracic thermodilution measurements,²⁷ although some studies have not found it to be as accurate in critically ill patients.^{28,29}

Transthoracic Echocardiography

Complete discussion of cardiac ultrasonography is beyond the scope of this chapter. However, transthoracic echocardiography (TTE) provides invaluable insight into cardiac function and has evolved into an extraordinarily useful diagnostic tool in the ICU. In particular, TTE can assist the intensivist in recognizing ventricular failure, hypovolemia, valvular disease, pulmonary embolism, cardiac tamponade, aortic dissection, and other cardiogenic contributions to shock.^{30,31} Recent recommendations from the American Society of Echocardiography recommend a limited, focused cardiac ultrasound (FoCUS) exam,

targeting assessment of biventricular function, volume status, and gross anatomic abnormalities. This exam can be rapidly performed at the bedside and provides useful information to guide management of the unstable patient.³²

Older studies, in which exams were interpreted by cardiologists, found TTE to be highly sensitive and specific for identifying cardiogenic shock, and it often led to changes in patient management.³³ There have yet to be randomized clinical trials investigating outcomes after use of focused critical care echocardiography, partly due to the often emergent nature of the need for examination but also due to the relatively novel use of TTE as interpreted by intensivists. Nevertheless, there are data to support the use of intensivist-performed TTE, particularly in the traumatically injured or putatively hypovolemic patient.³⁴ Furthermore, initial diagnostic evaluation of the hypotensive patient is significantly faster using TTE than by placing a pulmonary artery catheter (PAC) and usually provides comparable diagnostic information.^{35,36}

Beyond evaluation of cardiac structures, thoracic ultrasonography can be used to estimate volume status by using the ventilation-induced change in inferior vena cava (Δ IVC) diameter as a dynamic parameter of fluid responsiveness. Meta-analysis suggests a large Δ IVC is effective in identifying fluid responders, further corroborating the utility of TTE as a cardiovascular monitor in the ICU.³⁷

Traditionally, the utility of echocardiography in the ICU has been limited by the need for extensive specialized training in image acquisition and interpretation. As ultrasound technology has become more affordable and common, echocardiography has increasingly permeated into medical training. Indeed, after just a few hours of formal training, one study found ICU physicians were able to estimate basic aspects of cardiac function with reasonable accuracy using TTE.³⁸

TTE does have practical limitations. While the transthoracic exam can be performed quickly, it is logistically challenging to perform repeated exams to trend cardiac function over a short time frame; continuous examination is even more cumbersome. Furthermore, the exam itself is often limited by use of positive end-expiratory pressure (PEEP), unfavorable patient habitus, suboptimal positioning, or the presence of surgical dressings.³⁸

MINIMALLY INVASIVE MONITORS

Minimally invasive monitoring devices consist of those that require low-risk cannulation of peripheral veins or arteries or device insertion into natural orifices. While increasing the risk of patient harm, they overcome some of the limitations of noninvasive devices. For practical purposes, they are among the most feasible options for advanced cardiovascular monitoring in the ICU.

Partial Carbon Dioxide Rebreathing

The Fick principle is among the oldest concepts used to estimate CO. Traditionally, the Fick method involves measuring the ratio between oxygen consumption and the arteriovenous oxygen difference. However, this same principle can be applied to other respiratory gases. Carbon dioxide (CO_2) has a high diffusion capacity, is easily quantified, and is reliably produced in end organs, making it an ideal agent for substitution into the Fick equation. Assuming the partial pressure of end-tidal CO_2 approximates mixed venous CO_2 tension, CO can be calculated by periodically permitting CO_2 rebreathing (i.e., adding dead space to the ventilatory circuit) and measuring the change in end-tidal CO_2 as compared to measurement at a nonrebreathing time. This approach has been shown to correlate with cardiac index as derived from a PAC under most conditions. The CO_2 rebreathing technique is confounded by states of low tissue production of CO_2 (e.g., hypothermia), significant shunting, and very high CO. Furthermore, constant minute ventilation is required to ensure respiratory variation does not produce large swings in arterial CO_2 tension. This method is therefore not easily applied to spontaneously breathing patients.^{39,40,41}

The NICO system (Respironics, Murrysville, PA) is a popular device that measures CO using the Fick principle. It requires knowledge of arterial oxygen tension in order to account for intracardiac or intrapulmonary shunting, hence the designation as minimally invasive. Some studies have found the NICO monitor to be accurate at estimating CO when compared to thermodilution techniques,^{41,42} but others have found poor agreement between the two approaches.^{40,43} Nevertheless, the partial CO₂ rebreathing technique remains an option for measuring CO in patients who are not breathing spontaneously, can tolerate an increase in arterial CO₂, and do not require a PAC.

It is worth noting many investigations of novel cardiovascular monitors compare CO as measured by the investigational device to the clinical gold standard of using a PAC and indicator dilution. However, the Fick approach, after measurement of systemic oxygen consumption, is an actual gold standard in itself, as it reflects end organ oxygen utilization, normalization of which is the goal of hemodynamic optimization. Fick-determined CO often, but not always, correlates well with thermodilution-determined CO.^{44,45}

Arterial Pulse Contour Analysis

Measurement of CO by analyzing the peripheral arterial waveforms began to generate widespread interest in the 1950s,⁴⁶ was further refined in the 1990s,⁴⁷ and has emerged as one of the most popular approaches to advanced cardiovascular monitoring within the past decade. By analyzing the arterial pulse waveform, stroke volume is estimated, and a continuous display of hemodynamic metrics (e.g., stroke volume, cardiac index, systemic vascular resistance, and others) is provided. Estimating CO by arterial contour analysis is complex. Briefly, stroke volume is determined by calculation of the area under the arterial pressure waveform curve, with the assumptions that blood is a non-compressible substance which must flow forward following ejection from the left ventricle, the aorta pumps blood forward as it relaxes during ventricular diastole, and there is a linear relationship between pressure and the volume of blood in the arterial bed. Ambiguity enters the equation when determining the compliance and resistance of the arterial circuit. However, total resistance is unlikely to change significantly over a relatively short time (e.g., within a single cardiac cycle), and thus the area under the arterial waveform curve is proportional to total forward flow and hence to single-beat stroke volume. Commercial devices use proprietary algorithms to estimate vascular resistance and compliance using manual calibration or known physiologic data based on patient age, height, weight, and gender.⁴⁴ There are several devices which use pulse contour analysis to measure CO. The FloTrac Vigileo (Edwards Lifesciences, Irvine, CA), LiDCO (LiDCO Ltd., London, England), PiCCO (PULSION Medical Systems AG, Munich, Germany), and the PRAM/MostCare (Vytech Health, Padova, Italy) systems are among the most popular.

The FloTrac/Vigileo has been the most frequently studied of the pulse contour analysis systems and has had several software updates since its initial introduction in an effort to refine its accuracy. It is unique in that it does not require manual calibration but is autocalibrated using biophysical data to estimate vascular compliance and resistance. This leads to the potential for erroneous measurements, particularly in critically ill patients who may not have normal arterial system dynamics. While its exact algorithm is proprietary, its method of calculating CO is based on assessing the standard deviation of arterial pressure over time, with modification by the aforementioned biophysical variables. In an oversimplified view, FloTrac/Vigileo CO = PR × sd(AP) × X, where PR represents pulse rate, sd(AP) represents pulsatility using the standard deviation of the arterial pressure wave over a 20-second interval, and X is a constant that quantifies arterial compliance and peripheral vascular resistance.⁴⁸ The most recent FloTrac/Vigileo software generation does appear to be more accurate than its predecessors. However, all versions of this device are confounded by situations with low systemic vascular resistance or high CO (e.g., patients with cirrhosis undergoing liver transplant) and can have poor agreement with traditional methods of CO estimation.⁴⁹

The LiDCO system is an alternative device that has also been well studied. This device requires calibration using lithium hemodilution every few hours. In this technique, a very small dose of lithium is injected intravenously (peripherally or centrally) to generate a lithium concentration-time curve, as measured by a lithium-sensing electrode placed within an existing arterial catheter. With this technique, LiDCO CO = (lithium dose × 60)/(area × (1 – PCV)), where PCV is packed cell volume (which needs to be subtracted in the equation as lithium is only distributed in plasma and not within red cells).⁴⁸ Several studies have shown the lithium-dilution approach to be an accurate method of assessing CO, regardless of whether the lithium is injected centrally or peripherally.^{50,51} Studies evaluating LiDCO accuracy compared to PAC-measured CO have had mixed findings. With respect to critically ill patients, the LiDCO system has been deemed accurate in stable patients who have undergone cardiac surgery or liver transplant^{52,53} but not in a group of critically ill patients with a variety of causes of shock.^{49,54}

The PiCCO system is another pulse contour analysis monitor that requires frequent calibration and has been investigated in a relatively large number of trials. PiCCO calibration requires central venous catheterization and is based on thermodilution of the injectate, as detected by a centrally placed (i.e., axillary or femoral) arterial catheter. (Thermodilution calculation of CO is discussed in more detail in the next section.) The most recent iteration of the PiCCO software also takes the shape of the arterial waveform into consideration to estimate aortic compliance and peripheral vascular resistance. Briefly, PiCCO CO = cal × HR × ∫ [P(t)/SVR + C(p) × dP/dt]dt, where cal is the patient-specific thermodilution calibration value, HR is heart rate, P(t)/SVR is the area of the waveform, C(p) is arterial compliance, and dP/dt accounts for the shape of the waveform.⁴⁸ Of note, this transpulmonary thermodilution calibration technique compares favorably with CO estimation as measured by PAC thermodilution.⁵⁵ Recently, some authors have found acceptable agreement between PiCCO and PAC-derived CO measurements during cardiac surgery.⁵⁶ However, most studies have shown unacceptable discrepancies between PAC-derived CO and PiCCO.⁴⁹

The PRAM/MostCare device is unique among pulse contour analyzers in that it does not require calibration of any sort yet provides a constant readout of CO. It operates under a proprietary pressure-recording analytic method to continually calculate beat-to-beat stroke volume. It uses data from an arterial catheter but does not use input from assumed values of aortic elastance. In a very simplified explanation, PRAM CO = HR × [A/(P/t × K)], where HR is heart rate, A is the area under the systolic portion of arterial pulse curve, P/t evaluates systolic and diastolic pressure over time, and K represents instantaneous pulsatile acceleration of the arterial cross-sectional area. It is relatively new and has been less frequently studied than the preceding approaches to pulse contour analysis. There is significant disagreement among studies regarding the accuracy of PRAM/MostCare as compared to gold-standard approaches to CO assessment, so its efficacy remains unclear.⁴⁹

Regardless of the device used, all pulse contour analysis systems require relatively stable cardiovascular conditions to estimate CO. With rapidly changing conditions, such as occur in unstable critically ill patients, many of these systems lose accuracy and precision. Furthermore, they are subject to erroneous measurement in conditions in which vascular tone may be unusually abnormal (e.g., in the presence of vasoconstricting drugs to maintain a goal mean arterial pressure), during abnormal cardiac rhythms, or in conditions in which forward flow of arterial blood may not be guaranteed (e.g., in the presence of aortic regurgitation).⁴⁴ When subject to overall pooled analysis, these devices have been found to have unacceptably large error rates. Of the individual devices, only pooled analysis of LiDCO has shown reasonable agreement with PAC-derived measurements.^{25,49} Nevertheless, these monitors may still prove beneficial in ill patients who may be harmed by insertion of a PAC, as they are capable of analyzing hemodynamic trends over time, which may be more important than the definitive identification of a precise CO. Pulse contour analysis remains

a rapidly evolving area of cardiovascular monitoring and will likely continue to see increased utility in ICUs.

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) has become an invaluable tool for perioperative management of unstable surgical patients. It is an integral component of many cardiac surgical procedures, and there are well-defined guidelines for using intraoperative TEE.⁵⁷ Use of TEE for cardiovascular monitoring in the ICU is not yet routine but is increasingly common. It is often an important diagnostic modality when approaching the patient with shock who is not responding to standard therapy.⁵⁸

TEE avoids some of the limitations associated with TTE. Namely, high-quality images can often be obtained with reduced interference from patient habitus, position, or dressings. High PEEP, which can obscure the image, is also usually not a problem. Certainly there are limitations, as visualization of the left ventricle apex, portions of the left atrium, and flow across the tricuspid valve is not always easily achieved with TEE.⁵⁸ However, TEE can be rapidly performed and has been shown to frequently change patient management decisions in the ICU.^{59,60}

TEE is impractical for continuous cardiovascular monitoring. That being said, limited, goal-directed TEE exams performed over a short period of time at regular intervals can be useful to modulate therapy and assess response to interventions.^{61,62} Recently, miniaturized TEE probes have been used for hemodynamic assessment of critically ill patients with good diagnostic agreement compared to formal TEE. As of now, these miniaturized probes are only inserted periodically and removed after assessment, but they are easier to insert than full-size probes and may be safe for long-term monitoring.^{63,64} A proprietary investigational monoplane hemodynamic TEE device, the ImaCor ClariTEE (ImaCor Inc., Garden City, NY), is small in size and designed for continuous monitoring; it can remain in place for up to 72 hours. In a retrospective analysis, it was found to change therapy decisions after placement in nearly all instances of its use.⁶⁵ Further trials are necessary to determine how these less invasive TEE probes may influence patient outcome.

Doppler Ultrasound

Doppler ultrasound technology is a component of comprehensive echocardiograms based on changes in frequency that occur when ultrasound interacts with objects in motion (Doppler shift). Several devices exist that adapt the principles of Doppler echocardiography to function as cardiovascular monitors alone, rather than simply as diagnostic probes. These include the Ultrasound CO Monitor (USCOM, Sydney, Australia), CardioQ (Deltex Medical, Chichester, UK), and the HemoSonic 100 (Arrow International, Reading, PA). The USCOM is a noninvasive device that measures flow across the aortic or pulmonic valves via a handheld probe focused on the thoracic inlet or anterior chest wall. The CardioQ and HemoSonic 100 are esophageal probes that measure flow in the descending thoracic aorta. Regardless of manufacturer, all Doppler monitors measure CO over time, as calculated by the product of blood velocity multiplied by the cross-sectional area of the vessel being observed (often the descending thoracic aorta). In a pulsatile system where velocity changes throughout the cardiac cycle, velocity is summed as the velocity-time integral. Changes in the velocity-time integral reflect changes in CO, and these devices are somewhat protected from confounding caused by changes in systemic vascular resistance. The USCOM and CardioQ use proprietary algorithms to estimate vessel cross-sectional area. The HemoSonic 100 has a limited imaging tool to help measure aortic cross-sectional area and adjust the angle of the ultrasound beam relative to flow. These monitors do have several limitations. They periodically need to be refocused on the outflow tract of interest and cannot be used continuously. Improper positioning can potentially lead to incorrect aortic or pulmonary outflow tract area calculations. Additionally, abnormal relationships

between the thoracic inlet, chest wall, or esophagus and the aortic and pulmonic outflow tracts may lead to inaccurate velocity-time integral calculation.^{23,66}

These devices have not been investigated as extensively as some other modalities, and thus there are few high-quality data supporting their use. In a head-to-head comparison, there was significant disagreement between the USCOM and CardioQ systems.⁶⁷ Individually, however, they may be useful for monitoring a patient's CO trend over time. When used as part of a goal-directed strategy for optimization of perioperative fluid status, use of esophageal Doppler has been shown to be associated with fewer postoperative complications and a reduced length of hospital stay. It is unclear if these outcomes are unique to perioperative monitoring with esophageal Doppler or could be achieved using alternative dynamic assessment of volume status.⁶⁸

INVASIVE MONITORS

Invasive monitoring devices consist of those that require central venous or arterial cannulation. Invasive devices are typically reserved for patients who have specific pathologic states that mandate catheter-based assessment of cardiovascular function. Due to the complexity of this patient population and challenges associated with device insertion, these devices carry a realistic risk of infection, thrombosis, or mechanical injury.⁶⁹ If possible, the subclavian approach is preferred for central access; this carries a reduced risk of injury compared to jugular or femoral locations, though it does increase the risk of pneumothorax.⁷⁰

Central Venous Pressure Analysis

Measurement of right-sided cardiac pressure is easily accomplished after placement of a central venous line. Theoretically, assuming normal cardiopulmonary conditions, right atrial pressure should approximate left ventricular end-diastolic pressure and provide an estimate of left ventricular preload. Right atrial pressure as a static parameter has been used for more than 50 years to monitor fluid status, but it has been invalidated in many studies as an indicator of fluid responsiveness.⁷¹

Despite the limitations of central venous pressure analysis to guide resuscitation, placement of central venous lines is still necessary to deliver medication, measure venous oxygen tension, temporarily pace the heart, or treat gas embolism. Additionally, observing characteristic changes in peaks and descents in central venous pressure can be useful for diagnosing right-sided cardiac pathology such as arrhythmia, impaired diastolic relaxation, or tricuspid valvulopathy.⁷²

Pulmonary Artery Catheterization and Indicator Dilution

Introduced in 1970 by Swan and Ganz, the flow-directed PAC was among the first technologies available to allow intensivists to measure advanced hemodynamic variables.⁷³ By catheterizing the pulmonary vasculature, intensivists could now measure PCWP to estimate preload and assess CO frequently using indicator dilution. The indicator dilution approach to CO measurement involves measuring hemo- or thermodilution of an injectate as it passes from the right atrium (via a proximal catheter port) and enters the pulmonary circulation. Using this technique, $CO = [(T_b - T_i) \times V_i \times K] / (\int \Delta T_b \times dt)$, where T_b is the blood temperature, T_i is the injectate temperature, V_i is the injectate volume, K is a correction constant consisting of specific weight and specific heat of blood and injectate, and $\int \Delta T_b \times dt$ is the area under the thermodilution curve.⁷⁴ Upon introduction of this concept, it was assumed this approach could provide useful data not otherwise obtainable by less invasive examination. It was thought that would it lead to changes in management and clinical outcome. Thus, use of a PAC became a hallmark of critical care in the late 20th century.⁷⁵

The popularity of the PAC was in part due to the belief that the CO measured was accurate and that measurement of PCWP could be used

as a static indicator of volume status. However, recent work has found significant discordance between PAC- and Fick-calculated CO, especially in high-output states. Unfortunately, the lack of agreement between the methods occurs in clinically relevant conditions.⁴⁵ PAC-derived CO is prone to inaccuracy due to a variety of physiologic factors (e.g., loss of indicator solution, intracardiac shunting, tricuspid regurgitation, and respiratory variation), suggesting a possible reason for discordance between Fick- and PAC-calculated COs. Of note, transpulmonary indicator dilution, such as that employed by the LiDCO device, involves peripheral injection of an indicator solution and measuring dilution at a point distal to the heart (generally a peripheral artery). By virtue of the longer transit time, this may avoid some of the inaccuracy caused by respiratory variation.⁷⁴ Measurement of PCWP has been found to be equally fraught with challenges and can be inaccurate due to technical difficulties in wedging the catheter or zeroing the transducer. Furthermore, even when measured correctly, PCWP may not accurately estimate left ventricle end-diastolic pressure, especially in settings of reduced ventricular compliance, pulmonary hypertension, mitral valvulopathy, use of PEEP, or critical illness.⁷⁶⁻⁷⁸ Furthermore, using PCWP to optimize volume status has proven to be ineffective and has been superseded by dynamic variable assessment.⁷⁹

As evidence of the PAC's limitations accumulated, clinicians began to question the value of its routine inclusion in critical care. Certainly, inserting a PAC carries risks, not only those associated with potentially inaccurate estimations of hemodynamic variables but also the risks associated with central venous access (e.g., infection, pneumothorax, pain, and thrombosis) in addition to direct cardiac or pulmonary injury (e.g., dysrhythmia, heart block, pulmonary artery rupture, and pulmonary infarction). In 1996, the SUPPORT trial observed an increased risk of death and longer ICU stays in patients managed with PACs compared to propensity-matched controls.⁸⁰ A recent Cochrane meta-analysis including more than 5000 patients concluded PACs do not impact mortality, hospital length of stay, or cost of care.⁸¹

Much of the controversy surrounding the PAC, including its apparent lack of mortality benefit, has stemmed from studies that explicitly evaluate the impact of a PAC as a monitor alone. Many authors have expressed dissatisfaction with this approach. Their view is that the variables identified with a PAC must be coupled with goal-directed therapies, and it is these protocols that should be the focus of investigation when evaluating the impact of PACs on patient outcome. Indeed, several meta-analyses of studies that investigated perioperative therapeutic intervention protocols while monitoring hemodynamic variables using a PAC have found significant reductions in mortality, surgical complications, and postoperative organ dysfunction in patients with PACs compared to those without.⁸²⁻⁸⁴ However, these results may not be solely due to the use of a PAC for monitoring and may be achievable using other monitoring approaches. Furthermore, the mortality benefit seen in studies that use a PAC for monitoring may in fact be attributable to a hemodynamic support regimen of fluids and inotropes, as compared to studies without a PAC that have tended to use fluids alone.^{68,85}

Given the risks associated with PACs and the likelihood that goal-directed hemodynamic therapy can lead to clinical improvement using

other modes of cardiovascular monitoring, routine placement of a PAC is not recommended, even in high-risk perioperative situations. However, treatment of pulmonary hypertension and acute right heart failure necessitates monitoring pulmonary artery pressures in an effort to modulate therapy. Thus, these remain indications for a PAC.⁸⁶

CONCLUSION

Regardless of the technology or device chosen, use of cardiovascular monitoring devices should be tailored to the individual patient and circumstance. Stable, non-critically ill patients may derive the greatest benefit from relatively noninvasive approaches, with the understanding that the risk of imprecise or inaccurate data may be outweighed by the risk of harm from more aggressive approaches. Critically ill patients may require highly accurate, continuous observation of cardiovascular trends in order for the intensivist to respond rapidly and prevent further deterioration. In general, more invasive devices tend to be more precise and more accurate and thus may be indicated in this population. Ultimately, no particular approach is capable of providing direct patient benefit. Rather, it is the responsibility of the intensivist to choose a device or strategy that allows for recognition of hemodynamic derangement and encourages intervention when appropriate.

KEY POINTS

1. Monitoring devices are designed to measure global cardiovascular trends, often in an effort to accurately determine CO.
2. Dynamic, rather than static, parameters should be used to assess the cardiovascular response to an intervention, such as a fluid bolus.
3. The Fick method is the gold standard for measurement of CO, as this approach involves identification of end-organ oxygen exchange. Optimizing cellular metabolism is the goal of treatment for shock.
4. The clinical gold standard of measuring CO is that obtained by thermodilution via a PAC, as this is often more feasible than determination of systemic oxygen consumption.
5. More invasive systems, especially when they can be calibrated, offer a greater degree of accuracy and precision when calculating CO. Less invasive systems may confer a reduced risk of direct injury.
6. Critically ill patients have altered homeostasis, which may impair accuracy and precision of cardiovascular monitors.
7. In order to confer benefit, all monitoring devices require appropriate response by the intensivist when cardiovascular derangement is present.

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The safe and effective management of patients with acute respiratory failure requires accurate bedside monitoring of pulmonary function. This chapter focuses on the more common noninvasive techniques for monitoring pulmonary gas exchange, respiratory system mechanics, and breathing patterns. These techniques may lead to rapid assessment of patient respiratory function and appropriate clinical action.

PULSE OXIMETRY

Pulse oximetry is a microprocessor-based instrument that incorporates both oximetry and plethysmography to provide continuous noninvasive monitoring of the oxygen saturation of arterial blood (SpO_2). Often considered the “fifth vital sign,” pulse oximetry is one of the most important technologic advances for monitoring patients during anesthesia, in the intensive care unit (ICU), on the general ward, in the emergency department, and during a wide variety of procedures.¹⁻³ The pulse oximeter probe is embedded into either a clip or an adhesive wrap and consists of two light-emitting diodes on one side and a light-detecting photodiode on the opposite side. Either a finger or an earlobe serves as the sample “cuvette.” The tissue bed is transilluminated, and the forward-scattered light is measured. Pulse oximetry targets the signal arising from the arterial bed as light absorbance fluctuates with changing blood volume. Arterial blood flow causes signal changes in light absorption (the pulsatile component called *photoplethysmography*) that can be distinguished from venous and capillary blood in the surrounding tissues (the baseline, or direct current, component; Fig. 35-1).

Oximetry uses spectrophotometry to determine SaO_2 . According to the Beer-Lambert law, the concentration of a substance can be determined by its ability to transmit light.⁴ Oxygenated hemoglobin (HbO_2) and deoxygenated or “reduced” hemoglobin (HbR) species absorb light differently, so the ratio of their absorbencies can be used to calculate saturation. In addition, there are two minor hemoglobin (Hb) species: carboxyhemoglobin (COHb) and methemoglobin (MetHb). Fractional SaO_2 is the proportion of HbO_2 relative to all four hemoglobin species:

$$\text{HbO}_2 + \text{HbR} + \text{COHb} + \text{MetHb}$$

Measuring fractional hemoglobin requires a co-oximeter that incorporates four wavelengths to distinguish each species (Fig. 35-2). In contrast, oxygen saturation as determined by pulse oximeter (SpO_2) uses two wavelengths, so that it measures functional SaO_2 :

$$\text{HbO}_2 + \text{HbR}$$

Accuracy and Precision

Because pulse oximeters themselves cannot be calibrated, their accuracy is highly variable and dependent on both the calibration curve programmed into the monitor and the quality of signal processing.^{5,6} The ratio of absorbencies is calibrated empirically against SaO_2 measured by co-oximetry in normal volunteers subjected to various levels of oxygenation. Pulse oximeters are calibrated against measured SaO_2 values down to 70% (saturation below this level are determined by extrapolation).⁵ The resulting calibration curve is stored in the monitor's microprocessor and used to calculate the SpO_2 .⁶

The accuracy of the calibration curve depends on the laboratory testing conditions (co-oximeter used, range of oxygenation studied, and characteristics of sample subjects). Most manufacturers report an accuracy of $\pm 2\%$ at an SaO_2 greater than 70% and $\pm 3\%$ when the SaO_2 is 50% to 70%.² In normal subjects tested at an SaO_2 between 99% and 83%, pulse oximetry has a bias and precision that are within 3% of co-oximetry.⁷ However, under hypoxic conditions (SaO_2 78% to 55%), when the monitor must rely on extrapolated values, bias increases (8%) and precision deteriorates (5%).⁷ Likewise, in critically ill patients, pulse oximeters historically perform well when the SaO_2 is greater than 90% (bias of 1.7% and precision of $\pm 1.2\%$), but accuracy diminishes at an SaO_2 below 90% (bias of 5.1% and precision of $\pm 2.7\%$)⁸ (Fig. 35-3). Technologic advances over the past decade have apparently improved this performance; a recent study comparing pulse oximetry to co-oximetry reported a bias of 0.19% and a precision of $\pm 2.22\%$ over an SaO_2 range of 60% to 100%.⁹

Dynamic Response

Because pulse oximeters detect very small optical signals (and must reject a variety of artifacts), data must be averaged over several seconds, thus affecting the response time.⁵ Pulse oximeters may register a near-normal SpO_2 when the actual SaO_2 is less than 70%.⁵ A prolonged lag time is more common with finger probes than with ear probes^{5,10,11} and is attributed to hypoxia-related peripheral vasoconstriction.⁵ Bradycardia is also associated with a prolonged response time.¹¹

Sources of Error

Motion artifact and low perfusion are the most common sources of SpO_2 inaccuracies, which occur because the photoplethysmographic pulse signal is very low in these settings compared with the total absorption signal.^{12,13} The combination of motion artifact and low perfusion substantially lowers SpO_2 accuracy compared with either artifact alone.¹⁴ Causes of motion artifact include shivering, twitching, agitation, intraaortic balloon pump assistance, and patient transport.^{15,16} Signs of motion artifact include a false or erratic pulse rate reading or an abnormal plethysmographic waveform. Peripheral hypoperfusion from hypothermia, low cardiac output, or vasoconstrictive drugs may increase bias, reduce precision, and prolong the time to detect a hypoxic event.¹⁶ Newer technologies have helped reduce the incidence of these problems, but they have not been eliminated as a source of error. Relocation of the probe may be required to obtain a more accurate signal.

Despite recent technologic advances, there are still a number of factors that may affect the accuracy of the pulse oximeter. Table 35-1 lists the most common factors.

Dyshemoglobins and Vascular Dyes

Significant amounts of COHb or MetHb can cause errors in SpO_2 values. COHb and HbO_2 absorb equivalent amounts of red light, so carbon monoxide poisoning results in a falsely elevated SpO_2 because the pulse oximeter reports total Hb saturation and not just HbO_2 saturation. In the setting of carbon monoxide poisoning, the amount of COHb is elevated, resulting in a falsely high SpO_2 . The patient, however, could be experiencing profound hypoxemia. In contrast, MetHb causes

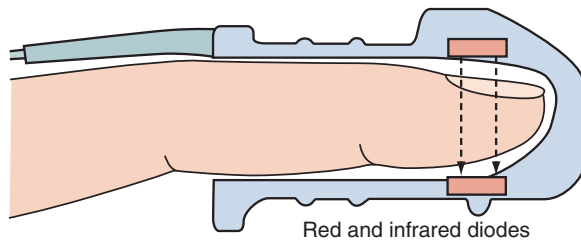


FIGURE 35-1 ■ Schematic depiction of the pulse oximeter light absorption signal. (Adapted with permission from Phillips Medical Systems, Carlsbad, California.)

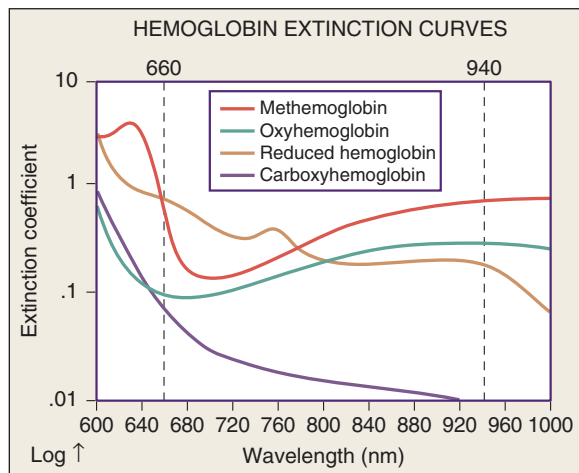


FIGURE 35-2 ■ Extinction coefficients of the four types of hemoglobin at the red and infrared wavelengths. Methemoglobin absorbs light at both wavelengths to an equal extent; absorption of red light by carboxyhemoglobin is similar to that of oxyhemoglobin. (From Tremper KK, Barker SJ. Pulse oximetry. *Anesthesiology* 1989;70:98-108.)

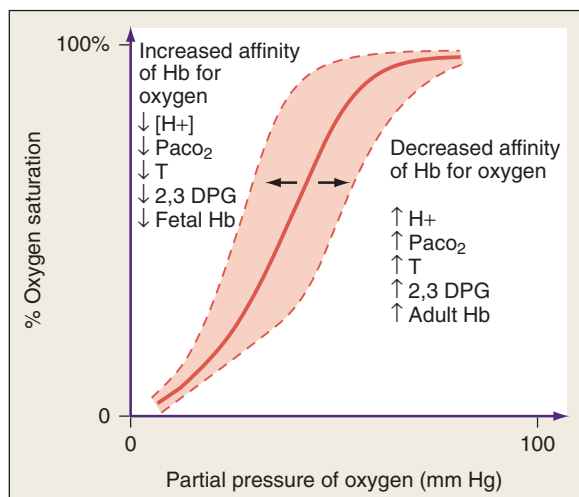


FIGURE 35-3 ■ Oxyhemoglobin dissociation curve relates oxygen saturation and partial pressure of oxygen in the blood. The curve is affected by many variables.

TABLE 35-1 Common Factors Affecting Pulse Oximetry Measurements

| FACTOR | EFFECT |
|----------------------------|---|
| Carboxyhemoglobin (COHb) | Slight reduction in accuracy of the assessment of oxygen saturation (SaO_2) by pulse oximetry (SpO_2) (i.e., overestimates the fraction of hemoglobin available for O_2 transport) |
| Methemoglobin (MetHb) | At high levels of MetHb, SpO_2 approaches 85%, independent of actual SaO_2 |
| Methylene blue | Transient, marked decrease in SpO_2 lasting up to several minutes; possible secondary effects as a result of effects on hemodynamics |
| Anemia | If SaO_2 is normal, no effect; during hypoxemia with Hb values less than 14.5 g/dL, progressive underestimation of actual SaO_2 |
| Ambient light interference | Bright light, particularly if flicker frequency is close to a harmonic of the light-emitting diode switching frequency, can falsely elevate the SpO_2 reading |
| Blood flow | Reduced amplitude of pulsations can hinder obtaining a reading or cause a falsely low reading |
| Motion | Movement, especially shivering, may depress the SpO_2 reading |
| Nail polish | Slight decrease in SpO_2 reading, with greatest effect using blue nail polish, or no change |
| Sensor contact | "Optical shunting" of light from source to detector directly or by reflection from skin results in falsely low SpO_2 reading |
| Skin pigmentation | Small errors or no significant effect reported; deep pigmentation can result in reduced signal |
| Tape | Transparent tape between sensor and skin has little effect; falsely low SpO_2 has been reported when smeared adhesive is in the optical path |
| Vasodilation | Slight decrease in SpO_2 |
| Venous pulsation | Artifactual decrease in SpO_2 |

substantial absorption of both red and infrared light, so the ratio approaches 1 (estimated SpO_2 of 85%).⁴ Significant MetHb causes falsely low SpO_2 values when the actual SaO_2 is greater than 85% and falsely high values when the SaO_2 is less than 85%.⁴ Administration of methylene blue or indocyanine green dyes for diagnostic tests causes a false, transient (1- to 2-minute) drop in SpO_2 to as low as 65%.^{17,18}

Nail Polish and Skin Pigmentation

Both dark skin pigmentation and dark nail polish interfere with absorption of the wavelengths used by pulse oximetry. Pulse oximeters thus have greater bias and less precision in black patients.⁸ Whereas an SpO_2 of 92% is sufficient to predict adequate oxygenation in white patients, a saturation of 95% is required in black patients.⁸ Dark nail polish can falsely lower SpO_2 , whereas red polish tends not to affect pulse oximetry accuracy.¹⁹ However, with newer technology, the negative effects of nail polish have been lessened. A recent study showed that there was an effect of dark nail polish on pulse oximetry readings, but it was not clinically relevant.²⁰ When nail polish cannot be removed, mounting the oximeter probe sideways on the finger yields an accurate reading.²¹

Ambient Light, Anemia, and Hyperbilirubinemia

Although pulse oximeters compensate for the presence of ambient light, the sensor should be shielded from intense light sources with an opaque material. Falsely low SpO_2 readings occur when even minor gaps exist between the probe and skin, allowing light reflected off the skin's surface to "shunt" directly to the photodiode.²² Xenon surgical lamps and fluorescent lighting can cause a falsely low SpO_2 .²³ Under

conditions of anemia (Hb 8 g/dL) and severe hypoxia (SaO₂ 54%), SpO₂ bias is markedly increased (−14%).²⁴ Hyperbilirubinemia does not affect SpO₂ directly.²⁵ However, carbon monoxide is a byproduct of heme metabolism, and icteric patients tend to have higher levels of COHb,²⁵ so SpO₂ may be falsely elevated.

Reflectance Pulse Oximetry

Reflectance pulse oximetry was designed to counter signal-detection problems associated with finger probes during hypoperfusion. The reflectance sensor is designed for placement on the forehead just above the orbital area, where superficial blood flow is abundant and less susceptible to vasoconstriction.²⁶ Whereas traditional probes work by transilluminating a tissue bed and measuring the forward-scattered light on the opposite side of the finger or earlobe, reflectance probes are constructed with the light-emitting diodes and the photodetector located on the same side. The photodetector measures the back-scattered light from the skin.²⁶ In addition, more liberal placement sites for reflectance pulse oximetry have allowed fetal monitoring during labor.²⁷ Intraesophageal SpO₂ monitoring is currently under investigation.²⁸ Anasarca, excessive head movement, and difficulty in securing the probe site are some of the problems encountered with reflectance pulse oximetry.²⁹ Light “shunting” from poor skin contact and direct sensor placement over a superficial artery are associated with artifacts.³⁰ Reflectance pulse oximetry is also limited by poor signal-to-noise ratio and variability among sites in the arrangement of blood vessels and tissue blood volume.³⁰ However, recent studies have shown reflectance pulse oximetry to be as effective as finger sensors in many situations.^{31–34}

Technologic Advances

Recent advances in signal analysis and processing have markedly improved SpO₂ accuracy during low perfusion states and reduced the problem of motion artifact.^{16,35} According to recent independent testing, these advances occur with pulse oximeters made by several manufacturers.³⁶ Durban and Rostow reported that new pulse oximeter technology can accurately detect SaO₂ in 92% of the cases in which traditional SpO₂ monitoring failed owing to low perfusion and motion artifact³⁷ (Box 35-1).

CAPNOMETRY

Capnometry consists of the measurement and numeric display of expired carbon dioxide (CO₂) at the patient's airway opening.³⁸ When a waveform plotting CO₂ against time or volume is also displayed, it is referred to as *capnography*, and the waveform is referred to as a *capnogram*.³⁸ Capnometry is most commonly used on patients receiving mechanical ventilation and works by passing infrared light through a sample chamber to a detector on the opposite side. CO₂ absorbs infrared light at a peak wavelength of approximately 4.27 μm.^{38,39} More infrared light passing through the sample chamber (i.e., less CO₂) causes a larger signal in the detector relative to the infrared light passing through a reference cell. The sample chamber is either connected directly to the Y-adapter of the ventilator circuit (mainstream) or by a sampling line at the Y-adapter that continuously aspirates gas into a sampling chamber located inside the monitor (sidestream).

Clinical Applications

Capnometric determination of the partial pressure of CO₂ in end-tidal exhaled gas (PETCO₂) is used as a surrogate for the partial pressure of CO₂ in arterial blood (PaCO₂) during mechanical ventilation^{40,41} (Fig. 35-4). Although widely available today, the utilization of PETCO₂ to represent PaCO₂ in ICUs remains unclear. While perhaps not an exact match for PaCO₂, PETCO₂ does provide a valuable trending tool. Also, with newer technologies, the accuracy of PETCO₂ measurements is improving. In a recent study, McSwain et al. showed strong correla-

BOX 35-1

American Association for Respiratory Care (AARC) Clinical Practice Guideline: Pulse Oximetry

INDICATIONS

- The need to monitor the adequacy of arterial oxyhemoglobin saturation.
- The need to quantitate the response of arterial oxyhemoglobin saturation to therapeutic intervention or to a diagnostic procedure (e.g., bronchoscopy).
- The need to comply with mandated regulations or recommendations by authoritative groups.

CONTRAINDICATIONS

- The presence of an ongoing need for measurement of pH, PaCO₂, total hemoglobin, and abnormal hemoglobins may be a relative contraindication to pulse oximetry.

PRECAUTIONS

- Pulse oximetry is considered a safe procedure, but because of device limitations, false-negative results for hypoxemia and/or false-positive results for normoxemia or hyperoxemia may lead to inappropriate treatment of the patient.
- Factors that may affect pulse oximeter readings include motion artifact, abnormal hemoglobins and methemoglobin, intravascular dyes, exposure of measuring probe to ambient light during measurement, low perfusion state, skin pigmentation, and nail polish or nail coverings with finger probe.

ASSESSMENT OF NEED

- When direct measurement of SaO₂ is not available or accessible in a timely fashion, an SpO₂ measurement may temporarily suffice if the limitations of the data are appreciated.
- SpO₂ is appropriate for continuous and prolonged monitoring (e.g., during sleep, exercise, bronchoscopy).
- SpO₂ may be adequate when assessment of acid-base status and/or PaO₂ is not required.

ASSESSMENT OF OUTCOME

- The following should be utilized to evaluate the benefit of pulse oximetry:
 - SpO₂ results should reflect the patient's clinical condition (i.e., validate the basis for ordering the test).
 - Documentation of results, therapeutic intervention (or lack of), and/or clinical decisions based on the SpO₂ measurement should be noted in the medical record.

MONITORING

- The monitoring schedule of patient and equipment during continuous oximetry should be correlated with bedside assessment and vital sign determinations.

From AARC clinical practice guideline: pulse oximetry. *Respir Care* 1992;37:891-897.

tions between PETCO₂ and PaCO₂ across a wide range of dead-space conditions.⁴² Capnometry is used for a variety of purposes, such as in the diagnosis of a pulmonary embolism, determination of lung recruitment response to positive end-expiratory pressure (PEEP), detection of intrinsic PEEP, evaluation of weaning, as an indirect marker of elevated dead-space ventilation, assessment of cardiopulmonary resuscitation, indirect determination of cardiac output through partial CO₂ rebreathing, verification of endotracheal cannulation, detection of airway accidents, and even determination of feeding tube placement.^{43–55} Guidelines for the use of capnometry/capnography are outlined by the American Association for Respiratory Care (Box 35-2).

Paco₂-PETCO₂ Gradient

Normal subjects have a PaCO₂-PETCO₂ gradient of 4 to 5 mm Hg.^{40,43,47,56–60} In critically ill patients, the PaCO₂-PETCO₂ gradient can be markedly elevated, with a tendency toward wider gradients in obstructive lung diseases (7–16 mm Hg) than in acute lung injury or cardiogenic pulmonary edema (4–12 mm Hg).^{46,47,61–63} A strong correlation between ΔPETCO₂ and ΔPaCO₂ ($r = 0.82$), along with minor bias and reasonable precision between PETCO₂ and PaCO₂, suggests that arterial blood gas monitoring may not be needed to assess ventilation unless the ΔPETCO₂ exceeds 5 mm Hg.⁴⁸ Nevertheless, several studies have found

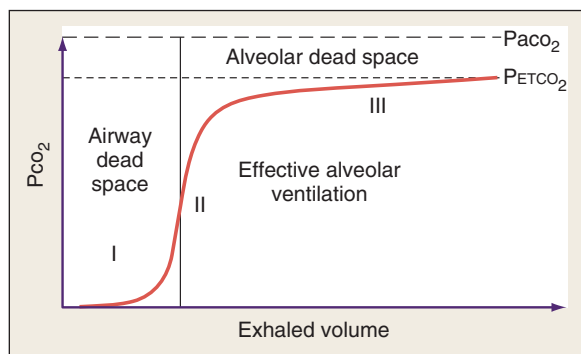


FIGURE 35-4 ■ Single-breath carbon dioxide waveform depicts carbon dioxide elimination as a function of the volume of gas exhaled. Phase 1 represents gas exhaled from the upper airways. Phase 2 is the transitional phase from upper to lower airway ventilation and tends to reflect changes in perfusion. Phase 3 is the area of alveolar gas exchange and represents changes in gas distribution. PETCO₂, partial pressure of end-tidal carbon dioxide.

that the Δ PETCO₂ often falsely predicts the degree and direction of Δ PaCO₂.^{58-60,63} Therefore, despite PETCO₂ monitoring, routine arterial blood gas analysis is still required in critically ill patients.

Several factors determine the PaCO₂-PETCO₂ gradient. Whereas PaCO₂ reflects the mean partial pressure of CO₂ in alveolar gas (PaCO₂), PETCO₂ approximates the peak PaCO₂.⁶⁴ During expiration, lung regions with high ventilation-to-perfusion ratios dilute the mixed CO₂ concentration so that PETCO₂ is usually lower than PaCO₂.⁶⁵ However, when CO₂ production is elevated (or expiration is prolonged), PETCO₂ more closely resembles mixed venous PCO₂, as a higher amount of CO₂ diffuses into a progressively smaller lung volume.⁶⁴ Thus, the PaCO₂-PETCO₂ gradient can be affected by changes in respiratory rate and tidal volume (VT) because of alterations in expiratory time and by CO₂ production and mixed venous CO₂ content.⁶⁴ In fact, it is not uncommon for PETCO₂ to exceed PaCO₂.⁶⁵ Inotropic or vasoactive drugs may affect the PaCO₂-PETCO₂ gradient in an unpredictable manner, either by increasing cardiac output and pulmonary perfusion (thereby reducing alveolar dead space) or by reducing pulmonary vascular resistance and magnifying intrapulmonary shunt by countering hypoxic pulmonary vasoconstriction.⁵⁸

Mechanical factors can cause either inconsistencies or inaccuracies in PETCO₂. The sample tubing length and aspirating flow rates used in sidestream capnometers affect the time required to measure changes in tidal CO₂ concentration.⁶⁶ At respiratory frequencies above 30 breaths/minute, capnometers tend to underreport the true PETCO₂.⁶⁷ This may occur because of gas mixing between adjacent breaths during transport down the sampling line and in the analysis chamber.⁶⁷ This problem can be avoided with mainstream analyzers, which provide near-instantaneous CO₂ measurement (less than 250 msec).⁶⁸

PaCO₂-PETCO₂ Gradient, Positive End-Expiratory Pressure, and Lung Recruitment

PEEP recruits collapsed alveoli, improves ventilation-perfusion matching, and reduces alveolar dead space, although excessive levels cause overdistention and increased alveolar dead space.⁶⁹ Because the PaCO₂-PETCO₂ gradient correlates strongly with the physiologic dead space-to-tidal volume ratio (VD/VT), this gradient may be useful in titrating PEEP in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).^{49,50} An animal model of ARDS found that stepwise application of PEEP progressively reduced the PaCO₂-PETCO₂ gradient and coincided with maximal or near-maximal improvements in oxygenation.⁶¹ However, PEEP applied beyond the lowest PaCO₂-

BOX 35-2 American Association for Respiratory Care (Aarc) Clinical Practice Guideline: Capnography/Capnometry During Mechanical Ventilation

INDICATIONS

- Capnography should not be mandated for all patients receiving mechanical ventilatory support, but it may be indicated for:
 - Evaluation of the exhaled CO₂, especially end-tidal CO₂ (PETCO₂).
 - Monitoring severity of pulmonary disease and evaluating response to therapy, especially therapy intended to improve the ratio of dead space to tidal volume (VD/VT) and the matching of ventilation to perfusion (V/Q) and, possibly, to increase coronary blood flow.
 - Use as an adjunct to determine that tracheal rather than esophageal intubation has taken place.
 - Continued monitoring of the integrity of the ventilatory circuit, including the artificial airway.
 - Evaluation of the efficiency of mechanical ventilatory support by determination of the difference between PaCO₂ and PETCO₂.
 - Monitoring adequacy of pulmonary, systemic, and coronary blood flow.
 - Estimation of effective (nonshunted) pulmonary capillary blood flow by a partial rebreathing method.
 - Use as an adjunctive tool to screen for pulmonary embolism.
 - Monitoring inspired CO₂ when CO₂ gas is being therapeutically administered.
 - Graphic evaluation of the ventilator-patient interface.
 - Measurement of the volume of CO₂ elimination to assess metabolic rate and/or alveolar ventilation.

CONTRAINDICATIONS

- There are no absolute contraindications to capnography in mechanically ventilated patients, provided the data obtained are evaluated with consideration given to the patient's clinical condition.

PRECAUTIONS AND POSSIBLE COMPLICATIONS

- With mainstream analyzers, the use of too large a sampling window may introduce an excessive amount of dead space into the ventilator circuit.
- Care must be taken to minimize the amount of additional weight placed on the artificial airway by the addition of the sampling window or, in the case of a sidestream analyzer, the sampling line.

ASSESSMENT OF NEED

- Capnography is considered a standard of care during anesthesia. The American Society of Anesthesiologists has suggested that capnography be available for patients with acute ventilatory failure on mechanical ventilatory support. The American College of Emergency Physicians recommends capnography as an adjunctive method to ensure proper endotracheal tube position.
- Assessment of the need to use capnography with a specific patient should be guided by the clinical situation. The patient's primary cause of respiratory failure and the acuteness of his or her condition should be considered.

ASSESSMENT OF OUTCOME

- Results should reflect the patient's condition and should validate the basis for ordering the monitoring.
- Documentation of results (along with all ventilatory and hemodynamic variables available), therapeutic interventions, and/or clinical decisions made based on the capnogram should be included in the patient's chart.

MONITORING

- During capnography, the following should be considered and monitored:
 - Ventilatory variables: tidal volume, respiratory rate, positive end-expiratory pressure, inspiratory-to-expiratory time ratio (I:E), peak airway pressure, and concentrations of respiratory gas mixture.
 - Hemodynamic variables: systemic and pulmonary blood pressures, cardiac output, shunt, and ventilation-perfusion imbalances.

From AARC clinical practice guideline: capnography/capnometry during mechanical ventilation. *Respir Care* 2003;48:534-539.

PETCO₂ gradient caused a secondary rise in the gradient, along with decreased cardiac output. Although a subsequent trial was unable to reproduce these findings in humans, another study found that the PaCO₂-PETCO₂ gradient narrowed (from 14 to 8 mm Hg) and oxygenation improved when PEEP was set at the lower inflection point of the

pressure-volume curve.^{45,62} When PEEP was set 5 cm H₂O above the lower inflection point, the PaCO₂-PETCO₂ gradient rose to 11 mm Hg, and cardiac output trended downward. In patients without a lower inflection point, the PaCO₂-PETCO₂ gradient did not change in response to PEEP. Thus, in a subset of ARDS patients, the PaCO₂-PETCO₂ gradient may be an effective way to titrate PEEP.

PETCO₂ Monitoring During Cardiopulmonary Resuscitation

Monitoring end-tidal CO₂ concentration is a reliable method for evaluating the effectiveness of cardiopulmonary resuscitation.⁷⁰ In animal models, PETCO₂ is strongly correlated with coronary perfusion pressure and successful resuscitation,⁷¹ whereas in humans, changes in PETCO₂ are directly proportional to changes in cardiac output.⁷² PETCO₂ during precordial compressions can distinguish successful from unsuccessful resuscitation, with values greater than 10 mm Hg⁷³ or greater than 16 mm Hg⁷⁴ associated with successful resuscitation.

Measurement of Dead-Space Ventilation

Ventilation-perfusion abnormalities are the primary physiologic disturbance in nearly all pulmonary diseases and the principal mechanism for elevated PaCO₂.⁷⁵ Dead-space ventilation (VD), the portion of VT that does not encounter perfused alveoli, directly impacts CO₂ excretion and is used as an indirect measure of ventilation-perfusion abnormalities. Physiologic VD represents the summation of anatomic-conducting airway and nonperfused alveolar components.

Physiologic VD/VT has historically been measured during a 3- to 5-minute exhaled gas collection into a 30- to 60-L Douglas bag. An arterial blood gas reading is obtained during the midpoint of the collection. VD/VT is calculated using the Enghoff modification of the Bohr equation, whereby the difference between PaCO₂ (a surrogate for the mean PaCO₂) and mean expired CO₂ tension (PECO₂) is divided by PaCO₂:

$$\frac{VD}{VT} = \frac{PaCO_2 - PECO_2}{PaCO_2}$$

The dead-space volume per breath or per minute can be determined by multiplying VD/VT by the simultaneously measured average VT or minute ventilation (\dot{V}_E)⁷⁶:

$$VD = \frac{(PaCO_2 - PECO_2)}{PaCO_2} \times VT \text{ or } VD = \frac{(PaCO_2 - PECO_2)}{PaCO_2} \times \dot{V}_E$$

By subtracting the physiologic VD per minute from the \dot{V}_E , the alveolar minute ventilation is obtained ($\dot{V}_A = \dot{V}_E - \dot{V}_D$). It can also be calculated as the volume of CO₂ produced per minute (\dot{V}_{CO_2}) divided by the PaCO₂:⁷⁶

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{PaCO_2} \times 0.863$$

Although expired gas collection with a Douglas bag is the classic method for measuring VD/VT, the gas collection system requires additional valving and connectors, making the procedure time-consuming and awkward. Metabolic monitors produce equally accurate, reliable results and are less cumbersome.^{77,78} The Douglas bag method and metabolic monitors, however, do share a limitation when used on a mechanically ventilated patient. During mechanical ventilation, gas is compressed in the circuit, which dilutes the fractional expired CO₂ concentration.⁷⁹ A correction factor can be used to offset the mathematical effects of gas compression. Volumetric capnography is an alternative method of measuring PECO₂ and VD/VT and has the advantage of being measured at the patient, thus eliminating the effects of compression volume contamination and the need to apply a correction factor.⁸⁰ In patients with ARDS, it has been shown that measurements of VD/VT using volumetric capnography are as accurate as those obtained through the use of a metabolic monitor.⁸¹ In addition, newer monitors incorporating capnography and pneumotachygraphy provide accurate single-breath determinations of VD/VT.⁸²

A significant source of measurement error for VD/VT is the contamination of expired gas with circuit compression volume.⁸³ During positive-pressure ventilation, part of the VT is compressed in the circuit, and during expiration, this gas mixes with CO₂-laden gas from the lungs. The dilution of the expired CO₂ results in a falsely elevated VD/VT that is directly proportional to the peak inspiratory pressure and circuit compliance. Clinically, correcting VD/VT for compression volume is done by multiplying the measured PECO₂ by the ratio of the ventilator-set VT to the VT delivered to the patient.⁸⁴ This requires determination of the ventilator circuit compliance.

Clinically, VD/VT may assist in the management of pulmonary disease in terms of both ventilator adjustments and diagnostic testing. Suter and colleagues found that VD/VT decreased as lung units were recruited but increased with lung overdistention during PEEP titration in ARDS.⁶⁹ A more recent study involving the use of dead-space calculations in ARDS showed that increased dead space is associated with a higher mortality in the early and intermediate phases of ARDS.⁸⁵ Fletcher and Jonson used VD/VT to optimize VT and inspiratory time settings during general anesthesia.⁸⁶ Measuring VD/VT may assist in identifying patients who can be removed from mechanical ventilation. Hubble and coworkers found that values less than 0.50 predicted successful extubation, and values greater than 0.65 identified patients at risk for post extubation respiratory failure.⁸²

One of the main clinical uses of VD/VT is to aid in the diagnosis of acute pulmonary embolism. VD/VT is comparable to radioisotopic lung scanning in detecting acute pulmonary embolism, with a value less than 0.40 suggesting that a significant embolus is improbable.⁸⁷ Single-breath estimates of alveolar VD are also capable of identifying patients with pulmonary embolus.⁸⁸ Increased physiologic VD/VT (greater than 0.60) was found to be significantly associated with mortality in patients with ARDS and in neonates with congenital diaphragmatic hernia.^{89,90} The findings that VD/VT is elevated early in the course of ARDS and is associated with increased mortality may be particularly useful. The efficacy of new therapies for ARDS may be judged, in part, by their ability to reduce VD/VT.

Transcutaneous Monitoring

Transcutaneous blood gas monitoring involves the use of a skin surface sensor to provide continuous noninvasive estimates of arterial PO₂ and PCO₂ (TcO₂ and TcCO₂, respectively). The sensor warms the skin to promote arterialization, as well as to increase the permeability of the skin to O₂ and CO₂ (Fig. 35-5). Elements of the sensor include a heating element, O₂ electrode, and CO₂ electrode. The electrodes measure the gas tensions in an electrolyte gel located between the sensor and the skin. Similar to end-tidal CO₂ (ETCO₂) monitoring and pulse oximetry, transcutaneous monitoring has the potential advantages over

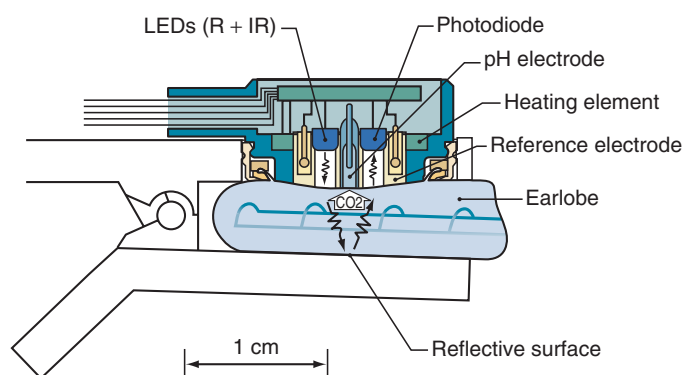


FIGURE 35-5 ■ A combined SpO₂/TcPCO₂ sensor at the earlobe. (From Eberhard P. The design, use, and results of transcutaneous carbon dioxide analysis: current and future directions. *Anesth Analg* 2007;105: S48-S52.)

direct arterial blood gas sampling of reducing the amount of blood drawn, time spent for analysis, and associated costs. $TcCO_2$ tends to be more reliable, most likely because of the greater diffusion capacity of CO_2 through the skin and the skin's own O_2 consumption.⁹¹ $TcCO_2$ has historically been used more frequently in neonatal and pediatric populations, but recent technologic advances have led to increased utilization in adults, despite the effects of a thicker epidermis. It has been shown to be particularly accurate in neonates because of their thin, poorly keratinized skin, which has fewer barriers to diffusion of capillary gases.⁹²

The gradient between $TcCO_2$ and $PaCO_2$ is influenced by skin perfusion and skin temperature. Thus, factors affecting cutaneous vasoconstriction (e.g., vasopressors, cardiac output, cutaneous vascular resistance) could potentially influence $TcCO_2$ measurements. Technical factors that can affect the accuracy of $TcCO_2$ measurements are similar to those of $ETCO_2$ monitoring and center around the inevitable gradient with $PaCO_2$.

The accuracy of transcutaneous arterial blood gas measurement in adults remains a point of debate. A number of studies have shown that $TcCO_2$ monitoring is accurate in adult patients with respiratory disorders.⁹³⁻⁹⁶ Some studies even suggest that $TcCO_2$ monitoring may be more accurate than $ETCO_2$ monitoring owing in part to the elimination of dead space.⁹⁷⁻⁹⁹ Conversely, some reports suggest that $TcPO_2$ is not accurate enough to be used clinically in the adult population or even in preterm infants.^{100,101}

The use of transcutaneous arterial blood gas measurement is increasing, but it should not take the place of invasive arterial blood gas measurement; it may have a place in trending oxygenation and CO_2 levels. However, care must be taken to ensure that variables that could affect the readings have been eliminated and that the unit is calibrated per the manufacturer's specifications, especially when erroneous readings are suspected.

ASSESSMENT OF PULMONARY MECHANICS

Assessment of basic pulmonary mechanics is crucial to monitoring pulmonary function during mechanical ventilation. It requires the measurement of VT , peak inspiratory flow rate, and four pressures: peak airway pressure, end-inspiratory plateau pressure, end-expiratory pressure in the circuit, and if intrinsic PEEP is suspected, end-expiratory pressure measured during an end-expiratory pause maneuver. From these variables, the compliance and resistance of the respiratory system are determined.

Compliance

Under conditions of passive mechanical ventilation, peak airway pressure denotes the total force necessary to overcome the resistive and elastic recoil properties of the respiratory system (i.e., both lungs and chest wall). Compliance is expressed as the ratio of volume added to pressure applied. Dynamic compliance is the ratio of volume added to the peak airway pressure (Paw) and includes the resistive forces in the tracheobronchial tree. A more useful measurement is that of static compliance. Static compliance requires the use of an end-inspiratory hold.¹⁰² During an end-inspiratory pause, peak airway pressure dissipates down to a stable plateau pressure. At the end of the inspiratory hold maneuver, "static" conditions usually exist (resistive forces have been eliminated), and the corresponding "plateau pressure" represents the elastic recoil pressure.

Dividing the VT by the plateau pressure ($Pplat$) minus the PEEP yields the static compliance of the respiratory system ($Crs\text{-stat}$).¹⁰³ Even at moderate levels of \dot{V}_E (greater than 10 L/min), dynamic gas trapping can occur (intrinsic PEEP) and, if suspected, $Crs\text{-stat}$ must be calculated using total PEEP ($PEEP_{tot}$) measured during an end-expiratory pause, rather than the PEEP applied at the airways¹⁰⁴:

$$Crs\text{-stat} = \frac{VT}{Pplat - PEEP_{tot}}$$

During patient-triggered ventilation, the assessment of pulmonary mechanics becomes more difficult because of the patient's spontaneous contributions, which may falsely raise or lower the plateau pressure. Obtaining an accurate measurement requires that the clinician perform the inspiratory hold when spontaneous efforts are absent and the pause will most likely be of shorter duration.

Resistance

Respiratory system resistance (Rrs) is the ratio of driving pressure to flow.¹⁰⁵ It is calculated as the difference between Paw and $Pplat$ divided by the preocclusion peak inspiratory flow rate (\dot{V}_I) and expressed as cm H_2O/L per second¹⁰⁶:

$$Rrs = \frac{Paw - Pplat}{\dot{V}_I}$$

Resistance is flow dependent because the driving pressure necessary to overcome resistance increases disproportionately to changes in \dot{V}_I (due to increased turbulence).¹⁰⁷ Therefore, respiratory system resistance can be accurately determined only with a constant inspiratory flow (square wave) pattern.¹⁰⁶

Compliance and Resistance in Normal and Pathologic Conditions

In mechanically ventilated normal patients, compliance is 57 to 85 mL/cm H_2O , and resistance is 1 to 8 cm H_2O/L per second.¹⁰⁸⁻¹¹⁰ Abnormalities in compliance and resistance in patients with acute respiratory failure are dependent on both the cause and severity of the disease. Patients with ARDS or cardiogenic pulmonary edema tend to have a low compliance (35 or 44 mL/cm H_2O , respectively) and an elevated resistance (12 or 15 cm H_2O/L per second, respectively).¹¹¹ In contrast, patients with chronic airway obstruction tend to have both a higher compliance (66 mL/cm H_2O) and a higher resistance (26 cm H_2O/L per second).¹¹¹

Dynamic Gas Trapping and Intrinsic Positive End-Expiratory Pressure

At end expiration, if the respiratory system remains above its relaxed position, gas gets trapped and the elastic recoil pressure in the lungs remains above baseline and is considered positive. This phenomenon is referred to as *intrinsic PEEP* ($PEEP_i$).¹¹² $PEEP_i$ can be measured by an end-expiratory circuit occlusion maneuver, whereby after a normal expiratory time elapses, both the inspiratory and expiratory ventilator valves close for 3 to 5 seconds, allowing alveolar pressure to equilibrate with the airway pressure (see Fig. 35-3).^{113,114} This pressure represents the average $PEEP_i$ throughout the lungs.^{113,115} However, it is important to keep in mind that different degrees of $PEEP_i$ may coexist in the lungs because of regional variations in time constants due to the underlying pathology.^{114,115} $PEEP_i$ is more common in mechanically ventilated patients with chronic obstructive lung diseases (in which dynamic hyperinflation slows elastic recoil) and patients who require high respiratory rates (which allow inadequate time for complete exhalation).

Pressure-Volume Curves

The static pressure-volume relationship can be used to analyze the elastic properties of the respiratory system and help guide mechanical ventilation.¹¹⁶ Pressure-volume (P-V) curves usually have a sigmoidal shape (Fig. 35-6). When inflation begins below functional residual capacity (FRC), there is relatively little volume change as transpulmonary pressure increases. This is referred to as the *starting compliance* and corresponds to the first 250 mL of volume change.¹¹⁷ It reflects either the relatively high pressure required to overcome small airway closure in the dependent lung zones or the relatively small area of aerated lung tissue as inflation commences.^{117,118} Typically this low-compliance segment in the P-V curve is followed by an abrupt slope change with a concave appearance that is termed the *lower inflection*

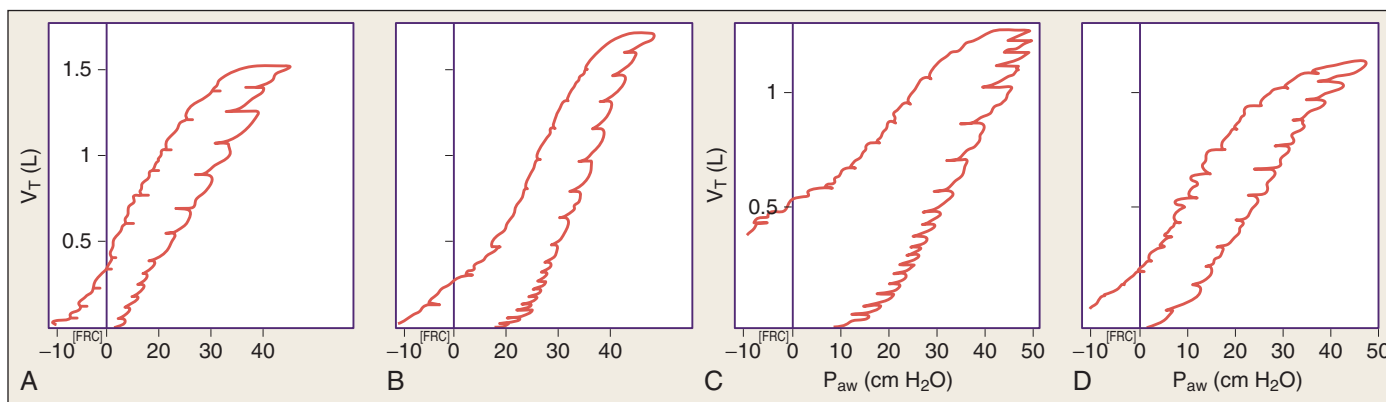


FIGURE 35-6 ■ Pressure-volume curves of the respiratory system of patients in various phases of acute respiratory distress syndrome. **A**, Decreased compliance and little hysteresis (early fibroproliferative phase). **B**, Almost normal compliance with large hysteresis (early exudative phase). **C**, Decreased compliance with large hysteresis (later exudative phase). **D**, Low compliance and little hysteresis (late fibroproliferative phase). (From Bigatello LM, Davignon KR, Stelfox HT. Respiratory mechanics and ventilator waveforms in the patient with acute lung injury. *Respir Care* 2005;50:235-245.)

point,¹⁰⁰ or Pflex.¹⁰¹ A common interpretation of the lower inflection point is that it signifies an abrupt reopening of collapsed peripheral airways and alveoli.^{116,118-120} Above the lower inflection point, the P-V curve becomes linear and is referred to as the *inflation compliance*.¹²¹ As the total lung capacity is approached, compliance decreases and the P-V curve becomes convex (bow-shaped). This is referred to as *end compliance*¹²¹ and is thought to signify the loss of distensibility at maximal inflation.¹¹⁸ This change point is termed the *upper inflection point*.¹²¹ As the lung is deflated, the linear portion of the curve is referred to as the *deflation compliance*, or *true physiologic compliance*, as it represents the elastic properties of the lung after full recruitment.¹²² As lung deflation proceeds below FRC, an inflection point often occurs on the deflation limb that represents small-airway closure.¹²² This airway closure tends to occur at a lower pressure than the lower inflection point on the inflation limb because the minimal force necessary to maintain patent airways is less than the pressure needed to recruit collapsed ones.¹²³

Constructing a Pressure-Volume Curve

There are three general approaches for creating the P-V curve: the supersyringe method, constant flow method, and multiple occlusion method.^{121,124,125} The supersyringe method involves the use of a large syringe that can accommodate up to 2 L of volume. At exhalation, insufflated volumes and the resulting pressures are recorded (after a 2- to 3-second pause at each point to eliminate the resistive forces) in a stepwise fashion (usually 100-mL increments).¹²⁵ Usually, when the airway pressure reaches the 40-cm H₂O range, inflation is stopped and deflation is performed the same way. Volume steps are plotted against the corresponding static pressure points on graph paper to obtain the curve. Respiratory system compliance is the slope of the inflation and deflation curves between the volumes of 0.5 and 1 L.¹¹⁹ The disadvantages of the supersyringe method are that it requires additional equipment, the patient has to be disconnected from the ventilator, and patient paralysis is required.

The constant flow method is available on some ventilators and involves the use of very low inspiratory and expiratory flows. The ventilator will then display the P-V plot. Higher flows, though, will allow the viscoelastic properties of the lung to shift the curve to the right. Disadvantages of this method include the fact that some ventilators cannot control expiratory flow (the deflation limb would be inaccurate) and, in most instances, the patient will require additional sedation so as not to contribute any spontaneous respiratory efforts.

The multiple occlusion method is also done with the ventilator. It involves periodically interrupting tidal breathing at different lung

volumes to obtain each P-V point. The ventilator, as was the case with the constant flow method, then displays the P-V plot. The advantages of this method are that both the inflation and deflation limbs are obtained, and the patient does not have to be disconnected from the ventilator. Sedation, paralysis, or both are still required with this method to prevent spontaneous respiratory efforts.

Determination of Lower and Upper Inflection Points

In clinical practice, the lower inflection point of the inflation limb is usually determined by the graphic technique.⁹⁷ First, a tangent is drawn extending the slope of the starting compliance. Another tangent is drawn extending the slope of the inflation compliance down toward the horizontal axis. Where the two tangents intersect, a third tangent is drawn down to the horizontal axis, and this point is considered the lower inflection point. The same technique can be used to determine the upper inflection point on the inflation limb, as well as the deflation limb's lower inflection point. Typically, PEEP is set 2 cm H₂O above the lower inflection point to ensure optimal lung recruitment, and VT is set below the upper inflection point to prevent lung injury from excessive stretch.^{116,126} P-V curves obtained through the use of a ventilator require visual interpretation of the inflection points. The problem with visual interpretation is that the inflection points are not always completely evident. This can lead to differing interpretations among clinicians.

Hysteresis

Hysteresis refers to the difference in compliance during inflation versus deflation. Compliance tends to be higher during deflation than inflation because higher pressures may be required during inspiration to recruit collapsed alveoli. This "extra" pressure is not required during deflation to prevent derecruitment. Ultimately then, the deflation limb may be more important for setting PEEP, since the deflation limb inflection point represents the point at which the alveoli will collapse.¹²⁷

ASSESSMENT OF BREATHING PATTERN AND CENTRAL DRIVE

Rate and Tidal Volume

Basic assessment of the respiratory pattern includes the measurement of respiratory rate and VT. A normal respiratory rate is 12 to 24 breaths/min, and mechanical ventilation is generally indicated when the rate exceeds 35 breaths/min.¹²⁸ A VT of 5 mL/kg is considered

sufficient to maintain unassisted breathing.¹²⁹ Tachypnea is often the earliest sign of impending respiratory failure, even when arterial blood gases remain within normal limits.¹³⁰ This may reflect the fact that muscle fatigue (which results from a mechanical workload that exceeds the power capacity of the ventilatory muscles) occurs before overt ventilatory pump failure.¹³¹ If untreated, a rapid, shallow breathing pattern can develop that will be progressively ineffective in maintaining acceptable arterial blood gases.¹³²

Of particular interest is the utility of breathing pattern in assessing the feasibility of weaning from mechanical ventilation. Typically, patients who fail to wean are more tachypneic (respiratory rate greater than 32 breaths/min) and have an abnormally low V_T (less than 200 mL).¹³³ The respiratory rate- V_T ratio, also known as the rapid shallow breathing index (RSBI), is a method that helps in evaluating readiness to wean. The RSBI is thought to be an accurate predictor of breathing effort.^{134,135} An RSBI threshold of less than 105 has both a high positive predictive value (0.78) and high negative predictive value (0.95) for the ability to maintain unassisted breathing.¹³⁶ Although the utility of RSBI has support from various studies,^{137,138} the original negative predictive value, at a cutoff greater than 105, may be too low according to some authors.^{138,139} While not an absolute predictor in and of itself, RSBI can be a valuable tool in helping to predict readiness to wean.

Central Ventilatory Drive

In some situations, clinicians may want to assess the central ventilatory drive. A heightened drive will increase the patient's work of breathing during mechanical ventilation.¹⁴⁰ Measuring the respiratory rate will give the clinician an indication of the central ventilatory drive but not the depth of the drive. Depth of the drive can be measured by a brief (100 msec) inspiratory occlusion after the onset of an effort, called $P_{0.1}$. Briefly occluding the airway at the onset of inspiratory

effort results in isometric contraction of the inspiratory muscles, so $P_{0.1}$ is independent of respiratory system mechanics.¹⁴¹ Measuring airway pressure at 100 msec indirectly reflects efferent motor neuron output. An increasing stimulus to the inspiratory muscles causes a more forceful contraction, with a proportional increase in pressure development. The selection of 100 msec is based on the fact that conscious or nonconscious perception of (and response to) sudden load changes requires approximately 250 msec.¹⁴² It is convenient that during mechanical ventilation, the lag associated with the trigger phase provides sufficient time to measure $P_{0.1}$.¹⁴³ Some ventilators¹⁴⁴ and pulmonary mechanics monitors¹⁴⁵ now measure $P_{0.1}$. Experimentally, $P_{0.1}$ has been used for closed-loop control of pressure support levels during weaning from mechanical ventilation.¹⁴⁶

At rest, $P_{0.1}$ is normally 0.8 cm H₂O, whereas in patients with respiratory failure, it can range from 2 to 6 cm H₂O, depending on the level of ventilatory support.^{143,145,147-150} $P_{0.1}$ correlates highly with a patient's work of breathing, and changes in $P_{0.1}$ (which occur with ventilator adjustments) show a high degree of sensitivity and specificity for corresponding changes in patient work.^{151,152} $P_{0.1}$ has been used to predict weaning and extubation success in patients recovering from acute respiratory failure. Levels exceeding 6 cm H₂O may predict weaning failure in chronic obstructive lung disease, whereas a $P_{0.1}$ greater than 4 cm H₂O may presage failure in ARDS.^{153,154}

During brief trials of unassisted breathing, a $P_{0.1}$ greater than 7 cm H₂O tends to describe patients requiring total ventilatory support and has been reported as a cutoff level in patients who ultimately fail a trial of extubation.¹⁵⁵ $P_{0.1}$ values between 4 and 7 cm H₂O may indicate patients who can be managed with partial ventilatory support, whereas a value less than 4 cm H₂O may indicate patients no longer in need of mechanical assistance.¹⁵⁴

A limitation of $P_{0.1}$ is that it dissociates from ventilatory drive when muscle weakness is present or hyperinflation alters the force-length relationship of the inspiratory muscles.

KEY POINTS

Pulse Oximetry

1. Because pulse oximeters cannot be calibrated, their accuracy is highly variable and dependent on both the calibration curve programmed into the monitor and the quality of signal processing.
2. Carboxyhemoglobin and oxyhemoglobin absorb equivalent amounts of red light, so carbon monoxide poisoning can result in falsely elevated oxygen saturation as measured by a pulse oximeter (SpO_2).
3. Motion artifact and low perfusion are the most common sources of SpO_2 inaccuracies.
4. Falsely low SpO_2 readings occur when even minor gaps exist between the probe and skin.
5. Pulse oximeters have greater bias and less precision in patients with dark skin pigmentation.

Capnometry

1. In normal subjects, the gradient between partial pressure of carbon dioxide in arterial blood and partial pressure of carbon dioxide in end-tidal exhaled gas (P_{aCO_2} - P_{ETCO_2} gradient) is 4 to 5 mm Hg, whereas in critically ill patients, the P_{aCO_2} - P_{ETCO_2} gradient can be markedly elevated and inconsistent, particularly in those with obstructive lung diseases (7 to 16 mm Hg).
2. The P_{aCO_2} - P_{ETCO_2} gradient is affected by changes in respiratory rate, tidal volume, carbon dioxide (CO_2) production, and mixed venous CO_2 content.

3. At respiratory frequencies above 30 breaths/min, capnometers tend to underreport the true P_{ETCO_2} .
4. In some patients with acute respiratory distress syndrome, the P_{aCO_2} - P_{ETCO_2} gradient may be an effective way to titrate positive end-expiratory pressure (PEEP).
5. During precordial compressions, P_{ETCO_2} can distinguish between successful and unsuccessful resuscitation, with values greater than 10 mm Hg associated with successful resuscitation.

Assessment of Pulmonary Mechanics

1. Distinguishing resistive from elastic recoil-related pressures in the lungs requires the introduction of an end-inspiratory circuit occlusion after tidal volume delivery.
2. In clinical practice, the pause time used for an end-inspiratory circuit occlusion is set at 0.5 to 1 second to limit any potential artifact from spontaneous breathing efforts that may falsely raise or lower the end-inspiratory plateau pressure.
3. The driving pressure necessary to overcome resistance increases disproportionately to changes in gas flow, so resistance can be determined accurately only with a constant inspiratory flow (square wave) pattern.
4. Intrinsic PEEP is measured by occluding both limbs of the ventilator circuit for 3 to 5 seconds at end-expiration, thus allowing alveolar pressure to equilibrate with airway pressure. This pressure represents the average intrinsic PEEP throughout the lungs.

Continued

KEY POINTS—cont'd

5. When using the pressure-volume curve of the respiratory system for lung-protective ventilation in patients with acute respiratory distress syndrome, PEEP is set 2 cm H₂O above the lower inflection point to ensure optimal lung recruitment, and tidal volume is set below the upper inflection point to prevent lung injury from excessive stretch.

Assessment of Breathing Pattern, Strength, and Central Drive

1. A threshold value of less than 105 for the respiratory rate/tidal volume ratio has both a high positive predictive value (0.78) and

high negative predictive value (0.95) for the ability to maintain unassisted breathing.

2. During brief trials of unassisted breathing, an inspiratory occlusion pressure 100 msec after the onset of effort ($P_{0.1}$) greater than 7 cm H₂O tends to signify patients requiring total ventilatory support and has been reported as a cutoff level in patients who ultimately fail a trial of extubation.

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Alberti A, Gallo F, Fongaro A, et al. $P_{0.1}$ is a useful parameter in setting the level of pressure support ventilation. *Intensive Care Med* 1995;21:547-553.

This paper describes the potential use of $P_{0.1}$, an indirect measurement of central respiratory drive and inspiratory effort, as a simple method for both titrating the level of mechanical ventilatory support and assessing weaning tolerance.

Falk JL, Rackow EC, Weil MH. End-tidal carbon dioxide concentration during cardiopulmonary resuscitation. *N Engl J Med* 1988;318:607-611.

This landmark paper introduced one of the most important clinical applications of capnography: the monitoring of spontaneous circulation and the effectiveness of precordial compressions in the setting of cardiac arrest. A sudden rise in end-tidal CO₂ concentration from approximately 1% to 3% (7 to 20 mm Hg) coincides with the return of spontaneous circulation.

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This case series report introduced one of the most crucial concepts and monitoring imperatives of invasive mechanical ventilation. This description of the mechanics and clinical implications of dynamic hyperinflation remains one of the most lucid in the critical care and pulmonary literature.

Tremper KK, Barker SJ. Pulse oximetry. *Anesthesiology* 1989;70:98-108.

This paper remains one of the best written on the subject of pulse oximetry. It provides clinicians with an elegant discussion of the history, physics, engineering, and clinical aspects of this technology.

■ References for this chapter can be found at expertconsult.com

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While arterial blood gas (ABG) data provide critical information to practitioners of critical care medicine, ABG measurement is the most frequently ordered test in intensive care units (ICUs), is overutilized, and is associated with burden to our patients (discomfort, blood loss) and healthcare system.¹⁻⁵ Therefore, appropriate understanding and use of this clinical test are important for optimal care of our patients. Although no randomized trials have been published to date, clinical studies looking at the utility of ABG testing in relation to clinical outcomes have reported mixed results and strongly suggest that ABG information be used within the clinical context in the ICU.⁶⁻⁸ The development of polarographic electrodes in the 1950s for oxygen (O₂) by Clark and for carbon dioxide (CO₂) by Severinghaus and Bradley, as well as Stow and coworkers, permitted measurement of the partial pressures of oxygen (Pao₂) and carbon dioxide (Paco₂) in arterial blood.⁹⁻¹¹ Cremer and colleagues developed the pH electrode in the early 20th century. ABGs remain the definitive method to diagnose, categorize, and quantitate respiratory, as well as metabolic, failure.¹²

WHY AM I OBTAINING AN ARTERIAL BLOOD GAS?

This should be the primary question to ask ourselves as part of our practice before reflexively ordering the next ABG upon encountering an unstable patient. As noted above, ABG measurement is the most frequently performed test in ICUs, and studies suggest that the presence of an arterial line is the most powerful predictor for obtaining an arterial blood sample for ABG, regardless of the Pao₂, Paco₂, Acute Physiology and Chronic Health Evaluation (APACHE) II score, or presence of a ventilator.^{1,13} In addition, there are no published guidelines and only a limited number of trials providing guidance to clinicians regarding the indications for sampling ABGs.¹⁴ Roberts et al., as well as Murphy, demonstrated that protocolized care was able to reduce the number of unnecessary ABGs with no negative effects on patient outcomes.^{1,4}

The indications for ABG analysis have to be guided within the clinical context, and recent technologies such as pulse oximetry and transcutaneous CO₂ detection will decrease the frequency of use of ABGs.^{15,16} Yet, we still need to give clinicians a “rule of thumb” regarding when to sample ABGs. As such, patients need ABG

- following endotracheal intubation and/or mechanical (invasive or noninvasive) ventilation,
- during the clinical course of acute respiratory distress syndrome (ARDS),
- when hypoxemic and/or hypercapnic respiratory failure is present,
- when acute circulatory failure is present, and
- during the management of complex acid-base disorders.

ARTERIAL BLOOD GAS SAMPLING

ABG samples are obtained either from an indwelling arterial catheter or from direct arterial puncture, and the blood is drawn into a syringe containing heparin. It used to be customary to flush a syringe with heparin and then to use that syringe to sample ABGs; however, research in adult, as well as pediatric, patients has shown that excess heparin significantly decreases the Paco₂, Pao₂, bicarbonate (HCO₃⁻), and base excess, while leaving the pH unchanged. Thus, excess liquid heparin falsely exaggerates the degree of metabolic acidosis with respiratory compensation.^{17,18}

While the most common site for arterial puncture is the radial artery, femoral and brachial arteries are also commonly used to sample arterial blood. Risks associated with arterial punctures are hematoma formation, ischemia to the upper or lower extremity, arterial injury, pseudoaneurysms, and arteriovenous fistulas.^{14,19-22} Once obtained, the arterial blood sample has to be processed immediately and correctly using the best laboratory practices to ensure quality. In addition to differences among laboratories, calibration discrepancies and contamination of electrodes with protein or other fluids may alter results.^{23,24}

Using the polarographic electrodes, Pao₂, Paco₂, and pH are directly measured; oxygen saturation (SaO₂) is calculated from standard O₂ dissociation curves or directly measured with a co-oximeter.^{9-12,25}

A co-oximeter is a blood gas analyzer that measures not just the partial pressure of gases but also the concentration of oxygen associated with different types of hemoglobin (Hb) based on their absorption spectra (Beer-Lambert law). The use of co-oximetry is usually indicated when

- a toxin is suspected,
- hypoxia fails to improve with the administration of oxygen,
- there is a discrepancy between the Pao₂ on a blood gas determination and the oxygen saturation determined by pulse oximetry (SpO₂), or
- a clinician suspects the presence of a dyshemoglobin, such as methemoglobin (MetHb) or carboxyhemoglobin (COHb).²⁶

Pulse oximetry, unfortunately, does not differentiate among the different types of Hbs. For example, in the case of MetHb, the Spo₂ may read 86%, but desaturation can be demonstrated with co-oximetry, recording 68% oxyhemoglobin and 32% MetHb.^{26,27}

The HCO₃⁻ concentration is calculated using the Henderson-Hasselbalch equation:

$$\text{pH} = \text{pK}_A + \log\left(\frac{[\text{HCO}_3^-]}{[\text{CO}_2]}\right),$$

where pK_A is the negative log of the dissociation constant of carbonic acid (HCO₃⁻).

The *base excess* is the quantity of strong acid required to titrate blood to pH 7.40 with a Paco₂ of 40 mm Hg at 37°C. In reality, acid is not titrated but calculated using a variety of nomogram.²⁸⁻³² Such calculations focus only on the metabolic sources for pH and [H⁺] changes. Bicarbonate is a similarly calculated value assuming Paco₂ at 40 mm Hg.

The following are some of the details one must take into consideration to avoid erroneous readings and interpretations:

1-Steady State

The sample of blood for ABG testing has to be collected when a patient reaches a steady state during the clinical course, especially to allow the arterial and alveolar gases to equilibrate. This may take up to 20 or 30 minutes in patients with chronic obstructive pulmonary disease (COPD).³³

2-Anticoagulants

As mentioned in the [Arterial Blood Gas Sampling](#) section, excessive heparin may affect Paco₂, Pao₂, HCO₃⁻, and base excess, while not interfering with the pH. Only 0.05 mL is required to anticoagulate 1 mL of blood, and knowing that the “dead space” volume of a standard 5-mL syringe is approximately 0.02 mL, it is reasonable to assume that

just having heparin in the dead space would be sufficient to provide anticoagulation of up to 2 mL of blood. New prefilled syringes (sodium or lithium heparin) overcome this problem.¹⁷

3-Processing Delay

While the blood sample resides in the syringe before analysis, the blood cells consume O₂ and produce CO₂. Red blood cell glycolysis could generate more lactic acid through the aerobic glycolysis and lower the pH.^{34,35} If the sample remains unanalyzed at room temperature for more than 15 minutes, there would be a significant increase in PaCO₂ and decrease in pH. When the sample is stored on ice, it can be processed up to 2 hours after collection without affecting the blood gas values, even on Mount Everest.³⁶⁻³⁹

4-Venous Sampling

If no arterial blood sample can be obtained, venous blood gas analyses would be of limited value; however, such a venous sample could give an estimate of the PaCO₂ and lactate concentration.^{40,41} This will be discussed later in the chapter.

There could be times when the intended arterial puncture results in inadvertent venous sampling. One can recognize venous sampling when

- the practitioner fails to observe a flash of blood during syringe filling,
- the blood gas results are not consistent with the clinical condition,
- there is an unexpectedly low Pao₂ and high Paco₂, or
- the Spo₂ by pulse oximetry is higher than the Sao₂ in the measured ABG sample.

5-Collection Equipment and Technique

If the dead space in the syringe were high, this would lower the PaCO₂. Additionally, a needle smaller than 25 gauge may cause hemolysis.

If there is an arterial line, one has to pay attention to the dead space of the system (priming volume from the sample port to the catheter tip) to prevent sample dilution. The adequate amount of blood to discard before obtaining the sample of blood for testing would be 2 times the dead space volume.³

6-Hyperventilation

Hyperventilation resulting from anxiety and/or pain may acutely alter the ABG results, producing deviations from baseline values.

7-Leukocytosis

Leukocytosis decreases the Pao₂ and pH and elevates the Paco₂ when analyzing a stored sample. This Pao₂ decrease is particularly noticeable in the presence of higher Pao₂ levels, is attributable to cellular oxygen consumption, and may be attenuated when samples are stored at colder temperatures.

8-Hypothermia

Blood gas values are temperature-dependent, and as the temperature decreases, the solubility of CO₂ increases and the partial pressure falls. Thus, if blood samples are warmed to 37°C before analysis (as is common in most laboratories), Pao₂ and Paco₂ will be overestimated and pH will be underestimated in hypothermic patients. The following correction formulas can be used:

- Subtract 5 mm Hg Pao₂ per 1°C that the patient's temperature is less than 37°C.
- Subtract 2 mm Hg Paco₂ per 1°C that the patient's temperature is less than 37°C.

- Add 0.012 pH units per 1°C that the patient's temperature is less than 37°C.

While there is extensive literature on the so-called pH-stat and alpha-stat assessments of ABGs, in summary, the *pH-stat* acid-base approach aims at maintaining the patient's pH in a constant range by managing pH at the patient's temperature. As in the formulas above, pH-stat is temperature-corrected. On the other hand, *alpha-stat* focuses on the ionization state of histidine, which is maintained by managing the standardized pH (measured at 37°C). Alpha (normally about 0.55) is the ratio of protonated imidazole to total imidazole on the histidine moieties in proteins. Alpha-stat is not temperature corrected—as the patient's temperature falls, the partial pressure of CO₂ decreases and solubility increases; thus, a hypothermic patient with a pH of 7.40 and a Paco₂ of 40 (measured at 37°C) will actually have a lower Paco₂ because of its lower partial pressure, and this will manifest as a *relative respiratory alkalosis*. In contrast, pH-stat, with its goal of maintaining a Paco₂ of 40 and pH of 7.40 at the patient's actual temperature, results in a higher Paco₂ (and *respiratory acidosis*).⁴³⁻⁴⁵

HYPOXEMIA, HYPOXIA, AND ARTERIAL BLOOD GAS ANALYSIS

We need to clarify the definitions of hypoxemia and hypoxia and the utility of different measures prior to analyzing the results of ABGs. The Pao₂ is primarily used to assess oxygenation, and it is reliable within a dynamic range between 30 to 200 mm Hg. However, Sao₂ is reliable within a much narrower range: between 30 and 60 mm Hg.⁴⁸ Measuring oxygen saturation by noninvasive pulse oximetry (Spo₂) or by ABG analysis (Sao₂) provides a better indication of arterial O₂ content than Pao₂, since only about 2% of blood O₂ is carried in the dissolved form and the greatest amount (98%) is carried by Hb. While using the Spo₂, one has to be cognizant of its shortcomings, including interference by indicator dyes used during certain procedures.^{49,50}

Hypoxemia is defined as a Pao₂ less than 80 mm Hg at 1 atm in adults breathing room air; *hypoxia* denotes tissue or cell level decreases in O₂. Thus, hypoxia (tissue or end-organ) in patients with hypoxemia depends on the severity of the hypoxemia and the ability of the cardiovascular system to compensate. Hypoxia is unlikely in mild hypoxemia (Pao₂ = 60-79 mm Hg). Moderate hypoxemia (Pao₂ = 45-59 mm Hg) may be associated with hypoxia in patients with anemia or cardiovascular dysfunction. Hypoxia is almost always associated with severe hypoxemia (Pao₂ < 45 mm Hg). While the Pao₂ might be low at 45 mm Hg, the mitochondrial O₂ partial pressure necessary to complete oxidative phosphorylation is around 0.5 to 3 mm Hg, several orders of magnitude lower, which may be the reason why some patients with cyanotic diseases and elite Mount Everest climbers without supplemental oxygen can have an average Pao₂ of 26 mm Hg, yet survive without significant end-organ injury.⁵¹⁻⁵⁸

Acute respiratory insufficiency occurs when the lungs no longer meet the metabolic demands of the body. It is divided into two types:

- Type I, hypoxemic respiratory insufficiency: Pao₂ ≤ 60 mm Hg when breathing room air at 1 atm pressure.
- Type II, hypercapnic respiratory insufficiency: Paco₂ ≥ 50 mm Hg.
- The tripartite information that can be gathered from ABG analyses includes (a) oxygen saturation and content, (b) CO₂ as a marker of ventilation, and (c) acid-base status. Here, we will discuss all three components.

Alveolar Ventilation

The Paco₂ reflects the CO₂ content of the sample. The CO₂ content is basically the balance between the quantity of CO₂ produced and the quantity excreted through alveolar ventilation (VA). It can be expressed by the equation:

$$\text{Paco}_2 \sim \text{CO}_2 / \text{VA}$$

VA is the portion of total ventilation that participates in gas exchange with pulmonary blood. If the metabolic rate remains unchanged, it is reasonable to assume that CO_2 production is in steady state. CO_2 homeostasis can then be simplified to:

$$\text{PaCO}_2 \sim 1/\text{VA}$$

Therefore, when steady state is reached (as discussed earlier in the chapter), PaCO_2 becomes a useful tool for assessing VA. If the PaCO_2 is >45 mm Hg, this is referred to as *alveolar hypoventilation*, and if the PaCO_2 is <35 mm Hg, it is called *alveolar hyperventilation*.

Oxygenation

Tissue oxygenation is dependent on the delivery of oxygenated blood (both dissolved as well as bound to Hb). The PaO_2 is the dissolved fraction that makes a very small contribution to O_2 delivery ($<2\%$), yet this fraction could be critical and useful in the setting of severe anemia.^{59,60} PaO_2 is dependent on the concentration of inspired oxygen (FiO_2), ventilation and perfusion (V/Q) matching, and venous oxygen saturation (SvO_2). The PaO_2 value has to be assessed within a clinical context, along with the FiO_2 and age of the patient.

Relationship Between PaO_2 and FiO_2

PaO_2 alone provides limited information about oxygenation and alveolocapillary gas exchange unless FiO_2 is also considered in the interpretation. In addition to FiO_2 , the other major determinant of PaO_2 is the degree of intrapulmonary shunting (Fig. 36-1). While PaO_2 and FiO_2 alone do not quantitate the intrapulmonary shunt (which is useful for the diagnosis and management of lung diseases and in guiding the approach to oxygen therapy and respiratory support), they provide an overall indication about the diagnosis, after which various formulas can be used for calculating the intrapulmonary shunt (Q_s/Q_t).

The classic “shunt equation” requires mixed venous blood sampling through a pulmonary artery catheter and the alveolar-arterial oxygen gradient equation (Box 36-1):

$$Q_s/Q_t = (C_c\text{O}_2 - C_a\text{O}_2)/(C_c\text{O}_2 - C_v\text{O}_2), \text{ where}$$

Q_s is blood flow through the shunt,

Q_t is total cardiac output,

$C_c\text{O}_2$ is pulmonary end-capillary O_2 content,

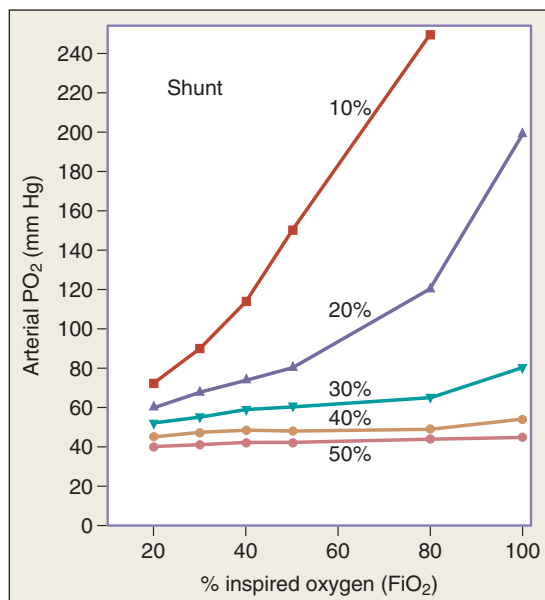


FIGURE 36-1 ■ The effect of increasing FiO_2 on PaO_2 according to shunt fraction.

$C_a\text{O}_2$ is arterial O_2 content, and

$C_v\text{O}_2$ is mixed venous O_2 content.

Clinically, the so-called P/F ratio ($\text{PaO}_2/\text{FiO}_2$) is most commonly used to approximately quantify the degree of V/Q mismatching. Since the normal PaO_2 in an adult breathing room air at an FiO_2 of 21% is 80 to 100 mm Hg, the normal value for $\text{PaO}_2/\text{FiO}_2$ ranges between 400 and 500 mm Hg. A $\text{PaO}_2/\text{FiO}_2$ ratio <200 most often indicates a shunt of $>20\%$. This ratio has also been incorporated since 1994 into the ARDS definition.⁶¹⁻⁶³ A notable limitation of the $\text{PaO}_2/\text{FiO}_2$ ratio is that it does not take into account changes in PaCO_2 at low FiO_2 .

Age

PaO_2 decreases with age (Box 36-1). For example, at an FiO_2 of 21% and 1 atm pressure, the PaO_2 is 85 to 90 mm Hg at 60 years of age, and this value decreases to 80 to 85 mm Hg at 80 years of age.

Acid-Base Balance

The normal diet generates volatile acid (CO_2) primarily from carbohydrate metabolism and nonvolatile acid (hydrogen ion [H^+]) from protein metabolism. The function of the homeostatic system is to maintain pH within a narrow range, and pH homeostasis is accomplished through the interaction of the lungs, kidneys, and blood buffers. VA allows for excretion of CO_2 , and the kidneys reclaim filtered HCO_3^- as well as excrete the daily acid load generated from dietary protein intake. Less than half of this acid load is excreted as *titratable acids* (i.e., phosphoric and sulfuric acids); the remaining acid load is excreted as ammonium. The blood pH is determined by the balance of these processes.⁶⁴

The current mainstream understanding of the acid-base system dates back to the 1950s, when the concepts of the Henderson-Hasselbalch equation were combined with the Brønsted-Lowry theory to create a *bicarbonate ion*-centered approach.^{65,66} In the late 1970s, Stewart repackaged the pre-1950 ideas of acid-base, including the Van Slyke definition of an acid, and used physical chemistry to generate a new understanding of acid-base balance.^{65,67} The resultant strong ion difference (SID) and concentration of weak acids (particularly albumin), push HCO_3^- into a minor role as an acid-base indicator rather than as an important mechanism:

$$\text{SID} = ([\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{2+}] + [\text{Mg}^{2+}]) - ([\text{Cl}^-] + [\text{lactate}])$$

Beware that SID is not the same as the anion gap (AG) and it contains [lactate], but SID does share a number of parameters with AG, and the trends of the two will often be close. The normal value for SID has not been well established, but the quoted range is 40 to 42 mEq/L. As the SID approaches zero, anions accumulate and the balance tilts toward acidity. This model makes it easier for clinicians to understand the “hyperchloremic acidosis” commonly observed following 0.9% saline administration and the systemic alkalosis of hypoalbuminemia (regarded as a weak acid).^{68,69}

Because of practical reasons, the HCO_3^- -centered approach is still commonly used over the Stewart approach to understand and manage acid-base balance.⁷⁰ The Henderson-Hasselbalch equation states that $\text{pH} = \text{pKa} + \log (\text{HCO}_3^-/\text{H}_2\text{CO}_3)$. If all constants are removed, the

BOX 36-1

Formulas for Evaluating Gas Exchange in Patients

Age-adjusted PaO_2 : Expected $\text{PaO}_2 = 0.3 (\text{age} - 25)$

Expected PaO_2 at 1 atm pressure is approximately 100 mm Hg. An approximation could be done as: Expected $\text{PaO}_2 = \text{FiO}_2 (\%) \times 5$

Alveolar-arterial gradient: $\text{AaDO}_2 = [\text{FiO}_2 \times (\text{barometric pressure} - 47)] - (\text{PaO}_2 + \text{PaCO}_2)$

Oxygenation index = $[(\text{mean airway pressure} \times \text{FiO}_2)/\text{PaO}_2] \times 100$

Dead space to tidal volume ratio: $\text{Vd/Vt} = (\text{PaCO}_2 - \text{PECO}_2)/\text{PaCO}_2$

The normal range is 20%-40%.

equation can be simplified to $\text{pH} \sim \text{HCO}_3^-/\text{PaCO}_2$. The HCO_3^- concentration is controlled mainly by the kidney and blood buffers, whereas PaCO_2 is regulated by the lungs adjusting the level of the volatile acid, H_2CO_3 , in the blood. Buffer systems can act within a fraction of a second to prevent excessive changes in pH. The respiratory system takes about 1 to 15 minutes, and the kidneys take many minutes to days to readjust the H^+ ion concentration.

The Anion Gap

According to the principle of electrochemical neutrality, total cations must equal total anions, and so when subtracting the commonly measured anions from the commonly measured cations, a fixed number should be obtained. The measured cations are in excess; mathematically, this “gap” is filled with unmeasured anions ensuring electrochemical neutrality. There is never a “real” AG because of the law of electrochemical neutrality; rather, AG is an expression of nonroutinely measured anions. AG is calculated using the following formula⁷¹:

$$\text{AG} = ([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-]) \quad (\text{normal AG} = 10 \pm 2 \text{ meq/L})$$

(Because of the low concentration of K^+ in the blood, it is not usually included in the calculation of AG.)

During critical illness, albumin typically decreases rapidly. Albumin is an important contributor of the “normal” AG; therefore, as the albumin concentration falls, it tends to reduce the size of the AG or have an alkalizing effect. Various corrections are available, of which Figge’s AG correction (AG_{corr}) is the most commonly used⁷¹:

$$\text{Albumin gap} = 40 - \text{apparent albumin (normal albumin} = 40 \text{ g/L)}$$

$$\text{AG}_{\text{corr}} = \text{AG} + (\text{albumin gap}/4)$$

STEPWISE APPROACH TO ACID-BASE DISORDERS

Step 1: Do a Comprehensive History and Physical Exam

History and physical examination can often give clues as to the underlying acid-base disorder (Table 36-1). For example, severe diarrhea could lead to loss of HCO_3^- with subsequent *non-AG metabolic acidosis*. Patients with COPD could have chronic respiratory acidosis

TABLE 36-1

Common Clinical Presentations and Associated Acid-Base Disorders

| CLINICAL PRESENTATION | ACID-BASE STATUS |
|--|---|
| Pulmonary embolism | Respiratory alkalosis |
| Shock | Lactic acidosis (metabolic) |
| Sepsis | Metabolic acidosis and respiratory alkalosis |
| Vomiting | Metabolic alkalosis |
| Diarrhea | Metabolic acidosis |
| Acute kidney injury | Metabolic acidosis |
| Cirrhosis | Respiratory alkalosis |
| Pregnancy | Respiratory alkalosis |
| Diuretics | Metabolic alkalosis unless thiazides are used |
| Chronic obstructive pulmonary disease | Respiratory acidosis |
| Diabetic ketosis | Metabolic acidosis (ketoacidosis) |
| Ethylene glycol (antifreeze) poisoning | Metabolic acidosis |
| Excessive 0.9% saline use | Metabolic non-anion gap acidosis |

because of decreased CO_2 removal with a compensatory metabolic alkalosis resulting in a normal pH.

Step 2: Order Simultaneous Arterial Blood Gas Measurement and Chemistry Profile

As mentioned in the previous section, the HCO_3^- in the ABG results is a calculated value; therefore, it is important to obtain a chemistry panel to have directly measured data. In addition, Na^+ and Cl^- will provide additional information about the volume status and SID.⁷²⁻⁷⁵

Step 3: Check the Consistency and Validity of the Results

Normal ABG results are provided in Table 36-2.

Step 4: Identify the Primary Disturbance

With the ABG results in hand, the practitioner then has to determine whether the patient is acidemic ($\text{pH} < 7.35$) or alkalemic ($\text{pH} > 7.45$) and what the primary cause is (metabolic, driven by HCO_3^- , or respiratory, driven by PaCO_2) (Table 36-3).

Step 5: Calculate the Expected Compensation

Any alteration in acid-base equilibrium sets into motion a compensatory response by either the lungs or kidneys. The compensatory response attempts to return the ratio between PaCO_2 and HCO_3^- to normal, with subsequent normalization of the pH. Compensation is usually predictable; the adaptive responses for simple acid-base disorders have been quantified experimentally⁷⁶ (Table 36-4). One has to then evaluate the compensatory responses and any secondary (uncompensated) acid-base disturbances.

Step 6: Calculate the “Gaps”

Calculate the Anion Gap

In high-AG metabolic acidosis, acid dissociates into H^+ and an unmeasured anion. H^+ is buffered by HCO_3^- , and the unmeasured anion

TABLE 36-2 Normal Acid-Base Values

| | MEAN | 1 \pm SD | 2 \pm SD |
|--------------------------|------|------------|------------|
| PaCO_2 (mm Hg) | 40 | 38-42 | 35-45 |
| pH | 7.4 | 7.38-7.42 | 7.35-7.45 |
| HCO_3^- (mEq/L) | 24 | 23-25 | 22-26 |

SD, standard deviation.

TABLE 36-3 Acid-Base Disorders

| DISORDER | DIAGNOSTIC CRITERIA |
|-------------------------------|--|
| Respiratory acidosis | $\text{PaCO}_2 > 45$ mm Hg |
| Respiratory alkalosis | $\text{PaCO}_2 < 35$ mm Hg |
| Acute respiratory acidosis | $\text{PaCO}_2 > 45$ mm Hg and $\text{pH} < 7.35$ |
| Chronic respiratory acidosis | $\text{PaCO}_2 > 45$ mm Hg and $\text{pH} = 7.36-7.44$ |
| Acute respiratory alkalosis | $\text{PaCO}_2 < 35$ mm Hg and $\text{pH} > 7.45$ |
| Chronic respiratory alkalosis | $\text{PaCO}_2 < 35$ mm Hg and $\text{pH} = 7.36-7.44$ |
| Acidemia | $\text{pH} < 7.35$ |
| Alkalemia | $\text{pH} > 7.45$ |
| Acidosis | $\text{HCO}_3^- < 22$ mEq/L |
| Alkalosis | $\text{HCO}_3^- > 26$ mEq/L |

TABLE 36-4 Compensation Formulas for Simple Acid-Base Disorders

| ACID-BASE DISORDER | COMPENSATION |
|-------------------------------|---|
| Metabolic acidosis | Change in $P_{aCO_2} = 1.2 \times \text{change in } HCO_3^-$ |
| Metabolic alkalosis | Change in $P_{aCO_2} = 0.6 \times \text{change in } HCO_3^-$ |
| Acute respiratory acidosis | Change in $HCO_3^- = 0.1 \times \text{change in } P_{aCO_2}$ |
| Chronic respiratory acidosis | Change in $HCO_3^- = 0.35 \times \text{change in } P_{aCO_2}$ |
| Acute respiratory alkalosis | Change in $HCO_3^- = 0.2 \times \text{change in } P_{aCO_2}$ |
| Chronic respiratory alkalosis | Change in $HCO_3^- = 0.5 \times \text{change in } P_{aCO_2}$ |

accumulates in the serum, resulting in an increase in the AG. In non-AG metabolic acidosis, H^+ is accompanied by Cl^- (a measured anion); therefore, there is no change in AG. Acid-base disorders may present as two or three coexisting disorders. It is possible for a patient to have an acid-base disorder with a normal pH, P_{aCO_2} , and HCO_3^- , and the only clue to an acid-base disorder being an increased AG. If the AG is increased by more than 5 meq/L (i.e., an AG > 15 meq/L), the patient most likely has a metabolic acidosis. Compare the fall in plasma HCO_3^- ($25 - HCO_3^-$) with the increase in plasma AG (ΔAG); these should be of similar magnitude. If there is a gross discrepancy (>5 meq/L), then a mixed disturbance is present:

The *anion gap* is calculated by subtracting the serum concentrations of Cl^- and HCO_3^- (anions) from the concentrations of sodium (cations):

$$([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$$

(Because of the low concentration of K^+ , it is not usually included in the calculation of AG.)

- If ΔAG is greater than the fall in HCO_3^- , this suggests that a component of the metabolic acidosis is due to HCO_3^- loss.
- If ΔAG is less than the fall in HCO_3^- , this suggests the presence of a coexistent metabolic alkalosis.

Osmolar Gap

Calculate the osmolar gap in patients with an unexplained AG metabolic acidosis to exclude ethylene glycol or methanol toxicity (Box 36-2):

The serum osmolality is calculated as:

$$2 \times (Na^+) + (Glucose)/18 + (BUN)/2.8,$$

where BUN = blood urea nitrogen (normal serum osmolality = 280–290 mOsm/kg H_2O).

The osmolar gap is defined as the difference between measured and calculated osmolality as

$$\text{Osmolar gap} = \text{Osmolality}_{\text{measured}} - \text{Osmolality}_{\text{calculated}} \\ (\text{normal} = < 10 \text{ mOsm/kg } H_2O)$$

COMMON ACID-BASE DISTURBANCES IN THE ICU

Metabolic Acidosis

The rate and degree of metabolic acidosis is mainly dependent on the underlying cause and the rapidity with which the condition develops. An acute, severe metabolic acidosis results in myocardial depression with a reduced cardiac output, decreased blood pressure, and decreased hepatic and renal blood flow; the cardiovascular system also becomes less responsive to vasopressor agents.⁷⁷ Reentrant arrhythmias and a reduced ventricular fibrillation threshold can occur.⁷⁸

The acute correction of metabolic acidosis has been a standard of care for intractable metabolic acidosis during acute coronary events. However, clinical trials have not shown improved outcomes, and acute

TABLE 36-5 Causes of Metabolic Acidosis

| INCREASED ANION GAP | NORMAL ANION GAP |
|----------------------|-----------------------|
| Acute kidney injury | Hypokalemic acidosis |
| Rhabdomyolysis | Hyperkalemic acidosis |
| Ketoacidosis | |
| Lactic acidosis | |
| Toxins: 5-oxoproline | |
| Beriberi | |

BOX 36-2 Causes of Increased Osmolal Gap

| | |
|-----------------|-----------------------------|
| Ethylene glycol | Alcohol |
| Methanol | Isopropyl alcohol (non-gap) |
| Mannitol | Sorbitol |
| Paraldehyde | Acetone |

correction can produce paradoxical central nervous system acidosis, which has led to its removal from advanced cardiac life support algorithms.^{79–81}

Metabolic acidosis in the critically ill patient requires an aggressive approach to the diagnosis and management of the underlying cause(s) (Fig. 36-2 and Table 36-5). In most patients, the cause(s) are clinically obvious, with lactic acidosis (tissue hypoxia or sepsis), ketoacidosis, and acute kidney injury (AKI) being the most common causes.^{82–84} In patients with an unexplained AG metabolic acidosis, drugs such as salicylates, methanol, or ethylene glycol toxicity should always be considered.^{85,86} Accumulation of 5-oxoproline related to the use of acetaminophen is a rare cause of AG metabolic acidosis.⁸⁷ Long-term use of lorazepam can result in the accumulation of its vehicle, propylene glycol, resulting in worsening AKI, metabolic acidosis, and altered mental status.^{88,89} Propylene glycol toxicity is typically observed after prolonged (>7 days), high-dose (average of 14 mg/h), continuous lorazepam infusion and can be recognized by an increased osmolal gap.⁹⁰ Similarly, first reported in children and then recognized also in adults, prolonged high-dose propofol (>100 $\mu\text{g/kg/min}$) is occasionally associated with the “propofol infusion syndrome.” This is characterized by rhabdomyolysis, metabolic acidosis, and renal and cardiac failure, requiring vigilance, early cessation of propofol, and use of an alternative sedative.^{91,92} It has been suggested that frequent assessment of creatinine kinase or a lipid panel would alert clinicians to impending propofol infusion syndrome.⁹³

The prognosis is related to the underlying disorder causing the acidosis. In almost all circumstances, the treatment of a metabolic acidosis involves treating the underlying disorder. Except in specific circumstances, there is no scientific evidence to support treating a metabolic or respiratory acidosis with sodium bicarbonate.⁹⁴ Furthermore, it is the intracellular pH that determines cellular function. The intracellular buffering system, including proteins, is much more effective than extracellular buffers in restoring pH to normal.^{95,96} Consequently, patients have tolerated a pH as low as 7.0 during sustained hypercapnia, without obvious adverse effects. Paradoxically, sodium bicarbonate can decrease intracellular pH in circumstances where CO_2 elimination is fixed. In addition, infusion of bicarbonate can lead to a variety of problems in patients with acidosis, including fluid overload, hypernatremia, and postrecovery metabolic alkalosis. Furthermore, studies in both animals and humans suggest that alkali therapy may only transiently raise the plasma HCO_3^- concentration. This finding appears to be related in part to the CO_2 generated as the administered bicarbonate buffers excess H^+ ions. Unless the minute ventilation is increased in ventilated patients, CO_2 elimination will not increase and

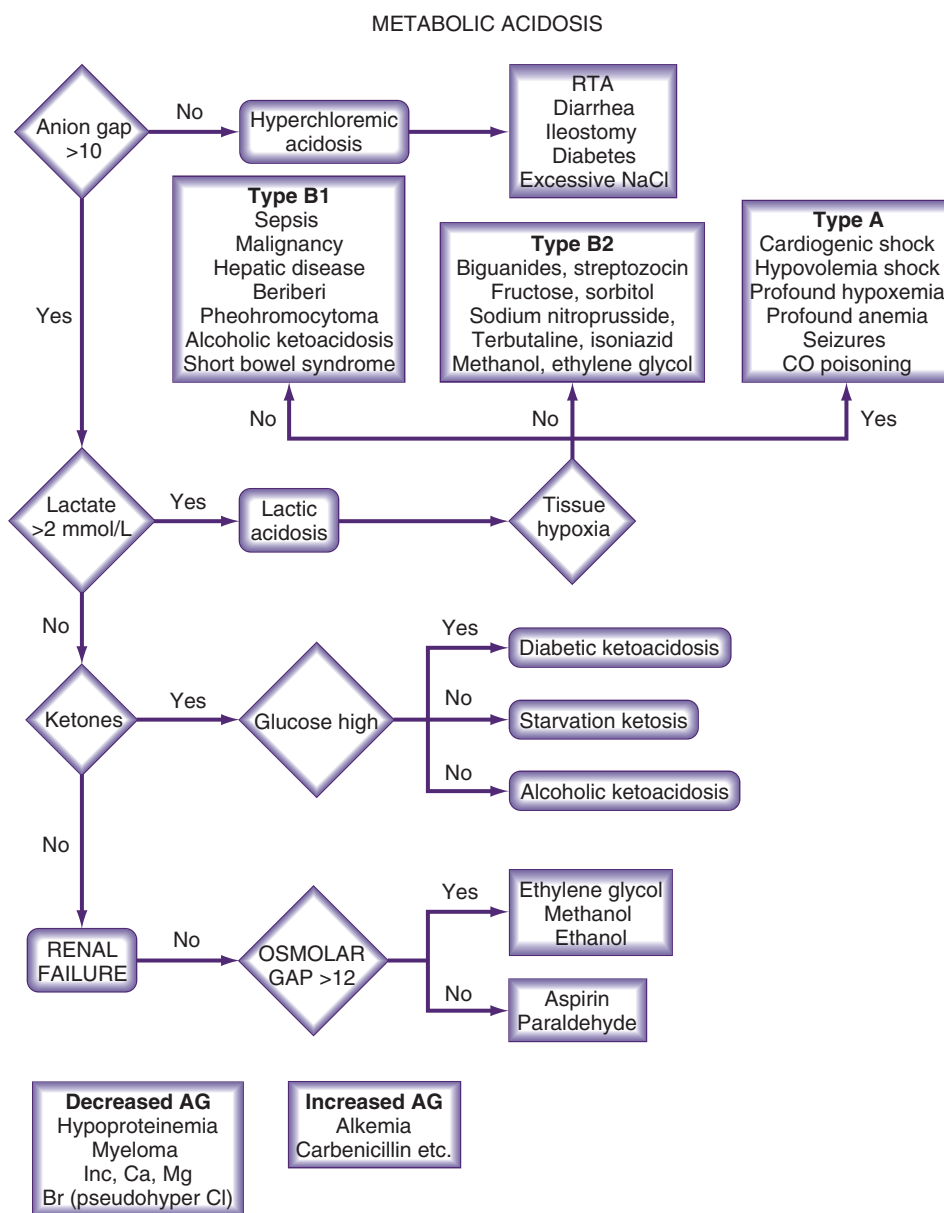


FIGURE 36-2 ■ Flowchart for diagnosing metabolic acidosis.

paradoxically will worsen the intracellular acidosis. Currently, there are no data to support the use of bicarbonate in patients with lactic acidosis.^{94,97}

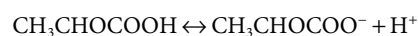
Sodium bicarbonate is frequently administered to “correct the acidosis” in patients with diabetic ketoacidosis (DKA). However, bicarbonate has been demonstrated to paradoxically increase ketone and lactate production.⁹⁸ Studies have demonstrated an increase in acetoacetate levels during alkali administration, followed by an increase in 3-hydroxybutyrate levels after its completion.^{98,99} In pediatric patients, treatment with sodium bicarbonate prolongs hospitalization.¹⁰⁰ In addition, bicarbonate may decrease cerebrospinal fluid pH, as the increased CO₂ produced by buffering acid crosses the blood-brain barrier, combines with H₂O₂, and regenerates H⁺. Therefore, the consensus is that adjunctive sodium bicarbonate is unnecessary and potentially disadvantageous in severe DKA.⁷⁹

Bicarbonate is considered life saving in patients with severe ethylene glycol and methanol toxicity. In hyperchloremic acidosis, endogenous regeneration of HCO₃⁻ cannot occur (HCO₃⁻ has been lost rather than buffered). Therefore, even if the cause of the acidosis can

be reversed, exogenous alkali is often required for prompt attenuation of *severe acidemia*. Bicarbonate therapy is, therefore, indicated in patients with severe *hyperchloremic acidosis* when the pH is <7.2; this includes patients with severe diarrhea, high-output fistulas, and renal tubular acidosis. To prevent hypernatremia, we suggest that 3 × 50 mL ampules of NaHCO₃⁻ (each containing 50 mmol of NaHCO₃⁻) be added to 1 L of 5% dextrose water and infused at a rate of 100 to 200 mL/h.

Lactic Acidosis

Lactate is a by-product of pyruvate, which is produced by lactate dehydrogenase (LDH). Either in hypoxia or during sepsis, lactic acid is preferentially produced. Lactic acid, like most substances with a pKa <4 (pKa 3.78), circulates almost entirely at physiologic pH as the freely dissociated anion, lactate (i.e., it releases its proton), strongly favoring the right side of the equation:



Hyperlactatemia refers to an elevated plasma concentration of lactate anions. In clinical practice, *lactic acidemia* is defined as a pH < 7.35, with a lactate concentration greater than 4 mmol/L. Lactic acidemia typically develops as a result of endogenously produced lactic acid, with lactate being measured as the dissociated base. During critical illness, the source of lactate is often believed to be ischemic tissues undergoing anaerobic metabolism, such as the gut and muscle. In addition to ischemia, the Warburg effect with dysregulated glycolysis is a major nonischemic cause of lactatemia.^{101,102} Furthermore, it should be noted that both the pH and AG are insensitive markers of an elevated lactate; patients with an elevated lactate may have a normal pH and AG.¹⁰³

D-Lactic Acidosis

Certain bacteria and viruses in the gastrointestinal tract may convert carbohydrates into organic acids or promote LDH activity.^{104,105} The two factors that make this possible are slow gastrointestinal transit (e.g., blind loops, obstruction) and a change of the normal flora (usually with antibiotic therapy).¹⁰⁶ The most prevalent organic acid is d-lactic acid. Since humans metabolize this isomer more slowly than l-lactate, and production rates can be very rapid, life-threatening acidosis can be produced.¹⁰⁷ The usual laboratory test for lactate is specific for the l-lactate isomer. Therefore, to confirm the diagnosis, plasma or urine d-lactate levels must be specifically requested. Urinary d-lactate is more easily tested.¹⁰⁸

Metabolic Alkalosis

Metabolic alkalosis is a common acid-base disturbance in ICU patients, characterized by an elevated serum pH (>7.45) secondary to plasma HCO_3^- retention. Metabolic alkalosis is usually the result of several therapeutic interventions in critically ill patients (Table 36-6). Nasogastric drainage, diuretic-induced intravascular volume depletion, hypokalemia, and use of corticosteroids are common causes of metabolic alkalosis in these patients. In addition, citrate in transfused blood is metabolized to HCO_3^- , which may compound the metabolic alkalosis. Overventilation in patients with type II respiratory failure may result in a posthypercapnic metabolic alkalosis. In many patients, the events that generated the metabolic alkalosis may not be present at the time of diagnosis.

Metabolic alkalosis may have adverse effects on cardiovascular, pulmonary, and metabolic function. It can decrease cardiac output, depress central ventilation, shift the oxyhemoglobin saturation curve to the left (thereby decreasing offloading of Hb-bound O_2), worsen hypokalemia and hypophosphatemia, and negatively affect the ability

to wean patients from mechanical ventilation. Increasing serum pH has been shown to correlate with ICU mortality. Correction of metabolic alkalosis has been shown to increase minute ventilation, PaO_2 , and mixed venous oxygen tension (SvO_2) and to decrease O_2 consumption. It is, therefore, important to correct metabolic alkalosis in all critically ill patients. In the case of cardiac arrest, it is also challenging to correct metabolic alkalosis in a rapid fashion.¹⁰⁹⁻¹¹¹

The first therapeutic maneuver in patients with a metabolic alkalosis is to replace any volume deficit with normal saline (0.9% NaCl) and correct electrolyte deficiencies. Aggressive potassium supplementation is warranted to achieve a serum $\text{K}^+ > 4.5$ mEq/L. If these interventions fail, ammonium chloride, hydrochloric acid, or arginine hydrochloride may be given.^{111,112} The disadvantage of these solutions is that they are difficult to use and require the administration of a large volume of hypotonic fluid. Extravasation of hydrochloric acid (even at 20-25 mmol/h) may result in severe tissue necrosis, which mandates that it be administered through a well-functioning central line. Acetazolamide is a carbonic anhydrase inhibitor promoting the renal excretion of HCO_3^- and has been demonstrated to be effective in treating metabolic alkalosis in ICU patients. A single dose of 500 mg is recommended. The onset of action is within 1.5 hours, with a duration of approximately 24 hours. Doses may be repeated.^{111,113-115}

VENOUS BLOOD GAS ANALYSIS

There is a strong correlation between arterial and venous blood pH and HCO_3^- levels in patients with DKA and uremia.^{114,115} In published studies, the difference between arterial and venous pH varied from 0.04 to 0.05, and the difference in bicarbonate levels varied from -1.72 to 1.88. However, the correlation between arterial and venous PCO_2 was relatively poor.¹¹⁶⁻¹¹⁸ Actually, this difference may be used to evaluate the adequacy of O_2 availability to the tissues (see below). Similarly, an excellent correlation has been demonstrated between mixed venous pH and HCO_3^- with arterial pH and HCO_3^- in critically ill patients.^{119,120} Yet, in shock states this does not hold true; the correlation between arterial and venous pH, HCO_3^- , and PCO_2 is poor.^{121,122} During cardiopulmonary resuscitation, for example, arterial blood pH was 7.41, while mixed venous blood pH was 7.15; the corresponding values for PCO_2 were 32 mm Hg and 74 mm Hg, respectively.^{123,124}

Once shock is resolved, ABG testing would not be necessary in patients without hypercarbia. Pulse oximetry and venous blood gas analysis would be enough to make clinical decisions. Furthermore, a venous blood gas can be useful to screen for arterial hypercarbia, as a venous $\text{PCO}_2 > 45$ mm Hg is highly predictive of arterial hypercarbia.¹²⁵

Mixed Venous/Central Venous Oxygen Saturation

Monitoring SvO_2 has been used as a surrogate for determining the balance between systemic O_2 delivery and consumption during the treatment of critically ill patients.¹²⁶ An $\text{SvO}_2 < 65\%$ is indicative of inadequate O_2 delivery. However, a mixed venous blood sample needs to be collected from the distal port of a pulmonary artery catheter, an invasive device that has not been shown to improve patient outcome. Therefore, most clinicians use as a surrogate the central venous oxygen saturation (ScvO_2).^{127,128}

There are multiple reasons why ScvO_2 and SvO_2 can differ. First of all, the vena caval blood streams into the right atrium and ventricle, and complete mixing only occurs during ventricular contraction. In addition, blood from the coronary sinus and Thebesian veins results in further discrepancies.^{129,130} Thus, SvO_2 is a better indicator of whole body balance of oxygen supply and demand, whereas ScvO_2 reflects changes in the upper body. In hemodynamically stable, healthy patients, ScvO_2 is usually 2% to 5% less than SvO_2 because of the high O_2 content of effluent venous blood from the kidneys.¹³¹ This changes during shock as blood is redistributed to the upper body at the expense of the splanchnic and renal circulations. In shock, ScvO_2 may exceed

TABLE 36-6 Causes of Metabolic Alkalosis

| LOW URINE CHLORIDE (VOLUME- OR SALINE- RESPONSIVE) | HIGH URINE CHLORIDE WITH HYPERTENSION |
|--|--|
| Gastric volume loss | Primary and secondary hyperaldosteronism |
| Diuretics | Apparent mineralocorticoid excess |
| Posthypercapnia | Liddle's syndrome (autosomal dominant, pseudoaldosteronism) |
| Villous adenoma (rare) | Conn's syndrome |
| Cystic fibrosis (if there has been excessive sweating) | Cushing disease |
| HIGH URINE CHLORIDE WITHOUT HYPERTENSION | |
| Bartter syndrome | |
| Gitelman syndrome (autosomal recessive hypokalemic metabolic alkalosis) | |
| Excessive bicarbonate administration | |

SvO₂ by up to 20%.¹³² This was also true for patients with cardiogenic, septic, and hemorrhagic shock.¹³³ Therefore, one has to assess these saturation values within the context of the clinical scenario.^{128,132,134-138} In patients with sepsis and liver failure, a low ScvO₂/SvO₂ is usually indicative of decreased cardiac output, and normal values do not necessarily exclude resuscitation or tissue oxygenation.¹³⁹⁻¹⁴¹ In liver failure, all pathologic collaterals may result in "arterialization" of the venous blood. In addition, cytopathic hypoxia may further decrease O₂ uptake and result in a "spuriously high" ScvO₂.¹⁴² Interestingly, patients dying of both sepsis and liver failure usually have a high ScvO₂/SvO₂.¹⁴³ In a recent goal-directed sepsis study, the mean ScvO₂ was 74% at enrollment, and less than 10% of patients required specific interventions to achieve values >70%.¹⁴⁴

In addition, a high mixed venous-to-arterial PCO₂ gradient is a predictor of decreased cardiac output and global tissue ischemia.¹⁴⁵⁻¹⁴⁷ This observation has been confirmed by Weil et al. and Androgué et al., who demonstrated that a high mixed venous-to-arterial PCO₂ gradient is a sensitive marker of global tissue ischemia during cardiogenic and septic shock.^{124,148-151} Recent work suggests that a central venous-to-arterial PCO₂ gradient >6 mm Hg is a reliable indicator of successful resuscitation in septic shock.¹⁵²

In summary, as a rule of thumb, venous blood gases cannot be substituted for ABG analysis in hemodynamically unstable patients and those with complex acid-base disorders. In these situations, both arterial and mixed venous/central venous blood gas analysis provides useful information.

KEY POINTS

1. Arterial blood gas (ABG) analysis is the gold standard for assessing oxygenation, ventilation, and acid-base status in critically ill patients, as long as it is obtained and interpreted within the clinical context.
2. Pulse oximetry can provide a surrogate measure of arterial oxygen tension (PaO₂). Venous pH and bicarbonate (HCO₃⁻) allow for an estimation of arterial pH and HCO₃⁻ in hemodynamically stable patients, yet one needs to be cautious during shock states. Venous carbon dioxide tension (PCO₂) is a poor proxy for arterial PCO₂. Venous blood gas analysis can be useful to screen for arterial hypercarbia, with a venous PCO₂ level > 45 mm Hg being highly predictive of arterial hypercarbia.
3. The indications for ABG sampling have not been well defined; however, an ABG should generally be performed on admission to the ICU, following endotracheal intubation, and as the clinical context changes.
4. ABG sampling does not have to be performed after each ventilator change or after each step during weaning from the ventilator.
5. Metabolic acidosis is serious; its etiology has to be determined and treatment initiated immediately.
6. In most clinical situations, sodium bicarbonate administration is of no therapeutic utility during metabolic acidosis.
7. In patients with a metabolic alkalosis, correct the volume and potassium deficit first, then initiate an acetazolamide and/or hydrogen chloride infusion.
8. Central venous oxygen saturation (S_{cv}O₂) and the central venous-to-arterial PCO₂ gap have utility in assessing the adequacy of resuscitation and oxygen delivery.

ANNOTATED REFERENCES

TRADITIONAL VS. NEW PERSPECTIVE ON ACID-BASE BALANCE

While the bedside clinician needs a handy tool to understand acid-base balance to help diagnose and manage patients appropriately, academic disagreements still exist regarding the topic of acid-base balance. In summary, the traditional approach suggests that the activity of H⁺ in a biological space is determined by the mass balance of H⁺, proton transfer reactions via proton donors (weak acids) and proton acceptors (weak bases), and the mass balance of proton donors and proton acceptors. (Arrhenius, Sorenson, Henderson, Hasselbalch, Bronsted and Lowry, Van Slyke, Lewis, Severinghaus, Astrup, Siggard-Andersen, Schwartz, and Relman).

In 1978, Stewart questioned the traditional dogma by proposing that a complex mixture of ions (Na⁺, K⁺, and Ca²⁺) regulate the activity of H⁺ over the physiologic pH range, nonvolatile proton donors and acceptors (albumin, phosphate, Hb, and metabolizable organic compounds) transfer H⁺ within the physiologic pH range, and the volatile bicarbonate-CO₂ buffer system is composed of CO₂, HCO₃⁻, H₂CO₃, and CO₃²⁻. The following are useful articles from the literature on the topic. Elbers PW, Van Regenmortel N, Gatz R. Over ten thousand cases and counting: acidbase.org is serving the critical care community. *Anaesthesiol Intensive Ther* 2015;47(5):441-448.

A new reference of a handy online web tool to help understand acid-base balance and a freely available textbook of Dr. Stewart. The web tool helps calculate the strong ion difference.

Kurtz I, Kraut J, Ornekian V, Nguyen MK. Acid-base analysis: a critique of the Stewart and bicarbonate-centered approaches. *Am J Physiol Renal Physiol* 2008;294(5):F1009-F1031.

The authors support the idea that the H⁺/HCO₃⁻ approach based on the Henderson-Hasselbalch equation is mechanistically more robust than the Stewart or strong ion approach. Accordingly, CO₂/HCO₃⁻ is useful in the hands of clinicians to help approach all acid-base derangements seen clinically; however, it is qualitative in nature and cannot quantify acid or base loads that result in metabolic acid-base disorders, despite the concomitant use of base excess information. These drawbacks led to the argument for a more quantitative measurement, the Stewart approach. However, both are "equilibrium equations" and have similar predictive value for clinical acid-base disorders, supporting the authors' opinion that their favorite approach is the Henderson-Hasselbalch equation.

OXYGEN TENSION: FROM A GLOBAL PERSPECTIVE TO A REGIONAL ASSESSMENT

The concept of partial pressure of oxygen measured in arterial blood gas analyses could be easily applied to oxygen tension measurements in regional perfusion. A recent work on brain tissue oxygen tension is relevant to the intensivist.

Rosenthal G, Hemphill JC 3rd, Sorani M, et al. Brain tissue oxygen tension is more indicative of oxygen diffusion than oxygen delivery and metabolism in patients with traumatic brain injury. *Crit Care Med* 2008;36(6):1917-1924.

The specific determinants of low brain tissue oxygen tension (P_{bt}O₂) following severe traumatic brain injury remain poorly defined; specifically, the question is whether P_{bt}O₂ reflects cerebral oxygen diffusion or cerebral oxygen delivery and metabolism. This group measured P_{bt}O₂ directly, as well as cerebral venous blood gases from a jugular bulb venous catheter. Following multiple logistic regression modeling, a strong association was detected between P_{bt}O₂ and diffusion of dissolved plasma oxygen across the blood-brain barrier, suggesting that P_{bt}O₂ reflects cerebral blood flow and the cerebral arteriovenous O₂ difference.

OTHER USES OF CO₂ MEASUREMENTS: EVIDENCE SUGGESTING THAT CO₂ COULD BE USED AS AN ENDPOINT FOR RESUSCITATION IN SEPSIS

Guzman JA, Dikin MS, Kruse JA. Lingual, splanchnic, and systemic hemodynamic and carbon dioxide tension changes during endotoxic shock and resuscitation. *J Appl Physiol* (1985) 2005;98(1):108-113.

The authors studied sublingual and intestinal mucosal blood flow and P_{co2} in a canine model of lipopolysaccharide-induced circulatory shock and resuscitation. Shock induced increased sublingual and splanchnic PCO₂, and the levels were nearly reversed after fluid resuscitation while systemic hypotension persisted. Changes in sublingual and splanchnic PCO₂ paralleled gastric and intestinal PCO₂ changes during shock but not during resuscitation. This and other work suggest the utility of PCO₂ in estimating tissue perfusion.

Mesquida J, Saludes P, Gruartmoner G, et al. Central venous-to-arterial carbon dioxide difference combined with arterial-to-venous oxygen content difference is associated with lactate evolution in the hemodynamic resuscitation process in early septic shock. *Critical Care* 2015;19:126.

Since normal or high central venous oxygen saturation (S_{cv}O₂) values cannot discriminate whether tissue perfusion is adequate, other markers of tissue hypoxia are required. The authors studied the ratio of central venous-to-arterial carbon dioxide difference (P_{cv}aCO₂ gap) to the arterial-venous oxygen content difference (C_{av}O₂) ratio to predict lactate evolution in septic shock. A high P_{cv}aCO₂/C_{av}O₂ ratio had a high predictive power for no improvement in lactate clearance. The receiver operating characteristic curve had an area under the curve of 0.82, and when the P_{cv}aCO₂/C_{av}O₂ ratio was set at 1.4 mm Hg · dL/mL O₂, it carried a sensitivity of 0.80 and specificity of 0.75 for lactate improvement. This ratio and PCO₂ could be used for predicting outcomes from sepsis.

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Tracheal intubation is a common, high-risk procedure. Risks associated with intubation in critically ill patients remain high and include prolonged hypoxemia, hemodynamic instability, cardiac arrest, and death. Over the past decade, significant improvements in patient safety have been reported for this procedure by employing skilled operators, a systematic approach to airway management, and advanced airway tools. The goal of this chapter is to provide a common, systematic approach using best evidence to maximize the success and safety of tracheal intubation in the intensive care unit (ICU).

AIRWAY MANAGEMENT CHALLENGES IN THE CRITICALLY ILL

Reported complication rates from tracheal intubation in the critically ill range from 4.2% to 22% and remain unacceptably high in comparison to operating room procedures.¹⁻⁵ Emergent ICU airway management cases leave little time to perform a thorough airway assessment and less time to plan when high-risk anatomic features are present. Cardiopulmonary disease makes preoxygenation more difficult, providing less apneic time during intubation before hypoxemia develops.⁶ Hemodynamic instability can limit the choice and dose of induction and paralytic agents that, combined with upper airway secretions, edema, and loss of muscle tone, can decrease glottic visualization. Other coexisting comorbidities, including obesity, increased intracranial pressure, and acute coronary syndrome can further complicate management of the critically ill during tracheal intubation.

TRAINING

Current airway management training is highly variable, even among anesthesia providers.⁷⁻¹⁰ A recent meta-analysis suggested that the level of training, as opposed to specialty, was the key factor for optimizing proper airway management.^{11,12} The appropriate volume and scope of airway training required, however, remains a topic in need of further research. Novices can obtain reasonable competence with direct laryngoscopy after 30 to 50 cases and may accelerate their skills using video-assisted instruction, but performance continues to improve even after 100 intubations.¹³⁻¹⁵ Box 37-1 provides a suggested list of airway management topics for training, but these recommendations are expert opinion only.¹⁶ The development of a vast array of advanced airway management devices has only complicated efforts to standardize training and approaches to ICU airway management. In a national survey of 180 American ICU and anesthesiology directors, only 70% had a difficult airway cart in their ICU, and 60% of the respondents reported that they had not been trained in the use of such equipment.¹⁷

INDICATIONS FOR TRACHEAL INTUBATION

Tracheal intubation is most commonly performed in critically ill patients with active or impending respiratory failure due to inadequate oxygenation and/or ventilation or for airway protection due to an inability to maintain a patent airway. Artificial airways can also facilitate secretion clearance and hyperventilation in the setting of an intracerebral herniation syndrome and can enhance the safe performance of procedures requiring conscious sedation in the setting of significant cardiopulmonary disease.

MAXIMIZING PATIENT SAFETY DURING TRACHEAL INTUBATION

The American Society of Anesthesiologists recommends that an airway assessment be performed before all intubations and emphasizes a systematic approach that maximizes oxygen delivery and considers an awake procedure, a variety of noninvasive techniques, and preservation of spontaneous ventilation.¹⁸ Other recent studies have also underlined the importance of a systematic approach to airway assessment, patient and equipment preparation, and procedure planning to maximize intubation success. Jaber et al. demonstrated that implementation of a protocolized ICU intubation bundle (Box 37-2) reduced complications by 25%.¹⁹ Improved patient safety and reduced need for emergent surgical airways have been achieved through implementation of a standardized, team-based approach that includes proactive identification of patients with known difficult airways, ready availability of advanced airway equipment, simulation-based airway skills and teamwork training, a mandatory bedside procedure checklist, and post-event debriefs.^{20,21} The APPROACH mnemonic (Box 37-3) is one structured checklist tool to ensure that these standardized interventions are consistently performed.²²

Airway Assessment

Common methods of airway assessment are limited in their ability to correctly identify difficult airways (positive predictive value, 4%-27%).^{23,24} The MACOCHA score, a seven-item validated prediction tool for the critically ill, is perhaps the most valuable tool for identifying high-risk patients.^{25,26}

Preoxygenation

Adequate preoxygenation is essential to maximize the time for intubation attempts. Use of a resuscitation bag, oral or nasal airway, positive end-expiratory pressure (PEEP) valve, high-flow nasal cannula system, or noninvasive positive pressure ventilation (NIPPV) can help improve and sustain patient oxygen saturation when standard bag-valve-mask ventilation proves challenging.^{27,28} Head of bed elevation may be particularly helpful to sustain apneic normoxia in patients with obesity, atelectasis, or reduced lung compliance, but apneic oxygenation using a nasal cannula during intubation was recently shown not to be beneficial.²⁹⁻³²

Preparation and Teamwork

The Fourth National Audit Project of the Royal College of Anaesthetists and Difficult Airway Society (NAP4) found that preparation, equipment, and communication errors were the most common causes of complications during airway management in ICUs and emergency departments in the United Kingdom.³³ These data underline the importance of deliberate planning and preparation to maximize patient safety and procedure success.

Patient positioning is especially important in ICU patients. Common methods include placing the patient in a supine position, moving them close to the head of the bed, and raising their head to or just below the level of the operator's xiphoid process. Provided there is no concern for neck injury, the patient's head is placed in a sniffing

BOX 37-1 Fundamental Airway Knowledge and Skills

Face mask ventilation, airway positioning
Laryngeal mask airway (LMA, including intubating devices)
Oral endotracheal intubation (direct laryngoscopy, DL)
Simple maneuvers (positioning, BURP*) to improve DL
Use of stylet, gum elastic bougie
Rapid sequence induction
Fiberoptic intubation via conduit (oropharyngeal airway, LMA)
Percutaneous cricothyrotomy

*BURP, Backwards, Upwards, and Rightwards Positioning.

From Goldmann K, Ferson DZ. Education and training in airway management. *Best Pract Res Clin Anaesthesiol* 2005;19(4):717–732.

BOX 37-2 ICU Intubation Bundle Used in a Large Multicenter Study to Improve Patient Outcomes

PREINTUBATION

1. Presence of two operators
2. Fluid loading (isotonic saline [500 mL] or hetastarch [250 mL]) in the absence of cardiogenic pulmonary edema
3. Preparation of long-term sedation
4. Preoxygenation for 3 min with NIPPV in case of acute respiratory failure (FiO_2 100%, pressure support ventilation level between 5 and 15 cm H_2O to obtain an expiratory tidal volume between 6 and 8 mL/kg and PEEP of 5 cm H_2O)

DURING INTUBATION

5. Rapid sequence induction: etomidate (0.2–0.3 mg/kg) or ketamine (1.5–3 mg/kg) combined with succinylcholine (1–1.5 mg/kg) in the absence of allergy, hyperkalemia, severe acidosis, acute or chronic neuromuscular disease, burn patients for more than 48 hours, and major crush injury
6. Sellick maneuver

POSTINTUBATION

7. Immediate confirmation of tube placement by capnography
8. Norepinephrine if diastolic blood pressure remains <35 mm Hg
9. Initiate long-term sedation
10. Initial “protective ventilation”: tidal volume 6–8 mL/kg of ideal body weight for a plateau pressure <30 cm H_2O

NIPPV, non-invasive positive pressure ventilation; PEEP, positive end expiratory pressure; FiO_2 , inspired oxygen fraction.

From Jaber S, Jung B, Corne P, Sebbane M, Muller L, Chanques G, et al. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Intensive Care Med* 2010;36:248–255.

position to align the oral, pharyngeal, and laryngeal axes for traditional direct laryngoscopy attempts. A rolled towel under the shoulders and a flat towel underneath the head can also help with alignment. Patients with known or suspected cervical injury should receive inline stabilization of the head and neck, which remain in a neutral position during intubation attempts.

Crew resource management principles important for an efficient airway management team include explicit role assignments, closed loop communication, and standardized equipment and medication preparation and positioning. Clear articulation of the primary and backup airway management plans and discrete oxygen cutoffs (which should prompt termination of intubation efforts and resumption of bag-valve-mask ventilation) provide shared situational awareness and guidance to maintain quality control and safety throughout the procedure. An empiric crystalloid bolus in the absence of decompensated heart failure and readily available vasopressors also reduce the risk of hypotension during intubation.¹⁹

Airway Pharmacology

Rapid sequence intubation is the standard of care in the emergency department due to its high rate of success.³⁴ Medication

BOX 37-3 The ACCP APPROACH to Airway Management

Assess the airway—it's all in your **HAND**

History of difficult intubation

Anatomic considerations

3-3-2 rule

Modified Mallampati Classification

Other risk factors for airway distortion, obstruction

Neck mobility

Difficult airway should be considered if concerns with any of the factors above

Preoxygenate using 100% oxygen, bag-valve-mask with PEEP valve

Prepare

Patient: Sniffing position, headboard off and patient head just below the intubator's xiphoid process

Medications: Free-flowing IV, premedication, induction, paralytic, and vasopressor agents

Right side: Suction, endotracheal tube with stylet and syringe attached

Left side: Laryngoscope handle, blades, oral and nasal airways, end-tidal CO_2 detector

Review team member roles, primary and backup intubation plans

Oxygen cutoffs: Identify signals to abort, reinstate bag-valve-mask ventilation

Administer medication, if indicated

Confirm endotracheal tube placement using two indicators (including end-tidal CO_2)

Hold endotracheal tube until secured

From American College of Chest Physicians Airway Management Program Curriculum, 2013.

BOX 37-4 Contraindications to Succinylcholine

History of malignant hyperthermia

Hyperkalemia

Upper, lower motor neuron lesions

Myopathy

Crush injury

Severe burns (>24 hours)

Prolonged immobility

administration in critically ill patients is more variable because of differences in provider comfort, hemodynamics, and concern for airway failure. Outside of a pulseless or unresponsive patient, however, selecting and preparing appropriate medications should be a routine part of intubation preparation and planning. Common agents, indications, and doses are summarized in [Table 37-1](#).³⁵ Drugs administered before induction are particularly useful in the setting of severe exacerbations of obstructive lung disease and significant intraocular or intracranial hypertension. Initial induction agent doses should be reduced by 25% to 50% in the elderly and in patients with hypotension, hypovolemia, or significantly impaired cardiac function. Propofol provides the best glottic visualization at full induction doses but causes significant hypotension. Etomidate has less associated hypotension and myocardial depression. It reduces adrenal steroidogenesis, but single doses do not appear to increase mortality even in septic patients.³⁶ Ketamine increases heart rate, blood pressure, and cardiac output and has been shown to provide similar intubating conditions and outcomes to etomidate in a large, prospective randomized trial.³⁷ Its use in the setting of increased intracranial pressure (ICP) is controversial.^{38,39}

The combination of an induction agent such as propofol with a paralytic has been shown to produce optimal intubating conditions.⁴⁰ The most commonly used agent is succinylcholine, a depolarizing muscle relaxant with a rapid onset of action and very short duration. In situations where succinylcholine may be considered unsafe ([Box 37-4](#)), rocuronium or atracurium will provide a similar onset of action but a much longer duration of paralysis. Use of rapid sequence intubation in the ICU remains controversial, but growing evidence suggests it is safe and effective when employed thoughtfully by an experienced operator.⁴¹

TABLE 37-1 Common Medications Used During Tracheal Intubation

| PREINDUCTION MEDICATIONS | | | | |
|--------------------------|--|--|---------------|---|
| DRUG | DOSE, COMMON INDICATIONS | CAUTIONS | | |
| Fentanyl | 2-3 micrograms/kg IV, 1-2 mins CAD, aneurysm, increased ICP | Hypotension Masseter, chest wall rigidity | | |
| Esmolol | 2-3 mg/kg IV Neurosurgery, head injury | Bradycardia Hypotension, bronchospasm | | |
| Lidocaine | 1.5 mg/kg IV, 2-3 min Asthma, COPD, increased ICP | Hypotension | | |
| INDUCTION MEDICATIONS | | | | |
| AGENT | ONSET (SECONDS) | DURATION (MINUTES) | DOSE | |
| Propofol | 9-50 | 3-10 | 0.5-2 mg/kg | |
| Etomidate | 30-60 | 3-5 | 0.2-0.3 mg/kg | |
| Ketamine | 60-120 | 5-15 | 2 mg/kg | |
| NEUROMUSCULAR BLOCKERS | | | | |
| AGENT | ONSET (SECONDS) | DURATION (MINUTES) | DOSE | OFF-LABEL DOSING |
| Succinylcholine | 30-60 | 5-15 | 1.0-1.5 mg/kg | Manufacturer's recommendation 0.6 mg/kg |
| Rocuronium | 45-60 | 45-70 | 0.6-1.2 mg/kg | |
| Atracurium | 60-90 | 35-70 | 0.4-0.5 mg/kg | |

From Reynolds SF, Heffner J. Airway management of the critically ill patient. *Chest* 2005;127:1397-1412.

■ INTUBATION TECHNIQUES

Recent years have seen the development of a wide array of commercially available airway equipment, with mixed availability and familiarity in many ICUs.¹⁷ Most experts recommend the selection of a limited list of airway tools most appropriate for a given ICU population to facilitate familiarity and training.

Direct Laryngoscopy

Current Macintosh and Miller blades are designed for rapid endotracheal tube placement. The Macintosh blade is broad and curved and includes a flange to displace the tongue to the left when the blade is introduced into the mouth from the right side (paraglossal approach). The blade is advanced toward midline, and the tip is directed into the vallecula once the epiglottis comes into view. Gentle blade traction will lift the epiglottis and expose the glottic aperture. The Miller blade is longer and straight with a slightly curved tip. It can be inserted using either a paraglossal or midline approach, and the distal end is used to directly lift the tip of the epiglottis. Care must be taken with both blades to apply caudal and anterior force, holding the laryngoscope handle near its base and keeping its angle less than 45 degrees to the patient to avoid dental damage. Blade sizes 3 or 4 are most appropriate for adult procedures. The broader surface of the Macintosh blade may provide better upward displacement of excess upper airway soft tissue, and the longer and narrower profile of the Miller blade may assist in the setting of narrow mouth opening or a long epiglottis. A stylet is generally used to help guide the ETT through the vocal cords and can be shaped with a distal bend to aid in tracheal placement.

Indirect Laryngoscopy Devices

Indirect laryngoscopy devices provide video or optical imaging using mirrors and prisms to improve glottic visualization in individuals in whom alignment of the airway axes is difficult. Some devices incorporate an acutely angulated blade (i.e., Glidescope, McGrath, C-Mac), while others incorporate a channel (i.e., AirTraQ, Pentax) to facilitate endotracheal tube placement through a more anterior glottis with the head in a neutral position.⁴²

Current literature suggests that indirect laryngoscopy offers little advantage in the average patient but affords high rates of intubation success in patients with difficult airway risk factors, obesity, or failed direct laryngoscopy attempts.⁴³⁻⁴⁷ This advantage does not appear to be uniform; the Airtraq optical laryngoscope, for example, has performed less favorably in difficult airways in the prehospital setting.⁴⁸ Videolaryngoscopy can also accelerate training performance with novices and provides a high rate of first-time success in the hands of less experienced intubators.⁴⁹⁻⁵¹ Each device has unique technical considerations that operators must be familiar with to maximize their potential benefit.

■ THE DIFFICULT AIRWAY

The definition of a difficult airway is the presence of clinical factors that complicate ventilation or intubation.¹⁸ The incidence of difficult airways encountered during emergent intubations is reported to be 10%.^{2,3}

The best management approach to a difficult airway in the ICU is not well studied. Until the many complex variables present in ICU airway management can be more systematically analyzed, the following suggestions represent the consensus opinion of one group of experts based on available data.⁵²

Emergency Airway Management: Extraglottic Airways and Cricothyroidotomy

Prolonged hypoxemia is the primary cause of most serious airway complications. If aggressive initial attempts to restore adequate oxygenation are not successful, early emergency airway management should be accomplished using either an extraglottic airway or cricothyroidotomy.

Extraglottic airways (EGAs, such as the Laryngeal Mask Airway and King tube) can be placed into the upper airway to reestablish adequate oxygenation and ventilation without significant technical expertise in many cases. Intubation through EGAs has proven successful following failed direct laryngoscopy and as a more rapid primary approach in patients with a predicted difficult airway.^{53,54} A number of current EGAs also provide the option of one-step intubation through

the device (Ambu Aura-i, CookGas LLC Air-Q/ILA, LMA Fastrach, and Classic Excel, i-Gel).

Surgical cricothyroidotomy is reserved for the emergency airway situation when an extraglottic airway cannot be effectively employed due to upper airway abnormalities, blood, or secretions that obviate proper placement and function. Cricothyroidotomy can be performed most rapidly using a rapid four-step technique.⁵⁵ Using a bougie through the neck incision to serve as an ETT guide has been shown to be successful even in the hands of the novice nonsurgeon.⁵⁶ A cricothyroidotomy kit that uses a Seldinger approach is also available but has been associated with longer time to placement.⁵⁷ Major complications include esophageal perforation, subcutaneous emphysema, and bleeding.

The Role of Advanced Airway Tools in Difficult Airway Management

If initial stabilization and oxygenation is possible, a rapid clinical airway assessment is essential to plan an appropriate and effective management strategy. Cooperative patients with slowly progressive respiratory failure and predicted difficult airways can be considered for awake intubation. More unstable or uncooperative patients can be managed with indirect laryngoscopy, gum elastic bougie, or an extraglottic airway.

Awake intubation provides the opportunity to preserve spontaneous respiration and prolong the available time for intubation attempts. Upright fiberoptic-assisted intubation through a Williams or Ovassapian intubating airway is a common and effective approach. Patients typically require a combination of nebulized or atomized lidocaine directed at the base of tongue and tonsillar pillars. Antisialagogues are frequently employed to aid visualization, and low-dose narcotics such as remifentanyl appear to be superior to dexmedetomidine when combined with low-dose midazolam for sedation.⁵⁸ Unfortunately, the 20-30 minutes required for appropriate airway preparation can be challenging in critical care practice, limiting broad-based application of this technique.

In the setting of a predicted difficult airway, indirect optical devices and videolaryngoscopes provide better glottic visualization and

maximize the opportunity of intubation success. In one large single institution study, a gum elastic bougie was the preferred method to successfully manage patients with incomplete glottic visualization and those for whom glottis intubation is not possible.² An intubating extraglottic airway is also an appropriate primary or rescue strategy.

CONCLUSION

Tracheal intubation in the ICU remains a high-risk procedure, and a systematic approach that emphasizes planning, preparation, and teamwork is necessary to maximize its outcome and safety. Although intensivists should maintain facility with direct laryngoscopy, there are growing data supporting the use of indirect laryngoscopy as both a primary and rescue technique in the ICU. In the setting of an emergency airway, an extraglottic airway or surgical airway should be rapidly employed. If oxygenation and ventilation can be reestablished, a wider variety of techniques can be considered. Until better evidence is available, ICU directors must apply these general principles to develop a safe and effective airway management program in their institution.

DISCLAIMER

The views expressed in this review are those of the author and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. government.

KEY POINTS

1. A systematic approach that emphasizes planning, preparation, and teamwork is the best proven method to reduce risks associated with airway management in the ICU.
2. An extraglottic airway should be employed early in the patient with inadequate oxygenation and ventilation.

■ References for this chapter can be found at expertconsult.com.

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Tracheotomy, one of the most commonly performed procedures in critical care, involves the surgical creation of an external opening in the tracheal wall to establish a stable airway. Usually, the stoma tract is kept open by inserting a tracheostomy tube with or without a cannula. The size and type of the cannula will depend on the context of the neurologic and respiratory impairment.

Opinions differ on whether the right term for the procedure is *tracheotomy* or *tracheostomy*; *tracheostomy* will be used here and is more common in the current literature and clinical practice.

Both surgical tracheostomy and percutaneous dilational tracheostomy (PDT) are performed in critical care patients with an upper airway obstruction or prolonged endotracheal intubation to facilitate airway management during long-term ventilation, enhance patient comfort (communication and airway clearance), enhance airway security, and reduce respiratory resistance (for faster weaning from mechanical ventilation).

■ INDICATIONS

Airway access for the treatment of an upper airway obstruction or mechanical ventilation can be obtained by either orotracheal intubation (OTI) or placement of a tracheostomy tube. During ventilation in general anesthesia or episodes of acute respiratory failure, patients are usually ventilated through an orotracheal tube, which can be easily and rapidly inserted into an initial airway device. Use of OTI minimizes acute surgical complications (e.g., bleeding, nerve and posterior tracheal wall injury) and late complications (e.g., wound infection and tracheal lumen stenosis) that may develop after the tracheostomy tube placement.

The introduction of the PDT by Ciaglia in 1985 as an alternative to a surgical tracheostomy attracted interest regarding its indications.¹ Initially, PDT was reserved for patients with few risk factors and favorable neck anatomy. However, with wider use, the indications expanded and PDT largely replaced surgical procedures. During the past decade, the use of PDT has increased, as has the use of tracheostomy for prolonged ventilation or treating upper airway obstruction secondary to trauma or surgery of the face and neck region.²

Recent studies have evaluated the effects of tracheostomy on long-term outcome. Frutos-Vivar et al. showed that tracheostomy was independently related to survival in the intensive care unit.³ Even if hospital mortality was similar between patients with and without a tracheostomy, there were significant differences in where the patients were discharged from the hospital. At home, mortality doubled for patients who required tracheostomy.

Moreover, many patients with tracheostomy require long-term care facilities. Therefore, because of its invasiveness and procedural risks, tracheostomy should be considered only when prolonged mechanical ventilation is expected.

■ ADVANTAGES OF TRACHEOSTOMY

European surveys investigating the use of tracheostomy in critically ill patients reveal the heterogeneity regarding techniques, timing, operator experience, and setting.⁴ Tracheostomy offers many clinical benefits for patients with respiratory failure or those requiring prolonged mechanical ventilation or airway protection because of neurologic

dysfunction. As compared with OTI, the safe anchorage provided by the tracheostomy tube reduces the risk of dislocation and potential accidental extubation, which could turn into an emergency in ventilated patients. Moreover, since the internal cannula is not affected by head and neck movement, the occurrence of lesions due to tracheal mucosal abrasion and laryngeal damage is low.

Besides allowing for easier draining of airway secretions and facilitating pulmonary toilet and oral hygiene, tracheostomy improves patient comfort by facilitating communication with family members and nurses and by reducing salivary stagnation in the larynx and pain during swallowing. Patients can be mobilized earlier and easier, with a faster return to oral feeding, shorter residence time of the nasogastric tube,^{5,6} and reduced risk of tracheoesophageal fistula formation.

Use of a tracheostomy tube can aid in weaning from mechanical ventilation, since the direct approach to the trachea (with an internal diameter greater than for the translaryngeal approach) and the minor length and absence of multiple curves all reduce airflow resistance. Moreover, it also allows for faster resumption of autonomous respiration, with reduced use of sedative agents, fewer days on the mechanical ventilator, shorter length of stay in the intensive care unit (ICU), and reduced use of resources.^{3,7,8} Although PDT continues to gain acceptance as the method of choice, no single technique has been shown to be superior to another in all clinical situations. Furthermore, PDT has a steep learning curve and requires mastery of procedural skills and extensive expertise.

■ COMPLICATIONS

Complications arising from tracheostomy maneuvers based on the time between the procedure and the onset of symptoms can be classified as intraoperative and postoperative (early and late complications, respectively). The frequency and severity of complications depend on tracheostomy technique, operator experience, patient anatomy, and pathophysiologic factors related to the degree of organ dysfunction, especially respiratory and coagulation deficits.

Procedure-related complications include desaturation and difficult cannula placement due to acute tracheostomy tube occlusion (generally because of the formation of a blood clot or mucous plug) or tube insertion into the wrong tract. Other early complications include hemorrhage, with bleeding controlled by local pressure or requiring exploration (with the conversion from PDT to another dilational technique or surgery in some cases) or desaturation due to subcutaneous emphysema with or without evidence of pneumothorax. Patients with severe bleeding should undergo a bronchoscopy for suspected tracheoesophageal fistula, but this complication is normally characteristic of late complications.

Common adverse events in the postoperative period or later include slight bleeding, controlled by local pressure, accidental cannula removal and the displacement (dislodged tracheal tubes within 7 days of insertion should be replaced with a tube the same size or smaller), and airway obstruction due to granuloma formation or infection or inflammation of the stoma.

Numerous uncontrolled case series have reported PDT complications, but there are few prospective comparative studies of complications associated with PDT and surgical tracheostomy or among different PDT methods. A meta-analysis by Freeman et al. found that

as compared with surgical tracheostomy, Ciaglia's and Grigg's techniques were associated with lower rates of stomal bleeding, infection, and postoperative complications.⁹ In a randomized trial with a double-blind follow-up comparing the outcomes and the short- and long-term complications of percutaneous translaryngeal tracheostomy (TLT) versus surgical tracheostomy, Antonelli et al. demonstrated lower bleeding rates with TLT, no evidence that TLT increases the risk of bacteremia caused by the spread of upper respiratory tract microbes, and similar long-term effects (physical and emotional) between the two procedures.¹⁰

SURGICAL TRACHEOSTOMY VERSUS PDT

Tracheostomy techniques are evolving and improving. Various PDT devices have been developed to minimize risk and simplify the procedure. Operator experience and the degree of patient complexity can influence the choice of technique in each case. Two basic tracheostomy methods are available: PDT and surgical tracheostomy. The choice of whether to use one or the other in a particular situation depends on available resources, operator experience, and patient factors.

SURGICAL TRACHEOSTOMY

Surgical tracheostomy is usually performed at the bedside in the ICU. Though more difficult because of suboptimal conditions of lighting, suction, sterility, and cautery, bedside tracheostomy avoids the need to transport the patient to the operating room, making it ideal for selected critically ill patients. In addition, it may be performed in the operating room prior to the neck or head surgery. Although PDT has become the procedure of choice in patients undergoing an elective tracheostomy, surgical tracheostomy remains the method of choice in selected critically ill patients with distorted neck anatomy, a history of prior neck surgery, history of cervical irradiation, recent maxillofacial or neck trauma, morbid obesity, a difficult airway, or marked coagulopathy.

The proportion of patients receiving a PDT or surgical tracheostomy varies across different practice settings. A surgical tracheostomy is largely performed in ICUs managed by surgeons, and PDT is preferred in ICUs managed by intensivists, while both techniques are adopted in medical and surgical ICUs.¹¹⁻¹⁶

PDT

Since the technique was first described by Ciaglia (using a guide wire),¹ new methods have been developed by combining the percutaneous nephrostomy multiple-dilator procedure and a variant of vascular access described by Seldinger in 1953. In 1990, Griggs described the guide wire dilator forceps technique (GWDF) (Portex Limited, Hythe, Kent, UK), an improvement on the Rapitrach method in which the forceps was inserted along the guide wire and opened to the size of the skin incision to dilate the trachea¹⁷ (Fig. 38-1). Ciaglia's initial serial multiple dilator technique (MDT) was revised in 1999 for use with a single tapered dilator (SSDT) with a hydrophilic coating. This permits, in a single step, the complete dilatation of pretracheal tissues known as the Blue Rhino technique (Cook Critical Care, Bloomington, IN, USA).¹⁸ In 1997, Fantoni described the translaryngeal method (TLT) (Mallinckrodt, Mirandola, Italy), which does not require the external compression of the tracheal tissues, in which the dilator is passed from the inner to the outer tracheal wall.¹⁹ In 2005, a screw-like device was designed to open the tracheal stoma (rotational dilation technique), which is useful in cases in which the view of the tracheal lumen is lost during bronchoscopy and minimizes the risk of posterior tracheal wall injury (PercTwist method, Rüschi GmbH, Kernen, Germany).²⁰

The Ciaglia Blue Dolphin system (balloon dilatational tracheostomy method) was introduced in 2008. It represents the latest technique derived from the Fogarty balloon embolectomy catheter used in



FIGURE 38-1 ■ Guide wire dilator forceps technique (Portex Limited, Hythe, Kent, UK). The operator shows the surgical forceps.



FIGURE 38-2 ■ Ultrasound in preoperative neck evaluation before performing a PDT or surgical tracheostomy.

vascular surgery. This device primarily generates a radial force to widen the tracheostoma in a single-step dilatation, minimizing bleeding and tracheal ring injury, while achieving good cosmetic results following decannulation.²¹

The success of PDT rests on the expertise of ICU specialists or surgeons in ICU settings (mixed medical and surgical, only medical or surgical). Moreover, the availability of different techniques should enable physicians to optimize the procedure in particularly challenging clinical scenarios, such as obesity, neurotrauma or vascular abnormalities with a high risk of bleeding, ultimately minimizing complications and allowing physicians to choose the method with which they feel most comfortable (Fig. 38-2).

A systematic review and meta-analysis of PDT in critically ill patients recently investigated the advantages of PDT versus surgical tracheostomy in relation to major and minor intraprocedural complications.²² The review included 13 randomized clinical trials (RCTs) published in the past 10 years on tracheostomy in medical, neurologic, or surgical ICU settings. The results demonstrated the equivalence of all techniques regarding the incidence of side effects and the rate of procedure success. The exception was TLT, which was associated with

more severe complications and the more frequent need for a conversion to a different tracheostomy technique.

TIMING OF TRACHEOSTOMY

Older guidelines recommended tracheostomy after 3 weeks of endotracheal intubation only if the extubation did not occur by 21 days.²³ However, defining and predicting the need for prolonged mechanical ventilation continues to pose a major methodologic challenge. With the exception of emergency procedures, the timing for performing a tracheostomy in patients requiring prolonged mechanical ventilation is controversial. However, the real issue behind the debate is how to measure the effectiveness of early tracheostomy and its effects on outcome.

A meta-analysis published in 2005 reported that early tracheostomy shortened the duration of mechanical ventilation and the length of ICU stay.²⁴ In their study involving 1044 patients, Fei Wang et al. suggested that tracheostomy timing did not significantly alter major clinical outcomes in critically ill patients.²⁵ Italian and French RCTs, published by Terragni and Trouillet, respectively, evaluated the benefits and risks of tracheostomy and the ability to identify early patients requiring prolonged mechanical ventilation.^{26,27} Both trials enrolled candidates for tracheostomy. In the first study, respiratory function was improved in a significant number of patients (43.3%) randomized to the late tracheostomy group so that tracheostomy was no longer necessary. Likewise, in the French study, only 27% of patients in the prolonged mechanical ventilation group underwent a late tracheostomy.

The TracMan U.K. randomized trial analyzed survival in early versus late tracheostomy and confirmed the results of the previous trials.²⁸ In the early group, 91.9% of the patients enrolled received a tracheostomy, whereas only 44.9% in the late tracheostomy group underwent a tracheostomy. No significant differences in mortality or other major secondary outcomes between the two groups were found.

Consequently, these results should convince clinicians that routine early tracheostomy does not necessarily reduce the incidence of ventilator-associated pneumonia (VAP), shorten hospital stay, or lower mortality. In general, a tracheostomy should not be performed earlier than 13 to 15 days of OTI.²⁹

Selected patients with neurologic injury can benefit from prolonged intubation because of their limited ability to clear secretions. Prolonged intubation in traumatic brain injury, however, is associated with a high incidence of pneumonia. Conversely, early tracheostomy after trauma reduces the length of ICU stay, days on mechanical ventilation, and incidence of VAP. In patients with infratentorial lesions, Qureshi et al. suggested performing early tracheostomy in patients with acute brain injury because of the low rate of successful extubation in this population.³⁰⁻³³ Although early tracheostomy in selected neurologic patients may reduce the length of ICU stay and pulmonary morbidity, the first 7-10 days after acute brain injury coincide with the highest incidence of intracranial hypertension. Therefore, the appropriate timing of tracheostomy in those patients must be related to the risk of severe intracranial hypertension.³⁴

TRACHEOSTOMY AND SAFETY

Adult tracheostomy can be performed in the operating room or at the bedside in the ICU. To improve PDT safety in different scenarios, suggested procedures to confirm tracheal puncture include a) ultrasound (US) for preoperative evaluation of the neck or during the intraoperative stage for monitoring needle progression through the trachea and b) bronchoscopy surveillance during the procedure, which is increasingly performed by intensivists in critical care. In our experience, PDT is a safe and easy procedure to perform at the bedside even in difficult situations by skilled intensivists with full technical support to minimize complications. For selected patients (e.g., those with distorted neck anatomy or history of prior neck surgery), a surgeon skilled in

the conventional open technique should be readily available even if the team is well trained in PDT.³⁵

BRONCHOSCOPY

Safety during the PDT procedure can be enhanced with bronchoscopy guidance to minimize complications. Several authors have recommended the use of bronchoscopy during PDT because it provides a direct visualization of the airway during tracheostomy tube placement. However, there is no clear consensus in the literature about its use. A recent study comparing the safety and efficacy of PDT procedures with or without bronchoscopy control found no difference in the time of tracheostomy, survival, ventilator-free days, length of ICU stay, or overall hospital stay between the two groups of trauma patients.³⁶ Differences in complications were not statistically significant, but there was a significant conversion rate to surgical tracheostomy among the patients who underwent PDT without bronchoscopy guidance.

Intraoperative endoscopic control has been shown to reduce complications associated with tracheostomy. Bronchoscopy guidance can improve the safety and efficiency by monitoring the placement of the tracheal puncture, the dilational procedure (preventing damage to the posterior tracheal wall and visualizing progression through the interannular membrane without breaking the tracheal rings), insertion of the tracheal cannula, and postprocedure control to detect intratracheal lesions and confirm the correct endotracheal placement³⁷ (Fig. 38-3).



FIGURE 38-3 ■ At the end of a PDT procedure, the cannula position inside the trachea is verified with a bronchoscope.

US AND PDT

In selected cases, however, even with fiber optic endoscopic control, a tracheostomy can result in serious complications due to the puncturing of venous or arterial vessels in patients with aberrant vascular anatomy. Patton et al. reviewed the incidence and sequelae of bleeding events as a complication of PDT.³⁸ They found that variations in venous (inferior thyroid vein) and arterial anatomy (thyroidea ima artery) led to serious bleeding events that required investigation with diagnostic US and/or radiologic examination before proceeding with PDT.

The presence of an abnormal branch of the innominate artery passing in front of the trachea near the area of a tracheostomy procedure can be detected by clinical evaluation (pulsatile swelling at the base of the neck), but an additional US evaluation could be useful to confirm the complexity of the tracheostomy procedure and may warrant switching to a surgical approach in some cases⁴ (Fig. 38-4).

US alone cannot replace bronchoscopy. Nonetheless, it may help to identify potential bleeding complications when evaluating the anterior neck region. In a recent study, Rajajee et al. reported on a US-guided PDT in a group of acute brain injury patients with morbid obesity or needing cervical spine precautions. US-guided PDT was successful in all cases.³⁹

Although US guidance is potentially promising, no RCTs have compared the safety or efficacy of preprocedural and real-time intraoperative US-guided PDT versus the current standard of care. Observational data suggest the use of US before tracheostomy to prevent vascular complications, but prospective RCTs are needed to evaluate its safety and efficacy in comparison with the traditional landmark-guided technique.⁴⁰

TRACHEO TRAINING

PDT has a steep learning curve.⁴¹ Training in PDT is usually performed on medical manikins or animal models owing to ethical and economic concerns.⁴²⁻⁴⁴ The pig model may provide a more realistic approach.⁴⁵ An Italian group tested the efficacy of the porcine model in developing the skills residents require for successful PDT. The model consisted of a larynx and trachea free from perilaryngeal and peritracheal tissues.⁴⁶ The resulting tissue block was then placed on a backing with an overlapping of sponge and plastic wrapping (simulating the skin) before being inserted into the manikin's neck.

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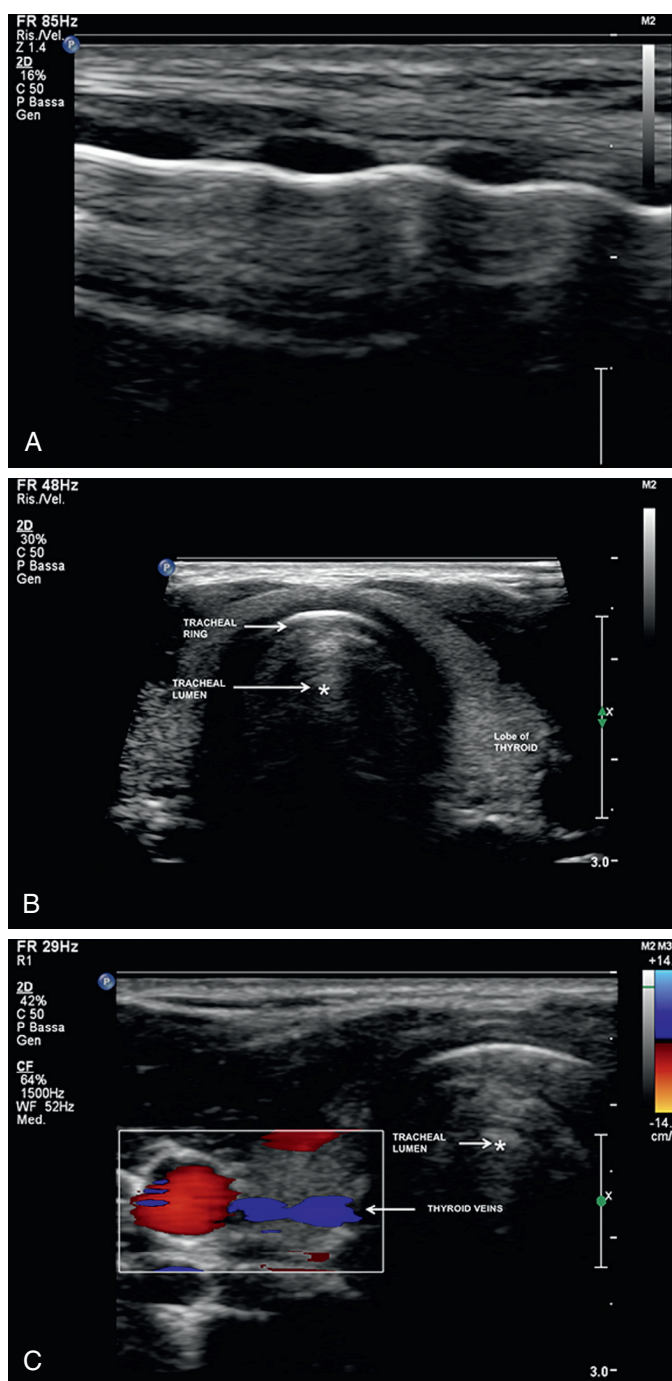


FIGURE 38-4 ■ Use of ultrasound to evaluate the anterior neck region may be a valid and economic support to improve preoperative assessment and identify potential bleeding complications during the procedure. **(A)** The sagittal ultrasound image is showing the upper four tracheal rings. **(B)** Transverse ultrasound image showing the anterior tracheal wall, tracheal lumen shadow, and thyroid gland. **(C)** Axial image of the trachea and surrounding structures with depiction of vascular structures (thyroid veins).

KEY POINTS

1. Surveys of tracheostomy use show wide heterogeneity in PDTs, timing, operator experience, and settings.
2. PDT continues to gain acceptance as the method of choice though no single technique has been shown to be superior to another.
3. PDT is not without complications as it has a steep learning curve and requires mastery of procedural skills and extensive expertise.
4. PDT has become the procedure of choice in patients undergoing elective tracheostomy. However, surgical tracheostomy remains the method of choice in selected critically ill patients presenting distorted neck anatomy, prior neck surgery, cervical irradiation, maxillofacial or neck trauma, morbid obesity, difficult airways, or marked coagulopathy.
5. The optimal timing of tracheostomy in patients requiring prolonged mechanical ventilation remains controversial. RCTs provide convincing evidence that a routine early tracheotomy may not necessarily improve the outcome but suggest that performing a tracheotomy when weaning fails must be tempered by the knowledge that many patients could improve with more time.

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Positive pressure mechanical ventilatory support provides pressure and flow to the airways to effect oxygen (O_2) and carbon dioxide (CO_2) transport between the environment and the pulmonary capillary bed. The overall clinical goal of mechanical ventilation is to maintain appropriate levels of O_2 and CO_2 content in the arterial blood while unloading the ventilatory muscles. An equally important goal is to provide this support without harming the lungs. Positive pressure mechanical ventilation can be applied through either an artificial airway or a tight-fitting mask (noninvasive ventilation, discussed in detail in Chapter 62).

DESIGN FEATURES OF MODERN MECHANICAL VENTILATORS

Most modern ventilators use high-pressure gas sources to drive gas flow.¹ Tidal breaths are generated by this gas flow and can be classified regarding what initiates the breath (trigger variable), what controls gas delivery during the breath (target or limit variable), and what terminates the breath (cycle variable).² In general, breaths can be initiated (triggered) by patient effort (assisted breaths) or by the machine timer (controlled breaths). Target or limit variables are either a set flow or a set inspiratory pressure. With flow targeting, the ventilator adjusts the pressure to maintain a clinician-determined flow pattern. In contrast, for pressure targeting, the ventilator adjusts flow to maintain a clinician-determined inspiratory pressure. Cycle variables are a set volume, flow, or a set inspiratory time. Breathes can also be cycled if the pressure limits are exceeded. Using this approach, breath delivery algorithms from modern mechanical ventilators can be broken into five basic breaths based upon trigger, target, and cycle criteria: (1) volume control (VC); (2) volume assist (VA); (3) pressure control (PC); (4) pressure assist (PA); and (5) pressure support (PS)² (Fig. 39-1).

The availability and delivery logic of the different breath types define the mode of mechanical ventilatory support.² The mode controller is an electronic, pneumatic, or microprocessor-based system designed to provide the proper combination of breaths according to set algorithms and feedback data (conditional variables). The five most common modes are volume assist-control (VACV), pressure assist-control (PACV), volume synchronized intermittent mandatory ventilation (V-SIMV), pressure intermittent mandatory ventilation (P-SIMV), and stand-alone pressure support ventilation (PSV).

Novel ventilator designs incorporate advanced monitoring and feedback functions into these controllers to allow continuous adjustments in mode algorithms as the patient's condition changes.³ The most common of these new feedback designs is the addition of a volume target feedback feature to PACV or PSV, termed the *pressure-regulated volume control* (PRVC) and *volume support* (VS), respectively. This feature adjusts the inspiratory pressure level to achieve the volume target. Feedback mechanisms of pressure-targeted breaths can also incorporate inputs (e.g., end tidal CO_2 , minute ventilation, or respiratory rate) in addition to tidal volume to adjust the inspiratory pressure (e.g., the proprietary "SmartCare" system).⁴

ADVERSE EFFECTS OF POSITIVE PRESSURE MECHANICAL VENTILATION

Ventilator-Induced Lung Injury

The lung can be injured when it is stretched excessively by positive pressure ventilation. The most well-recognized injury is an alveolar rupture, presenting as extraalveolar air in the mediastinum (pneumomediastinum), pericardium (pneumopericardium), subcutaneous tissue (subcutaneous emphysema), pleura (pneumothorax), and vasculature (air emboli).⁵ The risk of extraalveolar air increases as a function of the magnitude and duration of alveolar overdistention. Thus, interactions of the respiratory system mechanics and mechanical ventilation strategies (e.g., high regional tidal volume and PEEP; both applied and intrinsic) that produce regions of excessive alveolar stretch (i.e., transpulmonary distending pressures more than 40 cm H_2O) for prolonged periods, create alveolar units that are at risk for rupture.

Parenchymal lung injury not associated with extraalveolar air and can also be produced by mechanical ventilation strategies that stretch the lungs beyond the normal maximum capacity (i.e., "volutrauma" associated with transpulmonary distending pressures >30 cm H_2O).⁶⁻¹⁰ Pathologically, this manifests as diffuse alveolar damage and is associated with cytokine release¹¹ and bacterial translocation.¹²

In addition to being caused by simple overstretching of the lung, ventilator-induced lung injury (VILI) may have other determinants. Among these may be excessive tidal stretch (i.e., repetitive cycling of the lungs with tidal volumes larger than the normal 4 to 8-mL/kg ideal body weight)¹³ and a shear stress phenomenon that occurs when injured alveoli are repetitively opened and collapsed during the ventilatory cycle.^{9,14-16} Moreover, VILI may be worsened by increasing the frequency of excessive lung tidal stretching and from acceleration forces associated with rapid initial gas flow into the lung.¹⁷

VILI occurs clinically when low-resistance/high-compliance units receive a disproportionately high regional tidal volume in the setting of high alveolar distending pressures (see Fig. 39-2). Concerns regarding overdistention injury is the rationale for using "lung-protective" ventilator strategies that accept less than normal values for pH and O_2 partial pressure in exchange for lower (and safer) distending pressures and volumes.

Cardiac Effects

In addition to affecting ventilation and ventilation distribution, intrathoracic pressure changes resulting from positive-pressure ventilation can affect cardiovascular function.^{18,19} In general, as the mean intrathoracic pressure is increased, the right ventricular filling is decreased. This is the rationale for using volume repletion to maintain cardiac output in the setting of high intrathoracic pressure. In addition, high intrathoracic pressures can increase the right ventricular afterload, further compromising cardiac output. Conversely, elevations in intrathoracic pressure can improve left ventricular function because of an

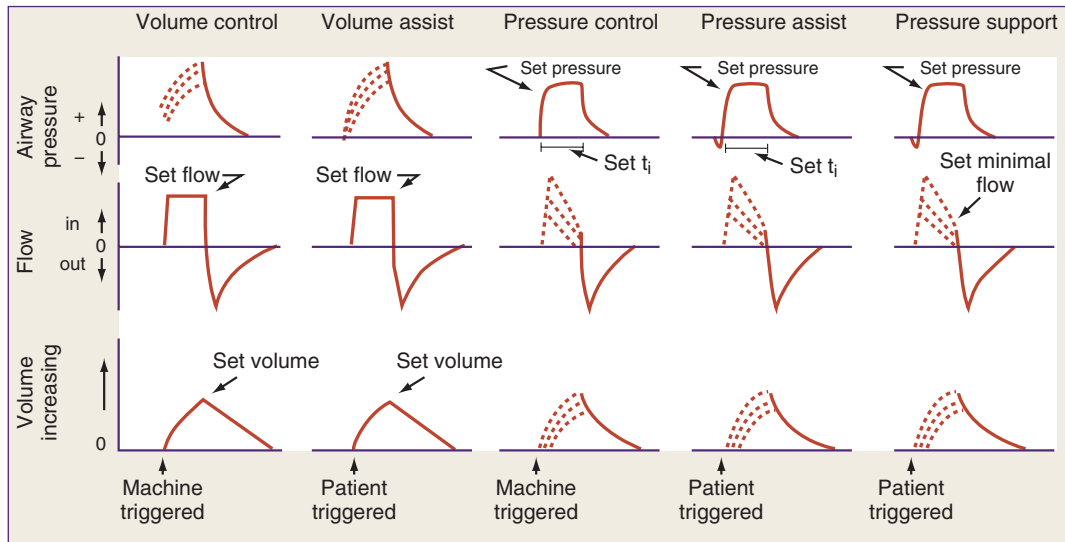


FIGURE 39-1 ■ Airway pressure, flow, and volume tracings over time depicting the five basic breaths are available on most modern mechanical ventilators. Breaths are classified by their trigger, target or limit, and cycle variables. (Adapted from MacIntyre NR. Mechanical ventilatory support. In: Dantzker D, MacIntyre NR, Bakow E, editors. *Comprehensive Respiratory Care*. Philadelphia: Saunders; 1995.)

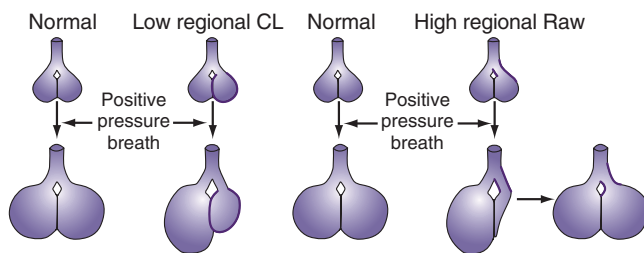


FIGURE 39-2 ■ Schematic effects of the ventilation distribution in two-unit lung models with homogeneous mechanical properties, abnormal compliance distribution, and abnormal resistance distribution. Note that in situations involving inhomogeneous lung mechanics, positive-pressure breaths are preferentially distributed to “healthier” regions of the lung and can produce regional overdistention even when a normal-sized global tidal volume is delivered. CL, lung compliance; Raw, airway resistance. (Adapted from MacIntyre NR. Mechanical ventilatory support. In: Dantzker D, MacIntyre NR, Bakow E, editors. *Comprehensive Respiratory Care*. Philadelphia: Saunders; 1995.)

effective reduction in the afterload.¹⁹ Indeed, the sudden release of intrathoracic pressure (e.g., during a ventilator disconnect or spontaneous breathing trial) can sometimes precipitate flash pulmonary edema because of the acute increase in afterload coupled with increased venous return.²⁰

Intrathoracic pressures can also influence the distribution of perfusion. The relationship between alveolar and perfusion pressures in the three-zone lung model can help to explain this.²¹ Specifically, the supine human lung is generally in a zone 3 (vascular distention) state. However, as the intraalveolar pressures rises, the zone 2 and zone 1 regions can appear, creating high \dot{V}/Q units. Indeed, increases in dead space (i.e., zone 1 of the lung) can be a consequence of ventilatory strategies using high ventilatory pressures or in the setting of high PEEP (either intrinsic or applied).

Positive pressure mechanical ventilation can affect other aspects of cardiovascular function. Specifically, dyspnea, anxiety, and discomfort from inadequate ventilatory support can lead to stress-related catechol

release, with subsequent increases in myocardial O_2 demands and risk of dysrhythmias. In addition, coronary blood vessel O_2 delivery can be compromised by inadequate gas exchange from lung injury coupled with low mixed venous O_2 partial pressure due to high O_2 consumption demands by the ventilatory muscles.

Patient-Ventilator Dyssynchrony

Patients can interact with all three phases of an assisted breath: (1) trigger, (2) flow delivery, and (3) cycle.²² Triggering dyssynchronies that manifest as unrecognized or delayed responses to the patient effort can be attributed to insensitive or unresponsive triggering mechanisms or intrinsic PEEP (PEEPi), causing an imposed triggering load on the respiratory muscles.²³ Excessive triggering (“double triggering”) may be derived from circuit motion artifacts, premature breath cycling, or the recently described “reverse” triggering observed during controlled breaths.²² Flow dyssynchrony occurs when the ventilator’s flow delivery algorithm is not matched by the patient effort and is more likely to occur during fixed flow breaths (i.e., flow targeted). Cycle dyssynchrony occurs when the breath cycling criteria are either inappropriately short or long on the duration of effort. Patients dyssynchronous with any of these phases will have unnecessary loads placed on their respiratory muscles, thereby increasing the risk of muscle fatigue. Moreover, dyssynchronous interactions produce discomfort and a sense of dyspnea.

There is no doubt that many dyssynchronies are subtle and of little clinical relevance, and significant dyssynchronies that produce severe patient discomfort are frequently cited indications for the administration of sedatives in many ICUs.^{22,23} Therefore, this may impact the ventilator duration as high sedation usage is linked to longer ventilator use.

Managing dyssynchronies can be a significant clinical challenge. Setting trigger sensitivity to be as sensitive as possible without auto-triggering is crucial. Judiciously, PEEPe in the setting of a triggering load from PEEPi can be helpful. Careful adjustments of flow magnitude, timing, and patterns (especially the use of pressure-targeted, variable-flow breaths) may help optimize flow and cycle synchrony. Finally, the newer interactive modes found for the proportional assist ventilation (PAV) and neurally adjusted ventilatory assist (NAVA) may offer help to optimize synchrony in the future.⁴

Oxygen Toxicity

Oxygen concentrations approaching 100% are known to cause oxidant injury to the airways and lung parenchyma.²⁴ The majority of the data supporting this concept, however, are derived from animal studies, and animals and humans often have different O₂ tolerances. It is unclear what the “safe” O₂ concentration or duration of exposure is in sick humans. Most consensus groups have argued that Fio₂ values less than 0.4 are safe for prolonged periods and that Fio₂ values greater than 0.8 should be avoided if possible.

Ventilator-Related Infections

Mechanically ventilated patients are at an increased risk of pulmonary infections for several reasons:^{25,26} (1) The natural protective mechanism of glottic closure is compromised by an endotracheal tube. This permits the continuous seepage of oropharyngeal material into the airways. (2) The endotracheal tube itself impairs the cough reflex and serves as a potential portal for pathogens to enter the lungs. This is particularly important if the circuit is contaminated. (3) Airway and parenchymal injury from both the underlying disease and management complications make the lung prone to infections. (4) The intensive care unit (ICU) environment itself, with its heavy antibiotic use and the presence of very sick patients in close proximity, poses a risk for a variety of nosocomial infections, often from antibiotic-resistant organisms.

Preventing ventilator-associated tracheobronchitis and pneumonia is critical because the length of stay and mortality are heavily influenced by their development.^{25,26} Handwashing and carefully chosen antibiotic regimens for other infections can have important benefits. Management strategies that avoid breaking the integrity of the circuit (e.g., circuit changes only when visibly contaminated) also appear to be helpful. Finally, the continuous drainage of subglottic secretions may be a simple way of reducing lung contamination with the oropharyngeal material.

APPLYING POSITIVE PRESSURE MECHANICAL VENTILATION

Tradeoffs

To provide adequate support while minimizing VILI, mechanical ventilation goals must involve tradeoffs. Specifically, the need for potentially injurious pressures, volumes, and supplemental O₂ must be weighed against the benefits of gas exchange support. To this end, a revision of the gas exchange goals has occurred over the past decade, including pH goals as low as 7.15 to 7.20, and O₂ partial pressure goals as low as 55 mm Hg, are now considered acceptable if the lung can be protected from VILI.²⁷ Ventilator settings are thus selected to provide at least this level of gas exchange support while simultaneously meeting two mechanical goals: (1) the provision of enough applied or “extrinsic” PEEP (PEEPe) to enlist the recruitable alveoli and (2) the avoidance of a PEEP–tidal volume combination that unnecessarily overdistends the lung regions at end inspiration. These goals embody the concept of a “lung-protective” mechanical ventilatory strategy,²⁸ and these principles guide the current recommendations for the specific management of parenchymal and obstructive lung disease.

Managing Parenchymal Lung Injury

Parenchymal lung injury describes disease processes that involve the air spaces and interstitium of the lung. In general, parenchymal injury produces stiff lungs and reduced lung volumes. In addition, the residual functional capacity is reduced, and the compliance curve is shifted to the right.²⁹ It is important to realize, however, that in all but the most diffuse diseases (e.g., diffuse cardiogenic edema), there are often marked regional differences in the degree of inflammation present and, thus, the degree of mechanical abnormalities that exist.^{29–32} This heterogeneity can have a significant impact on the effects of a particular

mechanical ventilation strategy. This is because delivered gases will preferentially go to the regions with the highest compliance and lowest resistance (i.e., the more normal regions) rather than to sicker regions with low compliance (see Fig. 39-2). A “normal-sized” tidal volume may thus be distributed preferentially to the healthier regions, resulting in a much higher regional tidal volume and the potential for regional overdistention injury.³⁰

Frequency–tidal volume settings for supporting a patient with parenchymal lung injury must focus on limiting end-inspiratory stretching. The importance of this limitation on improving the outcome has been suggested by several clinical trials.^{33,34} However, it was most convincingly demonstrated by the NIH ARDS Network trial that showed a 10% absolute reduction in mortality with a ventilator strategy using a pressure <30 cm H₂O and tidal volumes calculated on an ideal body weight of 6 mL/kg compared with 12 mL/kg.³⁵ As a result, the initial tidal volume settings should begin at a 6-mL/kg ideal body weight. Moreover, strong consideration should be given to further reducing this setting if plateau pressures, adjusted for any effects of excessive chest wall stiffness, exceed 30 cm H₂O. Increases in the tidal volume settings might be considered if there is marked patient discomfort or suboptimal gas exchange, provided that the subsequent plateau pressure does not exceed 30 cm H₂O. Respiratory rate settings are then adjusted to control the pH. Unlike in obstructive diseases (see later), the potential for air trapping in parenchymal lung injury is low if the breathing frequency is less than 35 breaths per minute and may not develop, even at frequencies exceeding 50 breaths per minute.

Although scaling tidal volume to ideal body weight is logical, recent studies have suggested that this may be overly simplistic in situations with extensive heterogeneous injury and little functioning lung (“baby lung”). Under these conditions, even a 6-mL/kg tidal volume may overdistend the remaining functional lung. To address this concern, strategies that scale the tidal volume to a measured functional residual capacity (i.e., targeting “lung strain”)³⁶ or to system compliance (i.e., limiting the tidal volume/compliance as expressed by the “driving pressure” or plateau pressure minus PEEP to <15 cm H₂O)³⁷ have been proposed. These approaches await outcome studies.

The choice of pressure-targeted or volume-targeted breaths often depends more on clinician familiarity with the two modes than on important clinical differences between them. In general, pressure-targeted breaths are preferable when an absolute pressure limit is desired in the circuit or when the patient effort is very active with variable flow demands. In contrast, volume-targeted breaths are preferable when it is critical to maintain a certain level of minute ventilation. The volume feedback features on pressure-targeted breaths may help combine the advantages of variable flow and a tidal volume target.

Setting the inspiratory time and the inspiratory–expiratory (I:E) ratio in parenchymal injury involves several considerations. The normal I:E ratio is roughly 1:2 to 1:4, and such ratios produce the most comfort and are the usual initial ventilator settings. Assessment of the flow graphic should also be performed to ensure that an adequate expiratory time is present to avoid PEEPi and air trapping. I:E prolongation beyond the physiologic range of 1:1 (inverse ratio ventilation or IRV) can be used as an alternative to increasing PEEPe to improve \dot{V}/\dot{Q} matching in severe respiratory failure.³⁸ A variation on IRV is airway pressure release ventilation (also known as *biphasic* or *bilevel ventilation*).³⁹ Airway pressure release ventilation (APRV) incorporates the ability to breathe spontaneously during the long inflation period of a pressure-controlled breath; a feature that may enhance alveolar recruitment and comfort. It must be emphasized, however, that although IRV/APRV strategies have a physiologic appeal, positive outcome studies supporting their use do not exist.³⁹

There are both mechanical and gas exchange approaches to setting the PEEP–Fio₂ combination to support oxygenation. Mechanical approaches often use either a static pressure–volume plot to set the PEEP–tidal volume combination between the upper and lower inflection points⁴⁰ or stepwise increases in PEEPe to determine the PEEPe level that yields the greatest compliance.⁴¹ A simpler mechanical approach that may reduce inflammatory cytokines involves analyzing

the airway pressure waveform during a set tidal volume with a constant flow breath (i.e., the “stress index”).⁴² If the pressure waveform demonstrates a steady increase, this implies that no recruitment-derecruitment or overdistention is occurring during the breath. In contrast, if the pressure waveform is concave upward, it suggests that overdistention is occurring; if the pressure waveform is concave downward, it implies derecruitment occurred during the previous exhalation. With any of these approaches, a recruitment maneuver could be used to recruit the maximal number of recruitable alveoli before setting the PEEP. FiO_2 adjustments are then set as low as clinically acceptable.

Since these mechanical approaches are time-consuming and technically challenging, gas exchange criteria are often used to guide the PEEP and FiO_2 settings. These generally involve algorithms designed to provide adequate values for the arterial partial pressure of O_2 while limiting PAO plateau pressures and minimizing FiO_2 (Table 39-1).⁴³ Note that constructing a PEEP- FiO_2 algorithm is usually an empiric exercise in balancing arterial O_2 saturation with FiO_2 and depends on the clinician’s perception of the relative “toxicities” of high thoracic pressures, high FiO_2 , and low arterial O_2 saturation. It is important to note that recent meta-analyses of three large trials comparing conservative versus aggressive PEEP- FiO_2 tables (mean PEEP of 7–9 cm H_2O versus mean PEEP of 14–16 cm H_2O) suggested a benefit to the more aggressive strategies in patients with more severe lung injury (i.e., $\text{PaO}_2/\text{FiO}_2 < 200$) and a benefit to the more conservative strategies in less severe lung injury.⁴³

Managing Obstructive Airway Disease

Respiratory failure from airflow obstruction is a direct consequence of increases in airway resistance. Airway narrowing and increased resistance leads to two important mechanical changes: (1) the increased pressures required for airflow may overload the ventilatory muscles, producing a “ventilatory pump failure,” with spontaneous minute ventilation inadequate for gas exchange, and (2) the narrowed airways create regions in the lungs that cannot properly empty and return to their normal resting volume, and PEEP_i is produced.⁴⁴ These regions of overinflation create dead space and place the inspiratory muscles at a substantial mechanical disadvantage, which further worsens muscle function. Overinflated regions may also compress healthier regions of the lung, impairing \dot{V}/\dot{Q} matching. Regions of air trapping and PEEP_i also function as a threshold load to trigger mechanical breaths.^{22,45,46}

Several gas exchange abnormalities can accompany worsening airflow obstruction. First, although there may be transient hyperventilation due to dyspnea in patients with asthma, worsening respiratory failure in those with obstructive lung disease is characterized by a falling minute ventilation as the respiratory muscles become fatigued in the face of airflow obstruction.⁴⁷ The result of this clinical situation is termed *hypercapnic respiratory failure*. Second, as noted earlier, regional lung compression and regional hypoventilation produce a \dot{V}/\dot{Q} mismatch that results in progressive hypoxemia. However,

alveolar inflammation and flooding are not characteristic features of respiratory failure due to pure airflow obstruction. Thus, shunts are less of an issue than in parenchymal lung injury. Third, overdistended regions of the lungs, coupled with underlying emphysematous changes in some patients, result in capillary loss and increase the dead space. This wasted ventilation further compromises the ability of the inspiratory muscles to supply adequate ventilation for alveolar gas exchange. Emphysematous regions have also reduced the recoil properties that can worsen air trapping. Finally, hypoxemic pulmonary vasoconstriction, coupled with chronic pulmonary vascular changes in some airway diseases, overloads the right ventricle, further decreasing the blood flow to the lung and making dead space worse.⁴⁷

Setting the frequency–tidal volume pattern in obstructive lung disease involves many considerations that are similar to those in parenchymal lung injury. Specifically, tidal volumes should be sufficiently low (e.g., 6-mL/kg ideal body weight) to ensure that the plateau pressure is <30 cm H_2O . However, in obstructive disease, clinicians should be aware that high *peak* airway pressures, even in the presence of acceptable values for plateau pressure, may transiently subject regions of the lung to overdistention injury due to a pendelluft effect (see Fig. 39-2). Similar to parenchymal lung injury, tidal volume reductions should be considered to meet the plateau pressure goals. Tidal volume increases can be considered for comfort or gas exchange, provided that the plateau pressure values do not exceed 30 cm H_2O . The set rate is used to control the pH. Unlike parenchymal disease, however, the elevated airway resistance and often low recoil pressures of emphysema greatly increase the potential for PEEP_i and air trapping, which limits the range of breath rates available.

The inspiratory–expiratory ratio in obstructive lung disease is set as low as possible to minimize the development of air trapping. For the same reason, approaches using IRV strategies are almost always contraindicated.

Since alveolar recruitment is less of an issue in obstructive lung disease than in parenchymal lung injury, the PEEP- FiO_2 steps in Table 39-1 should likely be shifted to a conservative strategy that emphasizes FiO_2 for oxygenation support. However, a specific role for applying PEEP in an obstructed patient occurs when PEEP_i serves as an inspiratory threshold load on the patient’s attempt to trigger a breath. Under these conditions, judicious application of PEEP_e (up to 75% to 85% of PEEP_i) can “balance” the expiratory pressure throughout the ventilator circuitry to reduce this triggering load and facilitate the triggering process.^{45,46} In general, PEEP_e below the PEEP_i level has little effect on the total PEEP. However, in rare circumstances, small amounts of PEEP_e have been shown to reduce PEEP_i and air trapping, presumably from splinting open collapsing small airways.⁴⁸

Managing Normal Lungs (Neuromuscular Injury and the Perioperative Setting)

The risk of VILI is thought to be lower in a mechanically ventilated patient with normal lungs because the lung mechanics are often near

TABLE 39-1 NIH ARDS Network PEEP- FiO_2 Tables

| CONSERVATIVE PEEP APPROACH | | | | | | | | | | | | | | | | |
|----------------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|-----|-----|-----|
| FiO_2 | 30 | 40 | 40 | 50 | 50 | 60 | 70 | 70 | 70 | 80 | 90 | 90 | 90 | 1.0 | 1.0 | 1.0 |
| PEEP | 5 | 5 | 8 | 8 | 10 | 10 | 10 | 12 | 14 | 14 | 14 | 16 | 18 | 18 | 20 | 24 |
| LIBERAL PEEP APPROACH | | | | | | | | | | | | | | | | |
| FiO_2 | 30 | 30 | 40 | 40 | 50 | 50 | 60 | 60 | 70 | 80 | 80 | 80 | 90 | 1.0 | 1.0 | |
| PEEP | 12 | 14 | 14 | 16 | 16 | 18 | 18 | 20 | 20 | 20 | 22 | 22 | 22 | 22 | 24 | |

Targets: Po_2 55–80, SpO_2 88%–95%. Move up one step if below target, down one step, if above target. FiO_2 , fraction of inspired oxygen; PEEP, positive end-expiratory pressure (cm H_2O). Data from the National Heart, Lung, and Blood Institute, National Institutes of Health.

normal, making regional overdistention less likely. More “generous” tidal volumes (e.g., up to 10 mL/kg IBW) are thus often used to improve comfort, maintain recruitment, and prevent atelectasis. Challenging these generous tidal volume practices, however, are a series of recent trials in the perioperative setting demonstrating that limiting plateau pressures and tidal volumes reduces postoperative respiratory complications.⁴⁹⁻⁵¹

Regardless of the tidal volume settings, maximal distending pressures should be monitored and kept as low as possible while still being compatible with the other goals noted earlier. Certainly, plateau pressure should always be kept well below 30 cm H₂O. Low levels of PEEP are often beneficial in preventing derecruitment (atelectasis) in these patients, who are often supine and incapable of secretion clearance or spontaneous sigh breaths.

Importantly, in the setting of severe CNS injury, concerns regarding the adverse effects of high intrathoracic pressure and high levels of PCO₂ may require adjustments to the basic lung-protective strategy (e.g., lower PEEP settings and higher minute ventilation settings).

Recovering Respiratory Failure: The Ventilator Withdrawal Process

Once the cause of respiratory failure stabilizes and begins to reverse, attention turns to the ventilator withdrawal process. Numerous evidence-based guidelines have focused on the pivotal role of spontaneous breathing trials (SBTs) in determining the need for continued mechanical ventilatory support.^{52,53} In general, once a patient has stabilized, has an adequate gas exchange, has low PEEP/FiO₂ needs, and is off vasopressors, daily SBTs should be initiated. Importantly, SBTs should be linked to a sedation minimization protocol for maximal success.

In patients comfortably tolerating an SBT for up to 2 h, an assessment should be made to determine if the artificial airway can be removed. In patients failing the SBT, comfortable forms of interactive ventilatory support should be provided until the next attempt at an SBT. This is usually the next day but may be more frequent in patients with rapidly recovering lung function (e.g., post anesthesia or drug overdose). Although the pressure-support mode is often used for this purpose, the pressure-assist control can also fill this role. When using pressure-assist control, the control rate is set quite low (or even to zero), and the inspiratory pressure is titrated to achieve comfort. Similar to pressure support, this approach is patient triggered and pressure targeted but is time cycled as opposed to flow cycling for pressure support.

More detailed discussions on the ventilator discontinuation process can be found in Chapter 63.

CONCLUSION

Positive pressure mechanical ventilatory support is a critical component in the management of patients with respiratory failure. However, it is important to note that this technology is supportive, not therapeutic, and it cannot cure lung injury. Indeed, the best we can hope for is to buy time by supporting gas exchange without harming the lungs.

Positive pressure mechanical ventilation is designed to provide substantial levels of respiratory support. The major goals are to unload the ventilatory muscles and optimize ventilation-perfusion matching to ensure adequate gas exchange. Important complications include ventilator-induced lung injury, cardiac compromise, oxygen toxicity, and patient discomfort. Applying ventilatory support often requires tradeoffs as clinicians attempt to balance gas exchange needs with the risk of these complications. Future innovations cannot focus simply on physiologic endpoints. Rather, innovations should demonstrate benefits in clinically relevant factors, such as mortality, ventilator-free days, barotrauma, and costs. Only then can we properly assess the often bewildering array of new approaches to this vital life-support technology.

KEY POINTS

1. Ventilator breath delivery is characterized by the trigger, target, and cycle variables.
2. The interaction of a positive-pressure breath and respiratory system mechanics is summarized by the equation of motion:
Airway pressure = (Flow × Resistance) + (Volume/System Compliance) + PEEP
3. The goal of positive pressure mechanical ventilation is to provide adequate gas exchange while protecting the lung from overdistention and recruitment-derecruitment injury.
4. Positive pressure mechanical ventilation in obstructive lung disease poses the additional risk of producing overdistention from air trapping.

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Acute kidney injury (AKI) is a common complication in critically ill patients admitted to the intensive care unit (ICU).¹⁻³ Recent epidemiologic data suggest that over 50% of ICU patients suffer from AKI and that up to 13.5% will be treated with renal replacement therapy (RRT).¹⁻³ Changes in patient characteristics, with admission of older patients with more comorbidities such as diabetes, cardiovascular disease, and hypertension, have resulted in a marked increase in the proportion of patients treated with RRT in the past decade.^{4,5} RRT has, therefore, become an essential and commonly used treatment option for ICU patients.

■ TECHNICAL ASPECTS OF RRT

RRT is most often delivered via extracorporeal techniques. Alternatively, the peritoneum of the patient can be used as a semipermeable exchange membrane. This latter technique is primarily used in resource-poor areas and seldom in developed countries.

Extracorporeal techniques can be done with different modalities (Table 40-1). These are named according to the duration of RRT and the technique used to exchange solutes and water (either diffusion or convection).

Diffusion and Convection

Exchange of waste products over a semipermeable membrane can occur via diffusion (hemodialysis [HD]) or convection (hemofiltration) (Fig. 40-1).

In diffusion, blood and dialysate flow countercurrent on both sides of the semipermeable membrane of the hemofilter. The driving force that moves solutes across the semipermeable membrane is the solute concentration gradient. Uremic toxins, such as blood urea nitrogen and creatinine, will have high blood concentrations and are absent in the dialysate. Other factors that determine the movement of solutes from the blood to dialysate are the diffusion coefficient of the membrane, its thickness, and its surface area. Diffusion is very efficient in removing small molecules, such as potassium, ammonium, and creatinine (<20 kDa); it is less efficient in removing larger solutes and water.

In hemofiltration, solutes and water are transported over the membrane by a difference in pressure between both sides of the membrane. Pressure forces the water and solutes from the blood compartment to the so-called effluent. The permeability coefficient of the membrane and the difference in pressure between both sides of the membrane determine the amount of fluid and solutes transported across the membrane via convection. The effluent rate is controlled by a pump. Hemofiltration is more efficient for removal of water and larger molecules (<60 kDa). In hemodiafiltration, both convection and diffusion are combined.

There are currently no data to suggest the superiority of diffusion over convection.

Duration of RRT

Intermittent hemodialysis (IHD) is a very efficient dialysis technique, performed during a 3- to 4-h period. Continuous renal replacement therapy (CRRT) is less efficient; it is conducted 24 h per day. Hybrid techniques, alternatively termed *sustained low-efficiency daily dialysis*

(SLEDD) or *extended daily dialysis* (EDD), have intermediate efficacy and are used 6 to 12 h per day.^{6,7}

Intermittent and hybrid therapies are performed with dialysis machines that are also used for chronic dialysis patients. These machines typically have more complicated interfaces and are, therefore, often managed by dialysis nurses. CRRT is most often performed with specially designed machines with a relatively simple interface, which are managed by ICU nurses.

Specific Aspects of a CRRT Circuit

Figure 40-2 illustrates the different aspects of CRRT, performed as continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF).

The dose of CRRT is by convention expressed as the clearance of urea, a small molecule that is not retained by the membrane in either HD or hemofiltration. The effluent rate, which is the volume of fluid produced by hemofiltration and/or HD, therefore equals the clearance of urea and, when corrected for body weight, can be used to express the dose of CRRT: dose of CRRT = effluent rate per hour per kg body weight (mL/kg/h). For a desired dose of 25 mL/kg/h in a 60-kg patient, the effluent rate will be $25 \times 60 = 1500$ mL/h. This effluent needs to be partly or completely replaced by another fluid; otherwise body fluid losses will be too high. The amount of effluent that is replaced will determine the fluid balance of the patient. This replacement fluid can be given prefilter (predilution), postfilter (postdilution), or as a combination of both. When the fluid is given by the postdilution mode, blood will concentrate while passing through the capillaries of the hemofilter. This may lead to clogging (partial clotting) and clotting of the capillaries, leading to decreased efficacy because fewer capillaries are available. To prevent this, a filtration fraction (the ratio of effluent flow over plasma flow) of <25% is advised. The filtration fraction is indicated on the dashboard of present-day CRRT machines. On the other hand, predilution administration will dilute the blood in capillary filters, leading to a decreased risk for clotting but also decreased clearance and efficacy.

Dose of RRT

In CRRT, the delivered dose should be 20 to 25 mL/kg/h of effluent. Two large prospective randomized studies compared this dose to a higher dose and found that outcomes were similar.^{8,9}

In intermittent RRT, the minimum delivered dose of dialysis should be 3 sessions per week lasting at least 4 h, with a blood flow of >200 mL/min and a dialysate flow of >500 mL/min or a Kt/V index of >3.9 per week, or maintenance of the predialysis urea concentration of 20 to 25 mmol/L.^{9,10}

Anticoagulation

Coagulation is one of the major barriers to effective extracorporeal therapies. When blood leaves the body, the coagulation cascade becomes activated, which can lead to thrombocyte activation, partial clogging (which lowers the effectiveness of dialysis), and even complete clotting/blockage of the dialysis/extracorporeal circuit (resulting in

TABLE 40-1 Renal Replacement Therapy Modalities

| MODALITY | ABBREVIATION | TREATMENT DURATION (per day) | BLOOD FLOW (mL/h) | DIALYSATE FLOW (mL/min) |
|--|--------------|---------------------------------|----------------------|----------------------------|
| Intermittent hemodialysis | IHD | 2-4 h | 150-450 | 300-600 |
| Hybrid techniques | | 6-12 h | 100-200 | 250-500 |
| • Slow low-efficiency daily dialysis | SLEDD | | | |
| • Extended Daily Dialysis | EDD | | | |
| • Prolonged Intermittent Renal Replacement Therapy | PIRRT | | | |
| Continuous Renal Replacement Therapy | CRRT | 24 h | 100-250 | 15-60 |
| • Continuous venovenous Hemodialysis | CVVHD | | | |
| • Continuous venovenous Hemofiltration | CVVH | | | |
| • Continuous venovenous Hemodiafiltration | CVVHDF | | | |
| Peritoneal dialysis | PD | 6 × 2-4 h | | |

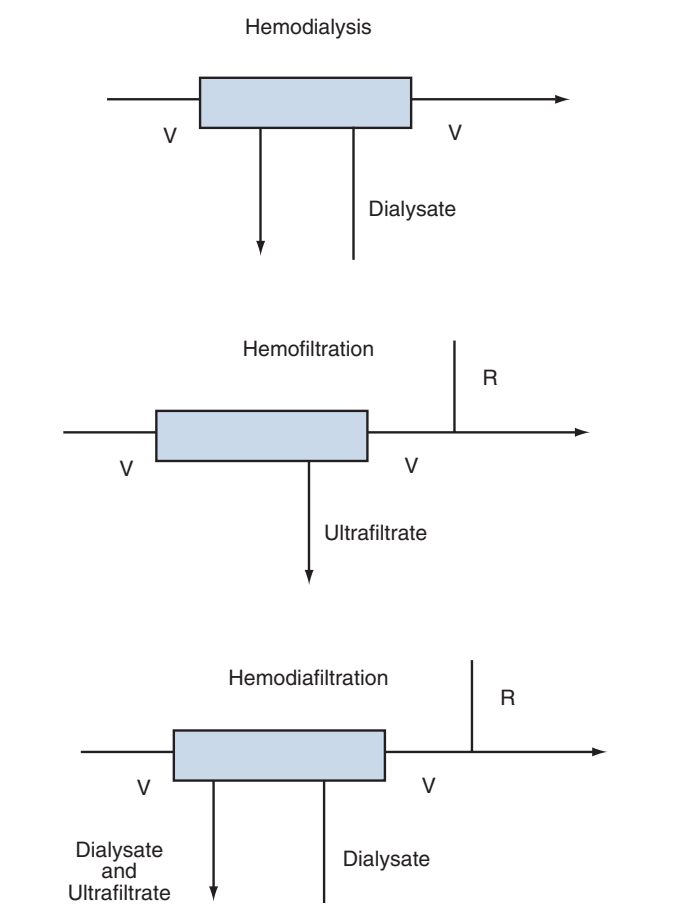


FIGURE 40-1 ■ Diffusion (as in hemodialysis) and convection (as in hemofiltration). V, venous blood prefilter and postfilter; R, replacement fluid.

loss of extracorporeal blood). Anticoagulation for RRT should be tailored according to the patient's characteristics and the modality chosen. The risk for coagulation rises with low blood flow or when the vascular access is not functioning well. Special attention is required for non-anticoagulant strategies to avoid coagulation of the circuit. Patients with a high hematocrit are at higher risk for clotting of the extracorporeal/dialysis circuit because of the higher viscosity of their blood. The local hematocrit in the filter rises when ultrafiltration is applied. Therefore, the filtration fraction (ratio of ultrafiltrate flow to blood flow) may not exceed 25% in postdilution RRT. In predilution mode, hemoconcentration is reduced by diluting the blood with

replacement fluids before the blood enters the filter. Blood products should be administered separately from RRT as much as possible. Prompt reaction to pump alarms is important to avoid interruption of blood flow. Careful circuit priming is fundamental. Circuits with a lot of blood-air contact due to the use of drip chambers are especially prone to clotting and require extra attention. There is no evidence pointing toward the efficacy of intermittently rinsing the circuit with saline flushes to prevent clotting.¹¹

- No anticoagulation strategy
Several authors described large series of patients treated without any form of anticoagulation during RRT for AKI (in up to 50%-60%).^{8,9} Especially in patients with a preexisting coagulopathy, an acceptable length of treatment can be reached, even without anticoagulant administration.¹² Risking circuit clotting, in the worst case leading to the loss of approximately 200 mL of extracorporeal blood and eventually also the venous access, may be defensible in patients with a high bleeding risk. Neither the effect of clogging on filter performance nor the consumption of coagulation factors in RRT without anticoagulation is well studied.
- Unfractionated heparin
Unfractionated heparin (UFH), the most widely used anticoagulant, has a half-life between 0.5 and 3.0 h in patients receiving dialysis.¹³ It has a rapid onset of action of approximately 3 to 5 min. Heparin acts by potentiating thrombin and inhibiting activated coagulation factor X (FXa). It is mostly administered as a prefilter infusion, by a variety of regimens, including single-dose, repeated-bolus, or constant-infusion methods. A possible administration scheme is to start with a bolus of 500 to 1000 units, followed by 500 to 750 units/h. Other authors suggest adapting the dose to the body weight, starting with a bolus of 10 to 20 units/kg/h, followed by a rate of 10 to 20 units/kg/h. This maintenance infusion would typically be stopped 30 min before the end of treatment. The dose must be altered for patients exhibiting coagulopathy or an increased bleeding risk. UFH can be easily monitored with routine laboratory tests, such as the activated partial thromboplastin time (aPTT) or activated coagulation time (ACT). Since heparin causes systemic anticoagulation, moderate anticoagulation targets are recommended for ICU patients (1.5-2 times prolongation of the aPTT, or baseline ACT plus 40%). If needed, heparin can be reversed with protamine. Heparin failure, resulting in clotting of the circuit, can be due to antithrombin deficiency or heparin neutralization by binding to plasma proteins. During heparin treatment, the thrombocyte count should be monitored, allowing timely detection of heparin-induced thrombocytopenia (HIT). Current guidelines suggest using heparin for intermittent RRT in patients without an increased bleeding risk, and in the presence of contraindications to citrate, which is used in continuous RRT.
- Low-molecular-weight heparins
Several studies have shown that low-molecular-weight heparins (LMWH) are effective and can be safely used for anticoagulation

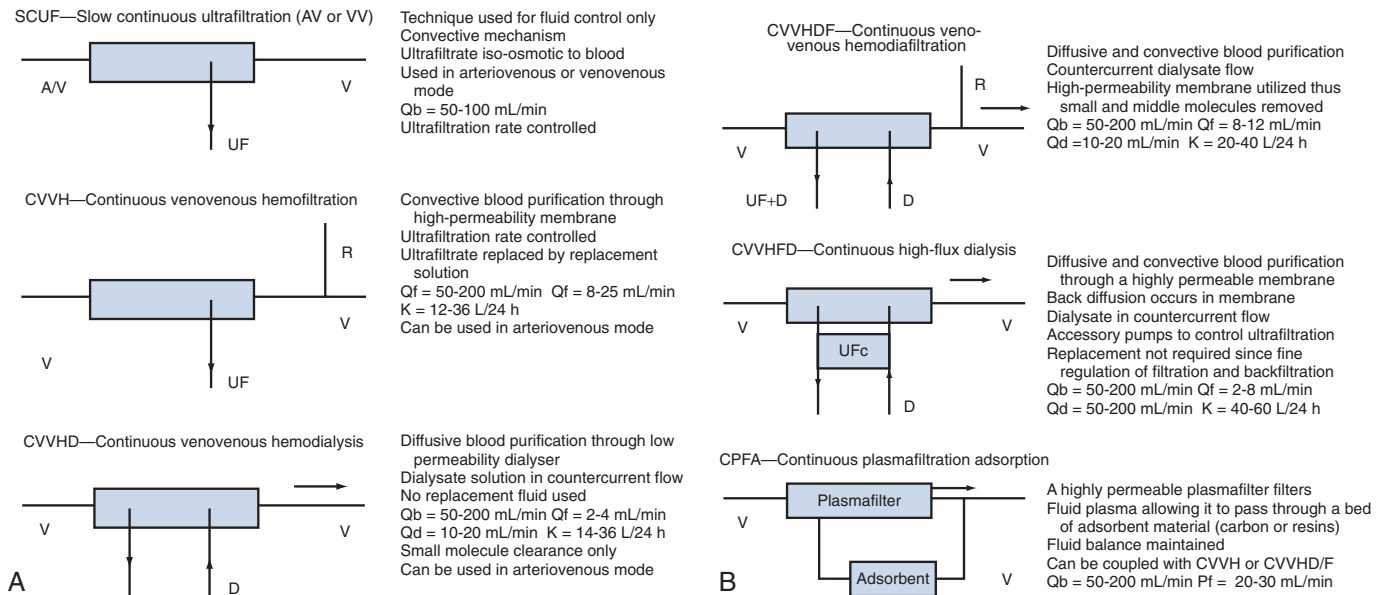


FIGURE 40-2 ■ Schematic representation and definitions of the different continuous renal replacement therapies according to standard nomenclature. Functional capabilities are described. A, artery; D, dialysate; K, clearance; Pf, plasma filtration rate; Q_b , arterial flow; Q_d , dialysate flow; Q_f , ultrafiltration rate; UF, ultrafiltrate; UFc, ultrafiltrate control pump; V, vein.

during chronic HD. LMWH are administered as a single bolus at the beginning of dialysis: immediately after the start of dialysis with postfilter administration or 5 min after the start with prefilter administration.¹⁴ They have a weight-based dosing, require no monitoring when used in short sessions, and have a reduced risk for HIT. The use of LMWH for IHD in AKI is increasing. LMWH are partially cleared during HD (especially with high-flux membranes), but periodic measurement of anti-Factor Xa levels may be useful with prolonged daily use.

- Citrate

The 2012 Kidney Disease Improving Global Outcomes Clinical Practice Guidelines for Acute Kidney Injury have recommended regional citrate anticoagulation as the preferred anticoagulation modality for continuous RRT in critically ill patients for whom it is not contraindicated.¹⁵ Citrate chelates calcium, an essential cofactor for many steps of the coagulation cascade. A whole range of protocols exist, using different dialysate/replacement fluids for the different RRT modalities. Prefilter infusion of citrate, either as a separate trisodium citrate solution or added to calcium-free predilution replacement fluid, lowers ionized calcium levels in the extracorporeal circuit to a level that achieves full blood anticoagulation (i.e., 0.3–0.4 mmol/L). In most protocols, the citrate dose is adapted according to the resulting postfilter circuit ionized calcium measurements, although recently, there has been some concern about the reliability of measurements obtained from point-of-care devices used for this purpose. Citrate and citrate complexes are partially removed in the effluent because of their low molecular weights (198 and 258, respectively) and high sieving coefficients. Citrate clearance is higher with dialysis than with CVVH, with extraction ratios from 20% to 60%, depending on the modality and dose of RRT. Calcium infusion is needed to replace calcium losses and maintain systemic ionized calcium levels within the normal range. The remaining citrate is metabolized in the liver, muscle, and kidney, producing bicarbonate and eventually leading to metabolic alkalosis. Most of the protocols compensate for this by administering a lower concentration of bicarbonate in the replacement fluid. In contrast, in patients with impaired citrate metabolism, acidosis can ensue. Other potential metabolic derangements include hyponatremia (due to metabolism of trisodium citrate),

hypomagnesemia (due to effluent losses in the form of citrate complexes), and hypocalcemia. Citrate accumulation can occur in patients with profound shock or severe liver failure, although recent studies have argued that citrate can be used safely in the latter.¹⁶ During citrate accumulation, there is a simultaneous increase of the total calcium and fall of the ionized calcium. The total calcium to ionized calcium ratio is the best marker for citrate intoxication. When this ratio exceeds 2.5, citrate administration must be stopped. Unintended rapid infusion of a hypertonic citrate solution, causing life-threatening hypocalcemia, is the main risk of citrate anticoagulation. In this situation, it is recommended that the citrate infusion be stopped, while continuing dialysis with a calcium-containing dialysate. In experienced hands, severe hypocalcemia-related complications seldom occur, and regional citrate anticoagulation has been shown to be safe. Treatment protocols should describe how to adjust flows under different conditions to prevent metabolic derangements. Compared with heparin, citrate is associated with lower risk of circuit loss, a lower incidence of filter failure, less bleeding, and lower transfusion rates. Furthermore, citrate is a source of energy and has potential anti-inflammatory effects.

- UFH and protamine

Regional anticoagulation can also be accomplished by the combination of UFH and protamine. Use of this strategy has decreased in parallel with the increasing popularity of citrate. Protamine has several side effects, such as anaphylaxis, hypotension, cardiac depression, leukopenia, and thrombocytopenia. Further, there may be the possibility of a rebound anticoagulant effect because of the shorter half-life of protamine compared with heparin. Regional anticoagulation with heparin-protamine is, therefore, no longer recommended.^{10,15,17}

- Platelet-inhibiting agents

Prostacyclin (PGI_2) and its analogue (nafamostat) inhibit platelet aggregation and adhesion. They have been used alone or in combination with heparin to improve filter survival. There is neither a great amount of data nor a lot of clinical experience with these medications for this purpose, and several guidance documents do not recommend their use in RRT. In addition to these drugs being expensive, there are safety concerns about hemodynamic stability

with the use of PGI₂, and about anaphylaxis, agranulocytosis, and hyperkalemia with the use of nafamostat.

Vascular Access

Vascular access is with a double-lumen catheter, preferably in the right jugular vein or a femoral vein. It is recommended that the subclavian approach not be used for vascular access of a catheter for RRT. Contact of the catheter with the vessel wall may lead to thrombosis and ensuing stenosis, and it may jeopardize the possibility for an arteriovenous fistula in case there is no recovery of kidney function and the patient remains dialysis-dependent. Thrombosis will be more likely to occur when the catheter has a trajectory with angulations, such as when it is inserted into the left jugular vein or subclavian veins.

For optimal blood flow rates, the tip of the catheter should be located in a large vein—that is, the inferior or superior vena cava. Therefore, for an adult, the optimal length of a catheter is 12 to 15 cm for the right jugular vein, 15 to 20 cm for the left jugular vein, and 19 to 24 cm for the femoral veins. There are several different designs of dialysis catheters. At present it is not clear which design is preferable. The outer diameter of catheters varies between 11F and 14F; larger catheter diameters will result in better blood flow rates.

INITIATION OF RRT

At present, the available evidence does not permit the proposal of strict guidelines for the timing of initiating RRT. If exposure to RRT were without risks, we would not wait until the development of absolute criteria. But very early initiation of RRT will expose the patient to potential hazards associated with insertion of the catheter (e.g., blood loss, thrombosis, catheter infection) and exposure to the extracorporeal circuit (e.g., air embolism, hypotension).¹⁸ If RRT offers support in patients with only mild or moderate AKI, early initiation may be beneficial. However, available data suggest no benefit in, for instance, modulation of the inflammatory response,^{19–21} and one study even showed harm when RRT was started very early in patients with severe sepsis or septic shock.²²

Cohort studies on the timing of RRT have shown a benefit from early initiation of RRT.²³ However, the few small prospective, randomized trials that evaluated early initiation of RRT did not show a benefit from early initiation.^{24–26} On the other hand, cohort studies also showed that late initiation is associated with worse outcomes.^{27–29}

Knowledge regarding the deterioration or recovery of kidney function within a certain time period would help us in determining the timing of RRT, especially when there are only relative criteria for initiating RRT (Table 40-2). A clinical risk assessment may identify patients at greater risk for further deterioration of kidney function. This may take into account such risk factors as age, chronic kidney disease, and severity of illness of the patient. Other tools that have been explored are measurements of specific kidney biomarkers and the furosemide stress test.^{30–36}

The kidneys are crucial for the removal of water and homeostasis of electrolytes and acid-base. Volume overload in an anuric patient and severe electrolyte and acid-base abnormalities are, therefore, absolute criteria for the initiation of RRT (Table 40-2).³⁷

CHOICE OF MODALITY OF RRT

Since the introduction of CRRT in the mid-1980s, there has been debate regarding the optimal modality of RRT. Several relatively small studies and meta-analyses showed that CRRT and IHD are associated with similar patient outcomes.^{38,39} However, the number of patients included in individual studies was relatively low, the baseline characteristics of the patients were different, and the techniques used (e.g., modalities, dose, initiation criteria) varied among studies, making comparisons difficult. Renal outcomes may, however, be better when CRRT is used. Cohort studies, as well as a comparison of the large prospective, randomized studies regarding dose, the ATN and RENAL

TABLE 40-2 Criteria for Initiation of RRT

| INDICATION | CHARACTERISTIC |
|--------------------------|---|
| ABSOLUTE CRITERIA | |
| Metabolic abnormality | BUN > 100 mg/dL (35.7 mmol/L) Hyperkalemia > 6 mmol/L with ECG abnormalities Hypermagnesemia > 8 meq/L (4 mmol/L) with anuria and absence of deep tendon reflexes |
| Acidosis | pH < 7.15 Lactic acidosis related to metformin use |
| Fluid overload | Diuretic-resistant |
| RELATIVE CRITERIA | |
| Metabolic abnormality | BUN > 76 mg/dL (27 mmol/L) Hyperkalemia > 6 mmol/L Dysnatremia Hypermagnesemia > 8 meq/L (4 mmol/L) |
| Acidosis | pH > 7.15 |
| Anuria/oliguria | AKI stage 1 AKI stage 2 AKI stage 3 |
| Fluid overload | Diuretic-sensitive |

AKI, acute kidney injury; BUN, blood urea nitrogen; ECG, electrocardiogram.

Modified from Gibney N, Hoste E, Burdmann EA, et al. Timing of initiation and discontinuation of renal replacement therapy in AKI: unanswered key questions. Clin J Am Soc Nephrol. 2008;3:876–880. Tab 1.

studies, suggest that CRRT is associated with better renal recovery and less end-stage kidney disease in survivors.^{8,9,40–42}

CRRT is performed with a lower extracorporeal blood flow and allows removal of fluid over a longer time period and a lower ultrafiltration rate, characteristics that enhance the hemodynamic tolerability of this technique. Hence, CRRT is often recommended for hemodynamically unstable patients,¹⁵ although studies in specialized centers could not demonstrate that CRRT was better tolerated than IHD in shock patients.⁴³

Intermittent techniques, however, use fewer resources since they allow for several treatments with one machine per day, and the dialysate and replacement fluid are produced by the dialysis machines, in contrast to the need to buy these special solutions for CRRT. Whether the cost of CRRT is greater than that of IHD or vice versa will depend on the specific setting.^{44,45} An important argument in favor of IHD and hybrid therapy is that these modalities will allow for mobilization of the patient during the off period. A recent meta-analysis suggests that hybrid therapies are associated with the same outcomes as CRRT, suggesting that increasing the length of intermittent treatment may combine the best of IHD and CRRT.⁴⁶ However, these data were compiled from a limited number of patients in primarily cohort studies, making this conclusion prone to bias.

SPECIAL INDICATIONS

Heparin-Induced Thrombocytopenia

Up to 3% of heparin-exposed patients develop antibodies directed against the complex of heparin and platelet factor 4, resulting in thrombocytopenia with or without thrombosis. If HIT is likely, all heparin administration, including LMWH, heparin-coated dialyzer membranes, and catheter locks containing heparin, must be stopped. Guidance documents recommend various options for anticoagulation during RRT in this circumstance: regional citrate anticoagulation or the use of direct thrombin inhibitors (such as argatroban or bivalirudin) or factor Xa inhibitors (such as danaparoid or fondaparinux).^{10,15,47}

Patients with High Serum Urea Concentration

When using acute RRT in a highly uremic patient (typically >175 mg/dL), precautions should be taken to prevent disequilibrium syndrome.

This rare neurologic condition is characterized by nausea, vomiting, restlessness, and headache. Some patients, however, may progress to seizures, coma, or death. The syndrome is believed to be primarily related to the decreased osmolality of the blood after the initiation of RRT, creating an osmotic gradient between the blood and the brain, which is compensated for by an influx of water into the brain compartment. To avoid brain edema caused by large variations in osmolality, several preventive measures can be taken, targeting a reduction in the plasma urea nitrogen of at most 40%. The dialysis dose can be reduced by lowering blood flow and dialysate flow, using a small dialyzer, and limiting the length of the treatment. The use of a sodium-enriched dialysate may further reduce the risk.⁴⁸

Patients with Intracranial Hypertension or Cerebral Edema

In patients with acute brain injury, AKI requiring RRT may worsen the neurologic status in several ways. The accumulated urea and solutes diffuse from the blood compartment to the brain cells, thereby increasing water uptake by the brain cells. Dysfunction in the blood-brain barrier reinforces this process. The shift of water into brain tissue, as a result of lowered tonicity of plasma with respect to the brain cells (as described in disequilibrium syndrome), may result in increased intracranial pressure causing cerebral hypoperfusion. This is exacerbated by decreased or absent autoregulation of cerebral blood flow due to the brain injury and eventual hypotension during RRT. Both hypotension and disequilibrium can be avoided by the slow progressive removal of fluids and solutes during CRRT, which is in this setting preferred over intermittent RRT. If the patient is also at increased risk for intracranial bleeding, locoregional citrate anticoagulation is recommended.¹⁷

Patients with Hyponatremia

If patients with severe chronic hyponatremia are treated with conventional RRT, the serum sodium concentration can be expected to increase rapidly, exposing patients to the risk of developing osmotic demyelination. High serum urea concentration may protect the brain against this.^{49,50} To avoid osmotic demyelination in patients with chronic hyponatremia, the treatment during a single dialysis session has to be adjusted to provide a rate of correction that does not exceed the generally recommended rate. The easiest way to do this is by choosing a low-efficiency RRT such as CVVH and to maintain the sodium concentration of the replacement fluid slightly higher than the serum sodium concentration. In the routinely available dialysate/replacement solutions, the variability in sodium content is limited. Adapting the sodium concentration can be established by adding sterile water to the replacement fluid bag. Diluting replacement fluid will also result in decreased potassium and bicarbonate concentrations and, therefore, may induce hypokalemia and acidosis. If only HD is available, one can use the lowest available concentration (130 mmol/L), reduce the blood flow rate markedly (to 2 mL/kg/min), and shorten the dialysis time.⁵¹

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■ References for this chapter can be found at expertconsult.com.

Prevention of Contrast-Induced Nephropathy

A single dialysis session removes 60% to 90% of contrast media from the blood,^{52,53} and one study argued that periprocedural CRRT may be beneficial in patients with chronic kidney disease.⁵⁴ However, meta-analyses including studies in patients without severe chronic kidney disease could not show a benefit for this strategy.^{52,55} Considering the possible complications, cost, logistical difficulties, and uncertain benefit, several guidelines do not recommend RRT for the prevention of contrast-induced nephropathy.^{15,56}

Patients with Severe Hemodynamic Instability

CVVHD, SLEDD, and continuous HD seem to be equivalent treatment strategies with regard to mortality, kidney recovery, and fluid removal for hemodynamically unstable patients.^{17,46,57–60} Treating those patients requires some precautions: less aggressive ultrafiltration; increasing dialysate sodium and calcium concentrations to 145 mmol/L and 1.5 mmol/L, respectively; adapting the dialysate temperature to obtain isothermal dialysis; connecting afferent and efferent blood lines simultaneously at the start of the procedure; raising the blood flow slowly; and using biocompatible membranes.¹⁷

Patients with Severe Lactate Acidosis

The key issue in the management of lactic acidosis is to treat the underlying cause. Continuous RRT can be performed in critically ill patients with severe lactic acidosis and AKI.⁶¹ Using continuous HD with bicarbonate dialysate, lactate concentrations can be lowered and the pH can be corrected. However, no adequately powered randomized, controlled trial with clinical outcome endpoints has yet evaluated RRT in this setting.⁶²

KEY POINTS

1. Uremia is the accumulation of uremic toxins of different molecular weights associated with pathogenicity secondary to kidney dysfunction.
2. Acute kidney injury (AKI) is a separate syndrome from chronic renal failure and should be approached in a distinct manner.
3. Specific indications exist for the initiation of renal replacement therapy (RRT) in AKI. Early initiation has been shown to be beneficial in cohort studies. The optimal timing of early is at present unclear and may differ in patient groups.
4. Multiple therapeutic modalities of RRT exist to treat AKI. No modality is clearly superior to another. Treatments should be tailored depending on the clinical scenario.
5. Knowledge of prescribed drug pharmacokinetics is important when dosing patients on RRT.

This article reports on the largest randomized prospective trial evaluating the dose of renal replacement therapy in the ICU. This article has set the standard for dialysis dose in the ICU.

RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009;361:1627–1638.
A landmark randomized clinical trial that shows the absence of beneficial effects of increasing the continuous renal replacement dose from 25 to 40 mL/kg/h.

VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008;359:7–20.
The largest clinical trial on "routine" renal replacement therapy delivery in the United States (using both intermittent and continuous techniques). According to these authors, intensive renal replacement approach does not improve survival.

Kellum JA, Ronco C. Dialysis: results of RENAL—what is the optimal CRRT target dose? *Nat Rev Nephrol* 2010;6:191–192.
An interesting commentary that tries to synthesize the results of the recent randomized trials on the issue of dialysis dose.

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■ PHYSIOLOGY AND PATHOPHYSIOLOGY

Temperature is a key determinant and a potential modifier of acute hypoxic and posthypoxic injury. This applies during and immediately following a period of ischemia and especially during reperfusion.¹⁻³ Experimental evidence suggests that the role of temperature in modifying ischemic injuries is equivalent to that of perfusion and oxygenation.⁴ The reason for this is that all destructive cascades that can be triggered by ischemia (summarized in Fig. 41-1) are temperature dependent—that is, they are markedly increased by fever and inhibited by mild hypothermia.¹⁻⁴ These processes, sometimes collectively called *reperfusion injury* or *postresuscitation disease*, can continue for hours to several days after the initial injury and can be retriggered by new episodes of ischemia. Most of these processes are temperature-dependent in a more or less dose-dependent fashion; for example, in the temperature range of 30–40°C the metabolic rate, oxygen consumption, and CO₂ production all increase by 7–10% per °C.^{2,5-6} Processes such as neuroinflammation, neuroexcitotoxicity, and apoptosis are all stimulated by fever and inhibited by hypothermia.² Temperature elevations also increase the permeability of the blood-brain barrier and lead to intracellular acidosis and production of toxic metabolites. In addition, seizure tendency can be increased by fever and mitigated by hypothermia.¹⁻²

Even under normal conditions, the average temperature in the (metabolically highly active) brain is slightly higher than core temperature.^{1,2} When fever occurs, brain temperature can rise well above the systemic temperature, especially in patients with acute brain injuries.^{2,7,8} This is due to excess heat generated by some of the ongoing destructive processes (indicated in orange font in Fig. 41-1), which include neuroinflammation, influx of excess calcium into injured brain cells leading to hypermetabolism, free radical production, and heat trapping in injured areas due to local edema formation and vascular blockage (*cerebral thermopooling*).² These processes lead to a general “overheating” of the brain, with additional temperature elevations in injured areas.² Numerous clinical studies have demonstrated that brain temperature exceeds core temperature by 1–2°C in patients with severe brain injury, with temperatures in injured areas exceeding core temperatures by up to 4°C.^{1,2,7,8} The higher brain temperature (especially in injured areas) can cause additional neurologic damage.² This has been conclusively demonstrated in numerous animal experiments, where experimentally induced brain injury increases significantly when animals are externally warmed; this phenomenon is independent of the initial severity of injury and is especially pronounced if hyperthermia coincides with a period of ischemia.^{1,2,9} Conversely, fever control mitigates brain injury in animal models, while inducing hypothermia provides additional neuroprotection.^{2,9}

Fever is a frequently occurring problem in patients with acute neurologic injury; in fact, the vast majority of these patients will develop fever during the course of their intensive care unit (ICU) stay. The most frequent cause is the so-called central fever, which is a direct consequence of the brain injury itself.^{1,2} However, brain-injured patients are also at a very high risk of infections; apart from the risk of complications such as aspiration pneumonia (due to decreased consciousness and diminished protective reflexes), brain injury can

directly induce immune dysfunction (mediated through the vagal nerve, with efferent signals inhibiting proinflammatory cytokine production), leading to an immunocompromised state with increased susceptibility to infections.¹⁰ Therefore, patients with acute brain injury may have central fever, infectious fever, or a combination of both, either simultaneously or sequentially.¹¹ Whatever the cause, the result is that the temperature set point is elevated, triggering the body’s mechanisms to increase core temperature; the patient thus develops fever.

As would be expected when studying pathophysiologic processes, hyperthermia (regardless of its cause) is independently associated with increased risk of adverse outcome in all types of acute neurologic injuries. Clinical studies in acute ischemic stroke (AIS), subarachnoid hemorrhage (SAH), intracranial hemorrhage (ICH), traumatic brain injury (TBI), and cardiac arrest have demonstrated independent correlations among fever and worse neurologic outcomes, higher mortality, and increased length of stay.¹ This has been documented in dozens of observational studies. For example, patients with AIS who develop fever have larger infarct volumes (OR, 3.23) and greater neurologic deficits (OR, 3.06),¹² increased risk of hemorrhagic transformation (OR, 7.3),¹³ and a 3.4- to 6-fold increase in risk of adverse outcomes.¹⁴⁻¹⁵ Fever in patients with cardiac arrest increases the risk of unfavorable outcomes by a factor of 2.3 per °C temperature increase above 37°C.¹⁶ In patients with ICH, the proportion of time spent at temperature higher than 37.5°C within the first 72 hours is independently associated with poor outcomes,¹⁷ and patients with fever have a significantly higher risk of hematoma expansion.¹⁸ In patients with SAH, fever is independently linked to adverse outcomes.^{19,20} Similar findings have been shown in patients with TBI.^{21,22} One study even reported that peak body temperature predicts mortality in patients without cerebral damage.²³

This large detrimental impact is partly explained by the pathophysiology outlined above, with brain temperature far exceeding core temperature and via heat trapping in injured areas.² The generalized increase in metabolic rate with corresponding increases in minute ventilation and oxygen consumption could also be detrimental, depending on the patients’ condition.^{2,24}

However, it should be noted that not all processes triggered by an episode of ischemia are harmful. For example, it has been shown that some degree of neuroinflammation can contribute to cellular repair after an ischemic insult.^{2,25} Furthermore, in some situations, the proinflammatory state that may be associated with fever can help the body fight infections. Fever can inhibit the growth of certain species of bacteria, while simultaneously stimulating immune cell function and enhancing antibody and cytokine synthesis.²⁶ Several studies suggest that suppression of fever with antipyretics in patients with influenza can adversely affect outcomes.²⁷

However, when the processes are uncontrolled and overwhelming, they are harmful and can lead to cell destruction and death. A useful analogy might be the process of infection and inflammation, where an immune response is needed to combat the infection but a cascade of inflammation (as is seen in septic shock) can overwhelm the organism and lead to death. In this situation, mitigating these processes can improve outcomes.

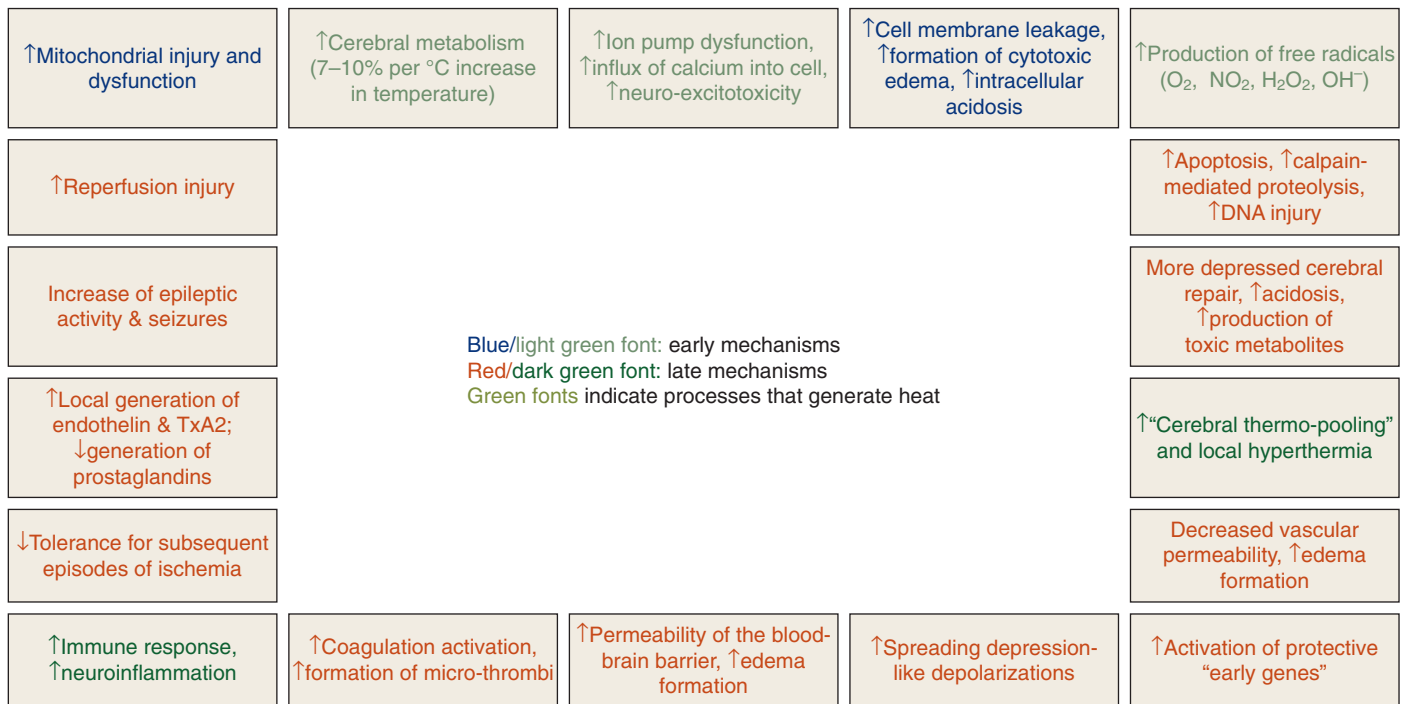


FIGURE 41-1 ■ Mechanisms underlying ischemia-reperfusion injury. (Adapted, with permission, from Polderman KH. Mechanisms of action, physiologic effects, and complications of hypothermia. *Crit Care Med* 2009;37:S186–S202.)

Thus, the potential benefits of fever should be weighed against the risks. This balance may shift even within the same patient, with protective effects of a febrile response outweighing harm in some phases of a disease, while harm outweighs benefits in other phases. The overwhelming majority of patients with acute brain injury is likely to suffer harmful consequences of fever and will benefit from strict fever control or even therapeutic hypothermia (see below).¹¹ As the destructive processes play out over periods of several days and can be restarted by new episodes of ischemia, maintaining an “appropriate” core temperature should be a key goal in care of critically ill patients, especially in those with acute neurologic injuries.^{1,2,11}

As with blood pressure and ventilation, an “optimal” temperature can be determined to suit the individual needs of the patient. Usually, this is normothermia, although in some situations (such as following anoxic brain injury), a below-normal temperature may provide additional benefits; meanwhile, in other situations (such as severe infections in non-brain-injured patients), a mild degree of hyperthermia may be beneficial.

CLINICAL EVIDENCE AND POTENTIAL INDICATIONS FOR TEMPERATURE CONTROL

Though randomized controlled trials (RCTs) assessing benefits of fever control are still lacking, based on the pathophysiologic data discussed above as well as dozens of observational studies showing a link between fever and adverse outcomes, maintaining normothermia is a widely accepted goal in patients with all types of acute brain injuries. Some observational and case-control studies in patients with SAH, AIS, and TBI have reported that aggressive temperature control using a combination of antipyretic drugs and mechanical cooling devices can indeed improve outcomes.^{28,29} Whether hypothermia can further improve outcomes compared to strict fever control remains a matter of debate.

Evidence for use of fever control and/or TH for specific types of injuries is briefly discussed below.

1. Neonatal Asphyxia

Seven multicenter RCTs in babies with perinatal asphyxia have reported significant improvements in neurologic outcomes when treated with TH (32–34°C for periods of 48–72 hours).^{30–36} Benefits in neurocognitive function persist on multiyear follow-up into middle childhood.³⁷ The estimated number needed to treat for the therapy is six. Eight nonrandomized trials have reported similar benefits. Based on these studies, the use of TH in neonatal asphyxia should be considered standard of care.

2. Cardiac Arrest

Two RCTs where patients were cooled to 32–34°C and 44 nonrandomized before-after studies have reported significantly improved outcomes in patients with witnessed cardiac arrest (CA) and an initial rhythm of ventricular fibrillation or ventricular tachycardia.^{38–39} A small RCT comparing cooling protocols of 32.0°C to 34.0°C reported significantly better results with 32°C.⁴⁰ In contrast, a large 2013 RCT found no difference between strict temperature control at 36.0°C compared to that at 33.0°C.⁴¹ The conclusions of this study have been criticized for problems such as prolonged time (10 hours) to target temperature, temperature fluctuations during the maintenance phase, excessively rapid rewarming, potential selection bias limiting generalizability, and other issues.^{42–44} Thus, although there is general agreement on the need for targeted temperature management after witnessed cardiac arrest, the precise target temperature is still being debated. Current guidelines from the American Heart Association (AHA) and Neurocritical Care Society strongly recommend using TH in all patients who have return of spontaneous circulation following witnessed out-of-hospital CA with an initial rhythm of ventricular fibrillation or pulseless

ventricular tachycardia and recommend considering TH for patients with witnessed asystole or pulseless electrical activity arrest.^{45,46} The AHA guidelines recommend strict temperature management with a relatively wide temperature range of 32–36°C, followed by strict fever control.⁴⁵

3. Acute Ischemic Stroke

As outlined above, there is compelling evidence suggesting harmful effects of fever in AIS. Experimental data suggest that mild hypothermia applied in the hours following injury significantly improves neurologic outcomes.^{1–2} Three feasibility studies have used TH in combination with treatments aimed at achieving reperfusion through administration of clot-dissolving drugs and/or mechanical thrombectomy.^{47,48} In these studies, application of TH appeared feasible and safe, though one study reported a high rate of pneumonia in the intervention group (though still with a nonsignificant trend toward better outcomes). Several other nonrandomized trials with a limited number of patients have studied TH as a treatment for brain edema in patients with large middle cerebral artery (MCA) strokes.¹ Outcomes were better compared to historical controls; however, use of TH for this indication has largely been replaced by surgical decompression for malignant MCA infarctions.

The use of TH for a limited period of time in combination with reperfusion appears to be a promising approach, but no large RCTs addressing this issue have been performed to date. Strict fever management after AIS should be the goal of care, with use of TH limited to clinical trials.

4. Traumatic Brain Injury

Experimental data and numerous clinical studies have shown that hypothermia can be used to control intracranial pressure and reduce brain edema in patients with TBI.¹ More than 30 clinical trials enrolling different categories of patients with severe TBI and using periods of cooling ranging from 24 hours to more than a week have shown conflicting results.¹ Several studies using TH in early stages of TBI have reported improved outcomes, while one larger RCT found similar outcomes with strict fever control compared to TH. Several meta-analyses have been conducted, which have suggested benefits when TH was used in early stages and for prolonged periods (>3 days) and when slow rewarming protocols were used.^{1,49} In contrast, a recent large trial using TH to treat refractory ICP rises in later stages of TBI reported significantly worse outcomes in the TH group.⁵⁰ Based on these conflicting results, strict fever control should be the goal in patients with severe TBI, while TH should be used only in the context of clinical trials.

5. Acute Myocardial Infarction

Numerous studies in different animal models (rats, rabbits, sheep, pigs, and dogs) have shown that cooling decreases myocardial injury and reduces infarct size in acute myocardial infarction (AMI).^{1,51–62} Reductions in infarct size ranged from 30% to 90% in these studies, depending on the animal model, area of the heart involved (more cardioprotection in anterior wall infarcts in some experiments), and duration of ischemia.^{51–62} Crucially, hypothermia is only effective when induced before reperfusion; in animal models, the effect is largely lost when cooling is initiated after or even during reperfusion.^{51–62}

Clinical studies attempting to use hypothermia in AMI have been limited by the difficulties in achieving hypothermia before reperfusion. A 2002 RCT randomized 42 patients to PCI with or without hypothermia and reported a nonsignificant infarct size reduction (2% vs. 8% of left ventricular mass).⁶³ Two subsequent RCTs failed to achieve target temperature in the majority of patients enrolled, although both studies found apparent benefits in those patients where core temperatures <35°C were reached before reperfusion (COOL-MI: infarct size 9.3% vs. 18.2%, $P = 0.05$, ICE-IT: 12.9% vs. 22.7%, $P = 0.09$).⁶⁴ However, the number of patients in these subgroups was small, and the subgroups

were not predefined. A subsequent small randomized feasibility trial and a subsequent larger trial (CHILL-MI) used a combination of cold fluid infusion and insertion of an endovascular cooling device to rapidly induce hypothermia. The CHILL-MI trial reported significant reductions in infarct size and lower incidence of heart failure at 45 days in patients with early anterior wall myocardial infarction (MI) who received a PCI within 4 hours⁶⁵; no benefits were seen if treatment was delayed longer, and no effect was noted in patients with inferior wall MI. As achieving low temperatures before reperfusion seems to be required to effect benefits in AMI, newer and more rapid cooling technologies may be required for this indication.⁶⁶

6. Other Potential Indications

Under the right circumstances, hypothermia can improve myocardial contractility (Table 41-1) and has been used in several small studies to treat cardiogenic shock.^{67–73} Several small case series have described the use of hypothermia to treat intracranial hypertension and hepatic encephalopathy in patients with acute liver failure.^{74–77} The appropriate target temperature and duration remain unclear, and in most studies, TH was used as a bridge to transplantation. Some case series and case control studies have reported successful use of hypothermia for adult respiratory distress syndrome,^{78,79} grand mal seizures,^{80,81} SAH,^{82–84} and spinal cord injury.⁸⁴ A larger study assessing TH for severe spinal cord injury is currently ongoing.⁸⁵ The use of TH in all these indications is still experimental, though fever control is regarded as standard of care.

PRACTICAL ASPECTS

Temperature can be increased by *conserving* heat (mainly through vasoconstriction of arteries in the skin) and by *generating* heat (mainly through shivering). Under normal circumstances, vasoconstriction begins at a core temperature of around 36.5°C; the reduction in heat loss resulting from cutaneous vasoconstriction is $\pm 25\%$.⁸⁷ The effectiveness of heat conservation and heat generation decreases with age; this is due to a less effective vascular response (i.e., less vasoconstriction), decreased ability to detect small temperature changes (leading to a slower counterregulatory response), and a lower basal metabolic rate.^{2,87} This means that in general, fever control and induction of hypothermia are easier to achieve and maintain in older patients than in younger ones.

Heat generation through shivering is usually much more active, and, therefore, more effective at temperatures close to the normal range than at temperatures that are several degrees below normal. In patients with a normal hypothalamic set point, the shivering threshold is $\pm 1^\circ\text{C}$ below the vasoconstriction threshold, or $\pm 35.5^\circ\text{C}$. The shivering response peaks at core temperatures around 35°C and decreases significantly at temperatures below 33.5–34°C; in most patients, shivering ceases completely at core temperatures around 31°C, though there is a wide variability among patients. There can be variability within the same patient as well if and when the hypothalamic set point changes (see below).^{2,87,88}

Shivering can be problematic for patient management. Sustained shivering can double the metabolic rate, thereby preventing effective temperature management. In addition, it increases oxygen consumption (by 40%–100%), breathing, and heart rate^{3,87}; furthermore, it induces a stress-like response with tachycardia, hypertension, and elevated intracranial pressure and has been linked to an increased risk of morbid cardiac events and adverse outcomes in the perioperative setting.^{1,3} Therefore, shivering should be aggressively and preemptively controlled, and shivering management should be an integral part of the temperature management strategy. Some common antishivering measures and drug regimens are listed in Table 41-2 and Box 41-1. As explained above, shivering will generally be most active at temperatures around 2°C below the hypothalamic set point (1°C below the skin vasoconstriction threshold).^{2,87} Febrile patients with acute brain injury are likely to have an *elevated* hypothalamic set point, so shivering will occur at significantly higher temperatures.

TABLE 41-1 Effects of Cooling on Key Physiologic Parameters

| | |
|--------------------------------|---|
| Cardiovascular and hemodynamic | <p>Mild hypothermia (32–34°C) decreases heart rate (unless there is a stress-mediated tachycardia, which may occur if the patient is shivering or is otherwise uncomfortable). Of note, the occurrence of hypothermia-induced bradycardia predicts better outcomes in patients following cardiac arrest.⁹²</p> <p>Experimental evidence suggests that mild hypothermia increases membrane stability, thereby decreasing the risk of arrhythmias and improving the likelihood of successful defibrillation. However, more profound (<28°C) hypothermia can increase the risk of arrhythmias, which may be refractory to antiarrhythmic drugs.⁸⁷ Therefore, care should be taken to keep core temperature $\geq 30^\circ\text{C}$. The effect on <i>myocardial contractility</i> is strongly dependent on heart rate. If the heart rate is allowed to decrease along with the temperature, myocardial contractility, as measured by systolic function, usually increases, although there may be a mild degree of diastolic dysfunction. If the heart rate is artificially increased through administration of chronotropic drugs or a pacing wire, myocardial contractility decreases.^{93–96}</p> <p>The hemodynamic effects of TH lead to a decrease in cardiac output (by about 25% when temperature decreases from 37 to 32°C). As metabolic rate will decrease by 35–50%, the balance between supply and demand is improved.</p> <p>Central venous pressure usually rises, and there is also an increase in arterial resistance and a slight rise in blood pressure. This rise in mean arterial pressure is caused by hypothermia-induced vasoconstriction of peripheral arteries and arterioles. This effect is absent or less pronounced in cerebral arteries, where the balance between cerebral blood flow and cerebral metabolism (as measured by oxygen and glucose utilization) is maintained or improved.</p> |
| Electrolytes | <p>Electrolyte disorders may develop especially in the induction phase of cooling, due to a combination of increased renal excretion and intracellular shifts.⁹⁷ Such electrolyte disorders can increase the risk of arrhythmias and have other adverse effects on outcome. Electrolyte levels should be monitored frequently in the induction and rewarming phases (Fig. 2) and maintained in the high-normal range. Potassium levels may rise during the rewarming phase, as potassium that was secreted into the cell in the induction phase is released. This is one of the reasons why rewarming should be done very slowly, giving the kidneys time to excrete the excess potassium. Hyperkalemia will not develop if rewarming is slow and if renal function is not grossly impaired.</p> |
| Other effects on metabolism | <p>Hyperglycemia. TH can decrease insulin sensitivity and reduce insulin secretion by pancreatic islet cells. Thus, patients treated with TH are at higher than average risk of developing hyperglycemia. Conversely, insulin requirements are likely to decrease during rewarming.</p> <p>TH leads to an increase in the synthesis of glycerol, free fatty acids, ketonic acids, and lactate, causing a mild metabolic acidosis in most patients that does not require treatment. In contrast to the pH levels measured extracellularly, <i>intracellular</i> pH levels increase slightly during cooling.</p> |
| Ventilation | <p>The TH-induced decrease in oxygen consumption and CO₂ production should lead to an adjustment in ventilator settings, and blood gases should be monitored frequently, especially during the induction phase. If ventilator settings are not adjusted, this can lead to hypocapnia and cerebral vasoconstriction.</p> <p>A complicating factor is that blood gas values are <i>temperature dependent</i>, and, as most blood gas analyzers warm blood samples to a temperature of 37°C, this should be accounted for prior to analysis; PO₂ and PCO₂ values should also be corrected for temperature. For example, in a patient with a core temperature of 30°C and pCO₂ determined to be 40 mm Hg in an uncorrected measurement, the temperature-corrected pCO₂ value would be 29 mm Hg. In the same patient with an uncorrected PO₂ of 100 mm Hg, the temperature-corrected value would be 73 mm Hg.</p> <p>Further, it is unclear whether target PCO₂ should be kept constant (e.g., at 40 mm Hg) regardless of the actual body temperature (<i>alpha-stat</i>) or corrected for the actual body temperature (so that the “true amount” of CO₂ increases during hypothermia: <i>pH-stat</i>). Which method is better for management of hypothermic patients has not been conclusively settled, but regardless of whether alpha stat or pH stat is used, the effect of temperature on PO₂ should always be taken into account. This also applies to measurements of mixed venous or venous saturation.</p> <p>If it is not possible to obtain blood gas results measured at the patients’ true core temperature, values can be estimated using the following rule of thumb: for pO₂, <u>subtract</u> 5 mm Hg for every 1°C below 37°C; for pCO₂, <u>subtract</u> 2 mm Hg for every 1°C below 37°C; for pH, <u>add</u> 0.012 points for every 1°C below 37°C.</p> |
| Infections | <p>Hypothermia impairs immune function and inhibits inflammatory responses. Indeed, this is one of the mechanisms through which TH can convey protective effects. A recent meta-analysis reported a mild increase in risk of ventilator-acquired pneumonia and bacteremia associated with TH. In patients treated with TH, assessment for infection should include machine workload (i.e., the energy expenditure of the cooling device to maintain target temperature). If energy expenditure increases and the patient is not shivering, this could indicate the presence of infection.</p> <p>Hypothermia also increases the risk of wound infections.</p> <p>Extra care should be taken in cooled patients to prevent bed sores, which are more likely to show progression and/or impaired healing. In addition, extra attention should be paid to catheter insertion sites and to any surgical wounds that may be present.</p> |
| Coagulation | <p>TH induces a mild bleeding diathesis, with increased bleeding time due to effects on platelet count, platelet function, the kinetics of clotting enzymes and plasminogen activator inhibitors, and other steps in the coagulation cascade. Standard coagulation tests will show no abnormalities unless they are performed at the patients’ actual core temperature. The risk of clinically significant bleeding induced by hypothermia in patients who are not already actively bleeding is very low. None of the large clinical trials in patients with TBI, SAH, stroke, or postanoxic coma have reported significantly increased risks of bleeding associated with hypothermia. Nevertheless, patients who are actively bleeding or have a high bleeding risk should not be cooled to temperatures <35°C.</p> |
| Drug clearance | <p>The half-life of many drugs, in particular those metabolized by the liver, can be significantly increased by TH. These include vasopressors (adrenalin and noradrenalin), benzodiazepines, fentanyl, remifentanyl, morphine, propofol, barbiturates, vecuronium, rocuronium, atracurium, phenytoin, nitrates, propranolol, and some volatile anesthetics. In most cases, the effect of hypothermia is to increase drug levels and/or enhance the effect of the drug.</p> <p>It is likely that the metabolism of other drugs with hepatic clearance will be affected by temperature in a similar way, based on their excretion mechanism. These mechanisms should be taken into account when treating patients under hypothermic conditions. Sedation and analgesia should be a specific focus of attention, especially considering that benzodiazepines and opiates can accumulate during hypothermia, complicating neurologic assessment after treatment.</p> |

TABLE 41-2 Medications (Sedating and Nonsedating) That Can Be Used to Control Shivering

| MEDICATIONS TO COMBAT SHIVERING | |
|--|--|
| NONSEDATING | SEDATING |
| Magnesium (MgSO ₄ , MgCl ₂) | Meperidine/pethidine |
| Buspirone | Opiates |
| Ondansetron | Quick-acting: fentanyl, remi-fentanyl; |
| Nefopam | Slow-acting: tramadol, morphine |
| Clonidine | Propofol |
| Ketanserin | Benzodiazepines (midazolam, temazepam, diazepam, etc.) |
| Urapidil | Dexmedetomidine |
| Phystostigmine | |
| Doxapram | |
| Paralytic agents | |

BOX 41-1 Examples of Antishivering Measures and Drug Regimens

POTENTIAL ANTISHIVERING MEASURES

Skin counterwarming is highly effective in most patients and can significantly reduce the dose of antishivering drugs (including sedation) required to manage shivering. This is particularly important when using TH in nonmechanically ventilated patients, such as when treating patients with AMI or AIS.

SOME COMMONLY USED ANTISHIVERING DRUG REGIMENS

Magnesium (bolus 4-8 g over 10-30 minutes, magnesium drip 0.5-1 g/hour; target serum levels up to 2-2.5 mmol/L (4.8-6 mg/dL); extra bolus if shivering is observed if serum level is not yet at target/maximum)

Buspirone 15-60 mg by mouth

Ondansetron 8-mg bolus (once)

Meperidine bolus 12.5-50 mg; some studies have used meperidine drips of 0.5-1.0 mg/kg

Fentanyl bolus 12.5-50 µg, drip 50-200 µg/hour

Dexmedetomidine 0.5-1 µg/kg loading dose, 0.2-1.0 µg/kg/hour maintenance dose

Addition of **acetaminophen** (paracetamol) and/or (in selected patients) **NSAIDs** can help reduce temperature (by between 0.3 and 0.7°C).

The most important physiologic changes associated with induction of hypothermia and some management strategies are listed in [Box 41-2](#). Temperature elevations have the opposite effects.

Another important parameter affecting ease and speed of cooling is body mass: obese patients are more difficult to cool, especially with surface cooling, due to the insulating properties of adipose tissue and because of the greater mass that requires cooling.

Finally, an issue that often confounds studies dealing with the efficacy of temperature management is that severe brain injury can significantly diminish or even obviate the thermoregulatory response; it is, therefore, much easier to cool patients with very severe brain injury (and absent shivering response) than those with less severe injury. Thus “easy” temperature control is, paradoxically, often a poor prognostic sign, whereas increased workload of cooling devices predicts better neurologic outcomes.^{2,87-88}

COOLING METHODS

Cooling technologies can be broadly divided into invasive (core cooling) and noninvasive (surface cooling) methods. [Figure 41-2](#) depicts “optimal” temperature control for a target of 32.0°C (see [Fig. 41-2, A](#)) and a target of 36.0°C (see [Fig. 41-2, B](#)), respectively.

BOX 41-2 Most Frequently Occurring Hypothermia-Induced Changes in Laboratory Measurements

Increase in serum amylase levels
Mild to moderate thrombocytopenia (platelet count 30-100 × 10¹²)
Increase in serum lactate levels (2.5-5 mmol/L)
Hyperglycemia (risk of hypoglycemia during rewarming when insulin requirements decrease)
Electrolyte disorders (low Mg, K, P, Ca)
Increase in liver enzymes (SGOT and SGPT)
Mild metabolic acidosis
Mild coagulopathy
Changes in blood gasses

The theoretical advantages of invasive cooling over surface cooling are as follows:

1. Some studies suggest greater speed of hypothermia/normothermia induction when core cooling is used; however, it is unclear whether more rapid induction improves outcome.
2. Invasive cooling has potentially fewer and smaller temperature fluctuations in the maintenance phase (see [Figs. 41-2, A and B](#)).
3. Some types of endovascular catheters allow continuous central blood temperature measurement.
4. There is no risk of surface cooling-induced skin lesions.
5. The patient is easily accessible—that is, there is no need to cover large areas of the skin to achieve cooling.
6. Less medication may be needed to control shivering because there is more effective shivering suppression with skin counterwarming (i.e., the entire surface area can be warmed using warm air, leading to a significantly diminished shivering response).^{2,6,87,88} In a related issue, there may be better tolerance and less shivering with endovascular cooling when TH is used in awake, nonintubated patients (e.g., for treatment of AIS or AMI to reduce infarct size).

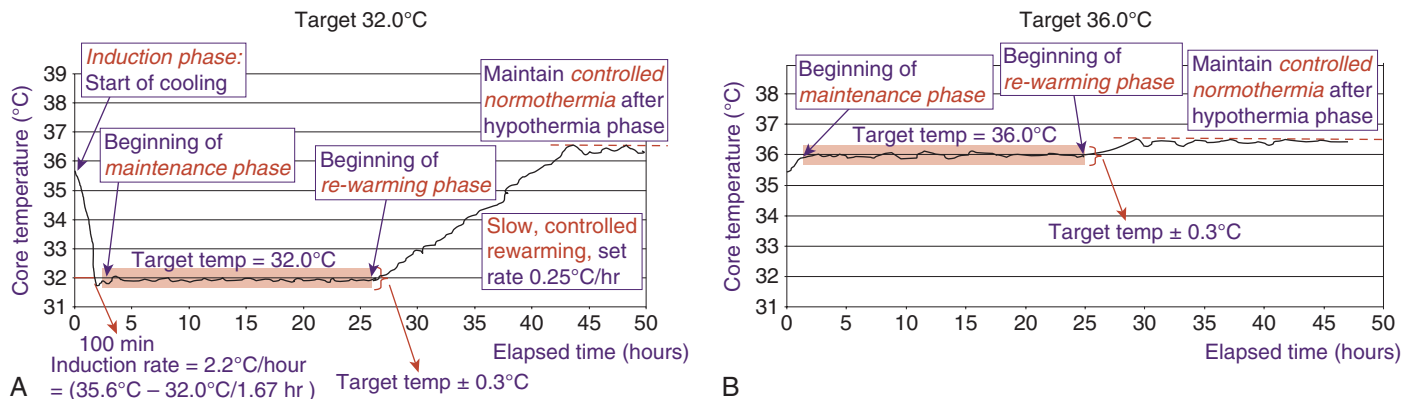
The theoretical advantages of surface cooling over invasive cooling are:

1. Ease of use; can be applied by nurses or nurse practitioners without intervention by a physician
2. No invasive procedure required
3. No delay in initiation of cooling, can be started immediately
4. (Compared to endovascular cooling) no risk of catheter-induced thrombus formation
5. Can be more easily applied outside the ICU setting
6. Combines better with infusion of refrigerated fluids (as this allows simultaneous cooling of both the core compartment and peripheral compartment of the body)

The available data on safety and efficacy of different cooling technologies are limited.^{87,88} Most published studies are small and have evaluated only a single cooling device or method; furthermore, comparative studies have often been retrospective or nonrandomized and/or have enrolled only small numbers of patients. Two large retrospective studies and one RCT suggested that invasive cooling has more rapid and effective temperature control and may help reduce nursing workload⁸⁹⁻⁹¹; in addition, these studies all reported nonsignificant trends toward more favorable outcomes with more accurate temperature control.

In summary, temperature is a key physiologic parameter in critically ill patients. It should be regarded in the same way (and controlling it granted the same importance) as blood pressure, heart rate, and ventilation parameters. As with these other parameters, normothermic values are desired, particularly if the patient has acute brain injury. As a general rule, fever should be avoided, which is easier said than done as the vast majority of these patients will develop fever as both a direct and indirect consequence of the neurologic injury. The availability of improved mechanical cooling devices has allowed improved and more accurate temperature control, and preliminary data suggest that this can lead to further improvements in outcomes.

Different stages of temperature management



The most common anti-shivering measures

- Skin counter-warming using forced air warming blankets.*
- Non-sedating drugs: magnesium (bolus 2–4 grams over 10–20 minutes if shivering occurs; drip with target serum levels up to 4–5 meq/dL; bolus of 2–4 grams IV in 5–20 minutes if shivering occurs); buspirone 15–30 mg;[†] clonidine 0.25–2 mcg/kg/hr.^{‡,§}
- Additional options WITH sedating effect: meperidine 25–100 mg bolus;[‡] opiates (preferably fentanyl bolus dose 25–100 mcg, drip 50–200 mcg/hr, or remi-fentanyl bolus 1 mcg/kg, drip 0.05–0.2 mcg/kg/min);^{‡,¶} dexmedetomidine bolus 0.5–1 mcg/kg in 10 min, drip 0.2–0.6 mcg/kg/hr;^{‡,¶} propofol drip 10–50 mcg/kg;^{‡,¶} benzodiazepines (midazolam, temazepam, or diazepam bolus and/or drips).^{‡,¶}

FIGURE 41-2 ■ “Optimal” temperature control. **A**, Temperature management with set target of 32°C. For the *induction phase* the aim is to get temperature below 34°C and down to the target temperature as quickly as possible. A small overshoot ($\leq 1^\circ\text{C}$) should be regarded as acceptable provided temperature remains $>30^\circ\text{C}$. For the *maintenance phase*, the target is tight control of core temperature, with minimal fluctuations (ideally never more than 0.3°C). The *rewarming phase* should be slow and controlled (warming rate 0.2–0.25°C/hour.). **B**, Temperature management with set target of 36°C. For the *induction phase*, the aim is to get temperature to 36.0°C as quickly as possible. For the *maintenance phase*, the target is tight control of core temperature, with minimal fluctuations (ideally never more than 0.2–0.3°C). More shivering is likely because the target temperature is closer to normal, leading to an enhanced shivering response. There is a greater risk of slipping into supra-normal (febrile) temperature range, especially because brain temperature exceeds core temperature by 1.0–2.0°C at this temperature. *Basic measure, should be used in all patients treated with TTM; if surface cooling used the noncooled areas should be warmed, especially face, hands, and feet. The (theoretical) warming effect on systemic temperature is negligible. Note: The efficacy decreases at higher core temperatures with lower core-skin gradients. [†]PO; [‡]IV; [§]Not available for IV use in the United States; [¶]Use generally limited to intubated patients. (Adapted, with permission, from Polderman KH. How to stay cool in the intensive care unit? Endovascular versus surface cooling. *Circulation* 2015;132:152–157.)

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Extracorporeal membrane oxygenation (ECMO), also frequently referred to as extracorporeal life support (ECLS), was first used in clinical settings for respiratory failure in 1972.¹ However, interest has grown substantially in the past 10-15 years, especially in the adult population (Fig. 42-1).

■ TECHNICAL ASPECTS

ECMO can be divided in venoarterial and venovenous modalities (Fig. 42-2).

Venoarterial ECMO

In the venoarterial mode, ECMO removes deoxygenated blood from the central venous system and returns pressurized, oxygenated blood to the systemic arteries. Access can be established directly in the right atrium and aorta via median sternotomy (central) or peripheral vessels (Fig. 42-2, C). Venous cannulation can be performed via the right internal jugular or femoral vein.

Access via the femoral artery is preferred in adults while infants often require carotid artery cannulation. The monitoring of distal blood flow in femoral vessel cannulation should be performed to prevent ischemia or compartment syndrome from venous engorgement. In femoral artery cannulation, a distal perfusion cannula can be placed retrograde and connected via a sidearm to the arterial tubing to provide distal perfusion (Fig. 42-2, A).^{2,3} An alternative approach to femoral cannulation involves sewing a 6- or 8-mm Dacron graft in an end-to-side fashion to the femoral artery to preserve distal flow into the leg.⁴ As flow from the femoral arterial cannulation is retrograde up the aorta, the native cardiac output will often supply the upper body. During severe respiratory failure, hypoxic perfusion to the upper body may result in a “blue upper body, red lower body” syndrome. If cerebral or cardiac oxygenation is deemed to be inadequate, a cannula can be placed into the venous system (usually the right internal jugular vein) and Y’ed into the arterial return from the ECMO circuit. Some portion of oxygenated blood can be directed into the right heart in this hybrid mode and improve oxygenation of the upper body. Similarly, a side graft of dacron⁵ can be used for the axillary arteries (Fig. 42-2, B). However, the upper extremities are more susceptible to hyperperfusion and the development of disabling compartment syndrome.⁶

Venovenous ECMO

In venovenous support, blood is both withdrawn and reinfused into the venous circulation. Thus, adequate cardiac function is required to deliver blood to the systemic circulation. Recirculation of oxygenated blood withdrawn back into the ECMO circuit prior to systemic delivery can severely impact the efficiency of the system. Recirculation can be limited by the return of oxygenated blood in a more proximal location when compared to the drainage (Fig. 42-2, E).

While the femoral veins have been typically utilized, cannulation of the neck vessels, including the internal jugular and the subclavian veins, can provide the patient with greater mobility and prove beneficial in rehabilitation.

A newer generation of cannulas includes the dual-lumen Avalon catheter (Maquet Corp.), which can drain blood from the inferior and superior venae cavae, as well as reinfuse oxygenated blood directly at the tricuspid valve orifice, reducing recirculation. The positioning of this cannula requires fluoroscopy or transesophageal echocardiography and added technical expertise in the manipulation and securing of the cannula^{7,8} (Fig. 42-2, D).

Physical Systems for ECMO

The ECMO system includes cannulas for inflow and outflow, a pump, an oxygenator, and a variety of diagnostic ports and monitors.

Pumps used for ECMO are of the centrifugal or roller types. While each has certain advantages, centrifugal pumps are now most common in adults and used in over 50% of pediatric patients. These pumps are easy to set up and initiate and are much more compact than roller systems. Potential advantages include ease of transport, decreased blood product destruction, and durability. Hemolysis and bleeding complications are lower in some reports and higher in others.

The new-generation membrane lungs made of polymethylpentene are low resistance, easy to prime, have excellent gas exchange, and are reliable often for weeks at a time. The oxygenators used for ECMO should be compact, have low priming volumes, and be reliable over prolonged periods of use.

MANAGEMENT OF ANTICOAGULATION AND BLOOD TRANSFUSION

Despite significant progress in ECLS technology over past decade, thrombosis, embolism, and bleeding remain leading causes of morbidity for patients on ECLS support.⁹⁻¹¹ Exposure of blood to nonbiologic surfaces activates both coagulation factors and platelets, resulting in a prothrombotic state. Intravenous unfractionated heparin (UFH) is the most frequently used anticoagulant that potentiates the activity of intrinsic antithrombin (AT). Moreover, the most commonly used assay to titrate the efficacy of UFH is activated clotting time (ACT). The typical goal of ACT for a patient on ECLS is in the range of 180-220 seconds.¹² Activated partial thromboplastin time (aPTT) assesses the intrinsic and common coagulation pathways. The goal of aPTT is usually between 50 and 70 seconds. In addition, anti-Xa monitoring for the heparin effect is replacing ACT in many centers, with goal levels of 0.3-0.7 IU/mL. No anticoagulation regimen has been shown to be more effective than another in preventing bleeding or clotting.

Patients with suspected heparin-induced thrombocytopenia (HIT) should be switched from heparin to a direct thrombin inhibitor (DTI) (e.g., bivalirudin or argatroban). Therapy with DTIs is typically guided by aPTT in the range 50-70 seconds.^{13,14}

While controversy regarding the goal hemoglobin or platelet count exists, the values commonly applied are provided below¹⁵:

| | |
|--------------------------------------|----------|
| • Platelets (cells/mm ³) | >40-50K |
| • INR | <1.6-1.7 |
| • Fibrinogen (mg/dL) | >100 |
| • Hemoglobin (g/dL) | >7-8 |

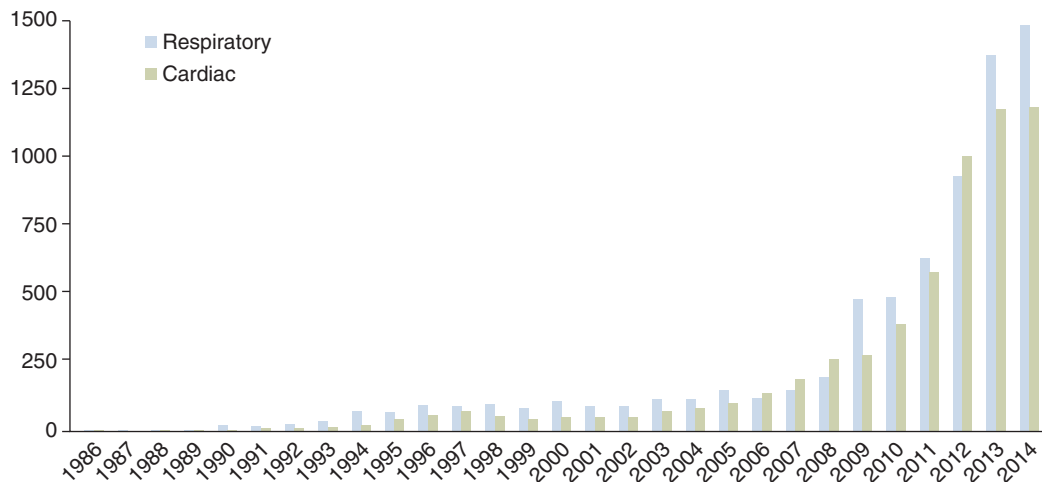


FIGURE 42-1 ■ Cardiac (green) and respiratory (blue) extracorporeal life support in adults (greater or equal to 16 years of age), by year in therapy. (Adapted from the Extracorporeal Life Support Organization, www.elso.org.)

ECMO IN RESPIRATORY FAILURE

The primary indication for application of venovenous ECMO is the presence of respiratory failure in the absence of cardiac dysfunction. Venous blood is removed from circulation and, after gas exchange, returns into the venous circulation already enriched with oxygen before entering pulmonary circulation.

ECMO in Acute Respiratory Distress Syndrome (ARDS)

Both the encouraging survival rates of adult ECMO during the H1N1 influenza epidemic and the CESAR trial (which noted increased survival at 6 months in patients receiving care and/or ECMO at an experienced center) have sparked interest for the use of ECMO in severe adult ARDS. Another randomized trial of early ECMO versus conventional therapy for severe ARDS is ongoing (EOLIA trial, NCT01470703) in response to criticism of the CESAR trial.^{9,16-20}

Typical triggers for ECMO initiation include severe hypoxemia, severe hypercapnia with uncompensated acidemia, and excessive airway pressures (Box 42-1). Ideal candidates for ECMO are young patients with severe ARDS and no other organ dysfunction. However, several recent reports of successful ECMO have been published in patients with a variety of comorbidities, multiorgan failure, sepsis, trauma, and hemorrhage.

The recent development of the RESP score, PRESERVE score, and others may prove to be beneficial in identifying optimal patients for ECMO and provide prognostic information.²¹ An online RESP score calculator can be found at <http://www.respscore.com/>.

Once a patient in severe ARDS is placed on ECMO, further management is directed at minimizing ventilator-induced lung injury (VILI) and providing “lung rest.” This approach typically includes pressure-controlled ventilation, limiting the peak inspiratory pressure under 20-25 cm H₂O, a high PEEP of 10-15 cm H₂O, respiratory rate of 6-10/min, and lowest FiO₂ possible.^{22,23} Patients will often have very low tidal volumes (2-4 cc/kg) due to poor compliance in injured lungs.²² Some experts suggest that the application of ECMO to the patients with severe ARDS should be instituted as early as possible to minimize VILI early in the course of the disease.²²

The use of spontaneous breathing modes, to the extent of extubation or early tracheostomy, is currently a trend, especially in adult patients. Minimization of sedation, avoidance of mechanical ventilation, and maintenance of physical activity allow early mobilization and

BOX 42-1

Indications for ECMO in Cases of Severe ARDS²²

Severe hypoxemia—P/F ratio < 50-80
 Severe hypercapnia associated with acidemia (pH < 7.15)
 Excessive end-inspiratory plateau pressure (>35-45 cm H₂O) in the presence of deep sedation and use of NMBS
 Failed proning maneuver
 Potentially reversible cause of respiratory failure
 Absence of conditions associated with poor prognosis

avoidance of deconditioning, which may hasten the recovery post ECMO and improve the long-term quality of life.

ECMO Use in Lung Transplantation

Over the past 5 years, several centers have reported the feasibility of ECMO in patients awaiting lung transplantation with favorable outcomes.²⁴⁻²⁶ An alternative to conventional VV-ECMO is the recently introduced arteriovenous pumpless lung support (iLA; NovaLung) that has been successfully used for hypercapnic respiratory failure and as a parallel low-resistance oxygenator in patients with severe PHTN and RV failure.²⁷

In the posttransplant period, ECMO has been successfully used to support patients with primary graft dysfunction (PGD).²⁸ Although ECMO substantially improves the survival of patients with PGD, allograft function remains considerably impaired in this cohort.²⁹

ECMO Use in COPD

Recently, ECMO and extracorporeal CO₂ removal (ECCO₂R) have been used in patients with chronic respiratory failure due to COPD exacerbation. ECCO₂R systems that utilize small single- or double-lumen catheters with low-flow pumpless or pump-driven circuits have been successfully used for the removal of 25%-50% of CO₂ that leads to a reduction of minute ventilation and the work of breathing.³⁰ In several small series, implementation of ECCO₂R has improved respiratory acidosis, prevented intubation, sped up liberation from mechanical ventilation, improved rehabilitation, and potentially decreased in-hospital mortality and length of stay.³⁰⁻³²

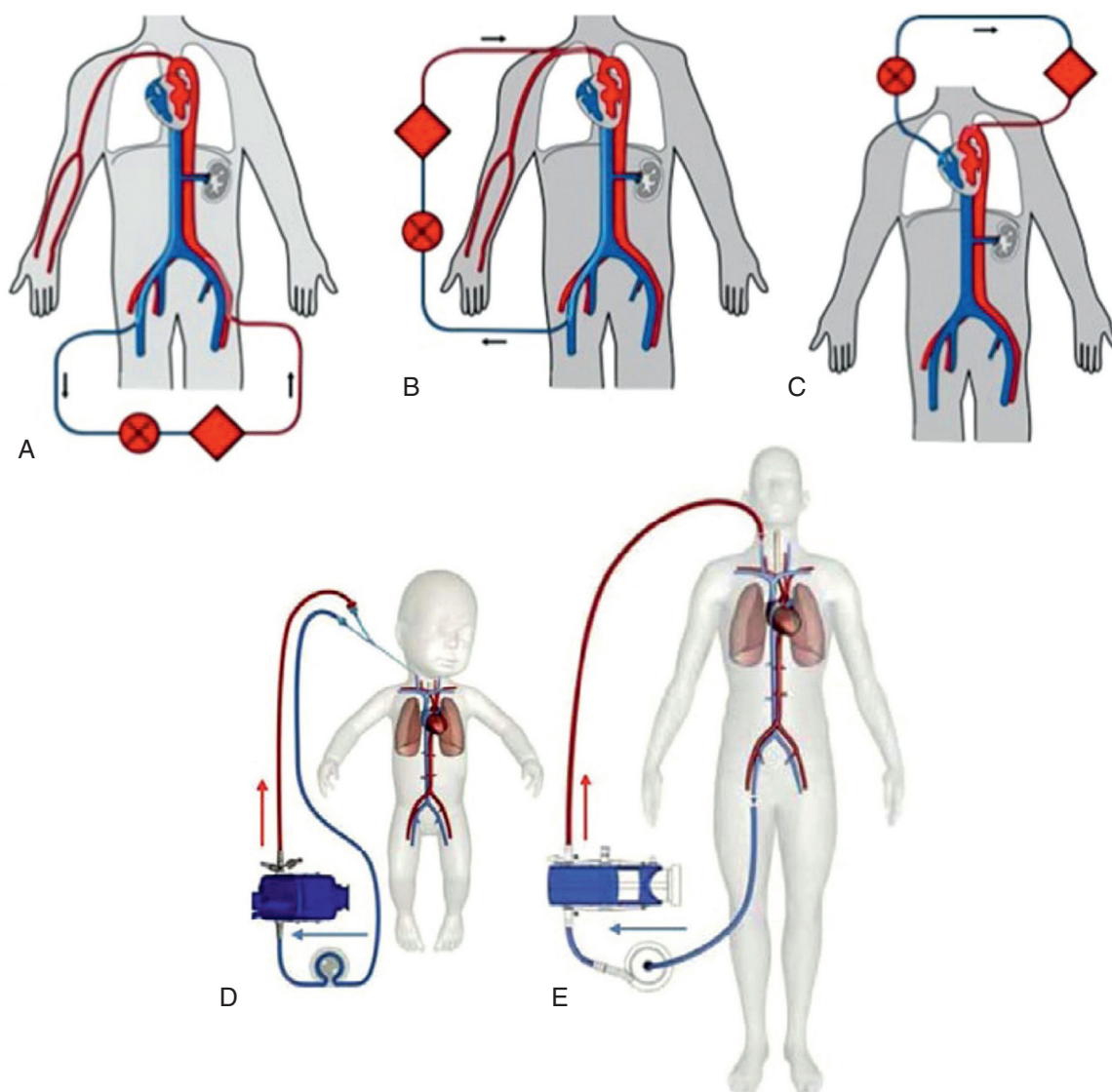


FIGURE 42-2 ■ Schematic of possible venoarterial (A-C) and venovenous (D,E) ECMO circuit configuration. (A) VA, peripheral, femorofemoral. (B) VA, peripheral, femoro-axillary cannulation. (C) VA, central cannulation. (D) VV, single, double-lumen cannula. (E) VV, two single lumen cannulas. ECMO, extracorporeal life support; VA, venoarterial; VV, venovenous. (Adapted from Sangalli F, Patroniti N, Pesenti A. ECMO—extracorporeal life support in adults. Springer, New York: 2014; Figs. 3-9 and 6-6.)⁶⁶

■ ECLS IN HEART FAILURE

Venoarterial extracorporeal support can be used to support the cardiovascular system in cases of cardiac or cardiopulmonary failure as described below.

Postcardiotomy Cardiogenic Shock (PCCS)

With the advent of new strategies for myocardial protection, rates of cardiogenic shock and the inability to wean from bypass have decreased to less than 10%.³³ If patients are unable to be weaned from cardiopulmonary bypass, existing cannulas for bypass can be connected to the ECMO circuit for central cannulation, while peripheral cannulation and chest closure may provide better hemostasis. As venoarterial ECMO increases the afterload of the left heart, rapid failure of the left ventricle can lead to left atrial distention, pulmonary edema, and hemorrhage. Decompression of the left heart can be facilitated with trans-

septal cannulation, and balloon septostomy to create an ASD, or direct LA venting.^{34,35}

The use of ECMO for PCCS is associated with a 25%-33% long-term survival rate, while up to 60% of patients are successfully weaned from ECMO.^{36,37} The majority of survivors recover adequate ventricular function to be weaned from ECMO within 72 hours. Conversion to a long-term assist device or consideration for heart transplant should be discussed if no recovery is obtained within the first 7 days of ECMO. Predictors of increased mortality include age > 70 years, high lactate levels, type A aortic dissection, double valve surgery, as well as presence of acute renal and liver failure.^{33,38}

Acute Myocardial Infarction (AMI)

Cardiogenic shock (CS) accompanies about 5%-7% of AMI. The use of ECLS in the presence of CS allows for the rapid stabilization of the myocardial oxygen supply-demand balance while maintaining

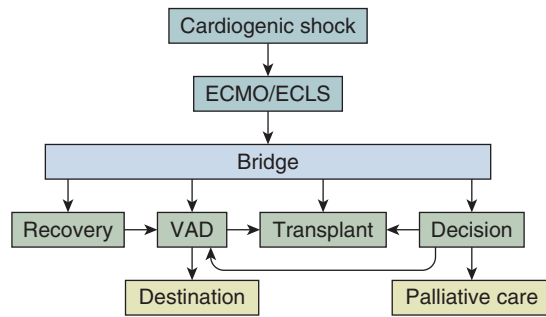


FIGURE 42-3 ■ Decision flow chart of ECLS use in cardiogenic shock/heart failure. VAD, ventricular assist device.

perfusion of the end organs. Once the patient is stabilized, every attempt for coronary revascularization should be made.³⁹ ECLS has been associated with a long-term survival rate between 28% and 35% in this group of patients. However, up to 60% of ECLS served as bridge to VAD or transplants.^{9,40}

End-Stage Heart Failure

Patients in NYHA class IV or INTERMACS class 2 heart failure who are inotrope-dependent or have acute decompensation may require cardiac support as a bridge to transplantation or the placement of a ventricular assist device. ECMO can provide adequate perfusion and reverse organ dysfunction serving as a “bridge to decision” when the suitability of the patient for long-term mechanical circulatory support (MCS) is unclear. Multiple reports suggest good results of ECMO serving as a bridge to transplantation or VAD implantation in patients with end-stage heart failure with a long-term survival rate of 36%-39%^{41,42} (Fig. 42-3).

Myocarditis

Patients with viral myocarditis typically present with new onset of severe single organ failure (cardiac) and have a very good prognosis for recovery. Venoarterial ECMO is used for circulatory support in such patients as recovery often occurs within days to weeks. Overall, the reported survival of patients with fulminant myocarditis supported with ECLS is between 63% and 70%, with 4%-10% of patients bridged to heart transplantation.^{43,44}

Extracorporeal Cardiopulmonary Resuscitation (ECPR)

Over 4800 patients in the ELSO registry have received ECMO during active cardiopulmonary resuscitation (ECPR), with a survival of 35%-37%. Adults have the lowest survival rate of 27%-30%.^{45,46} ECPR is used in several scenarios of profound cardiovascular collapse: stabilization and maintenance of hemodynamics after cardiac arrest and the successful return of spontaneous circulation (ROSC) during in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA). Several studies have reported ECLS use in 23%-41% of patients after CPR and ROSC. Compared to patients who were supported with ECLS in the absence of CPR, these groups had a two-fold increased risk of an unfavorable outcome.⁴⁷

Despite a higher mortality rate in patients placed on ECLS during CPR, several studies have shown a benefit of a 30-day survival up to 34%.⁴⁸ Time to ECMO from the initiation CPR has shown to be associated with the outcome while other reports find no difference in the outcome with CPR up to 60 minutes. Thus, adequacy of CPR is likely more important than the actual duration. Therefore, an assessment of the patient and a decision regarding the initiation of ECLS should be

performed by an experienced practitioner within 10-15 minutes of IHCA, with the assumption that the ECLS team and resources are available to initiate ECLS within 20-45 minutes.

The outcomes of patients with OHCA are historically poor, with survival in the range of only 10%-12%.^{39,49} However, a recent report from Australia noted a survival of 56% in out-of-hospital arrest patients who received bystander CPR and ECMO cannulation in the ED and a 60% survival in those with inpatient arrest.

Emerging Indications for ECLS

The successful use of ECLS in adult sepsis, sepsis-induced cardiomyopathy, and toxic shock syndrome has been reported in past decade.^{50,51} Recently, two large series have confirmed that ECLS should be considered in patients with refractory septic shock, demonstrating a survival rate of 23%-71%.^{36,52}

ECMO has been successfully used in patients with trauma,⁵³ severe drug intoxication,⁵⁴ and diffuse alveolar hemorrhage due to systemic disease.³⁷ It is considered the gold standard for rewarming following an accidental hypothermic cardiac arrest.^{55,56}

WEANING FROM ECMO

Weaning of VA ECMO is guided by improving hemodynamic echocardiography (TTE or TEE) at a reduced flow. Pulmonary artery catheters may also provide valuable information if present. Many patients require low doses of vasoactive agents to facilitate weaning. Careful assessment of biventricular function, hemodynamics, and the metabolic profile at a low flow or during a “clamp off” trial is mandatory. Clamping patients off of ECMO support provides the best indication of the adequacy of cardiopulmonary function. After some time (often 1-2 hours) at low flow (1 L) or clamped off from ECMO, if adequate hemodynamics, tissue perfusion, and gas exchange are obtained, decannulation is performed.⁵⁷

Weaning from VV ECMO should be initiated when the gas exchange and lung compliance begin to improve. Ventilator settings may be increased but remain at protective levels, and FiO_2 is increased to a maximum of 0.5-0.6. As the lung membranes are very efficient at removing carbon dioxide, the complete cessation of gas flow and “capping” of the lung membrane is required to fully evaluate the patient’s ability for gas exchange. Once the patient maintains stable gas exchange with minimal ECMO support and acceptable ventilator settings, ECMO can be discontinued.²² A recent international survey found that 16% of patients were removed from ECMO while not on a ventilator.

COMPLICATIONS

ECMO is highly invasive and has the potential for serious complications. The most common mechanical complication of adult respiratory ECMO is a failure of the oxygenator (16%), followed by cannula problems (7.7%). Bleeding and thrombosis remain the most common patient complications, and intracranial hemorrhage or thrombosis is the most devastating patient-related complication.⁹ Interestingly, complication rates are similar for respiratory or cardiac failure indications (Table 42-1). In a recent study of more than 1400 patients placed on VV-ECMO, the most frequent patient-related complication was hemorrhage.¹⁰ Cerebral infarction or hemorrhage occurred in 4%-6% of patients, with more than 20% of patients having confirmed documented infections. While circuit rupture rates have declined from 17% in the 1980s to less than 2% recently, the incidence of clot formation within the circuit has increased. Clinically relevant thrombosis was noted in 75% of postmortem exams, although clinicians identified only one-third of these events.

A recent meta-analysis of ECLS use for cardiac failure exhibited significant rates of ECLS-related complications.¹¹ Acute kidney injury was reported in 55% of patients, with 46% requiring renal replacement therapy (RRT). Major bleeding and significant infection occurred in

TABLE 42-1 Incidence and Outcomes of Complications for Adult ECLS

| COMPLICATION | PADEN, 2013 | | BROGAN, 2014 | CHENG, 2014 |
|------------------------|------------------|--------------|--------------|---------------------------------|
| | RESPIRATORY ECLS | CARDIAC ECLS | RESPIRATORY | CARDIAC |
| MECHANICAL | | | | |
| Oxygenator failure | 16.1 | 15.1 | | Not reported |
| Tubing rupture | 0.3 | 0.2 | 0.6 | |
| Pump malfunction | 2.1 | 0.7 | | |
| Cannula problems | 7.7 | 4.4 | | |
| Circuit clot | | | 18 | |
| PATIENT-RELATED | | | | |
| ICH | 3.9 | 1.7 | | |
| Stroke | | | 5 | 5.9 |
| Cannula site bleeding | 17.2 | 20.9 | | 41 (bleeding reported combined) |
| Surgical site bleeding | 16.7 | 25.5 | 31 | |
| GI bleeding | | | 4.8 | |
| Pulmonary hemorrhage | | | 9 | |
| Cardiac tamponade | 2.6 | 5.7 | | |
| Clinical seizures | 1.1 | 2.1 | 2 | |
| Acute renal injury | | | | 55.6 |
| Requiring RRT | | | 45 | 46 |
| Infection | | | 22.5 | 30.4 |
| LE ischemia | | | | 16.9 |
| LE fasciotomy | | | | 10.3 |
| LE amputation | | | | 4.7 |

(Adapted from Paden ML, Conrad SA, Rycus PT, Thiagarajan RR, ELSO Registry. Extracorporeal Life Support Organization Registry Report 2012. ASAIO J 2013;59(3):202-10; Brogan TV, Thiagarajan RR, Rycus PT, Bartlett RH, Bratton SL. Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multicenter database. Intensive Care Med 2009;35(12):2105-14; and Cheng R, Hachamovitch R, Kittleson M, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. Ann Thorac Surg 2014;97(2):610-6.)

41% and 30% of patients, respectively. A significant proportion of patients developed complications related to vascular cannulation, including 17% with lower extremity ischemia, of which 10% resulted in compartment syndrome and fasciotomies and 4.7% required amputations of the lower extremities.

PEDIATRIC ECMO/ECLS

The application of ECMO to pediatric patients has become commonplace in many centers throughout the world. Current data on the diagnoses and outcomes of the over 50,000 neonates and children receiving ECMO is presented in Table 42-2. The largest growth of ECMO use in children remains in the cardiac failure population. Compared to 10 years ago, the use of ECMO as a bridge to transplant or long-term ventricular assist devices is now also viewed as a viable technique. Children undergoing ECMO during active cardiac arrest and resuscitation also form an increasingly larger group of patients, with an overall survival of 35%-40% over time.

One factor that is noted in pediatric ECMO is the increasing complexity of patients who receive ECMO support (Fig. 42-4).⁵⁸⁻⁶⁰ A review from the ELSO found that patients with comorbidities before ECMO increased from 18% to 47% between 1993 and 2007.⁵⁸ While such patients had decreased survival as compared to patients without comorbidities, 40%-50% survived to hospital discharge. Factors associated with increased mortality from this report are shown in Table 42-3. The willingness of clinicians to apply ECMO to groups previously shunned is also noted in the number of patients with an underlying malignancy who are now receiving ECMO support. Such patients now comprise 1% of the pediatric ECMO cases, an amount three times larger than in years past, with an overall survival to discharge of 48%.⁶¹⁻⁶⁴

Other factors that may relate to the expansion of ECMO to groups previously excluded may be the advent of new technology. The ELSO

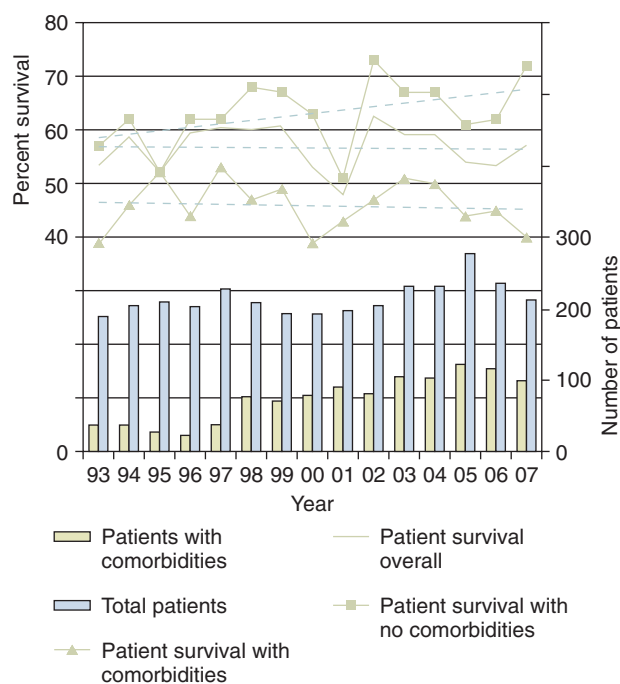


FIGURE 42-4 ■ Pediatric patients treated with extracorporeal membrane oxygenation for acute respiratory failure by year. Dashed lines represent a linear trend. (From Zabrocki LA, Brogan TV, Statler KD, Poss WB, Rollins MD, Bratton SL. Extracorporeal membrane oxygenation for pediatric respiratory failure: survival and predictors of mortality. Critical Care Medicine, 2011;39(2), 364-370. Fig. 1.)

TABLE 42-2 Demographics of ECMO Patients

| OVERALL OUTCOMES | | | | | |
|---|----------------|------------------|------------------|----------------------------|------------|
| | TOTAL PATIENTS | SURVIVED ECLS | | SURVIVED TO DC OR TRANSFER | |
| NEONATAL | | | | | |
| Respiratory | 27,728 | 23,358 | 85% | 20,592 | 74% |
| Cardiac | 5,810 | 3,600 | 62% | 2,389 | 41% |
| ECPR | 1,112 | 712 | 64% | 449 | 40% |
| PEDIATRIC | | | | | |
| Respiratory | 6,569 | 4,327 | 66% | 3,760 | 57% |
| Cardiac | 7,314 | 4,825 | 66% | 3,679 | 50% |
| ECPR | 2,370 | 1,313 | 55% | 976 | 41% |
| ADULT | | | | | |
| Respiratory | 7,008 | 4,587 | 65% | 4,026 | 57% |
| Cardiac | 5,603 | 3,129 | 56% | 2,294 | 41% |
| ECPR | 1,657 | 639 | 39% | 471 | 28% |
| TOTAL | 65,171 | 46,490 | 71% | 38,636 | 59% |
| NEONATAL RESPIRATORY RUNS BY DIAGNOSIS | | | | | |
| | TOTAL RUNS | AVERAGE RUN TIME | LONGEST RUN TIME | SURVIVED | % SURVIVED |
| CDH | 7,228 | 254 | 2549 | 3,691 | 51% |
| MAS | 8,684 | 133 | 1327 | 8,128 | 94% |
| PPHN/PFC | 4,800 | 155 | 1176 | 3,696 | 77% |
| RDS | 1,546 | 136 | 1093 | 1,300 | 84% |
| Sepsis | 2,856 | 143 | 1200 | 2,084 | 73% |
| Pneumonia | 376 | 249 | 1002 | 218 | 58% |
| Air leak syndrome | 133 | 171 | 979 | 98 | 74% |
| Other | 2,496 | 183 | 1843 | 1,519 | 61% |
| PEDIATRIC RESPIRATORY RUNS BY DIAGNOSIS | | | | | |
| | TOTAL RUNS | AVERAGE RUN TIME | LONGEST RUN TIME | SURVIVED | % SURVIVED |
| Viral pneumonia | 1,450 | 317 | 2968 | 940 | 65% |
| Bacterial pneumonia | 686 | 284 | 1411 | 402 | 59% |
| Pneumocystis pneumonia | 35 | 373 | 1144 | 18 | 51% |
| Aspiration pneumonia | 304 | 249 | 2437 | 208 | 68% |
| ARDS, postop/trauma | 185 | 248 | 935 | 115 | 62% |
| ARDS, not postop/trauma | 550 | 304 | 3086 | 297 | 54% |
| Acute respiratory failure, non-ARDS | 1,186 | 255 | 2429 | 641 | 54% |
| Other | 2,306 | 219 | 2465 | 1,195 | 52% |

Run time in hours. Survived = survival to discharge or transfer based on number of runs.

(Data adapted from the ECMO Registry of the Extracorporeal Life Support Organization [ELSO], Ann Arbor, Michigan, January, 2015. www.elseo.org.)**TABLE 42-3** Multivariate Odds Ratios for Survival in Pediatric Respiratory ECMO

| | ADJUSTED ODDS RATIO | CONFIDENCE INTERVAL |
|-----------------------|---------------------|---------------------|
| Asthma | 0.37 | 0.18-0.75 |
| ARDS/Sepsis | 1.53 | 1.11-2.11 |
| Pertussis | 1.71 | 1.05-2.77 |
| Fungal pneumonia | 5.88 | 1.18-29.32 |
| Treatment before 2001 | 1.22 | 1.03-1.44 |
| Age > 10 years | 1.37 | 1.10-1.71 |
| Ventilation > 14 days | 2.55 | 1.90-3.42 |
| VV ECMO | 0.66 (vs. VA) | 0.56-0.77 |

(Data from Zabrocki, LA, Brogan, TV, Statler, KD, Poss, WB, Rollins, MD, Bratton, SL. Extracorporeal membrane oxygenation for pediatric respiratory failure: survival and predictors of mortality. Crit Care Med 2011;39(2):364-70).

registry has found that approximately two-thirds of children with respiratory failure (>30 days of age) now receive VV support. While venovenous ECMO requires adequate cardiac function, many patients with pre-ECMO vasoactive needs often have a reversal of mild to moderate cardiac dysfunction once improved oxygen delivery and reduced mechanical ventilator settings occur with ECMO initiation. The advantages of VV support in children remain similar to adults, and while the long-term benefits of this approach over venoarterial access remain to be proven, initial data suggest that VV support is associated with improved survival and decreased complications.⁶⁴

As in adults, universally validated criteria for ECMO initiation do not exist. A consensus conference on pediatric acute respiratory distress syndrome was recently held and the results published. One severity tool, the oxygenation index, was recommended as a serial measure of the severity of lung injury. While OIs of >40 were often used in the past, new data suggest that mortality increases at levels >16. When combined with another variable of lung injury, pulmonary dead space, OIs of >16 with dead space of >23% resulted in an observed mortality risk of 53% (Khemani, R., personal communication). These findings, combined with the increased ease of applying ECMO, have led to a discussion as to whether ECMO should be applied at OI severity scores

much lower than in the past. A case-by-case discussion of the potential benefit of ECMO versus risk is also practiced.

Another change in pediatric ECMO is that survival based on the pre-ECMO duration of mechanical ventilation is equivalent up to 14 (and even 21 in one series) days, as opposed to 7 days historically.⁵⁸ The potential reversibility of the underlying injury is now a larger factor in ECMO candidacy than pre-ECMO ventilator duration. In a similar fashion, prolonged duration of ECMO for weeks or months is also acceptable if the process is thought to be reversible, or if the patient is being bridged to a lung or heart transplant. Unlike adults, young children can grow new alveoli and overcome lung damage. Prolonged ECMO duration and an emphasis on rehabilitation have led to the latest change in support techniques, that of maintaining the patient in an awake and mobile state. However, managing infants and children in such a manner has unique difficulties. These difficulties are often highlighted during the emergence phase from heavy levels of narcotics, benzodiazepines, and a potential neuromuscular blockade that may have been in place in the pre-ECMO period. Transitioning to an awake and interactive status requires commitment and collaboration among bedside medical staff, family, and ancillary services (e.g., child life and physical therapy). The use of less sedating medications (e.g., dexmedetomidine), while expensive, may be helpful. As with adults, many centers are advocating extubation and ambulation of children during ECMO support, while others choose to maintain some level of mechanical ventilator support (often using spontaneous breathing modes but focusing on nontoxic levels of support) via a tracheal tube or tracheostomy. Percutaneous tracheostomy can be performed safely at the bedside if the medical staff does not prefer extubation and the ECMO course is likely to be long. Enteral feeding is advocated, as is physical therapy to maintain muscle strength.

Long-term follow-up to identify deficiencies and institute early intervention is required. Reports indicate that up to 50% of children surviving ECMO have neurodevelopmental abnormalities, although severe disability is rare. Behavioral concerns (ADD, learning disabilities), slightly lower IQ, and hearing loss appear to be the most common.

ETHICAL CONSIDERATIONS

Ease of application and accessibility are increasing in the patient populations who are placed on ECMO, and the durability of systems now allow prolonged support. Determining futility is difficult, and long-term outcomes, resource use, and efficacy remain issues to be resolved in the future.⁶⁵

KEY POINTS

1. Venovenous extracorporeal membrane oxygenation (ECMO) is used in patients with isolated respiratory failure and relies on preserved cardiac function, whereas venoarterial ECMO provides both respiratory and cardiac support and is frequently referred to as extracorporeal life support (ECLS).
2. Venovenous respiratory ECMO is successfully used in adult patients with severe refractory ARDS, in patients with end-stage lung disease as a bridge to transplant, and in cases of severe primary graft dysfunction (PGD) following lung transplantation.
3. Low-flow extracorporeal CO₂ removal systems (ECCOR) are used in severe hypercarbic forms of ARDS and in patients with COPD exacerbation.
4. Venoarterial cardiac ECLS is used as a bridge system to recovery, ventricular assist device (VAD), or heart transplant in patients with cardiogenic shock due to ACS, myocarditis, or end-stage heart failure, with best survival in patients in the myocarditis group.
5. ECPR (extracorporeal cardiopulmonary resuscitation) is a powerful tool used to stabilize patients in refractory cardiac arrest; however, survival remains low.
6. Complications of ECMO are not uncommon and include systemic infections, cerebrovascular accidents (CVAs) both hemorrhagic and embolic in origin, bleeding, and limb ischemia. Technical complications have declined over time.
7. Well-defined criteria for appropriate patient selection for ECMO initiation do not exist at present.

References for this chapter can be found at expertconsult.com.

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Critically ill patients typically have anorexia and are frequently unable to take oral diets. Therefore, micronutrients and macronutrients should be prescribed as enteral or parenteral nutrition.¹

The catabolic response of critical illness is characterized by inflammatory and endocrine stress responses that may induce increases in resting energy expenditure (REE) and urinary nitrogen excretion.²

Nutritional intake may be insufficient and lead to accumulated energy and protein deficits. This can result in a reduction of the lean body mass (LBM) to an extent of 1 kg per day.³ Both low admission LBM, severe skeletal muscle wasting, and ICU-acquired weakness are associated with a prolonged need for mechanical ventilation and increased infectious morbidity and mortality rates.^{4,5}

Anorexia is likely a maladaptive response as animal and human studies have shown trophic effects of enteral nutrients on gut mucosa integrity and improved outcomes.⁶

Nutritional support for adult ICU patients aims at reducing energy and protein deficits without inducing overfeeding, sufficient micronutrient intake, and preserving gut integrity. Several large nutrition trials with high-quality data have led to some consensus. However, many controversies persist.^{6,7}

NUTRITIONAL RISK ASSESSMENT

Most nutritional assessment instruments, such as the MNA, SGA, SNAQ, NRS-2002, and MUST scores have not been developed for ICU patients and rarely have been specifically validated.⁸

A novel method, the NUTRITION Risk in the Critically ill (NUTRIC score) has been made available.⁹ A conceptual model links starvation, inflammation, nutritional status, and outcomes (Fig. 43-1). Low scores (0-4) predict a low malnutrition risk, and high scores (5-9) identify patients with increased ventilation duration and mortality that are most likely to benefit from nutrition therapy (Table 43-1).

Patients with a higher body mass index (kg/m^2 ; BMI) demonstrate better ICU and hospital survival due to poorly understood mechanisms.¹⁰ Low skeletal muscle area, as assessed by CT scan, is a risk factor for mortality in ventilated patients, independent of gender and APACHE-II score. Moreover, muscle mass was a primary predictor of mortality, while BMI was not.¹¹ Preserving LBM is a primary target of nutritional therapy.

REFEEDING SYNDROME

Refeeding syndrome refers to biochemical and clinical symptoms, as well as metabolic abnormalities due to shifts in electrolytes and fluid imbalance in malnourished patients undergoing refeeding by oral, enteral, and/or parenteral feeding.¹²

It is characterized by low concentrations of predominantly intracellular ions; phosphate, magnesium, and potassium, in addition to abnormalities in glucose metabolism, sodium levels, and water balance associated with morbidity and mortality.¹³ Thiamine deficiency can also occur.¹⁴

The incidence of refeeding syndrome is unknown due to the lack of a universal definition. Plasma electrolytes and glucose should be measured before feeding and any deficiencies corrected during feeding. Whenever marked hypophosphatemia occurs after the start of feeding, intake should be reduced to 500 kcal per day for 48 hours.^{15,16}

ENTERAL NUTRITION

Tube feeding or enteral nutrition (EN) is administered as a special liquid food mixture containing proteins, carbohydrates, fats, vitamins, and minerals, through a tube into the stomach or small bowel.

Feeding Tubes

Nasogastric or naso-enteral tubes are placed into the stomach or bowel through the nose. To prevent sinusitis or nasal decubital ulceration, orogastric and oro-enteral tubes are also used. A tube directly placed through the skin into the stomach or bowel is called a *gastrostomy* or *jejunostomy*.

Nasogastric tubes may be used depending on composition: PVC tubes up to 10 days, PUR up to 6-8 weeks, and silicone tubes for 6 weeks to 3 months.

Blenderized Tube Feeds

Low-cost blenderized tube feeds ("home brew") are used in some parts of the world. Macronutrient content is usually highly variable, often conflicting with daily recommendations.¹⁷ Moreover, there is a high contamination risk, physical and chemical instability, and high osmolality and viscosity, potentially enhancing intolerance.

Commercially Available Tube Feeds

Tube feeds are available as canned powder to dissolve, liquid containing glass bottles, or self-collapsible packages. Closed feeding systems involve the use of sterile feeding containers that are spiked with feeding sets. Closed feeding systems use connectors that prevent a connection to intravenous lines and reduce the contamination risk, and the hanging time can be increased up to 24 hours. Higher contract price and increased waste of closed systems leads to higher daily costs. However, after adjusting for nursing time and feed contamination costs, the total costs are lower.¹⁸

Compositions of Tube Feeding

Nutrient concentrations of formulas vary from 1.0-2.0 kcal/mL. Calorically dense formulas are used in patients requiring fluid restriction. Polymeric high-protein formulas have higher protein to nonprotein energy ratios and aid in achieving protein requirements in obese patients while preventing energy overfeeding. There is no evidence that hydrolyzed protein (peptide-based) formulas are superior with respect to tolerance, absorption, or outcome.¹⁹

Fibers

There are feeds with and without fibers. Sources of fiber in EN include soluble and insoluble fibers. Soluble fibers (e.g., pectin and guar) are fermented by colonic bacteria and enhance colonic sodium and water absorption to treat EN-associated diarrhea. Insoluble fibers (e.g., soy polysaccharide) increase fecal weight and peristalsis and decrease the fecal transit time.²⁰ Frequently, mixtures of fibers are used.

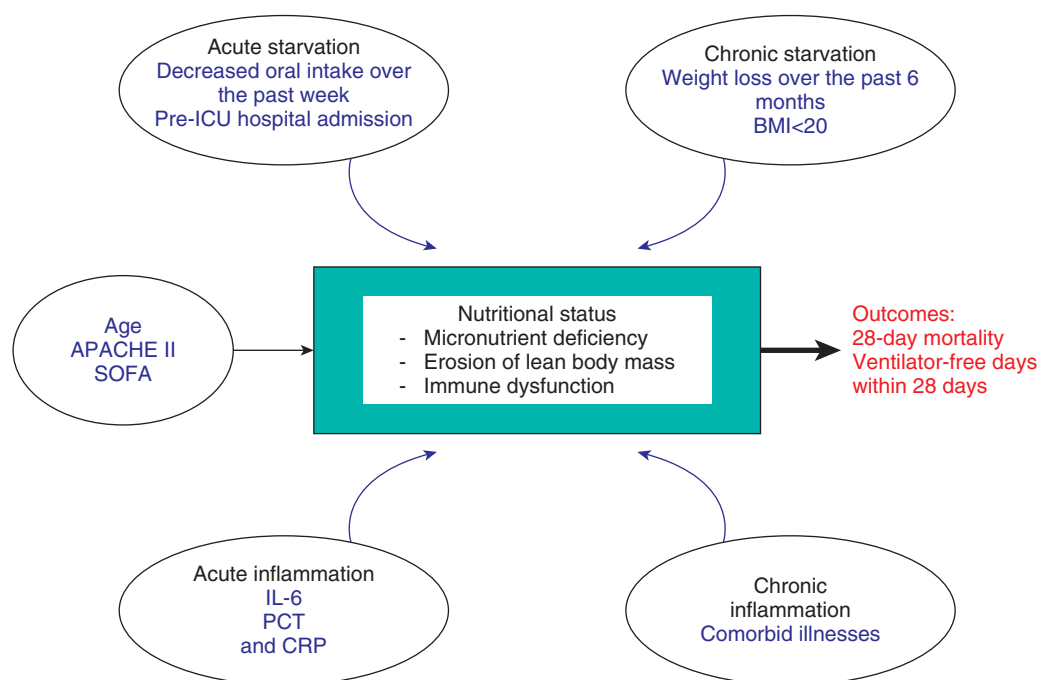


FIGURE 43-1 ■ Several factors are involved in the nutritional status of the critically ill at the time of ICU admission. Nutritional status is related to chronic and acute starvation, acute and chronic inflammation and disease severity. (From Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Critical Care*. 2011;15(6):R268.)

TABLE 43-1 Modified* Nutric Score Variables

The NUTRIC Score is designed to quantify the risk of critically ill patients developing adverse events that may be modified by aggressive nutrition therapy. The score, of 1-9, is based on five variables that are explained below.

| VARIABLE | RANGE | POINTS |
|-------------------------------------|-------|--------|
| Age (years) | <50 | 0 |
| | 50-75 | 1 |
| | >75 | 2 |
| APACHE-II score (points) | <15 | 0 |
| | 15-20 | 1 |
| | 20-28 | 2 |
| | >28 | 3 |
| SOFA-score (points) | <6 | 0 |
| | 6-10 | 1 |
| | >10 | 2 |
| Number of comorbidities | 0-1 | 0 |
| | >2 | 1 |
| Days from hospital to ICU admission | 0-1 | 0 |
| | >1 | 1 |

*IL-6 was part of the original scoring system (acute inflammation); however, it was often not routinely available as it contributed very little to the overall prediction of the NUTRIC score. The modified score is depicted.

From Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Critical Care*. 2011;15(6):R268.

Disease-Specific Feeding Formulas

Renal formulas have lower protein concentrations, as well as potassium and phosphate levels. Hepatic formulas have increased amounts of branched-chain amino acids (e.g., valine, leucine, and isoleucine) and reduced amounts of aromatic amino acids (e.g., phenylalanine, tyro-

sine, and tryptophan). Diabetic formulas have lower carbohydrate, higher fat content, and variable types of carbohydrates (e.g., oligosaccharides, fructose, cornstarch, and fiber). In pulmonary formulas, some carbohydrate calories are substituted with fat calories to limit CO₂ production and improve ventilation. ARDS formulas combine antioxidants with borage and fish oils, to supplement gamma-linoleic acid (GLA), and eicosapentanoic acid (EPA).

In patients with chyle leakage, low-fat or medium chain triglycerides (MCT), or enriched feeds are recommended. MCT does not require lymphatic transport.

Overall, for all disease-specific feeding formulas, strong evidence to improve outcome is lacking.²¹

Allergies

The majority of adverse reactions to food are nonimmunologic in origin, with lactose intolerance being the most common. Documented food allergies in adults are likely lower than 8%-10%, and most enteral feeds are gluten-free. For specific allergies, soy-free, casein-free, whey-free, and egg-free feeds are available.

Contraindications to Enteral Nutrition

In general, EN is safe when contraindications are carefully reviewed (Box 43-1). They are related to obstruction, bowel perforation, and ischemia. Many critically ill patients are at risk of splanchnic hypoperfusion due to circulatory redistribution. It is essential to provide adequate fluid therapy before commencing EN. There is no definition of hemodynamic stability associated with safe enteral feeding. However, retrospective data show that early EN in patients on vasopressor treatment is safe and improves outcome.²¹ Patients should have stable blood pressures without the need to increase vasopressors, with acceptable ScVO₂ and/or plasma lactate levels or other indicators of adequate blood flow. For most patients this will be within 6-12 hours after admission, still meeting the window of early EN (24-28 hours).

Timing of Initiation

By definition, early EN is initiated within the first 24-48 hours after hospital admission. ICU admission is considered to be the starting moment for ICU patients. Observational studies show that early EN is superior to late initiation (>48 hours) and is therefore recommended in the guidelines.²² The practical inability to initiate early EN may reflect the severity of illness. Therefore, large randomized trials on early EN versus delayed nutrition are warranted.

BOX 43-1 Contraindications to Enteral Nutrition

ABSOLUTE CONTRAINDICATIONS

- Intestinal obstruction
- Ongoing splanchnic ischemia
- Small bowel fistulas that cannot be bypassed by the feeding tube
- Hemodynamic instability*

RELATIVE CONTRAINDICATIONS

- Active gastrointestinal hemorrhage
- Early stages of short bowel syndrome
- Severe malabsorption

*Enteral nutrition may worsen ischemia due to hypoperfusion of the gut and lead to necrosis and bacterial overgrowth.

Full Versus Trophic Enteral Nutrition

The optimal dose of nutritional support is heavily debated. Permissive under-, trophic, trickle, and hypocaloric feeding are frequently used and confusing.

Permissive underfeeding suggests a lower nutritional intake (e.g., calories, proteins, and micronutrients) is acceptable. Hypocaloric feeding implies that only energy intake is lower. Trophic feeding has no clear definition, although it is accepted to represent an enteral intake of 10-20 mL/h or 500-1000 kcal/day.

Recent trials on trophic and full nutritional support were summarized and did not demonstrate benefits of either strategy, suggesting that trophic feeding could be sufficient (Table 43-2).²⁴ However, most studies included relatively young, well-nourished (high BMI) patients with low nutritional risk (NUTRIC score < 5). In the only trial with a higher nutritional risk, trophic feeding was associated with more infections. Functional outcomes in all studies were not investigated, although the long-term outcomes have been shown to be associated with feeding adequacy.²⁵

Stoppages

Interruptions in feeding for various reasons are frequent, resulting in intakes less than the prescribed amounts. Administering target volumes over 20 hours to circumvent this problem or to increase infusion rate after stoppages can be recommended.²⁶

TABLE 43-2 Randomized Trials on Trophic and Full Nutritional Support

| STUDY | YEAR | PATIENTS (N) | BMI (KG/M ²) | NUTRITIONAL RISK | MEAN DAILY CALORIES | MEAN DAILY PROTEINS | OUTCOME |
|----------|------|-----------------|---------------------------|------------------------------|---|--|--|
| AUTHOR | | TROPIC VS. FULL | TROPIC VS. FULL | MEAN ESTIMATED NUTRIC SCORE* | TROPIC VS. FULL | TROPIC VS. FULL | TROPIC VS. FULL |
| Arabi I | 2011 | 120/120 | 28.5 ± 7.4/ 28.5 ± 8.4 | 4-5 | 1066.6 ± 306.1/1251.7 ± 432.5 kcal/day | 47.5 ± 21.2/43.6 ± 18.9 g/day | Infections: Sepsis episodes 44.2/46.7% (<i>P</i> = 0.70) 28-day mortality: 18.3/23.3%; (<i>P</i> = 0.34) Hospital mortality: 30.0%/42.5%; (<i>P</i> = 0.04) |
| Rice | 2012 | 508/492 | 29.9 ± 7.8/ 30.4 ± 8.2 | 4-5 | 400/1300 kcal/day | 0.3-0.4/1.0-1.2 g/kg/day ⁻¹ | Infections: Bacteremia 11.6/9.3 (<i>P</i> = 0.24) Ventilator-free days (28 d): 14.9/15.0 (<i>P</i> = 0.89) 60-day mortality: 23.2/22.2 (<i>P</i> = 0.77) |
| Petros | 2014 | 46/54 | 28.6 ± 6.5/ 27.1 ± 6.8 | 5-6 | 11.3 ± 3.1/19.7 ± 5.7 kcal/kg/day ⁻¹ | 0.4/0.8 g/kg/day ⁻¹ | Infections: 26.1/11.1% (<i>P</i> = 0.046) ICU mortality rate: 21.7%/ 22.2% (NS) Hospital mortality: 37.0/31.5% (<i>P</i> = 0.67) |
| Charles | 2015 | 41/42 | 32.9 ± 2.0/ 28.1 ± 0.9 | 3-4 | 982 ± 61/1338 ± 92 kcal/day | 86 ± 6/83 ± 6 g/day | Infections: 70.7/76.2% (<i>P</i> = 0.57) Hospital mortality 7.3/9.5% (<i>P</i> = 0.72) |
| Arabi II | 2015 | 448/446 | 29.0 ± 8.2/ 29.7 ± 8.8 | 4-5 | 835 ± 297/1299 ± 467 kcal/day | 57 ± 24/59 ± 25 g/day | Infections: 35.9/37.9 (<i>P</i> = 0.54) 90-day mortality: 27.2/28.9% (<i>P</i> = 0.58) |

*Based on mean study data for both groups, the modified NUTRIC-score was estimated.

Adapted from McClave SA, Martindale RG, Vanek VW, McCarthyM, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN Parenter Enteral Nutr. 2009;33(3):277-316. Table 2.

Gastric Residual Volume

The increased gastric residual volume (GRV) amount aspirated from the stomach following administration of feed represents feeding intolerance. Risk factors for delayed gastric emptying include gastroparesis, diabetes mellitus, gastric outlet obstruction, (postoperative) ileus, trauma, or sepsis, and medications affecting gastric motor function (e.g., opioids). Aspiration of gastric contents should be prevented, although the GRV thresholds are non-evidence based. Recommendations have gradually increased up to 500 mL/6 h, and GRV can be reinfused or discarded. Discarded GRV reduces feeding efficacy.

Proton pump inhibitors reduce gastric secretions.²⁷ Prokinetic medications are used to improve gastric emptying, such as metoclopramide (e.g., 4 × 10 mg and erythromycin 2 × 200 mg) either alone or combined. They are safe when QTC intervals are monitored and used for up to 7 days, and tachyphylaxis is common.²⁸ Two trials demonstrated that the omission of GRV measurement does not increase the aspiration incidence. Moreover, allowing a large GRV increases the amount of feeding administered. To abandon the GRV measurement is debated, and if all strategies fail, a postpyloric feeding tube can be inserted as often as small intestinal functions are normal.²⁹

Postpyloric Feeding

Immediate postpyloric feeding may facilitate the early increase of EN, and evidence of superiority is lacking. However, the reduced aspiration risk has been clearly demonstrated.³⁰ Postpyloric tubes are placed by duodenal endoscopy or using electromagnetic tube placement or self-advancing nasal-jejunal devices. Selection of modality, timing, and success of positioning are related to patient factors, operator experience, and logistics. Criteria to monitor postpyloric feeding are provided (Box 43-2) as monitoring jejunal feeding is complex.

Complications of Enteral Nutrition

Most complications associated with EN are minor, but some can be serious. Complications can be categorized into problems encountered during the placement of tubes (e.g., tracheal/pulmonary misplacement and epistaxis) and during delivery: clinical and metabolic problems (e.g., refeeding syndrome, high GRV, vomiting, aspiration, diarrhea, azotemia, hypernatremia, and dehydration or hyperglycemia), and nutritional problems (e.g., tube obstruction and bacterial contamination).

Aspiration

There is no consistent relationship between gastric residual volumes and aspiration. Aspiration may occur with low GRV; it occurs signifi-

cantly more often when the volumes are high.³¹ Head-of-bed elevation can be recommended, although whether 45° head-of-bed elevation is superior to 25°-30° elevation remains unproven.

Routine GRV monitoring in ventilated patients to prevent aspiration is debatable as omitting measurements does not transfer into higher ventilator-associated pneumonia rates.³²

Diarrhea

Critically ill patients may develop diarrhea for various reasons (Box 43-3). During the first 14 ICU days, at least 1 day of diarrhea was observed in 14% of patients. Delivering >60% of the energy target by EN, antibiotics, and antifungal drugs are risk factors.³³ Of the diarrhea episodes, 89% lasts 4 days or less. EN *per se* was not a risk factor, while anecdotal improvements have been reported when using fiber-enriched nutrition or hydrolyzed protein formulas.³⁴

Constipation

The prevalence of lower gastrointestinal tract paralysis leads to an increased fecal transit time; (>5 days) is common and in some series up to 90% is seen. Opioid administration is associated with delayed defecation. Prophylactic or therapeutic laxatives and/or fiber-enriched enteral nutrition (prebiotics) is recommended. Both lactulose and polyethylene glycol are more effective in promoting defecation than the placebo. Early defecation is associated with a shorter length of stay.³⁵

Protocols

Evidence-based nutrition protocols designed to improve enteral feeding have been shown to improve feeding adequacy and outcome.^{36,37} Developing a protocol is recommended (Fig. 43-2).

BOX 43-3

Common Causes of Diarrhea in Critically Ill Patients

MEDICATION

Antibiotics
H₂-receptor antagonists, antacids
Drugs: significant amounts of sorbitol, magnesium, or hypertonic medications
Laxative use (unintended)

GASTROINTESTINAL DYSFUNCTION

Gastric or small bowel resection
Inflammatory bowel disease
Pancreatic insufficiency
Radiation enteritis
Sprue
Protein-losing gastroenteropathies
Bowel impaction (paradoxical)

MALNUTRITION

Hypoproteinemia
Micronutrient deficiencies

ENTERAL NUTRITION-ASSOCIATED

Excessive feeding rate, concentration, volume, or osmolality
Adaptation in malnourished patients or those whose gastrointestinal tract has not been used recently
Intolerance or allergy to feeding formula

INFECTION

Clostridium difficile enterocolitis
Opportunistic gastrointestinal infection
Significant amounts of contaminated feeding formula
Altered gastrointestinal flora

ENDOCRINE DYSFUNCTION

Diabetes mellitus
Hyperthyroidism
Hypocortisolism

BOX 43-2 Monitoring Postpyloric Feeding*

MONITOR

- GRV volume and aspect
- Abdominal distention
- Fecal transit time
- Intra-abdominal pressure (optional)

CRITERIA TO STOP POSTPYLORIC FEEDING

- Major feeding admixture in gastric aspirate suggesting back-flow
NB: gastric aspirate without tube feed admixture is not a reason to stop irrespective of volume
- Major abdominal distention
- Uncontrolled vomiting
- Obstruction ileus
- Intraabdominal pressure > 20 cm H₂O
- Severe diarrhea

*Before starting postpyloric feeding, check for general contraindications to enteral nutrition (Box 43-1)

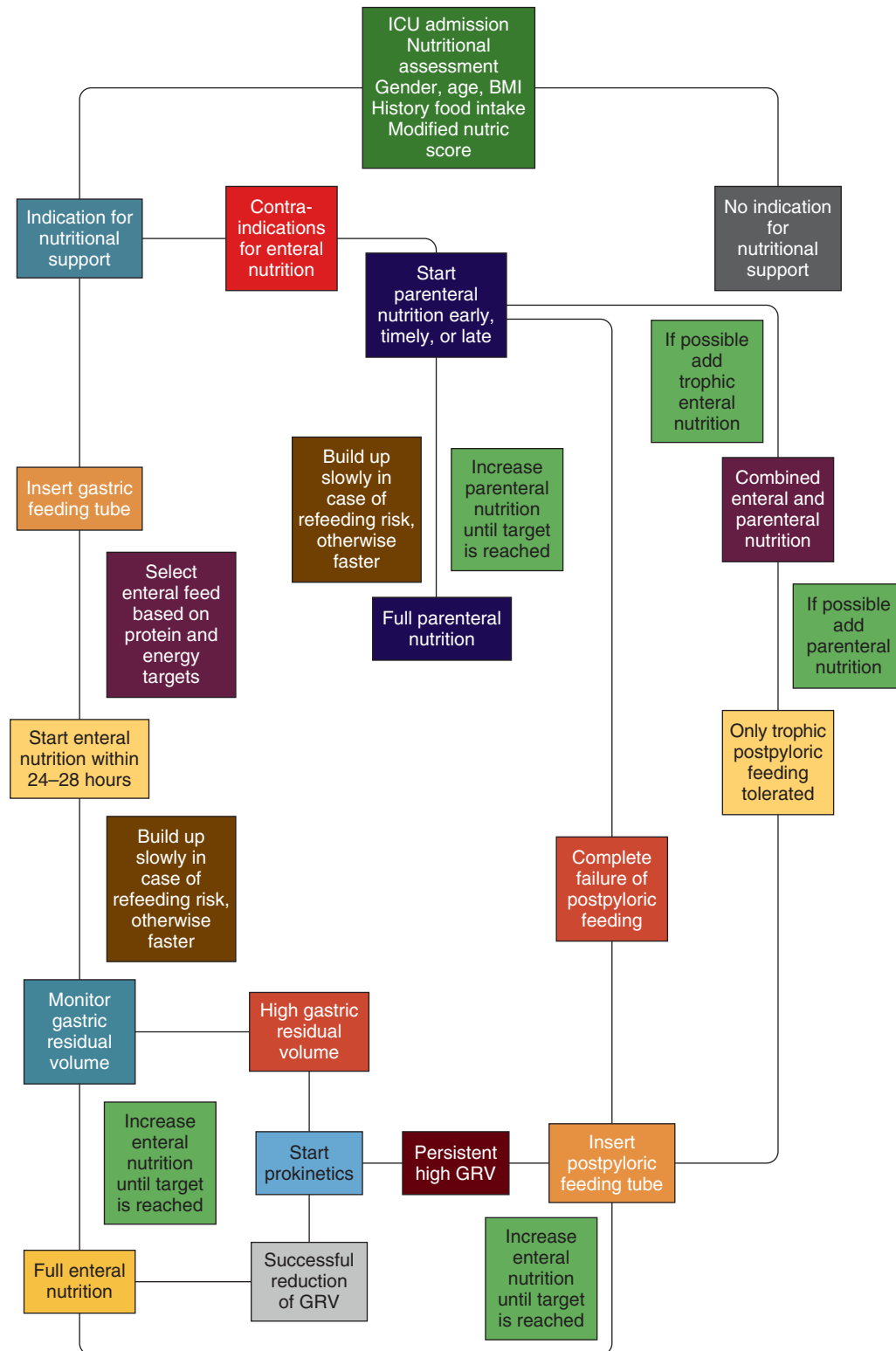


FIGURE 43-2 ■ Nutritional support flow chart.

PARENTERAL NUTRITION

Total parenteral nutrition (TPN) supplies all daily nutritional requirements by the parenteral route (via a central venous catheter or venous peripherally inserted central catheter [PICC-line]). Partial or supplemental parenteral nutrition (SPN) aims to close the gap in the intake when EN does not reach the targets.

Composition

The optimal PN composition depends on the clinical situation, energy, and protein needs, as well as electrolyte abnormalities and the risk of fluid overload.

The liquid food mixture of standard PN comprises amino acids (apart from glutamine for reasons of stability), carbohydrates (e.g.,

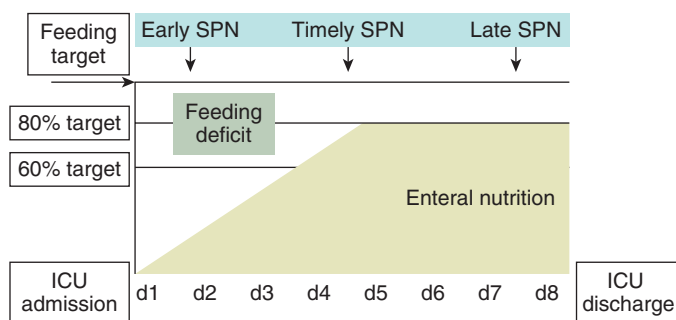


FIGURE 43-3 ■ Timing of supplemental parenteral nutrition to prevent feeding deficit.

dextrose/glucose), and lipid emulsions (e.g., soybean, olive or fish oil-based) and is infused from multi-chamber or single-chamber sterile infusion bags.³⁸ Trace elements are added to meet daily recommended allowances. In the absence of EN vitamin, K supplementation among other vitamins is important. In the case of hepatic complications (hyperbilirubinemia) interruption of lipid emulsion is recommended, and the optimal lipid emulsion still is debated. The omega-3 fatty acids in the fish oil have antiinflammatory effects, omega-9 fatty acids in the olive oil have neutral immune effects, and omega-6 fatty acids in soybean oil are proinflammatory. Soybean-based emulsions should be avoided.⁶

Timing of SPN Initiation

Nutrition guidelines present divergent advice regarding the timing of SPN ranging from early SPN (<48 h after admission) to postponing SPN until day 8 after ICU admission. Others have studied starting SPN after 3 days (timely; Fig. 43-3).

One RCT found a higher percentage of living ICU discharge at day 8 in the late SPN group, but there were no differences in ICU and in-hospital mortality. No other RCT found differences in ICU or in-hospital mortality rates. Contradicting results were found for ICU and hospital length of stay, infection rates, nutrition targets, duration of ventilation, glucose control, duration of renal replacement therapy, muscle wasting, and fat loss.

It is reasonable to assume that there are no clinically relevant benefits of early SPN. Considering infectious morbidity and potential slower organ failure resolution, and higher acquisition costs, the early administration of SPN cannot be recommended.³⁹

In severely malnourished patients, early SPN should be considered, and initiation can be delayed for 5-8 days in others.⁴⁰

Complications

Several complications are related to PN use (Box 43-4), and most can be prevented by catheter sepsis prevention and the close monitoring of glucose and electrolytes, fluid status, triglycerides, as well as liver and renal laboratory tests.

Parenteral Nutrition Versus Enteral Nutrition

EN was considered to be superior over PN. The Calories trial that compared 2400 patients randomized into EN or PN, changed this assumption.⁴¹ No differences in infections and mortality were found, and less vomiting and hypoglycemia were observed during PN. No differences in caloric intake were found to be due to the build-up of parenteral intake. Possibly due to better glucose control, preventing overfeeding and better central catheter care complications were similar to EN. EN remains a first-line therapy, but in cases that targets cannot be reached, it is safe to commence PN.

BOX 43-4 Complications of Parenteral Nutrition

CATHETER-RELATED

- Bleeding
- Pneumothorax
- Central line-associated bloodstream infection
- Obstruction
- Thrombosis, embolism

METABOLIC

- Refeeding syndrome
- Overfeeding
- Glucose abnormalities (hyperglycemia or hypoglycemia)
- Hyperlipidemia (hypertriglyceridemia)
- Liver dysfunction (increased transaminases, bilirubin, and alkaline phosphatase)
- Hepatomegaly
- Hyperammonemia
- Abnormalities of serum electrolytes and minerals
- Vitamin and mineral deficiencies
- Elevated BUN

CIRCULATORY

- Volume overload

ADVERSE REACTIONS

- Dyspnea
- Cutaneous allergic reactions
- Nausea
- Headache
- Back pain
- Sweating
- Dizziness

GALLBLADDER-ASSOCIATED

- Cholelithiasis
- Gallbladder sludge
- Cholecystitis (acalculous)

CALORIC REQUIREMENTS

Energy requirements in critical illness are unknown. Underfeeding (<80% of energy target) and cumulative energy deficit and overfeeding (>110% of target) are associated with increased morbidity (e.g., infections) and mortality. An optimum energy intake is estimated at 85% of the REE target.⁴² This lower optimum may result from endogenous energy production that cannot be abolished by providing energy.

Formulas to Estimate Energy Expenditure

Energy requirements are estimated based on patient characteristics before admission. However, requirements differ for each patient and day and should be preferably adjusted according to indirect calorimetry, although not widely available and often technically difficult or impossible to apply. Data from 160 variations of 13 predictive equations compared with indirect calorimetry measurements demonstrated 38% underestimated and 12% overestimated energy expenditure (>10%). Differences from minus 43% to 66% above indirect calorimetry values in individual patients were observed.⁴³

Guideline Recommendations for Daily Energy Intake

International societies have recommended intakes ranging from 20-25 kcal/kg per day in the acute phase, and 25-30 kcal/kg in the recovery phase. Additionally, it was suggested to prescribe hypocaloric feeding in critically ill obese (BMI > 30 kg/m²) patients, 60%-70% of the target energy requirements, or 11-14 kcal/kg of the actual body weight or 22-25 kcal/kg of the ideal body weight.^{1,44}

Indirect Calorimetry

Using a metabolic cart, REE can be measured with indirect calorimetry by measuring oxygen consumption (VO_2) and carbon dioxide production (VCO_2). Every liter of oxygen consumed is equivalent to 5 kcal. Weir introduced an equation to calculate REE:

$$\text{REE} = [\text{VO}_2 (3.941) + \text{VCO}_2 (1.11)] 1440 \text{ min/day}.$$

REE provides better energy targets than formulas, and the respiratory quotient (RQ) (CO_2 -production/ O_2 -consumption) is indicative of substrate use. RQ is 1.0 when the fuel is a carbohydrate, 0.8 for protein, and 0.7 for fat; normal RQ is 0.80. $\text{RQ} > 1.0$ may indicate overfeeding. Inaccuracies can arise from air leaks (e.g., circuit or pneumothorax). As O_2 sensors are inaccurate at the higher FiO_2 levels (>0.6) application in pulmonary failure is limited. Additionally, high PEEP levels of circuit compressibility cause volume changes and measurement errors.

The Tight Calorie Control Study (TICACOS), involving 130 ventilated patients, compared EN with an energy target determined by indirect calorimetry or $25 \text{ kcal/kg}^{-1}/\text{day}^{-1}$ and showed that indirect calorimetry leads to higher mean energy and protein intake, resulting in a trend toward improved hospital mortality. However, the duration of ventilation and ICU stay was increased.⁴⁵ The uptake of metabolic carts is emerging, and studies are ongoing.

Nonnutritional Calories

Typically, nutritional calories are evaluated; however, some calories may go unnoticed.

Glucose and dextrose-containing infusions and drugs, propofol (lipid-based), and trisodium citrate used for extracorporeal circuit anticoagulation during renal replacement therapy provide non-nutritional caloric intake, potentially inducing overfeeding.

PROTEIN REQUIREMENTS

Critical illness cause increased protein turnover and the loss of LBM. There is growing evidence demonstrating the importance of protein and amino acid provisions, and it is likely that nutritional proteins have an impact on the preservation of muscle mass, resulting in better patient outcomes.⁴²

Guideline Recommendations for Daily Protein Intake

Several nutritional societies provide slightly different recommendations; however, they can be summarized as to provide 1.2–2.0 g protein/kg if the BMI $< 30 \text{ kg/m}^2$, 2 g/kg ideal body weight if BMI 30–40 kg/m^2 , and 2.5 g/kg ideal body weight if the BMI $> 40 \text{ kg/m}^2$.^{2,121,44}

SPECIFIC MACRONUTRIENTS

Enriched or supplemented (par)enteral nutrition with supposed immune-modulating macronutrients (e.g., glutamine, arginine, and fish oil) have frequently been studied.³⁴ Pharmaconutrition suggests that specific nutritional components may exert pharmacologic effects to modulate the immune response.

Contrasting international recommendations, the MetaPlus trial demonstrated no effect of a cocktail of macronutrients (e.g., glutamine and fish oil) and micronutrients (e.g., selenium, vitamins C and E, and zinc) on the primary endpoint of infections.⁴⁶ Moreover, increased long-term mortality among medical patients was observed. In the REDOXs trial, no clinical benefit of glutamine and antioxidants was found, and a trend toward increased mortality at 28 days, as well as significant increases in-hospital and 6-month mortality in glutamine-supplemented patients, was found.⁴⁷

Since then, the safety of immune-modulating ingredients has been questioned. Benefits are limited or absent, and potential harm is involved. Use of unbalanced compositions is not recommended.⁴⁸

Glutamine

Glutamine is the most abundant plasma amino acid. In critical illness, plasma levels can be low. However, this is not always the case. Non-essential amino acids can be synthesized from other amino acids. Low levels in ICU patients are considered to be conditionally deficient, too low for the actual condition disease state. As low admission plasma glutamine was associated with increased mortality, supplementation was considered.

Positive effects are based on results from older, smaller, and mainly single-center studies. Recent studies have challenged the conditional deficiency hypothesis, both in mechanistic studies and in recent randomized trials (MetaPlus and REDOXs). Low levels could potentially reflect an adaptive response. Glutamine supplementation may only be considered while monitoring plasma levels and should be avoided as serious safety issues are involved.⁴⁹

Arginine

Another amino acid considered to be conditionally deficient is arginine. Data from 30 trials in 3000 patients after major surgery exhibit reduced infectious morbidity of arginine supplementation and a reduced length of stay. Before surgery, 5–7 days of arginine (12–15 g/day) may be beneficial. However, harm was observed in severe sepsis patients. Excessive nitric oxide production increasing mortality risk was the suggested mechanism. For sepsis patients, arginine-supplemented EN should be avoided.³⁴

Fish Oil

We lack studies showing associations of low baseline EPA and docosahexaenoic acid (DHA) levels and outcome. Smaller studies combined borage and fish oils (GLA/EPA) with antioxidants in ARDS, suggesting a benefit.²¹ The large OMEGA-EN trial (e.g., omega-3 fatty acids, EPA, DHA, GLA, and antioxidants) in ARDS patients was prematurely terminated for not reducing ventilator-free days and a higher 60-day in-hospital mortality trend ($P = 0.054$).⁵⁰ At present, it is unclear whether fish oil confers benefits and does not increase harm.

SPECIFIC MICRONUTRIENTS

The exact recommended daily allowances (RDAs) for antioxidants, trace elements, and vitamins in ICU patients are not known. Many patients have low admission plasma levels. During the ICU stay, this may worsen as RDAs are only available in 1500 mL of EN, and many patients have lower intakes. In PN, trace elements and vitamins must be added. However, whether supraphysiological dosages should be prescribed is inconclusive.

Antioxidants and Trace Elements

A meta-analysis of 21 RCTs on combined antioxidant supplementation showed significant reductions in mortality, ventilation duration, and a trend toward reduction in infections with no effect on ICU or hospital LOS. Most of the included RCTs were small studies (<100 patients), which were inadequate to detect important effects on mortality. The positive signal emerges only after statistically aggregating these smaller trials.⁵¹ In an unadjusted analysis, a recent retrospective study suggests an increased mortality associated with selenium supplementation.⁵²

Vitamins

Few data are available via vitamin supplementation in ICU patients; however, whether low plasma levels reflect deficiency is not known. Hyperlactatemia may reflect thiamine deficiency, and supplementation is recommended.⁵³ Supplementation may also be indicated in case of alcohol abuse, severe malnutrition, or refeeding risk.

Vitamin D supplementation was studied using high-dose supplementation (540,000 IU followed by monthly doses of 90,000 IU for 5

months). No effect on hospital LOS, hospital mortality, or 6-month mortality was found. Lower hospital mortality was observed in severe vitamin D deficiency (≤ 12 ng/mL), requiring further study. Remarkably, many patients on high-dose supplementation did not exhibit normalized plasma levels of 25-hydroxyvitamin D.⁵⁴

There is a lack of dose-finding studies for most vitamins in critically ill patients. Moreover, we do not know whether normalizing plasma levels translates into a better outcome.

■ PREBIOTICS AND PROBIOTICS

The World Health Organization has defined probiotics as “live microorganisms, which confer a health benefit on the host.”⁵⁵ Prebiotics (fibers) are food for probiotics that are nondigestible by humans. Prebiotics stimulate the growth of beneficial bacteria. Symbiotic supplements contain both probiotics and prebiotics.

Critical illness leads to alterations of the gut microbiota, leading to a loss of commensal flora and the overgrowth of potentially pathogenic bacteria. Probiotics restore the microbiota bacterial balance and improve the immune function, as well as the gastrointestinal structure and function.⁵⁶

Bacterial translocation of probiotics has been reported anecdotally. Since the PROPATRIA trial,⁵⁷ which showed increased mortality among probiotic-treated pancreatitis patients due to gut ischemia, safety concerns have been expressed.

A meta-analysis of 13 RCTs did not demonstrate a reduction in the ventilation duration or lower ICU or hospital mortality rates. However, a reduced incidence of ICU-acquired pneumonia and ICU LOS was found.⁵⁸ In a recent Cochrane analysis, the effect on pneumonia was questioned due to the low-quality studies that were included.⁵⁹ Identification of which ICU patients could benefit from probiotics is unclear.

KEY POINTS

1. ICU admission lean body mass and cumulative protein and energy deficit are associated with outcome.
2. Admission nutritional assessment using the NUTRIC-score facilitates selection of patients who benefit from nutritional support.
3. Refeeding syndrome, as identified by hypophosphataemia after resuming nutrition, should lead to caloric restriction for 2 days and gradual introduction of calories.
4. Enteral feeding is preferred over parenteral nutrition and should be initiated early (24-48 hours after ICU admission) to preserve gut condition.
5. Absolute contraindications for enteral nutrition are intestinal obstruction, perforation, and ischemia.
6. Hemodynamic instability is only a temporary contraindication for enteral feeding; feeding can commence when stable vasopressor infusion is achieved.
7. In well-nourished patients with low NUTRIC-scores, trophic feeding is associated with similar outcomes as full nutritional support.
8. Measuring gastric residual volume reduces feeding efficiency; therefore it should be abandoned or high GRV up to 500ml/6 hours should be accepted.
9. Critical care nutrition protocols improve feeding adequacy.
10. Gastrointestinal symptoms such as diarrhea are common during an ICU stay; however, they are frequently due to other causes than enteral feeding.
11. There are no clear benefits of supplemental parenteral nutrition within 5 days of ICU admission.
12. Formulae to estimate energy expenditure are inaccurate; therefore indirect calorimetry is recommended.
13. Caloric overfeeding should be prevented; therefore nonnutritional calories from propofol, dextrose, and citrate infusion should be considered as an energy source.
14. Protein intake should be at least 1.2 gram/kg per day, with higher recommendations in patients with greater BMI and protein loss due to renal replacement therapy.
15. Based on contradictory results from clinical trials, pharmaconutrition with glutamine, arginine, and fish oil cannot be recommended.
16. Recommended daily allowances for vitamins and trace elements in critical illness are unknown; however, supplementation should be considered in patients on parenteral nutrition or enteral nutrition intake below 1500 kcal/day.
17. Although prebiotics and probiotics seem to be safe in most ICU patients, proven benefits in targeting gut microbiota with these strategies are lacking.

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Clinical Pearls:

1. Clinical nutritional support must minimize tissue loss, optimize tissue repair, and minimize metabolic overloading.
2. Pushing nutritional intake beyond recommended levels may create additional metabolic stress.
3. Enteral nutrition support is generally considered the preferred route for nutrition, yet parenteral nutrition may be necessary to meet the need of critically ill children.

Nutritional support is a central therapy in the management of critically ill children. Patients of differing ages and conditions have fundamental differences in nutrient requirements and utilization. Our well-intended efforts to “increase” nutritional support may at times lead to greater harm than benefit through the provision of protein, carbohydrate, and fat far beyond what the critically ill child can utilize. In addition, metabolic complications such as total parenteral nutrition (TPN)-associated cholestasis, hepatic steatosis, and catheter-related infections are morbidities that have arisen with the advent of advanced nutritional support methods.

Recent reviews of the literature on nutritional support for critically ill children detail the lack of definitive studies to guide practice based upon scientific evidence.^{1,2} Therefore, many of the recommendations rest upon “good practice” principles based on expert consensus and the avoidance of known harm whenever possible. Those best practices are contained in the American Society of Parenteral and Enteral Nutrition (A.S.P.E.N.) guidelines for supporting children in the pediatric intensive care unit (PICU).³

Nutritional support has three primary goals. The first is the preservation of lean body mass to minimize the consequences of catabolism during critical illness. The second goal is the provision of suitable substrates to maintain or restore immune function and tissue repair. The third goal is the prevention of nutrition-related complications, including aspiration risks, in patients receiving enteral nutrition and the avoidance of nutrient-induced organ overload whether through excess carbohydrate (e.g., increased CO₂ production and hepatic steatosis) or excess protein/nitrogen load to the liver and kidney. This chapter provides the critical care clinician with a basic understanding of the issues necessary for providing effective and safe nutrition to critically ill children and those recovering from life-threatening illness.

IMPACT OF PHYSIOLOGIC STRESS IN CHILDREN

Life-threatening illness, sepsis, burns, trauma, and major surgical procedures elicit dramatic systemic inflammatory responses via activation of the immune system, clotting mechanisms, and the endothelium. The patient's ability to withstand the metabolic responses to such stresses and ultimately to reverse the process is central to recovery.⁴⁻⁶

The initial response to injury involves activation of endothelial and priming inflammatory cells such as neutrophils, macrophages, and lymphocytes. Such activation occurs through proinflammatory mediators, including tumor necrosis factor, interleukin-2, histamine, eicosanoids, heat-shock proteins, free radicals, platelet-activating factor, and tryptases.⁷ The same signals that activate the endothelium lead to vascular permeability changes and the activation of clotting mechanisms. Simultaneously, alterations in hepatic and peripheral protein metabolism occur, constituting acute phase changes.⁸ Proinflammatory

stimuli also play a role in regeneration and repair, and the timing of interventions is important.^{9,10} In response to injury, a range of neuro-humoral reactions occur, forming the classic “stress response,” which includes elevation of levels of growth hormone, endogenous catecholamines, glucagon, and cortisol. Gluconeogenesis occurs through the release of glycerol and gluconeogenic amino acids from the periphery, followed by their conversion to glucose in the liver and kidney. Hyperglycemia frequently is associated with this state and may induce glycosuria and an osmotic diuresis. Insulin activity is impaired at the tissue level, leading to so-called insulin resistance in the face of the powerful gluconeogenesis driven by stress hormones.

The breakdown of protein is a central theme in the body's response to stress. Hepatic uptake of amino acids increases for the conversion to glucose and the production of acute-phase proteins. Hepatic synthesis of other proteins, such as albumin and prealbumin, declines.¹¹ Urea-genesis increases, and nitrogen is liberated in the form of uric acid, creatinine, and urea. These catabolic changes account for the dramatic increase in nitrogen wasting seen during stress states. One of the major consequences of life-threatening physiologic stress is the net depletion of body protein representing the somatic protein pool (e.g., skeletal muscle mass) and functional tissues contained in the visceral protein pool (e.g., plasma proteins, enzyme systems, antibodies). With protein catabolism rates elevated by up to twofold, synthesis does not keep pace, and a state of negative nitrogen balance ensues.¹² In the resolution of the inflammatory response, the patient's immune system plays a central role in the recovery of wound healing and immune competence.¹³ The syndrome of multiple organ dysfunction seen in critically ill patients likely is due in part to the inability of the immune system to downregulate the inflammatory response to injury in specific organs. Additionally, acquired mitochondrial dysfunction leads to ineffective cellular energy production.¹⁴ Nutrition support of a critically ill patient is thought to be essential to achieve recovery, minimizing the subsequent period of convalescence.

The body's response to withholding feeding (i.e., starvation) in healthy individuals is qualitatively and quantitatively different from that seen when nutrient intake is absent during critical illness. In simple starvation, the body's regulatory mechanisms for sparing lean tissue and using triglycerides as the primary energy source are intact. Under the influence of the stress response, rapid depletion of lean tissues occurs, with the oxidation of amino acids, carbohydrates, and fats as energy substrates.

NUTRITION ASSESSMENT OF THE CRITICALLY ILL CHILD

Nutrition assessment of hospitalized children is a central part of the initial examination and evaluation. Undernutrition in developed countries is most frequently found in hospitalized children in the setting of chronic illness.¹⁵ In a multicenter study, over 30% of children admitted to the PICU had evidence of severe malnutrition.¹⁶ Conversely, an estimated 17% of children in the United States aged 2 to 19 years were identified as obese in 2011-2012.¹⁵ Yet obesity is not an indicator of nutritional adequacy, but excessive calorie intake is. Obese children may have access to calorically dense yet poor nutritional quality foods and can present with micronutrient deficiencies, including vitamin D, B₁₂, and iron.¹⁷⁻¹⁹ Excess body weight is often falsely interpreted as well

nourished, while we recognize that a 10% weight loss from baseline indicates severe acute malnutrition.¹⁵ The presence of preexisting severe malnutrition may complicate critical care management through the presence of marasmus cardiomyopathy, severe intracellular energy deficiency, and the development of refeeding disequilibrium when nutrients are provided in the PICU.²⁰⁻²² Skilled clinicians, including pediatric-trained registered dietitians/registered nutritionists (RD/RDN), must fully assess critically ill children for the presence of malnutrition to avoid known complications of refeeding.

The initial nutrition evaluation consists of assessing the patient's anthropometric measurements (weight, height, midarm circumference) and historical evidence for recent weight loss and nutrient intake.¹⁵ Nutrition history should include the presence and duration of nausea, vomiting or diarrhea, fever, frequent infections, fatigue, food aversion, abdominal discomfort, and feeding intolerance. The Centers for Disease Control (CDC) recommends that the World Health Organization (WHO) growth data charts be used to evaluate growth data in children 0-2 years of age and the CDC growth data charts used for children 2-20 years of age.^{23,24} Genetic and ethnic background should be taken into consideration. The presence of genetic syndromes (e.g., Down or Turner syndrome) and the child's birth status (e.g., prematurity, growth restricted) may also affect the child's growth, and disease-specific growth comparison data curves may help to establish the degree of variance from similar populations.

Clinicians caring for children who will experience more than a few days of hospitalization must be especially aware of the potential for acquired nutritional depletion. Potential sources of error exist in interpreting anthropometric measurements. Such errors are primarily related to changes in body water associated with acute critical illnesses in children, as in conditions producing capillary leak syndrome or defects in renal water clearance.

No nutrition-related serum biomarkers have been proven to identify malnutrition or predict clinical outcomes.²⁵ Frequently, serum proteins decrease during acute critical illness without reflecting preceding malnutrition. This phenomenon is seen frequently when capillary leak syndrome occurs in the first days following PICU admission in patients with sepsis, burns, surgical interventions, and ischemia-reperfusion injury. Through the loss of endothelial barrier function, large molecules such as albumin that are normally three to four times more concentrated in the vascular compartment than in the interstitial fluid, move into the extravascular space, lowering their concentration without a concomitant decrease in the total body pool of albumin. This effect may be very pronounced in patients who have received large volumes of crystalloid fluid during resuscitation. The synthesis of acute-phase proteins is increased, while the synthesis of albumin (half-life, ~20 days) and prealbumin (half-life, 2 days) is decreased.²⁶ These changes may be seen within 6 hours of the onset of severe physiologic stress. In infants followed after cardiac surgery, the return of CRP levels to less than 2 g/dL is associated with return to an anabolic state, with improving prealbumin levels.¹⁵ Such positive changes herald the impending return to a state of growth and tissue accretion.

Energy Expenditure

Nutritional support for critically ill children differs fundamentally from conventional nutrition for healthy children. Estimates of caloric and protein requirements during acute illness and recovery indicate that children have greater requirements for both calories and protein on a body weight basis when compared to critically ill adults. Yet, during periods of critical illness, the utilization of nutrients for growth is markedly inhibited by the hormonal response to stress and the circulating inflammatory mediators. Critically ill children may have a lower energy expenditure during mechanical ventilation and sedation because of their reduced movement and a transient absence of growth.¹⁵ In critically ill children, many investigators have found the resting energy expenditure (REE) to be less elevated than previously expected, leading to a risk of overfeeding.^{27,28} Thus, sedated, critically ill children with decreased activity levels can be at risk for overfeeding when using

standard age-appropriate equations for healthy children.²⁹ One of the most important points for clinicians prescribing nutritional support is to provide calories in a thoughtful manner based upon the available clinical guidelines and *avoid excess caloric intake* during the acute phase of illness.

Energy needs are determined using predictive equations or indirect calorimetry (IC). Although many predictive equations exist, their accuracy for determining energy requirements, particularly in critically ill children, is not clear.^{30,34} Predictive equations derived from healthy, nonhospitalized patients have been shown to overestimate the measured energy expenditure. Even equations developed for use in critically ill children fail to consistently predict REE when compared to measured energy expenditure using indirect calorimetry (IC).^{3,30} Because of the dynamic metabolic changes that occur during critical illness, the gold standard for determining energy metabolism is IC.³¹ Equations for estimating REE and TEE are summarized in Table 44-1.

Indirect calorimetry determines the resting energy expenditure (MREE) and respiratory quotients (RQ) by measuring whole-body oxygen consumption (VO_2) and the metabolic production of carbon dioxide (VCO_2).^{11,29,31} As in adult nutritional assessment, the *respiratory quotient* ($\text{RQ} = \text{VCO}_2/\text{VO}_2$) reflects substrate oxidation. The physiologic range for the RQ in humans is 0.67-1.2; any value much outside this range suggests an invalid study.³² RQ correlates with the percent calories provided/percent calories required, with mixed fuel use generally between 0.85 and 0.95; values greater than 1 indicate net fat synthesis.¹¹ Indirect calorimetry (IC) is well established in clinical nutrition but has been difficult to perform with consistent results in children. The lack of suitable equipment to perform IC in children has been a major obstacle to its widespread application.

Through indirect calorimetry, it has become clear that patients with similar clinical appearances may have widely differing metabolic rates when adjusted for age and weight.^{3,27,33-35} The differences may be as great as 300%, suggesting the potential for severe over- or under nutrition depending upon the values assumed.²⁸ Total energy expenditure (TEE) can vary depending on the route of nutrition delivery (enteral vs. parenteral), activity, progressive ventilation weaning, wound losses and intermittent pain and anxiety. Patients should be reassessed as their clinical status changes and adjustments are made to nutritional support. Most clinicians must rely upon information provided in published studies to guide the delivery of calories since most will not have a means of determining the REE by IC.³⁶

TABLE 44-1 Equations for Estimating Total Energy Expenditure (TEE) in Critical Illness

RESTING ENERGY EXPENDITURE (REE) Kcal/DAY

| | |
|-------------|---------------------------------------|
| 0-3 years | $61 \times \text{kg} - 54$ |
| 3-10 years | $23 \times \text{kg} + 500$ |
| 10-18 years | Male: $17.5 \times \text{kg} + 650$ |
| 10-18 years | Female: $12.2 \times \text{kg} + 745$ |

*Stress Factors:
Multiply REE by stress factors to estimate *total energy needs*:
Surgery: 1.1-1.5
Cardiac Failure: 1.2
Sepsis/Fevers: 1.2-1.6
Head Injury: 1.3
Trauma: 1.1-1.8
Burns: 1.5-2.5

REE adapted from World Health Organization. Energy and Protein Requirements. Report of a Joint FAO/WHO/UNU Expert Consultation. Technical Report Series 724. World Health Organization, Geneva, 1985.

Stress factors adapted from The ASPEN Pediatric Nutrition Support Core Curriculum 2010.

*Critically ill patients who are sedated, with minimal movements, and receiving ventilation support may have energy needs very close to the calculated REE. Multiplying by stress factor may exceed metabolic needs.

Protein

The high rate of protein turnover during critical illness is associated with an increase in ureagenesis and urinary nitrogen loss, which may amount to as much as 1-2 g/kg/day of protein equivalent. To minimize nitrogen loss, proteins or amino acids must be administered in amounts sufficient to replace losses, with additional protein to synthesize new tissue. Table 44-2 provides guidelines for the administration of protein to children in the PICU during different phases of illness. Nitrogen balance in response to nutrition support represents a continuum. In one study, the authors found that nitrogen balance was obtained at an intake of 2.8 g/kg/day.³⁷ Positive nitrogen balance was only achieved with amino acid infusion rates at the upper end of those typically used by clinicians. Of equal importance is the provision of calories in sufficient quantity to assure that protein can be used for synthesis rather than oxidized as an energy substrate.

In disease states with altered nitrogen clearance—for example, hepatic and renal failure—a decrease in protein support may be necessary to avoid excessive ammonia production and/or urea formation. Only in the rare incidence of hepatic encephalopathy should protein be limited, although severe protein restriction may impair hepatocyte regeneration and exacerbate malnutrition. With renal failure, urea clearance will increase dramatically once dialysis is initiated, allowing better nutrition to be provided. However, amino acid losses across the dialysis membrane can be substantial.³⁸

Fluids

Maintenance fluids for most patients can be estimated by conventional formulas based on body weight as follows. For each kilogram body weight from 0-10 kg, provide 100 mL/kg/day. For each kilogram body weight from 10-20 kg, add 50 mL/kg/day. For each additional kilogram of body weight over 20 kg, add 20 mL/kg/day. Thus, for a 25-kg child, maintenance daily fluid is 1600 mL/day $([10 \text{ kg} \times 100 \text{ mL/kg/day}] + [10 \text{ kg} \times 50 \text{ mL/kg/day}] + [5 \text{ kg} \times 20 \text{ mL/kg/day}])$.³⁹ Fluid needs increase with fever or persistent tachypnea due to increased insensible fluid losses. Additional fluids must be provided when abnormal losses are present as with diarrhea, nasogastric drainage, or from wound loss in burns or from other sites. The replacement fluid composition is based on the content of sodium, potassium, bicarbonate, and chloride lost and conforms to conventional surgical and medical guidelines for fluid replacement. Typically, maintenance fluids should provide sodium (3-5 mEq/kg/day) and potassium (2-3 mEq/kg/day) salts as well as a modest amount of glucose (5% or 10% if <6 months of age).

TABLE 44-2 Guidelines for Protein Support in Critically Ill Children

| PROTEIN: g/kg/DAY | | | |
|-----------------------|------------------|-------------------------------|--|
| AGE | RDA ^a | CRITICAL ILLNESS ^b | RENAL DISEASE* (PREDIALYSIS-DIALYSIS) ^c |
| 0-6 months | 1.52 | 3 | 1.5-2.1 |
| 7-12 months | 1.2 | 2-3 | 1.7-1.7 |
| 1-3 years | 1.05 | 2 | 1.05-1.5 |
| 4-13 years | 0.95 | 1.5-2 | 0.95-1.35 |
| Greater than 14 years | 0.85 | 1.5 | 0.85-1.2 |

Adapted from the protein guidelines in the references below:

^aRecommended Dietary Allowance, Food and Nutrition Board, Institute of Medicine, National Academies.

^bASPEN Clinical Guidelines: Nutrition Support of the Critically Ill Child. JPEN. 2009;33(3):260-276.

^cNational Kidney Foundation. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 Update. Am J Kidney Dis 2009;53(Suppl. 2):S1-S124.

*Protein needs in critical illness are elevated; thus patients with renal dysfunction may require greater protein provision than non-critically ill children with renal disease.

Recent trends in providing electrolytes has favored a *balanced* electrolyte solution containing acetate salts of 1-2 mEq/kg/day to minimize the development of hyperchloremia caused by the large chloride load contained in fluids and medications. The provision of glucose in maintenance fluids is intended to spare lean tissue and prevent hypoglycemia, especially in infants with low glycogen stores.

NUTRITION SUPPORT RECOMMENDATIONS FOR THE CRITICALLY ILL CHILD

Enteral Nutrition Support

The decision to provide nutrition via a parenteral or enteral route depends upon the anticipated time to resumption of normal dietary intake, the available routes of nutrient administration, underlying metabolic or endocrine conditions, and the existence of organ dysfunction. In all critically ill patients with a functioning gastrointestinal tract, enteral nutrition is the preferred mode of nutrition support.³ Table 44-3 reviews the indications and contraindications for enteral feedings. Enteral nutrition is associated with lower rates of nosocomial infections and reduced mortality.¹¹ Enteral nutrition is thought to support intestinal integrity and the intestinal microbiome.³⁹ In addition, the avoidance of central venous access reduces the risk of central line-associated infections.

Early enteral nutrition, *even at low volumes*, can support intestinal function, reduce hepatic cholestasis, and reduce infection rates.⁴⁰ Gastric feedings are generally preferred in preterm infants, even during periods of critical respiratory illness.^{3,41} In the PICU, concerns for gastric reflux and aspiration of gastric contents favor postpyloric enteral feeding to reduce aspiration risk.³ Transpyloric feeding tubes can be placed at bedside by experienced clinicians⁴² or under fluoroscopic guidance. Metoclopramide or erythromycin can facilitate placement of a transpyloric tube when gastric motility is impaired. Even when a transpyloric feeding tube cannot be placed, continuous enteral feeding via a nasogastric tube may confer most of the benefits.⁴⁴

During critical illness, continuous drip feedings may be better tolerated than bolus feedings, especially in patients with significant respiratory distress and/or hypoactive bowel function. Continuous feeding is always required with postpyloric tube placements. Breast milk is the optimal nutrient source for critically ill infants and can be delivered by feeding tube. Specialized supplements can be added to breast milk to increase the nutrient density to better meet the needs of critically ill infants. Modern enteral nutrition formulas for critically ill children are lactose free, may contain medium-chain triglycerides, and contain ample proteins to meet their increased needs. Adult formulas may be appropriate in critically ill children greater than 10 years of age. A variety of formulas exist, and the availability may vary from country to country. The hospital dietitian is best prepared to help select the most suitable formula.

Infusion rates are typically begun conservatively at ~1 mL/kg/hr, with a stepwise increase every 4 to 6 hours as tolerated up to the desired final rate. Clinicians must maintain vigilance for evidence of feeding intolerance. In patients with altered tissue perfusion, enteral feedings may be feasible, yet caution should be exercised in patients requiring high doses of vasopressors.⁴⁰ Any signs of marked abdominal distention, profuse diarrhea, emesis, or the development of a new metabolic acidemia may indicate the need to hold enteral feedings and assess the abdomen before reinstituting feeds.⁴⁴

Parenteral Nutrition

One of the great achievements of clinical nutrition science has been the development of safe and effective nutrient support by the intravenous route. Parenteral nutrition (PN) has been invaluable in the survival of premature infants, children with congenital or acquired bowel defects, and those who do not tolerate enteral nutrition due to

TABLE 44-3 Indications and Contraindications for Enteral Feeds in Critical Illness

| INDICATIONS (TIMING OF INSTITUTING FEEDS) | CONTRAINDICATIONS | RELATIVE CONTRAINDICATIONS |
|---|--|--|
| INABILITY TO CONSUME ADEQUATE ORAL NUTRITION WITHIN AN ACCEPTABLE TIME FOR AGE AND NUTRITIONAL STATUS Malnutrition on Admission <ul style="list-style-type: none"> 0-2 years: <3 days 3-10 years: 3-5 days >10 years: 5-7 days Well Nourished on Admission <ul style="list-style-type: none"> 0-2 years: 3 days 3-10 years: 5 days >10 years: 7 days Hypermetabolic Condition <ul style="list-style-type: none"> Cyanotic heart disease Severe trauma Sepsis/SIRS ARDS Thermal injury Inability to Take Oral Nutrition <ul style="list-style-type: none"> Oral/laryngeal/esophageal carcinomas Congenital malformations Neurologic disorders | DYSFUNCTIONAL GASTROINTESTINAL TRACT <ul style="list-style-type: none"> Severe ileus High output intestinal fistulas Severe necrotizing pancreatitis Intestinal ischemic injury Intractable emesis Severe secretory diarrhea SPECIAL CIRCUMSTANCES <ul style="list-style-type: none"> Expressed desires of family for no artificial nutrition End-stage disease or terminal illness wherein supportive therapies are discontinued and nutrition will not contribute to comfort measures. | CONDITIONS IN WHICH ENTERAL FEEDING TUBES MAY RISK SECONDARY INJURY <ul style="list-style-type: none"> Neutropenia patients without established enteral access Facial and/or neck trauma (unable to place enteral feeding tubes) CONDITIONS THAT MAY LIMIT TOLERANCE BUT THAT ARE NOT ABSOLUTE CONTRAINDICATIONS TO ENTERAL FEEDS <ul style="list-style-type: none"> Short bowel syndrome Intestinal fistulas <ul style="list-style-type: none"> May attempt enteral feeding if fistula is in distal bowel (ileum or colon) May attempt with fistulas in the proximal bowel with enteral access distal to the fistula Feeds should be discontinued if fistula output becomes excessive with the initiation of feeds. |

Data from Enteral Nutrition in Adult and Pediatric Patients. JPEN J Parenter Enteral Nutr. 2002;26:1:13A-138SA.

malabsorption, surgery, or other causes of bowel dysfunction. PN should be considered in any patients who cannot tolerate enteral feedings. However, PN may come with a significant morbidity in terms of iatrogenic electrolyte and acid-base disturbance, cholestasis, hepatic fibrosis following prolonged use, and increased risk of bacterial and fungal infections. The goals of PN support during critical illness need to be clarified and kept realistic to avoid adding unnecessary metabolic stress to already compromised pulmonary, renal, and hepatic function. The timing for institution of PN intervention should be carefully considered and corresponds to those given under enteral nutrition indications in Table 44-3. Excess PN may contribute to organ dysfunction and should be avoided: *More than recommended is not better for these patients.*

Parenteral nutrition is composed of dextrose, amino acid solutions, electrolyte salts and minerals, added vitamins and trace elements, and sterile water. Some PN pharmacies will add lipids to the mixture as a 3-in-1 solution, or they may be delivered as separate infusions. Due to the high osmotic content and risk of extravasation injury, *peripheral* parenteral nutrition solutions are not recommended to exceed 900 mOsm/L, which limits *peripheral* solutions to dextrose 12.5 g/100 mL and amino acids 2 g/100 mL.⁴³ Central venous access will allow for more concentrated solutions, typically up to 25 g/100 mL dextrose and 5 g/100 mL amino acids. Parenteral nutrition solutions may not be compatible with some intravenous medications. Consulting a pediatric pharmacist regarding compatibility is prudent.

Glucose is the primary energy source for the brain, erythrocytes, and renal medulla. Infants and malnourished children have lower glycogen body content and may develop hypoglycemia during periods of fasting. Most PICU protocols include intravenous fluids with low-dose dextrose (5-10 g/100 mL) to reduce catabolic losses and support essential glucose needs in critical illness. Once parenteral nutrition is initiated, the cellular energy requirements of most critically ill children can be met, and euglycemia can be maintained through the infusion of 5-8 mg/kg/min of dextrose. This range represents ~25-40 kcal/kg/day of carbohydrate calories and is a close first approximation of the *basal* cellular energy expenditure seen in many hospitalized children. Glucose infusion rates less than 2 mg/kg/min may lead to hypoglycemia or starvation ketosis. When infusion rates exceed 10-12 mg/kg/min of glucose, net lipogenesis and hyperinsulinemia may ensue

which can further complicate clinical management.⁴³ While an occasional patient may become acutely hyperglycemic or experience dramatic electrolyte changes following the initiation of PN, most patients will tolerate it well and can be advanced to full PN within a few days. Insulin is used as needed to achieve acceptable glucose levels, generally <240 mg/dL. Close glucose monitoring during insulin infusion is required to avoid episodes of hypoglycemia.

Specific amino acid solutions developed for neonates contain taurine, tyrosine, cysteine, and histidine, which are advantageous for select newborns and young infants with biliary disease, sepsis, or under high physiologic stress. These solutions contain increased branched-chain amino acids that are conditionally “essential-for-age” in infants and decreased amounts of nonessential amino acids. In premature infants or those on prolonged PN, intravenous carnitine supplementation has been advocated to aid in triglyceride clearance through enhanced β -oxidation of fatty acids.⁴⁵ In older children, conventional amino acid solutions designed for adult patients provide adequate dietary nitrogen.

Critically ill children have a high rate of fat oxidation; thus, fatty acids are a prime source of energy in metabolically stressed children.³ Intravenous lipid emulsions were originally developed to prevent essential fatty acid deficiency, which can arise in a matter of days in critically ill children.³ Provision of only 4% to 5% of total calories as essential fatty acids containing fat emulsions will prevent essential fatty acid deficiency.³ Calories from fat should not exceed 20% to 30%, with a maximum of 2-4 g/kg/day of intravenous lipids. A 20% lipid emulsion is the preferred source of intravenous fat and provides 2 kcal/mL. For pediatric patients, lipid emulsions are administered continuously unless rising plasma triglyceride levels suggest inadequate clearance. This condition may be seen during sepsis, with increased generation of triglycerides from high carbohydrate infusion and increased peripheral lipolysis. Recent research suggests that the current lipid products, derived primarily from soy oils, may increase inflammation and contribute to parenteral nutrition-associated liver disease.⁴⁶ Current research indicates the combined use of olive and fish oils may produce less associated inflammation; however, these products are not currently approved for use in the United States. Table 44-4 presents the accepted guidelines for prescribing PN and for determining the glucose infusion rate (GIR) and advancement of PN support based on weight.

TABLE 44-4 General Guidelines for Dosing Pediatric Parenteral Nutrition

| | MINIMUM DOSE | ADVANCE BY | MAXIMUM DOSE | CALORIES/kg/DAY |
|------------------------|--|--|---|---|
| Dextrose | 7-10 g/kg/d (GIR 5-7) Typically 10 g/100 mL | Add +2-4 g/kg/d (+GIR 1-3) Add + 2.5-5 g/100 mL | 14-17 g/kg/d (GIR 8-12) 15-25 g/100 mL | 3.4 kcal/g 27-41 kcal/kg/day |
| Amino acids | 1-2 g/kg/d Typically 2 g/100 mL | 0.5-1 g/kg/d Add + 0.5-1 g/100 mL | 2-4 g/kg/d 2-5 g/100 mL | 4 kcal/g 8-20 kcal/kg/day |
| Lipids 20% solution | 0.5-1 g/kg/d = 2.5-5 mL/kg/d | +0.5-1 g/kg/d = +5 mL/kg/d | 0.5-3 g/kg/d = 2.5-15 mL/kg/d | 10 kcal/g (2 kcal/mL) 5-30 kcal/kg/day |

Calculate glucose infusion rate (GIR):

Dextrose g/100 mL \times volume (mL/kg/day) \div 1.44 = mg/kg/min

(1.44 = 1440 mL/day \div 1000 mg/g dextrose)

SHOULD NUTRITION SUPPORT BE PROTOCOL DRIVEN?

Multicenter studies suggest that frequent interruptions in nutrition support can significantly impair nutrition delivery. However, patients who received a higher percentage of their prescribed enteral nutrition experienced an improved 60-day survival.¹⁶ Research indicates that feeding protocols may enhance the delivery of nutrition, decrease the use of PN, increase tolerance of enteral nutrition, and shorten the time to reach goal nutrition.^{44,47} The recommendations are for early institution of enteral feeding via NG or transpyloric route, planned rate of advancing feedings (e.g., every 4 hours, if tolerated), and the caloric goal. However, a recently published multicenter trial suggests that early PN increased morbidity from infection compared to starting 1 week after admission (18% early vs. 10% late), although mortality was no different between the early and late groups.⁴⁸ Thus, early PN may carry risks with little proven benefit.

SUMMARY

Nutritional support of critically ill children is a central part of intensive care medicine. The complexity of pediatric disease and the wide range

of ages and body conditions, as well as the multiple options for nutrient delivery necessitate close collaboration between physicians and pediatric dietitians who are familiar with children's nutrition requirements during critical illness. Although PN support has associated risks, it can offer lifesaving treatment to patients with dysfunctional gastrointestinal tracts. Enteral nutrition continues to be the preferred route of nutrition whenever possible, even in small amounts, as it offers multiple clinical benefits during critical illness.

KEY POINTS

1. Increasing nutritional intake beyond recommended levels may create additional metabolic stress.
2. A significant degree of benefit from nutrition will be seen by simply avoiding starvation through the provision of a portion of the estimated nutritional needs by enteral or parenteral route.
3. Clinical nutritional support must minimize tissue loss, optimize tissue repair, and minimize metabolic overloading.

ANNOTATED REFERENCES

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Joffe A, Anton N, Lequier L, Vandermeer B, Tjosvold L, Larsen B, et al. Nutritional support for critically ill children. *Cochrane Database Syst Rev* 2009;2:CD005144.

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Bed rest has historically been prescribed as an adjunct to the treatment of acute illness and rehabilitation after surgery. Even as physicians and researchers began to realize the “evil sequelae of complete bed rest”²¹ in both medical and surgical patients, the therapy remained commonplace in the intensive care unit (ICU). Indeed, healthcare providers in the ICU have traditionally focused their attention on normalizing the physiologic derangements that threaten their patients’ survival. However, therapeutic advances and improvements in the management of critically ill patients have improved the outcomes in this patient population.²⁻⁴ As survival from critical illness has improved, the long-term complications and associated therapies have become more apparent. A large proportion of these patients experience long-term cognitive, psychological, and physical disability, with less than half of critical illness survivors returning to work 1 year after ICU discharge.⁵⁻⁸ Early mobilization and ambulation of critically ill patients are feasible, safe, and effective interventions that result in improvements in physical functional and neuropsychiatric outcomes.⁹⁻¹⁵

■ THE PHYSIOLOGY OF BED REST

Bed rest has, at one time or another, been promoted as a therapy for almost all ailments. Hippocrates suggested that all pain could be relieved by bed rest.¹⁶ However, as early as the 1940s, it was recommended that “the physician ... always consider complete bed rest as a highly unphysiological and hazardous form of therapy.”²¹ Nonetheless, it was not until recently that the medical community began to acknowledge the ill effects of complete inactivity and immobility during critical illness.

Inactivity and immobility have profound effects on skeletal muscle. Disuse leads to reduced protein synthesis, accelerated proteolysis, and increased apoptosis, ultimately resulting in a catabolic state, atrophy, and clinical weakness.^{17,18} In a study of young, healthy volunteers, 28 days of bed rest resulted in a 0.4 ± 0.1 -kg loss of lean leg mass and a $22.9 \pm 3.5\%$ reduction in leg extension strength.¹⁹ When healthy volunteers were subjected to 28 days of bed rest and hydrocortisone to achieve plasma cortisol levels mimicking trauma or critical illness, leg extension strength decreased even further ($28.4 \pm 4.4\%$, $P = 0.012$), and the loss of lean leg mass was increased threefold compared to bed rest alone (1.4 ± 0.1 kg, $P = 0.004$).²⁰ Therefore, it is apparent that both immobility and the hormonal effects of critical illness contribute to increased weakness in ICU patients.

■ NEUROMUSCULAR WEAKNESS IN THE ICU

Neuromuscular weakness is a common complication of critical illness. Approximately half of ICU patients with sepsis, multiorgan failure, or prolonged mechanical ventilation have electrophysiologic evidence of neuromuscular dysfunction.²¹ In patients with both sepsis and multiorgan failure, the incidence can be as high as 100%.²² Electrophysiologic weakness is evident as early as 18-24 hours into the onset of a critical illness.^{22,23} Clinical evidence of weakness is evident in a smaller but significant portion of ICU patients.²⁴

The differential diagnosis of neuromuscular weakness in the ICU is long and includes critical illness neuromyopathy, an umbrella term that includes critical illness neuropathy, critical illness myopathy, and neuromuscular junction disorders. ICU-acquired weakness (ICUAW) is defined as bilateral symmetric limb weakness and is the clinical manifestation of critical illness neuromyopathy. It typically presents as flaccid quadriplegia with hyporeflexia or areflexia, although the cranial nerves are usually spared.²⁵ This weakness increases the duration of mechanical ventilation, prolongs ICU and hospital length of stay (LOS), and increases mortality.^{21,26}

A number of risk factors have been implicated in the development of ICUAW. These include the systemic inflammatory response syndrome, sepsis, multiorgan failure, renal replacement therapy, catecholamine administration, and hyperglycemia.²¹ The relationship between ICUAW and other factors, such as age, gender, corticosteroids, or neuromuscular blocking agents is inconsistent.^{4,21,24,27-29} Unfortunately, there have been few investigations of interventions to prevent ICUAW. With ill-defined or unmodifiable risk factors and a lack of preventive measures, ICUAW has become common in survivors of critical illness and has serious long-term consequences. Indeed, survivors of the acute respiratory distress syndrome report poor functional status at 1-year post discharge despite the normalization of pulmonary function tests. Secondary to muscle loss, weakness, and fatigue, only 49% of these patients were able to return to work within 1 year of their critical illness.⁷ Five years after ICU discharge, 100% of survivors reported subjective weakness and decreased exercise capacity compared to before ICU admission.⁸ Similarly, survivors of severe sepsis with no functional limitations prior to ICU admission developed significant limitations in their ability to perform activities of daily living and continued to develop functional limitations at a more rapid rate following hospital discharge.⁵ Early mobilization and ambulation have been suggested as one possible intervention to prevent the weakness and functional decline associated with critical illness.

■ EARLY MOBILIZATION AND AMBULATION IN THE ICU

Safety and Feasibility

Multiple studies have confirmed the safety and feasibility of physical therapy in the medical ICU population.^{9,10,12,30,31} Morris et al. performed a prospective cohort study of 330 patients in a university-based medical ICU and showed that an ICU mobility team was able to initiate an early mobilization protocol within 48 hours of mechanical ventilation, without observing any adverse events or accruing increased cost.³⁰ Similarly, in a study by Pohlman et al., patients were successfully mobilized as early as one day after the initiation of mechanical ventilation.⁹ Physical therapy was successfully provided to 90% of medical ICU days during mechanical ventilation, despite a potential barrier to mobilization (e.g., acute lung injury, administration of vasoactive medications, delirium, renal replacement therapy, or obesity) present in 89% of the sessions. Minor adverse events, such as oxygen desaturation, increased heart rate, agitation, or ventilator dyssynchrony, occurred in 16% of sessions but required cessation in only 4%. No

unplanned extubations occurred. More recently, a prospective observational study of 1110 medical ICU patients, in which 5267 physical therapy sessions were conducted on 4580 patient days, revealed a physiologic abnormality or potential safety event in only 0.6% of sessions.¹² Only 4 (0.1%) of these occurrences required additional treatment or increased cost, and LOS was not increased. Furthermore, ICU rehabilitation programs aimed at reducing the time from ICU admission to physical therapy are sustainable in the long term. A recent study evaluating the effect of an ICU rehabilitation program in a medical ICU showed a sustained decrease in time to mobilization over a 5-year period.³²

Few studies have evaluated the safety and feasibility of early mobilization and ambulation in surgical ICU patients, where issues, such as wound healing, fractures, weight-bearing limitations, incisional pain, must be considered. A prospective observational study of early mobilization in a surgical ICU showed that early mobilization can occur safely as early as ICU day 1, without significant adverse events.³³ In a retrospective study of early mobilization in a trauma and burn ICU, Clark et al. reported no adverse events with physical therapy.³⁴ A subsequent review of the evidence for early mobilization in critically ill trauma patients concluded that there is a lack of evidence in this population but outlined injury-specific guidelines.³⁴ Early mobility also appears to be safe in the neuro intensive care unit (neuro-ICU) population. Indeed the implementation of a comprehensive mobility initiative in a neuro-ICU resulted in a 300% increase in mobility among patients, with no significant adverse events, such as falls or inadvertent line disconnections.³⁵ Furthermore, case reports suggest that even patients with left ventricular assist devices³⁶ and those on extracorporeal membrane oxygenation³⁷⁻⁴⁰ can safely participate in physical therapy programs. At our institution, we routinely ambulate patients on extracorporeal membrane oxygenation and extracorporeal life support systems.

Importantly, one commonly cited barrier to early mobilization and ambulation is the femoral catheter, which has recently been shown to be safe in the setting of physical rehabilitation. Indeed, in a cohort of 239 patients with femoral venous, arterial, or hemodialysis catheters, 101 patients received physical therapy interventions for a total of 253 sessions over 210 ICU days.⁴¹ The highest daily activity level was standing or walking, which occurred on 23% of days, and no adverse events were reported. However, of note, only 6 (6%) of patients had femoral hemodialysis catheters and none of these patients achieved a level of standing or walking. Another cohort of 77 patients with 92 femoral catheters underwent a total of 210 physical therapy sessions with 630 mobility activities and similarly found no adverse events. However, ambulation accounted for less than 10% of mobility activities, and it is unclear if any patients with hemodialysis catheters stood or walked.⁴² Therefore, femoral catheters need not be viewed as a barrier to mobilization, but caution must be taken with femoral hemodialysis catheters until there is more convincing evidence of safety.

Outcomes

The strongest evidence to support the benefit of early mobilization and ambulation can be obtained from two randomized controlled trials. Burtin et al. randomized 90 medical and surgical ICU patients on ICU day 5 to bedside ergometry with standard treatment, including respiratory physiotherapy and active motion sessions of the upper and lower limbs compared to standard treatment alone.⁴³ At hospital discharge, a 6-minute walking distance and the subjective feeling of well-being were significantly higher in the treatment group. Schweickert et al. randomized 104 medical ICU patients who had been on mechanical ventilation for less than 72 hours, to either daily sedation interruption and early exercise/mobilization or daily sedation interruption with therapy as ordered by the primary medical team.¹³ Patients in the intervention group had less delirium, more ventilator-free days, and an increased return to independent functional status at the time of hospital discharge.

Observational studies have also shown that early mobilization and ambulation are associated with decreased ICU and hospital LOS,^{30,44,45} as well as decreased delirium⁴⁵ without an increase in cost.³⁰ Early mobilization and ambulation can even lead to cost savings.⁴⁶ In the trauma and burn population, early mobilization and ambulation have been associated with decreased airway, pulmonary, and vascular complications, including ventilator-associated pneumonia and deep vein thrombosis.³⁴ In the neurosurgical ICU, increased mobility resulted in decreased restraint use, infections (including ventilator-associated pneumonia), decreased ICU, and hospital LOS.³⁵ Several specialty societies now recommend aggressive rehabilitation in the critically ill.^{47,48}

IMPLEMENTATION AND MONITORING

Implementation of an early mobilization and ambulation program is an iterative process that requires a structured approach, transdisciplinary team, collaborative environment, and support from administration and senior management. The use of a vetted framework, such as the Plan-Do-Study-Act (PDSA) model, the six sigma model,⁴⁹ or the 4-step model for large-scale knowledge translation suggested by Pro-novost et al.⁵⁰ increases the likelihood of success and sustainability of an intervention.

Planning and Engaging Phase

The first stage begins with summarizing and publicizing the evidence for early mobilization, including its safety, feasibility, sustainability, and effectiveness. Next, an interdisciplinary team, including physicians, nurses, physical therapists, respiratory therapists, senior executives, and other stakeholders, should be created. This team works with the frontline staff to navigate the early mobilization process and ensure a supportive and collaborative culture within the unit. Culture is of utmost importance, as “unnecessary immobilization” has been shown to occur frequently in ICUs where early mobilization is not ingrained in the culture.⁵¹ The team should then create a protocol for early mobilization, explicitly defining inclusion and exclusion criteria with the goal of capturing as many patients as possible and avoiding unnecessary exclusions. Of course, clinicians should consider each patient’s baseline, current clinical status, and clinical trajectory within the context of the prespecified criteria. Fig. 45-1 provides a sample algorithm for the delivery of physical therapy in critically ill patients.⁴⁵ Note that the type of physical activity performed depends on the status of the individual patient. Various methods of physical activity have been used successfully in the ICU, including traditional activities, such as sitting on the edge of the bed, standing, sitting in a chair, and ambulating. However, other activities, such as cycle ergometry⁴³ and even video games,⁵² are also safe and feasible. Careful consideration of certain populations (e.g., trauma patients, neurosurgical patients, patients with open abdominal wounds) should be given⁵³ and may require consultation with specialty services to delineate the appropriate activity level for these patients. Additionally, the team should consider whether early mobilization will be implemented on its own or as a part of a larger bundle of care processes. This includes the awakening and breathing, coordination, delirium monitoring and management, as well as early exercise and mobility (ABCDE) bundle^{11,53} or the ABCDEF bundle, which also encompasses family engagement.⁵⁴

Once a preliminary protocol has been identified, a sample patient can be used to assess workflow and potential barriers. Potential barriers should be discussed with all stakeholders, as perceived barriers may differ among disciplines. Table 45-1 describes a number of potential barriers to early mobilization and ambulation in addition to associated solutions.^{45,55} Note that these barriers include not only patient-related variables (e.g., the presence of lines, tubes, and drains) but also organizational, cultural, and environmental barriers. The latter include the lack of appropriate equipment (e.g., portable monitors and ventilators) and default bed rest orders. Cost is also a commonly perceived barrier,

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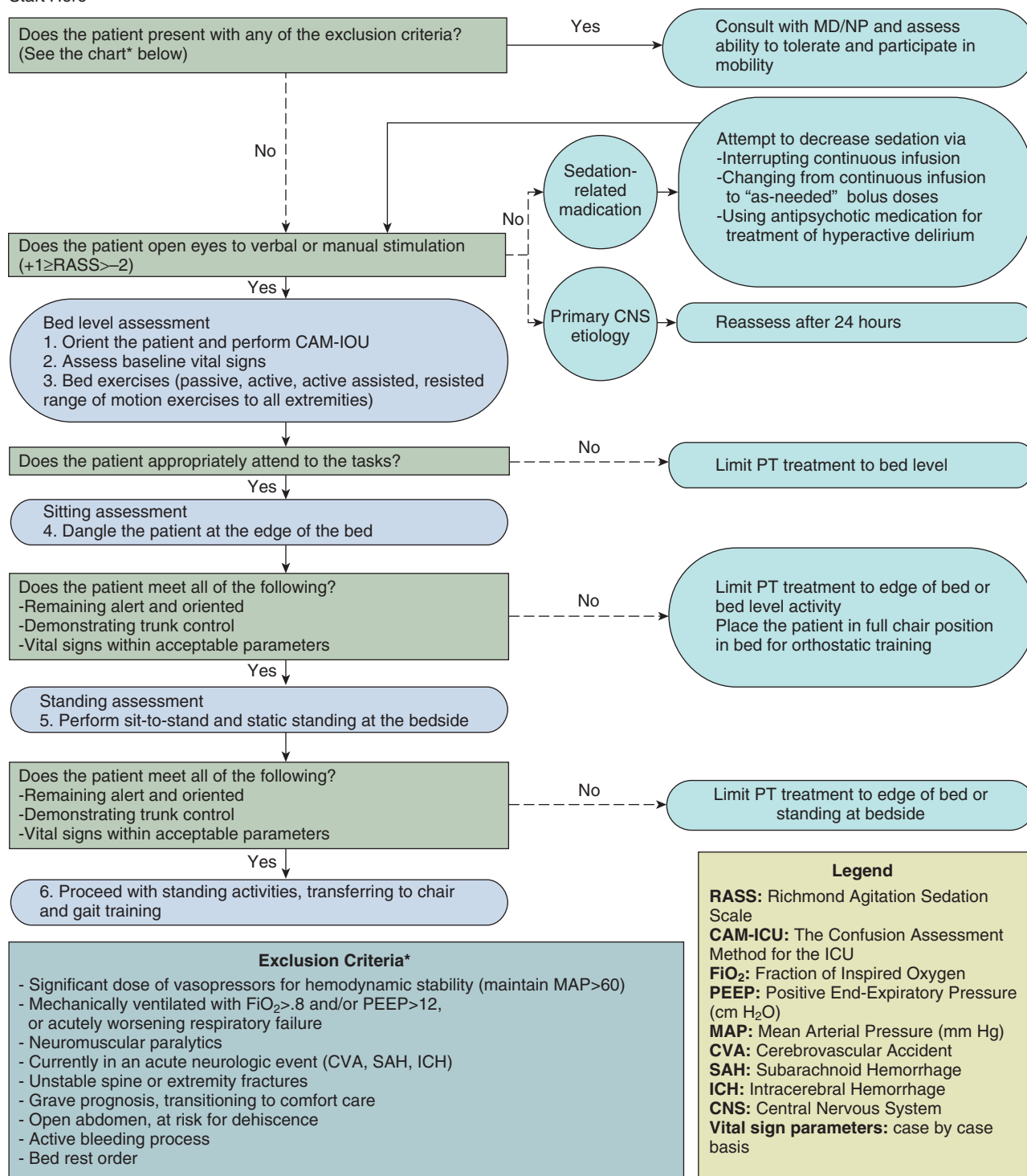


FIGURE 45-1 ■ Sample daily mobility assessment and treatment algorithm. MD = doctor of medicine; NP = nurse practitioner; RASS = Richmond Agitation-Sedation Scale; PT = physical therapy; CAM-ICU = the Confusion Assessment Method for the Intensive Care Unit; PEEP = positive end-expiratory pressure; MAP = mean arterial pressure; CVA = cerebrovascular accident; SAH = subarachnoid hemorrhage; ICH = intracerebral hemorrhage.) (Reprinted with permission from Critical Care Medicine/ Lippincott Williams & Wilkins (page S73, Fig. 45-1).⁴⁵

TABLE 45-1 Potential Barriers to Early Mobilization and Suggested Solutions

| BARRIER | SOLUTION |
|--|---|
| Endotracheal tubes, central venous catheters, other lines and drains | Secure device Train staff in best practices |
| Hemodynamic derangements | Educate staff on evidence of safety Provide specific exclusion guidelines |
| Sedation | Integrate daily sedation holiday into PT/OT protocol Encourage sedative administration on as-needed basis instead of continuous infusion Use validated sedation scoring system to evaluate sedative needs |
| Delirium | Normalize sleep-wake cycle Expose patient to sunlight during daytime hours Redirect patient frequently Minimize benzodiazepines and narcotics Monitor for delirium with validated scoring system |
| Inappropriate equipment | Purchase necessary equipment (portable monitors, portable ventilators) Consider options for bedside or in-room PT/OT if equipment purchase is not feasible |
| Insufficient staffing | Hire additional personnel Reorganize staff (example: shifting one nurse from night to day shift since PT/OT more likely to occur during the day) Train and utilize nursing students and PT students taking ICU elective Implement technologic solutions to maximize staff efficiency |
| Lack of physician referrals for physical therapy | Streamline physical therapy orders Use computerized order entry Make default activity order “ad lib” Perform joint PT/nursing/ICU team rounds to identify patients appropriate for mobilization Implement automatic referral to PT/OT |
| Fear of intervention/cultural roadblock | Create ongoing dialogue to address stakeholder concerns Educate staff on safety and benefits of intervention Incorporate early mobilization into ICU culture |
| Lack of leadership | Recruit transdisciplinary team Identify physician champion Include senior management/hospital administrators |

Data from Lipshutz et al.⁵⁵ and Engel et al.⁴⁵ ICU, intensive care unit; OT, occupational therapy; PT, physical therapy.

particularly among hospital administrators, despite evidence that early mobilization can be implemented with no additional cost and may be cost saving.⁴⁶

The planning and engaging phase also includes the development of a measurement plan and specification metrics used to evaluate the program. These can be either process or outcome measures. Process measures include the percent of patients being referred to physical therapy, the number of physical therapy sessions occurring per ICU day, and the time from ICU admission to ambulation. Possible outcome measures include the highest activity level achieved, incidence or duration of delirium, functional status at the time of ICU discharge, ICU or hospital LOS, cost, patient and family satisfaction, hospital discharge destination, and mortality. The metrics chosen should be easily measured and reproducible. Ideally, data should be collected both before and after implementation of the program to ensure that a pre-post analysis can be performed. Adverse events should also be defined and recorded to ensure that the program is safe for patients, family, and staff.

Executing Phase

Pilot testing the program in a subset of ICU beds may be prudent to help identify issues and optimize the protocol prior to dissemination

to all critically ill patients. Unit-based marketing campaigns advertising and supporting the initiative should precede the initial rollout to alert providers and remind staff of the benefits of physical therapy in the ICU. Members of the interdisciplinary team should be readily available to encourage and support frontline providers, answer questions, and quell anxieties associated with ambulating critically ill patients. Additionally, team members should continuously request feedback on the implementation process and the algorithm in use. In addition, they should also attempt to identify barriers not previously recognized, with the goal of making changes rapidly to address concerns and improve the program. Early achievements should be applauded and celebrated, with staff, patients, and families acknowledged for their efforts.

Evaluating and Improving Phase

The evaluation phase continues indefinitely. Evaluation can be both qualitative (e.g., in the form of informal interviews, focus groups, and surveys) or quantitative. The quantitative assessment is composed of the metrics previously defined in the planning phase. One feasible and reliable way to evaluate the success of an early mobilization and ambulation program is to use an ICU mobility scale. Hodgson et al. recently developed and validated an 11-point mobility scale.⁵⁶ This scale

TABLE 45-2 ICU Mobility Scale

| CLASSIFICATION | DEFINITION |
|---|---|
| 0 Nothing (lying in bed) | Passively rolled or passively exercised by staff, but not actively moving |
| 1 Sitting in bed, exercises in bed | Any activity in bed, including rolling, bridging, active exercises, cycle ergometry, and active assisted exercises; not moving out of bed or over the edge of the bed |
| 2 Passively moved to chair (no standing) | Hoist, passive lift, or slide transfer to the chair, with no standing or sitting on the edge of the bed |
| 3 Sitting on edge of bed | May be assisted by staff, but involves actively sitting on the side of the bed with some trunk control |
| 4 Standing | Weight bearing through the feet in the standing position, with or without assistance. This may include use of a standing lifter device or tilt table |
| 5 Transferring bed to chair | Able to step or shuffle through standing to the chair. This involves actively transferring weight from one leg to another to move to the chair. If the patient has been stood with the assistance of a medical device, they must step to the chair (not included if the patient is wheeled in a standing lifter device) |
| 6 Marching on spot (at bedside) | Able to walk on the spot by lifting alternate feet (must be able to step at least 4 times, twice on each foot), with or without assistance |
| 7 Walking with assistance of 2 or more people | Walking away from the bed/chair by at least 5 m (5 yards) assisted by 2 or more people |
| 8 Walking with assistance of 1 person | Walking away from the bed/chair by at least 5 m (5 yards) assisted by 1 person |
| 9 Walking independently with a gait aid | Walking away from the bed/chair by at least 5 m (5 yards) assisted by a gait aid, but no assistance from another person. In a wheelchair-bound person, this activity level includes wheeling the chair independently 5 m (5 yards) away from the bed/chair |
| 10 Walking independently without a gait aid | Walking away from the bed/chair by at least 5 m (5 yards) without a gait aid or assistance from another person |

Reprinted with permission from Hodgson et al. and Heart & Lung/Elsevier (page 21, Fig. 45-1).⁵⁶

(Table 45-2) describes the highest level of activity achieved by a patient on a given day, ranging from a score of 0, which indicates no activity (patient lying in bed), to 10, which indicates being able to walk independently without an assistance device. In a study of 100 medical, surgical, and trauma ICU patients, the scale was a feasible tool with high interrater reliability among nurses and physical therapists of various levels. Other important metrics include the incidence of

delirium, ICU and hospital LOS, hospital discharge destination (i.e., home versus rehabilitation facility or skilled nursing facility), and the incidence of adverse events. Ongoing improvement should take place in response to issues, staff concerns, or poorly performing metrics. Metrics that improve initially and then show a decrement indicate a problem with sustainability and should trigger an in-depth review of the program and re-engagement of the frontline staff.

KEY POINTS

1. A large proportion of survivors of critical illnesses experience long-term cognitive, psychological, and physical disability, with less than half of survivors returning to work by 1 year after ICU discharge.
2. Prolonged periods of inactivity and immobility lead to reduced protein synthesis, accelerated proteolysis, and increased apoptosis. This ultimately results in a catabolic state, atrophy, and clinical weakness.
3. Early mobilization and ambulation have been suggested as possible interventions to prevent the weakness and functional decline associated with critical illness.
4. Early mobilization is safe, feasible, and sustainable in various ICU populations.
5. The intervention is beneficial, decreasing the incidence and duration of delirium, decreasing ICU and hospital LOS, improving functional status, and increasing the likelihood of being discharged home from the hospital.
6. Early mobilization therapy should be considered in all critically ill patients.

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Weakness from inactivity and critical illness is seen commonly in intensive care unit (ICU) patients, occurring in about 57% of patients in at-risk populations.^{1,2} ICU-acquired weakness (ICUAW) develops from inactivity, inflammation, and metabolic abnormalities. Patients' underlying illnesses, safety concerns, the presence of management devices [e.g., intravenous (IV) catheters, endotracheal tubes, thoracostomy tubes], and treatment of pain and anxiety with narcotics and sedation suppress patient activity and further contribute to weakness. The impact of inactivity is powerful, and measurable weakness manifests after just a few days of inactivity.³ In ICUAW, the combination of inactivity, inflammation, and metabolic abnormalities can cause patients to lose 3% to 11% of their strength per day.⁴

CLINICAL MANIFESTATIONS OF ICUAW

The classic case of ICUAW involves a patient with ventilator-dependent respiratory failure and septic shock, requiring several days of sedation, mechanical ventilation, and vasopressors. After the resolution of shock, the patient demonstrates symmetric limb weakness that can manifest as decreased handgrip or leg strength. Such a patient may develop symmetric diaphragmatic weakness, leading to failure to meet criteria for mechanical ventilation liberation despite effective treatment for the initial cause of respiratory failure.

However, ICUAW can develop in any patient, whether or not he or she has respiratory failure or shock. Symmetric limb and diaphragmatic weakness are the most widely identified characteristics. Patients may also demonstrate symmetric sensory loss, muscle atrophy, and decreased deep tendon reflexes, while their facial muscles are often spared.^{5,6} Differential diagnoses include Guillain-Barré syndrome, drug- or metabolism-induced neuropathies, myasthenia gravis, uremia, diabetes, electrolyte abnormalities, brainstem or spinal cord injuries, and epidural abscesses.⁵ Warning: patients with asymmetric findings require additional evaluation to rule out causes of unilateral neuropathy, such as stroke or pressure-induced neuropathy (e.g., pressure over the ulnar or peroneal nerves).

In patients requiring mechanical ventilation, ICUAW may have an even more prolonged effect. Generalized weakness can be tenacious and persistent. Patients often have difficulty recovering normal walking speed and other activities of daily living; limitations on their functional status continue for up to 5 years or more after discharge from the ICU.^{2,4,7,8}

DIAGNOSIS OF ICUAW

A diagnosis is often made by physical examination alone. However, this can be difficult in patients on mechanical ventilation or in those who are otherwise unable to interact with the examining physician. Such patients sometimes require additional testing to rule out other causes. A recent ATS Consensus conference recommends using the Medical Research Council (MRC) scale of Manual Muscle Testing (MMT) as part of the physical examination, even though there are limitations posed by the ordinal scale and the possibility of missing other subtle early changes in distal muscles.^{9,10} The MRC scale is a 6-point assessment of muscle strength that requires full patient cooperation and is graded as follows: 0, no visible contraction; 1, visible contraction without movement; 2, movement of limb, but not against

gravity; 3, movement of limb against gravity; 4, movement of limb against gravity and resistance; and 5, normal power.

MMT is performed on three muscle groups in both the upper and lower extremities. The following movements are included:

- Shoulder abduction (moving the elbows laterally away from the body)
- Elbow flexion
- Wrist extension
- Hip flexion
- Knee extension
- Ankle dorsiflexion

Patients who score 48 or less out of a possible 60 (an average of 4 or less on each group joint) are defined as having ICUAW.^{6,11} Other assessments can include hand dynamometry, which measures hand-grip strength.

Electrophysiologic testing can confirm the suspected diagnosis using nerve conduction studies and electromyography. These tests can be helpful in patients who are unable to follow along with physical examination. In particular, in patients with unexplained failure to liberate from mechanical ventilation, such testing can identify ventilator-induced diaphragmatic dysfunction, a presentation of ICUAW. Electrophysiologic studies are typically reserved for special circumstances that require a diagnosis for management decisions, as they can cause pain and discomfort and require trained staff. Nerve and muscle histology can confirm the diagnosis, but this is rarely indicated because of the risks of biopsy and limited potential benefits.

CLASSIFICATION OF ICUAW

ICU patients can develop pathologic changes in muscles and nerves. As the duration of inactivity increases, disuse leads to physical changes at the cellular level, contributing to diminished action potentials both within nerves and across the neuromuscular junction, resulting in diminished force of contraction, loss of myosin, and muscle atrophy. Simultaneously, the systemic inflammation and metabolic abnormalities of the underlying critical illness cause disruption of microcirculation with damage to nerves and muscles. The nerves can develop dysfunctional nutrient transport. These muscles can develop further atrophy, myosin loss, or even mild rhabdomyolysis. To characterize how individuals are affected, ICUAW can be classified according to physical findings, electrophysiologic testing, or biopsy. Although three distinct classifications exist and are described below, the prevention of ICUAW in all forms responds to early mobilization.

Critical illness polyneuropathy (CIP) affects the distal axonal sensory and motor nerve, impacting both limb and respiratory muscles. Electrophysiologic testing shows reduced amplitude in both muscle and sensory nerve action potentials with normal or mildly reduced nerve conduction velocity.^{6,12}

Critical illness myopathy (CIM) demonstrates both decreased muscle mass and contractility due to decreased myosin in relation to actin and increased proteolysis as compared to protein synthesis. Electrophysiologic testing shows decreased sensory or muscle nerve action potential amplitudes are decreased.^{5,12}

Critical illness neuromyopathy (CINM) demonstrates characteristics of both CIP and CIM on nerve conduction studies and electromyography.^{11,12}

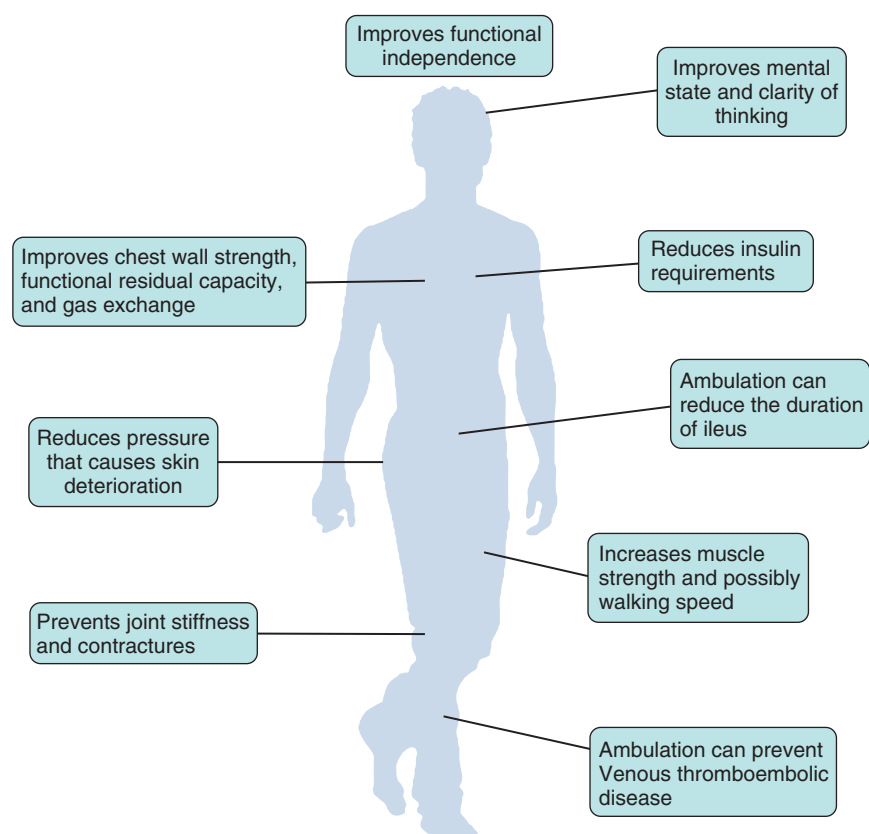


FIGURE 46-1 ■ Benefits of early mobilization.

RISK FACTORS FOR ICUAW

In general, patients are at increased risk the longer they remain mechanically ventilated or on bed rest. Their level of acuity and organ dysfunction also plays a role.¹³ For each day of bed rest, there can be up to a 3% to 11% decrease in strength.⁴ In randomized controlled trials, hyperglycemia was associated with increased risk of ICUAW. Incidence decreased when glucose levels were more closely controlled with insulin protocols in most cases, but not all studies are consistent.^{1,11,14} Corticosteroid usage and neuromuscular blockade were at one time considered to be risk factors; however, more recent studies suggest that they are not. The weakness attributed to corticosteroid impact may actually have resulted from hyperglycemia secondary to the steroid effect on insulin levels.¹¹ Other possible but unconfirmed risk factors include administration of aminoglycosides, female sex, and the use of total parenteral nutrition.¹¹

PREVENTION OF ICUAW

Advantages of Early Mobilization

Prevention of ICUAW by early mobilization is the most important treatment for patients. This should occur before the diagnosis, as soon as safety criteria are met, because early mobilization can have the most benefit for the patient and prevent atrophy secondary to inactivity. Early mobilization programs have been shown to increase patients' functional independence at the time of discharge,¹⁵ yielding improved 6-minute-walk scores and overall perceived well-being.^{16–18} Early mobilization interventions improved patients' metabolic status as evidenced by a decrease in the exogenous insulin required to maintain blood glucose control.¹⁹ Other benefits of early mobilization shown in trials include shortened duration of delirium, reduced need for mechanical ventilation, and shortened stays in the ICU and

TABLE 46-1

Safety Criteria Considerations to Avoid Mobility

- Mean arterial blood pressure <65 mm Hg or target range
- Systolic blood pressure >200 mm Hg
- Heart rate <40 to 50 or >140 beats/min or out of individualized target range
- New arrhythmia
- Patient requires medium or high dose of vasopressor support
- Oxygen requirement of >80%
- PEEP >10 to 15 cm H₂O
- Respiratory rate >35/min for more than 60 seconds
- Oxygen saturation above 90% before initiation
- Oxygen saturation below 85% for >60 seconds or decreasing more than 10% during exercise
- Pain scale rating >7 for more than 5 minutes or equivalent assessment if patient is intubated (i.e., grimacing)
- New-onset chest pain
- Pale appearance, diaphoresis, or feeling acutely ill
- Elevated intracranial pressure
- Agitation
- Undergoing renal replacement therapy
- Active seizures or alcohol withdrawal
- Concern for myocardial ischemia

Adapted from Parry 2012, Needham, D 2010, Schweickert 2009, Hodgson 2013.^{16,18,22,23}

hospital.^{17,18} In practice, it can improve patients' mental clarity and motivation to recover and reduce the possibility of joint stiffness and contractures. Sitting up in a chair and standing can improve gas exchange and functional residual capacity, while ambulating can reduce the skin pressure that can lead to pressure ulcers and the risk of deep vein thrombosis (Fig. 46-1).

Early mobilization can be performed safely in medical and surgical intensive care units by combining clinical judgment with close attention to safety criteria (Table 46-1). In randomized trials, adverse events

such as patient falls, blood pressure fluctuations, and hypoxemia severe enough to require suspension of the treatment occurred in less than 1% of the mobilization sessions.²⁰

Implementation of Early Mobilization in ICU Patients

A multidisciplinary team approach is important to promote working together by physicians, nurses, therapists, and other staff to ensure patient safety and participation. Performing early mobilization interventions on critically ill patients who may be mechanically ventilated is generally considered safe but still requires clinical judgment, individualized safety assessment, and monitoring.²¹ Safety assessment criteria should include oxygen requirements, oxygen saturation, respiratory rate, levels of positive end expiratory pressure, blood pressure, vasopressor requirements, heart rate, intracranial pressures, and other conditions and treatments. See Table 46-1 for details.

Other safety considerations can be tailored to the patient. Additional cardiac concerns include the presence of severe or critical aortic stenosis and dependency on a transvenous or epicardial pacemaker. The presence of other devices, such as a femoral intraaortic balloon pump, extracorporeal membrane oxygenation, pulmonary artery catheterization, or a thoracostomy tube, needs to be considered. Post-surgical or trauma considerations include the presence of a significant unstable fracture or a large, open abdominal or chest wound. Neurologic considerations include elevated intracranial pressure, status post craniectomy, lumbar or subgaleal drain, spinal precautions prior to clearance, active spinal cord injury, vasospasm after aneurysmal clipping, or seizures. Additional medical concerns include bleeding, hypothermia protocol, hyperthermia, and active signs of suboptimal organ perfusion (e.g., elevated lactic acid).²³

Patients should also be assessed for level of consciousness, delirium, and their ability to follow commands. A calm and alert level of consciousness is preferred, as patients who are too drowsy or agitated may

have difficulty following directions. Delirium can be assessed using the Confusion Assessment Method for the ICU (CAM-ICU).²⁴ If patients are not at the appropriate level of consciousness or are delirious, they can be considered for passive range of motion exercises in the upper and lower extremities. Staff or trained family members can perform passive range of motion in the upper and lower extremities. Minimizing the use of sedation and narcotic infusions while maintaining comfort can reduce delirium and improve the level of consciousness and the ability to follow commands.¹⁸

When patients are not delirious and are calm, alert and able to follow commands, they should be ready for active rehabilitation therapy. Physical therapists or other trained staff can conduct early mobilization sessions. Occupational therapy sessions may also be indicated based on personalized need if patients require assistance with finer motor movements.²⁵ Patients will vary significantly in their strength level, ranging from 0-5 on the MRC scale. Personalized therapy sessions are personalized depending on strength and functional abilities and often incorporate a graduated intensity program and up to five to seven sessions per week.

Rehabilitation includes assistance to perform the following activities:

- Transition from lying to sitting on the edge of the bed
- Transition from sitting to standing
- Transfer from standing to sitting in a chair
- Walking with assistance
- Walking independently
- Climbing stairs

In patients who demonstrate more severe deconditioning and weakness, additional strengthening rehabilitation exercises are indicated. These include active trunk and upper and lower extremity exercises that are introduced in a graduated manner.^{17,26} Such programs are often implemented in a multidisciplinary approach with involvement by physical therapists, nurses, and nursing assistants. See Figure 46-2, which is based on modified work by Hanekom et al.

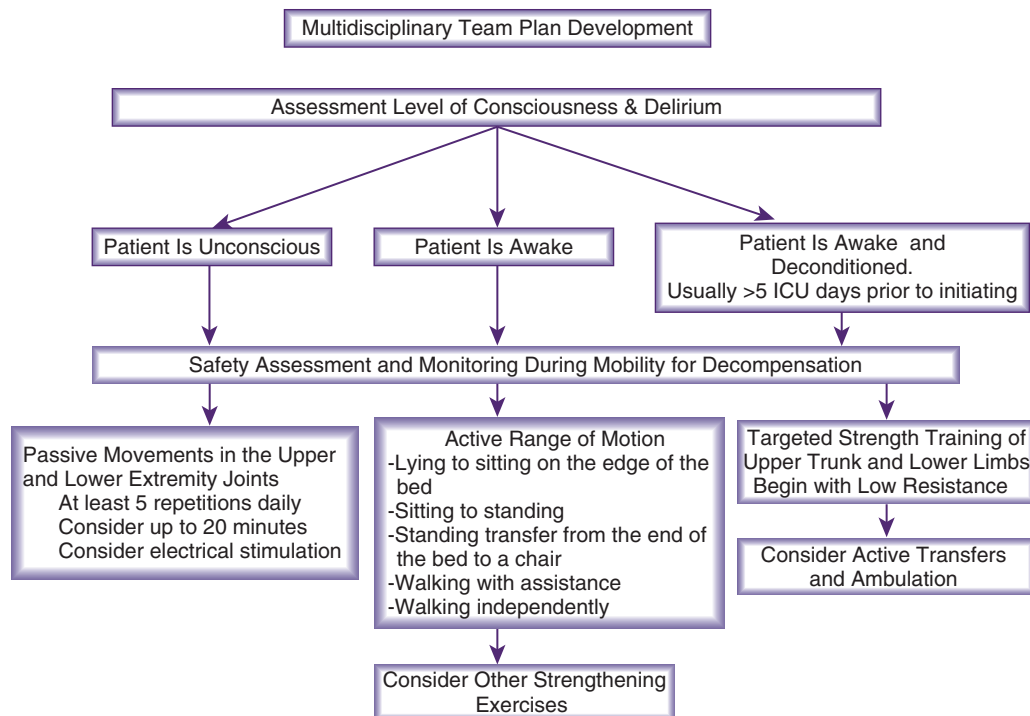


FIGURE 46-2 ■ Implementing early mobilization. (Adapted from Hanekom S, Gosselink R, Dean E, et al. The development of a clinical management algorithm for early physical activity and mobilization of critically ill patients: synthesis of evidence and expert opinion and its translation into practice. Clin Rehabil 25[9] 771–787, 2001.)

Additional Considerations for Prevention of ICUAW

Glycemic Control

Adequate maintenance of glucose control may prevent the development of CIP and CIM. Subanalyses of two randomized controlled trials compared patients with strictly regulated blood sugar to a control group; using electrophysiologic testing, the relative risk of developing ICUAW was more than 20% lower in patients with strictly controlled glucose. Glucose control can minimize the risk of ICUAW in patients who develop hyperglycemia subsequent to receiving corticosteroids.^{14,15,27} While these glucose studies demonstrate theoretical benefits, there is debate about whether the associated risks of hypoglycemia with tight glucose control are justified.¹¹

Inspiratory Muscle Strength Training

Patients who are unable to liberate from mechanical ventilation due to ICUAW may benefit from inspiratory muscle strength training, inhaling against a device that provides resistance to inspiration. In one trial, patients with tracheostomies who required intermittent ventilation received inspiratory muscle strength training of 6-10 resisted breaths repeated four times daily. This trial demonstrated strengthened inspiratory muscle strength and a 25% increase in successful liberation from mechanical ventilation compared to the control group.²⁸

Transcutaneous Electrical Stimulation

Transcutaneous electrical stimulation of the extremities is an intervention that can be used in both unconscious and awake patients and may be of benefit with or without additional active exercises. A limited trial involving daily application of transcutaneous electrical stimulation for 55 minutes to the lower limbs demonstrated improved strength and muscle mass.²⁹ Other small trials also demonstrated improved muscle strength; while debate over the evidence is ongoing, these trials assert that transcutaneous electrical stimulation in conjunction with physical therapy appears to improve outcomes.^{20,30}

Cycle Ergometry

A cycle ergometer is a stationary cycle that offers both active and passive exercise options to a patient. It can provide adjustable resistance for active strengthening or, depending on the patient's ability, can provide passive range of motion to prevent contractures in a weak or paralyzed patient. Patients can use a cycle ergometer while in bed. Research trials have demonstrated improvements in muscle mass.²⁰

CONCLUSION

Patients develop ICUAW disuse atrophy, as well as metabolic and inflammatory injury to the muscles and nerves leading to symmetric

limb weakness and, potentially, diaphragmatic weakness. The duration of inactivity is the leading risk factor, despite the various pathophysiology and electrophysiology findings. The short-term implications of ICUAW include prolonged mechanical ventilation and ICU length of stay. In the long term, weakness and decreased physical abilities can persist for 5 years or more after ICU discharge.

Early mobilization should be initiated as soon as safely possible. Waiting to initiate mobilization can make a significant impact on short- and long-term morbidity. Early mobilization requires close monitoring to ensure patients are able to safely initiate and follow through with the rehabilitative exercises. Most patients can, at the very least, receive passive range of motion exercises and graduated active rehabilitation as they recover from their critical illness. Early mobilization of patients with regular sessions, up to 6-7 times a week, can prevent the morbidity of ICUAW and improve physical health outcomes.

KEY POINTS

1. ICUAW develops from a combination of deconditioning, inflammation, and metabolic disorders.
2. ICUAW manifests with symmetric limb and/or diaphragm weakness with other possible findings that can include sensory loss.
3. Other diagnoses should be considered if the patient has unilateral or facial weakness or the severity is out of proportion to their risk factors.
4. Days of bed rest is the most important risk factor and potentially modifiable with early mobilization. Other important risk factors include the level of acuity and hyperglycemia.
5. Minimizing the use of sedation to promote consciousness for active rehabilitation is important.
6. Early mobilization with 5 to 7 sessions per week can improve patients' strength, physical functioning, and reduce the risk of other comorbid conditions.
7. Early mobilization should be started as soon as it is safe by incorporating the existing criteria.
8. A multidisciplinary team approach is important to implement a graduated and individualized approach for mobilization and physical rehabilitation.

■ References for this chapter can be found at expertconsult.com.

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Little can be done to reverse the primary brain damage caused by an insult; however, one of the major factors influencing outcome in patients with acute brain injury is the additional brain damage that occurs from secondary injury processes. Intracranial hypertension and cerebral ischemia are the most significant secondary injury processes that can be monitored and treated in the intensive care unit (ICU). In addition, secondary ischemic insults of extracerebral origin (e.g., arterial hypotension, hypoxemia) can be prevented or treated before they become severe enough to injure the brain. The purpose of advanced monitoring of the brain in the ICU is to detect these secondary insults, allowing for a more informed, individualized approach to treatment.

MONITORING NEUROLOGIC STATUS

The clinical approach to a patient with a neurologic problem requires the physician to have a specialized anatomic and physiologic knowledge of the nervous system. Daily evaluation of neurologic and mental status should be included in the neuromonitoring protocol. Neuro-monitoring should include the Glasgow Coma Scale (GCS) score, function of pyramidal and extrapyramidal systems, status of cranial nerves, function of the cerebellum and spinal cord whenever possible, and any changing trend in the neurologic status. In critically ill patients, such a complete neurologic evaluation can sometimes be unreliable or impossible because of the use of sedatives and the need for intubation and ventilatory support as part of the medical treatment of the neurologic problem. However, in the nonsedated patient, the recently devised Full Outline of Unresponsiveness (FOUR) score, which measures ocular and limb responses to commands and pain, pupillary responses, and respiratory pattern,¹ may provide a more complete assessment of brainstem function. The FOUR score has been shown to have good interrater reliability and prognostic content for some neurologic conditions.² However, experience with this instrument is still limited as compared to the GCS. Current evidence suggests that both the GCS and FOUR score provide useful and reproducible measures of neurologic state and can be routinely used to chart trends in clinical evaluation. Pupillary evaluation is a strong predictor of outcome that must be integrated into the daily GCS evaluation. However, poor interrater reliability exists among practitioners when it comes to pupillary assessment. New devices like the handheld pupillometer provide objective measurement of pupillary response and diameter, but more clinical experience is needed to determine if they should be included as a standard of care.³

Along with neurologic examination, information about vital signs and key laboratory values should be immediately available in a 24-hour record sheet or electronic medical record. Assessment of pain and sedation can be challenging in the context of brain injury. New evidence recommends the use of validated and reliable scales such as the Sedation-Agitation Scale (SAS) and Richmond Agitation Sedation Scale (RASS),⁴ as these provide workable solutions in some patients.

"Wake-up tests" in patients with intracranial hypertension pose significant risks⁵ and show no proven benefits in terms of duration of mechanical ventilation, length of ICU and hospital stay, or mortality rate in patients with neurologic disorders.

The GCS is used as a standardized scale for recording neurologic status in the ICU. The Glasgow Outcome Scale (GOS) has been the

standard outcome tool for neurocritical care. New tools such as the Neurological Outcome Scale for TBI (NOS-TBI) have been adapted for traumatic brain injury (TBI) patients from the National Institutes of Health Stroke Scale (NIHSS).⁶ This scale has demonstrated adequate predictive validity as well as sensitivity to change compared with gold-standard outcome measures and may enhance prediction of outcome in clinical practice and research.⁷

INTRACRANIAL PRESSURE AND CEREBRAL PERFUSION PRESSURE

The threshold that defines normal or raised intracranial pressure (ICP) is uncertain, but normal resting ICP in an adult is considered to be less than 10 mm Hg. Intracranial hypertension is generally accepted to be an ICP greater than 20 to 25 mm Hg. In the 2007 Guidelines for the Management of Severe TBI, an ICP threshold above 20 to 25 mm Hg was adopted as a level III recommendation to initiate treatment to reduce ICP in patients with severe life-threatening head injury.⁸ Recently, the necessity of ICP monitoring was questioned by the BEST-TRIP trial.⁹ No significant difference in outcome was observed when treatment of patients with severe TBI was guided either by ICP monitor or by clinical/imaging judgment. However, the results are specific to certain populations and may not be generalizable. ICP treatment is important, and in circumstances where adequate resources are available, such treatment is best achieved by the combined use of ICP monitoring, clinical examination, and imaging modalities.¹⁰

Cerebral perfusion pressure (CPP) is the difference between the mean arterial blood pressure (MAP) and ICP. Under normal physiologic conditions, an MAP of 80 to 100 mm Hg and an ICP of 5 to 10 mm Hg generate a CPP of 70 to 85 mm Hg.¹¹ Cerebral blood flow (CBF) is determined by both CPP and cerebrovascular resistance (CVR) according to the formula $CBF = CPP/CVR$.

Under normal circumstances, the brain is able to maintain a relatively constant CBF of approximately 50 mL per 100 g/min over a wide range of CPP (60 to 150 mm Hg).¹² Following injury, the ability of the brain to pressure autoregulate can be impaired, and CBF is often dependent on CPP.

The recommendations for an adequate CPP have changed over time and may in part be associated with the variability in how MAP is measured.¹³ Moreover, management strategies based on targeting CPP rather than ICP have not enhanced outcomes.¹⁴ The current recommendation in TBI is to target CPP values within the range of 50 to 70 mm Hg.¹⁵ CPP values less than 50 mm Hg increase the risk of cerebral ischemia and hypoperfusion, while therapies required to maintain CPP values greater than 70 mm Hg have been associated with an increased risk of acute respiratory distress syndrome (ARDS).¹⁶ However, individual assessment may be needed to determine the ideal CPP values for specific populations.¹⁷

Intracranial Pressure Monitoring Devices

The current gold standard for ICP monitoring is the ventriculostomy catheter or external ventricular drain (EVD), which is a catheter inserted in the lateral ventricle, usually via a small right frontal burr hole. This ventricular catheter is connected to a standard pressure transducer that must be maintained at a specific level. The reference

point for ICP is the foramen of Monro, although in practical terms, the external auditory meatus is often used as a landmark. Advantages of EVDs include the ability to measure global ICP and to perform periodic in vivo external calibration and therapeutic CSF drainage and sampling. However, intraventricular catheters are also associated with the highest rate of infection among the ICP monitors. Several microtransducer-tipped ICP monitors are now available on the market for clinical use (e.g., Camino ICP monitor, Codman microsensor, Hummingbird ICP, and Neurovent-P ICP monitor). These catheter-based transducers can measure pressure directly in the brain parenchyma. Although there are fewer risks of infection and intracranial hemorrhage with these catheters, the main disadvantage is that only the Hummingbird ICP can be calibrated in vivo; after preinsertion calibration, they may exhibit zero drift (degree of difference relative to zero atmospheres) over time.¹⁸

Noninvasive ICP monitoring devices have been developed to reduce the risk associated with invasive monitors. Such technologies include displacement of the tympanic membrane,¹⁹ optical detection of cerebral edema,²⁰ transcranial Doppler pulsatility index, and magnetic resonance of the optic nerve sheath.²¹⁻²⁴ So far, none of these methods has provided accuracy sufficient to replace invasive monitors.

ICP Waveforms

The normal ICP waveform consists of three arterial components superimposed on the respiratory rhythm. The first arterial wave is the percussion wave, which reflects the ejection of blood from the heart transmitted through the choroid plexus in the ventricles. The second wave is the tidal wave, which reflects brain compliance; and the third wave is the dicrotic wave that reflects aortic valve closure. Under physiologic conditions, the percussion wave is the tallest, with the tidal and dicrotic waves having progressively smaller amplitudes. When intracranial hypertension is present, cerebral compliance is diminished. This relationship is reflected by an increase in the peak of the tidal and dicrotic waves exceeding that of the percussion wave (Fig. 47-1).

Complications

Among the complications related to ICP monitoring, intracranial hemorrhage and infections are the most common. Less frequent complications are malfunction, malposition, and obstruction. Although these complications generally do not produce long-term morbidity in patients, they can cause inaccurate ICP readings and may increase hospitalization costs by requiring replacement of the monitor.

The incidence of infection for ICP devices is reported to be 1% to 27%,²⁵ depending on the type of device. In 2004, Anderson investigated complications associated with use of an ICP fiberoptic device (Camino) alone and in combination with an EVD catheter; the infection rates were 1.8% and 7.9%, respectively.²⁶ Several other factors have been identified that may affect the risk of EVD infection: the use of prophyl-

actic parenteral antibiotics; presence of other concurrent systemic infections; presence of intraventricular or subarachnoid hemorrhage (SAH); duration of monitoring; open skull fracture, including basilar skull fractures with CSF leak; leakage around the ventriculostomy catheter; and repeated flushing of the EVD. Routine exchange of ventricular catheters and prophylactic antibiotic use for EVD placement are not recommended to reduce infection rates.²⁷ However, placement of ICP monitors should be done under the most sterile possible conditions, minimizing excessive manipulation and flushing. Although there is evidence that antibiotic-impregnated catheters may decrease infection rates, more trials should be conducted to evaluate the beneficial effect on clinical outcome.²⁸

The second most common complication related to ICP monitoring is intracerebral hemorrhage; the risk is very low, with an average incidence of 1.1%.

JUGULAR VENOUS OXYGEN SATURATION

Placement of a jugular venous oxygen saturation ($Sjvo_2$) catheter involves retrograde insertion into the internal jugular vein of a catheter equipped with an oxygen sensor at the tip. The catheter is similar to the type used for CVP monitoring but is directed cephalad into the jugular bulb.²⁹ The tip of the catheter must be placed above the C1-C2 vertebral bodies to avoid contamination with blood coming from the facial vein. Correct positioning of the catheter can be confirmed with a lateral skull x-ray (Fig. 47-2). The incidence of complications related to the $Sjvo_2$ catheter is low but includes carotid artery puncture, hematoma formation, infection, thrombosis, and increased ICP that may arise during catheter insertion or with prolonged monitoring.

The development of in vivo reflectance oximetry using fiberoptic catheters has allowed continuous monitoring of $Sjvo_2$ without the need for continuous blood sampling, except for calibration purposes.³⁰ Changes in $Sjvo_2$ should be confirmed by measuring the oxygen saturation in a blood sample withdrawn from the jugular venous catheter, and the catheter should be recalibrated if the difference is more than 4% to increase the duration of good-quality records.^{29,31}

Side of Jugular Catheterization

The International Consensus on Multimodal Monitoring in Neurocritical Care recommends that the catheter site placement be based on the diagnosis, the type and location of brain lesions, and technical feasibility.¹⁰ If the strategy is to use $Sjvo_2$ as a monitor of global oxygenation, then cannulating the dominant jugular vein is logical because it is most representative of the whole brain. The dominant internal jugular vein is the larger of the two veins as determined by ultrasound imaging or by ICP response to venous compression. However, if the strategy is to identify the most abnormal oxygen saturation, then the side with the most severe injury should be cannulated.³²

Normal Jugular Venous Oxygen Saturation

$Sjvo_2$ reflects the global balance between cerebral oxygen delivery (supply) and the cerebral metabolic rate of oxygen (demand). When arterial oxygen saturation, hemoglobin concentration, and the hemoglobin dissociation curve remain stable, $Sjvo_2$ generally parallels changes in CBF. Values defining the normal range of $Sjvo_2$ are usually considered to be 50% to 54% for the lower range and 75% for the upper range.^{30,33} Multiple pathologic clinical scenarios may cause an increase or decrease in $Sjvo_2$ values (Table 47-1). A large number of studies have assessed the role of jugular venous saturation monitoring in patients with severe TBI. In 1992, Sheinberg et al. demonstrated that single or multiple episodes of jugular venous desaturation were associated with a higher mortality rate.³⁴ However, high $Sjvo_2$ values indicating low cerebral oxygen extraction have also been associated with poor outcome,³³ and an elevated mean arteriojugular oxygen content difference has been associated with a better outcome.³⁵ Because $Sjvo_2$

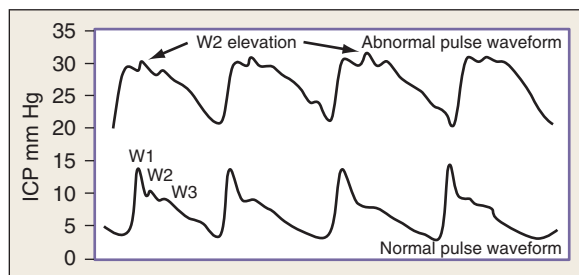


FIGURE 47-1 ■ (Upper tracing) Normal intracranial pressure (ICP) waveform and its components, W1 (percussion wave), W2 (tidal wave), and W3 (dicrotic wave). (Bottom tracing) As ICP increases, distinctive waveform changes occur (e.g., elevation of the second pulse wave and “rounding” in the ICP waveform).

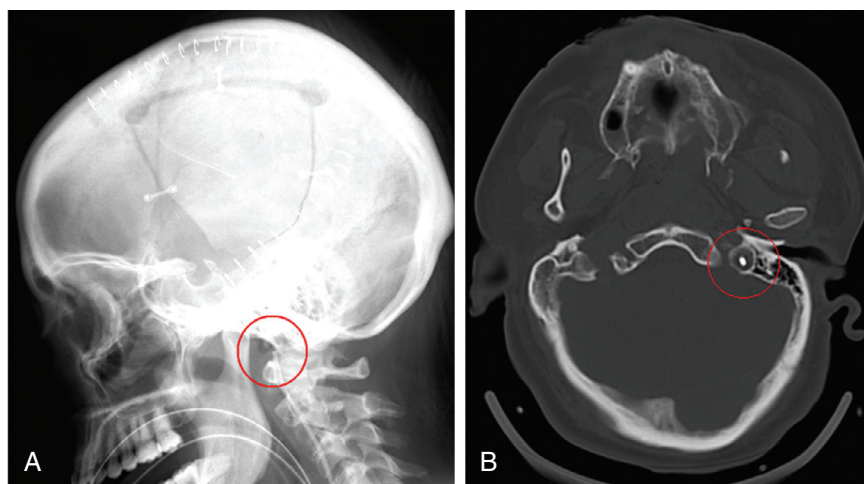


FIGURE 47-2 ■ **A**, Lateral skull x-ray confirming adequate SjvO₂ catheter placement at the C1-C2 level. **B**, Head computed tomography scan showing the catheter tip correctly placed at the jugular venous bulb level.

TABLE 47-1

Clinical Conditions Associated With Alterations in SjvO₂ Values

| | |
|-----------------------------|--|
| Increased SjvO ₂ | Restricted oxygen diffusion or extraction due to neuronal infarction or inflammation Decreased cerebral metabolism Increased systemic oxygen supply due to hyperoxia Hyperemia |
| Decreased SjvO ₂ | Local or systemic hypoperfusion (e.g., intracranial hypertension, shock or prolonged hypotension, vasospasm) Decreased systemic oxygen supply (e.g., low PaO ₂) Increased cerebral metabolism or oxygen extraction (e.g., seizures, fever) |

provides only information of a global state of cerebral oxygenation, focal ischemic areas are not evaluated with this technique. According to the most recent consensus for brain oxygen monitoring and thresholds, evidence supports the use of SjvO₂ along with clinical indicators and other monitoring modalities for accurate prognostication.¹⁰

■ LOCAL OR REGIONAL MONITORING

Transcranial Doppler Flow Velocity and Flow Volume

Transcranial Doppler (TCD) ultrasonography is a noninvasive monitoring technique that measures blood flow velocity in one of the major arteries at the base of the brain. A 2-MHz pulsed ultrasound signal is transmitted through the skull (usually through the temporal bone) and, using the shift principle, measures red cell flow velocity. Flow volume is directly proportional to flow velocity and can be calculated by multiplying the velocity by the cross-sectional area of the vessel insonated. Cerebral vasospasm is a major cause of disability after SAH and TBI, with similar incidence in both groups.³⁶ The incidence of critical regional CBF reductions due to vasospasm are seen progressively when flow velocities above 120 cm/sec are present by TCD examination.³⁷ Angiography remains the gold standard for diagnosing cerebral vasospasm, but TCD ultrasonography gives a noninvasive alternative for daily bedside monitoring of the CBF dynamics. The

Lindegaard ratio (middle cerebral artery-to-extracranial internal carotid artery flow velocity ratio) helps in differentiating vasospasm from hyperemia; vasospasm is considered to be present if the Lindegaard index is greater than 3:1.³⁸ In hyperemia, the flow velocity for both intracranial and extracranial vessels increases, whereas in vasospasm, high flow velocity is seen only in intracranial vessels, resulting in a high ratio.

Vasospasm following TBI or SAH has an impact on morbidity and mortality. Frequently, the first clinical sign is a deterioration in the neurologic examination, which occurs too late to reverse the process. TCD ultrasonography may identify changes in flow velocity that can precede these clinical findings and may lead to further diagnostic assessment and therapy. The major drawback of TCD ultrasonography is that it is operator dependent, though color-coded TCD provides improved accuracy of measurement.

TCD studies have high specificity for the confirmation of brain death. Brief systolic forward flow spikes with reversed or absent diastolic flow found bilaterally or in three different arteries are accepted TCD criteria for supporting the diagnosis of brain death.³⁹

Brain Tissue Oxygen Partial Pressure

A major limitation of SjvO₂ technology is that regional ischemia cannot be identified. Following TBI and other neurosurgical conditions, regional differences in CBF occur commonly, giving brain tissue oxygen partial pressure (Pbto₂), which measures oxygen levels in the local area of brain surrounding the catheter.

Pbto₂ is measured using a polarographic Clark-type electrode at the tip of a catheter placed in the brain parenchyma. The Clark electrode polarographic probe has a semipermeable membrane covering two electrodes. In the presence of dissolved oxygen crossing the membrane, an electric current is generated and then transferred to a monitor for interpretation. Temperature is also needed to calculate the oxygen tension. Brain temperature rather than core temperature is preferred for this purpose, and a sensor is incorporated into the Pbto₂ catheter.⁴⁰

Normal values for Pbto₂ are 20 to 40 mm Hg; levels below 10 to 15 mm Hg are considered critical, and intervention should be considered.⁴¹ The likelihood of death following a severe TBI increases the longer the Pbto₂ remains below 15 mm Hg and with any occurrence of Pbto₂ below 6 mm Hg.⁴²

Correct probe placement and depth into the region of interest are key for successful monitoring of Pbto₂. Two general strategies have been used for placement of this probe. Some recommend placement

of the probe into relatively normal brain tissue so that the Po_2 values reflect global brain oxygenation. Changes in Pbto_2 correlate well with changes in Sjvo_2 when the sensor is inserted into noncontused areas of the brain. Others recommend placement of the probe into penumbral tissue so that Po_2 values reflect oxygenation in the most vulnerable areas of the brain. Regardless of the strategy used, the Po_2 values must be interpreted with the understanding that the values measure only the local tissue surrounding the catheter. Pbto_2 monitoring is safe and provides accurate data for up to 10 days and can be used to guide pharmacologic, hemodynamic, or respiratory therapy.⁴³ For TBI patients, Pbto_2 monitoring has been incorporated into an overall management strategy, along with ICP and other standard monitoring. Decreased mortality in TBI patients managed using a Pbto_2 -targeted management strategy (maintaining $\text{Pbto}_2 > 25$ mm Hg) has been reported.⁴⁴ Narotam et al. also reported an improved 6-month clinical outcome over the standard ICP/CPP-directed therapy when treatment of cerebral hypoxia with a Pbto_2 -directed protocol (>20 mm Hg) was aggressive.⁴⁵ Treating a reduced Pbto_2 should be first directed to any underlying causes of inadequate cerebral oxygen delivery. Such corrections might include increasing CPP (reducing ICP, increasing MAP), improving arterial oxygenation, transfusions for a low hemoglobin concentration, reducing fever, or treating subclinical seizures. If an underlying cause for the low Pbto_2 is not found, or if Pbto_2 remains low after optimizing oxygen delivery, obtaining a follow-up CT scan of the head might be considered to assess whether a delayed hematoma or hemorrhagic contusion has developed. A sustained (>30 min) Pbto_2 of 0 mm Hg and no response to oxygen challenge are consistent with brain death,⁴⁶ although care related to interpretation in this regard is needed depending on the location of the probe or potential probe malfunction.

Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) is based on the fact that light in the near-infrared range (700–1000 nm) can pass through skin, bone, and other tissues relatively easily. Oxygenated hemoglobin, deoxygenated hemoglobin, and cytochrome *aa3* have different absorption spectra (650–800 nm). Changes in the absorbance of near-infrared light as it passes through these compounds can be quantified using a modified Beer-Lambert law, which describes optical attenuation. The main advantage of NIRS is that it is a noninvasive method for estimating regional changes in cerebral oxygenation. However, its clinical use is limited by an inability to differentiate between intracranial and extracranial changes in blood flow and oxygenation. This shortcoming adversely affects the reliability of the readings⁴⁵ and causes an inconsistent association between monitoring of decreased oxygenation and neurologic outcome.⁴⁷ Currently, there are no studies providing evidence that NIRS use alone can influence outcomes in adult neurocritical care.

Electroencephalogram

An electroencephalogram (EEG) depicts the spontaneous electrical activity of the cerebral cortex and is generated mainly by the summation of excitatory and inhibitory postsynaptic potentials of cortical neurons. It does not reflect activity in subcortical levels, cranial nerves, or the spinal cord. The electrical signal is amplified, filtered, and then displayed as either 8 or 16 channels (8 channels per hemisphere) to give an accurate representation of electrical activity throughout the cortex. EEG activity is usually interpreted in terms of frequency, amplitude, and location (focal or generalized activity).

EEG is the most frequently used electrophysiological technique in the ICU. EEG offers information about brain electrical activity and is essential to detect seizures. The presence of seizures, including duration and response to therapy, may predict outcome after coma with or without known acute brain injury in the ICU setting.⁴⁸ A relatively high incidence of nonconvulsive seizures (NCSz) occurs in the ICU (approximately 30%); such seizures can only be detected with EEG.

Setting a low threshold for obtaining an EEG must be considered in patients with acute brain injury and unexplained alteration of consciousness. EEG is urgently needed in patients with convulsive status epilepticus who remain unresponsive after one hour of administering what should represent adequate antiepileptic treatment. Continuous EEG (cEEG) is also strongly recommended in patients undergoing therapeutic hypothermia and within 24 h of rewarming to exclude NCSz in all comatose patients after cardiac arrest.⁴⁹

Continuous or long-term EEG is usually preferred over routine EEG recordings, as routine EEG will miss NCSz in approximately half of those with seizures when compared to prolonged monitoring.⁵⁰ Quantitative EEG algorithms have been developed to support the time-consuming expert review of cEEG recordings in the ICU setting. However, none of these techniques has reliably replaced the invaluable role of the expertly trained electrophysiologist.

Microdialysis

Microdialysis is a technique for sampling the extracellular space of a tissue. This method is based on the diffusion of water-soluble substances through a semipermeable membrane. Small molecules ($<20,000$ D) from the extracellular fluid can diffuse across the membrane and enter the perfusate. Conversely, substances that have been added to the perfusate can diffuse across the membrane to gain entry to the tissue. The degree of permeability of the membrane determines the molecular weight of the substances that cross it.

The concentration of substances in the dialysate depends on the flow rate and chemical composition of the perfusate, the length of the dialysis membrane, the type of dialysis membrane, and the diffusion coefficient of the tissue. The recovery of a particular substance is defined as the concentration in the dialysate divided by the concentration in the interstitial fluid. If the membrane is long enough and the flow slow enough, the concentration in the perfusate will be the same as that in the interstitial fluid (i.e., 100%). The parameters that are commonly used in clinical studies (i.e., 10-mm membrane, perfusion with Ringer's solution, and flow rate of 0.3 $\mu\text{L}/\text{min}$) provide an *in vivo* recovery rate (extrapolation to zero flow method) of approximately 70%.⁵¹

The technique of cerebral microdialysis allows continuous and online monitoring of changes in brain tissue chemistry. As with brain tissue oxygenation monitoring, microdialysis involves inserting a fine catheter (diameter 0.62 mm) into the brain. The dialysate, which is collected in vials that are exchanged every 10 to 60 minutes, is then analyzed using sensitive assays.

The key substances measured by microdialysis can be categorized as follows:

1. Energy-related metabolites (glucose, lactate, pyruvate, adenosine, xanthine)
2. Neurotransmitters (glutamate, aspartate)
3. Markers of tissue damage and inflammation (glycerol)
4. Exogenous substances (administered drugs)

Metabolite variations over time can help with clinical management and are not limited to markers of ischemia but allow monitoring of energy metabolism in the brain as well. In TBI, cerebral microdialysis may contribute to prognostication.⁵² In SAH, microdialysis has provided an understanding of poor energy substrate transport and of markers of late cerebral ischemia. Cerebral microdialysis has a very low complication rate. Nonetheless, there are a number of limitations regarding its clinical use, including its focal measurement and the fact that it discloses different metabolite concentrations when inserted into pathologic versus preserved brain areas. Therefore, microdialysis should be interpreted based on the location as defined by postinsertion CT. Currently available techniques can be cumbersome for bedside monitoring and interpretation, providing delayed rather than real-time data. Microdialysis when used with multimodality monitoring may enhance the understanding of brain physiology. Similarly, when used for research, it may provide new understandings of pathophysiologic mechanisms and treatment modalities that directly affect brain metabolism and function.

KEY POINTS

1. Evaluation of neurologic and mental status should be included in the monitoring protocol whenever possible.
2. The ventriculostomy catheter remains the preferred device for monitoring intracranial pressure (ICP) and is the standard against which all new monitors are compared.
3. The two major complications of ICP monitoring are ventriculitis and intracranial hemorrhage.
4. The simplest measure of cerebral perfusion is cerebral perfusion pressure (CPP). For equivalent levels of CPP, cerebral perfusion is impaired more by decreases in blood pressure than by increases in ICP.
5. Transcranial Doppler (TCD) ultrasonography is a noninvasive monitor that provides indirect information about cerebral blood flow (CBF) in one of the major arteries at the base of the brain. In the absence of vessel stenosis, vasospasm, or changes in arterial blood pressure or blood rheology, pulsatility reflects the distal cerebrovascular resistance.
6. The Lindegaard (hemispheric) index is the ratio of flow velocity in the middle cerebral artery and the internal carotid artery. The mean hemispheric index in normal individuals is 1.76 ± 0.1 , and pathologic values suggestive of vasospasm are generally above 3.
7. Normal values for P_{bto_2} are 20 to 40 mm Hg, and critical reductions are below 10 to 15 mm Hg.
8. The use of electroencephalograms (EEGs) in the ICU to detect early subclinical seizures may help reduce mortality and morbidity in status epilepticus. Continuous EEG monitoring is also useful in detecting ischemic cerebral events, including vasospasm following subarachnoid hemorrhage (SAH) and intracranial hypertension after TBI.

■ References for this chapter can be found at expertconsult.com.

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Altered states of consciousness are a common reason for the admission to intensive care units (ICUs). Few problems are more difficult to manage than the unconscious patient, because there are many potential causes of an altered mental status, and the time for diagnosis and effective intervention is short. *Consciousness* is defined as the state of awareness of the self and the environment. Consciousness requires two intact and interdependent physiologic and anatomic components: (1) arousal (or wakefulness) and its underlying neural substrate, the ascending reticular activating system (ARAS) and diencephalon, and (2) awareness, which requires the functioning cerebral cortex of both hemispheres. Most disorders that acutely disturb consciousness are impairments of arousal that create circumstances under which the brain's capacity for consciousness cannot be accurately assessed. In other words, failure of arousal renders it impossible to test awareness.

Alterations in arousal may be transient, lasting only several seconds or minutes (following seizures, syncope, and cardiac dysrhythmia), or sustained, lasting hours or longer. Four terms describe disturbed arousal of a patient. *Alert* refers to a normal state of arousal. *Stupor* describes a state of unarousability in which strong external stimuli can transiently restore wakefulness. Stupor implies at least a limited degree of cognitive activity accompanies the arousal, even if transient. *Coma* is characterized by an uninterrupted loss of the capacity for arousal. The eyes are closed, sleep/wake cycles disappear, and even vigorous stimulation elicits only reflex responses at best. *Lethargy* describes a range of behaviors between arousal and stupor. Only the terms *alert* and *coma* have enough precision to be used without further qualification; a coma has gradations in depth, but this cannot be accurately assessed once the patient no longer responds to external stimuli. Stupor and coma imply an acute or subacute brain insult. The cerebral reserve capacity is large, and thus, altered consciousness reflects either diffuse and bilateral cerebral dysfunction, failure of the brainstem-thalamic ARAS, or both. All alterations in arousal should be regarded as acute and potentially life-threatening emergencies.

The evaluation of a comatose patient demands a systematic approach with directed diagnostic and therapeutic endeavors; time should not be wasted on irrelevant considerations. Urgent steps are required to minimize permanent brain damage from reversible causes. Patient evaluation and treatment must occur simultaneously. Such an approach demands an understanding of the pathophysiology of consciousness, and mechanisms by which it may be deranged.

ANATOMY, PATHOLOGY, AND PATHOPHYSIOLOGY

Consciousness depends on an intact ARAS in the brainstem and adjacent thalamus, which acts as the alerting or awakening element of consciousness, together with a functioning cerebral cortex of both hemispheres, which determines the content of that consciousness.^{1,2} The ARAS lies within a more or less isodendritic core that extends from

the medulla through the tegmentum of the pons to the midbrain and paramedian thalamus. The system is continuous caudally with the reticular intermediate gray matter of the spinal cord and rostrally with the subthalamus, hypothalamus, anterior thalamus, and basal forebrain.³ The ARAS itself arises within the rostral pontine tegmentum and extends across the mesencephalic tegmentum and its adjacent intrathalamic nuclei. ARAS functions and interconnections are considerable, and likely contribute to more than only a cortical arousal system. The specific role of the various links from the reticular formation to the thalamus has yet to be fully identified.⁴ Furthermore, the cortex feeds back on the thalamic nuclei to contribute to an important loop that amplifies arousal mechanisms.^{5,6}

The ascending arousal system contains cholinergic, monoaminergic, and γ -aminobutyric acid (GABA) systems, none of which has been identified as the arousal neurotransmitter.^{2,7,8} Acute structural damage to, or metabolic/chemical disturbance of, either the ascending brainstem-thalamic activating system or the thalamocorticothalamic loop can alter the aroused attentive state. Consciousness depends on the continuous interaction between the mechanisms that provide arousal and awareness. The brainstem and thalamus provide the activating mechanism, and the cerebrum provides full cognition and self-excitation. The content of consciousness is best regarded as the amalgam and integration of all cognitive function that resides in the thalamocortical circuits of both hemispheres. Altered awareness is due to the disruption of this cortical activity by diffuse pathology. Focal lesions of the cerebrum can produce profound deficits (e.g., aphasia, alexia, amnesia, and hemianopsia), but only diffuse bilateral damage sparing the ARAS and diencephalon can lead to wakeful unawareness. Thus, there are two kinds of altered consciousness: (1) altered arousal due to dysfunction of the ARAS-diencephalon and (2) altered awareness due to bilateral diffuse cerebral hemisphere dysfunction.

Four major pathologic processes can cause such severe global, acute reductions of consciousness.^{1,9} (1) In the presence of diffuse or extensive multifocal bilateral dysfunction of the cerebral cortex, the cortical gray matter is diffusely and acutely depressed or destroyed. Concurrently, the cortical-subcortical physiologic feedback excitatory loops are impaired, with the result that brainstem autonomic mechanisms become temporarily profoundly inhibited, producing the equivalent of acute "reticular shock" below the level of the lesion. (2) Direct damage to the paramedian upper brainstem and posterior-inferior diencephalic ascending arousal system blocks normal cortical activation. (3) The widespread disconnection between the cortex and subcortical activating mechanisms acts to produce effects similar to both conditions 1 and 2. (4) Diffuse disorders, usually metabolic in origin, concurrently affect both the cortical and subcortical arousal mechanisms, although to a different degree according to the cause.

Structural Lesions Causing Coma

Intracranial mass lesions that cause a coma may be located in the supratentorial or infratentorial compartments. From either location, impaired arousal or coma is caused by the compression of the brainstem-hypothalamic activating mechanisms secondary to swelling and the displacement of deep-lying intracranial contents. The ultimate event occurs either by halting the axoplasmic flow or by sustained neuronal depolarization due to ischemia or hemorrhage. Factors

[†]This chapter is dedicated to Dr. Plum, who passed away prior to the publication of this edition of the textbook.

important to the degree of the loss of arousal are the rate of development, location, and ultimate size of the lesion. Cerebral mass lesions distort the intracranial anatomy and thereby alter the cerebrospinal fluid (CSF) circulation and blood supply to the brain. These changes result in an increased bulk of the injured tissue and a reduction in intracranial compliance. Intercompartmental pressure gradients result in herniation syndromes that are not necessarily associated with large increases in intracranial pressure (ICP). Sustained or evolving mass lesions can disturb cerebral vascular autoregulation, which results in transient vasodilatation. This in turn causes recurrent increases in ICP, with the additional compromise of cerebral blood supply to the injured regions.

Two herniation syndromes demonstrate the mechanism by which supratentorial lesions induce a coma. The rate of evolution of a mass dictates whether the anatomic distortion precedes (in slowly evolving lesions) or parallels the patient's deterioration of wakefulness. *Transtentorial herniation* can be central or predominantly unilateral. Central herniation results from caudal displacement by deep midline supratentorial masses, large space-occupying hemisphere lesions, or large uni- or bilateral compressive extraaxial lesions with compression of the ARAS. The progressive rostral-caudal pathologic and clinical stages of this herniation syndrome were outlined.¹ Pathologically, the bilateral symmetric displacement of the supratentorial contents occurs through the tentorial notch into the posterior fossa. Alertness is impaired early, pupils become small (to 3 mm) and reactive, and bilateral upper motor neuron signs develop. Cheyne-Stokes breathing, grasp reflexes, roving eye movements, or the depressed escape of oculocephalic reflexes are the typical clinical manifestations. In the absence of effective therapy at this diencephalic stage, herniation progresses caudally to compress the midbrain, leading to a deep coma and fixed midposition (3-5 mm) of the pupils, signifying sympathetic and parasympathetic interruption. Spontaneous eye movements cease, and the oculocephalic and oculocephalic reflexes become difficult to elicit. Spontaneous extensor posturing may also occur. Once this stage is reached, full recovery is unlikely. As the caudal compression-ischemia process advances, the pontine and medullary function becomes destroyed, with variable breathing patterns and absent reflex eye movements. Finally, autonomic cardiovascular and respiratory functions cease as the medullary centers fail.

Uncus herniation results from laterally placed hemisphere lesions, particularly of the temporal lobes, that cause side-to-side cerebral displacement as well as transtentorial herniation. Focal hemisphere dysfunction (e.g., hemiparesis, aphasia, seizures) precedes unilateral (usually ipsilateral) compression paralysis of the third cranial nerve. An early sign of uncus herniation is an ipsilateral (rarely contralateral) enlarged pupil that responds sluggishly to light, followed by a fixed, dilated pupil and an oculomotor palsy (eye turned downward and outward).¹ The ipsilateral posterior cerebral artery can become compressed as it crosses the tentorium and causes ipsilateral occipital lobe ischemia. Progressively, the temporal lobe compresses the midbrain, with the loss of arousal and bilateral or contralateral extensor posturing. Ipsilateral to the intracranial lesion, hemiparesis may develop if the opposite cerebral peduncle becomes compressed against the contralateral tentorial edge. Abnormal brainstem signs become symmetric, and herniation proceeds similarly to central herniation as rostrocaudal brainstem displacement progresses.

Infratentorial lesions cause coma by displacement, compression, or direct destruction of the pontomesencephalic tegmental activating system. Displacement of the medulla downward that is sufficient to push the brainstem and cerebellar tonsils into the foramen magnum causes cardiorespiratory collapse. Acute intrinsic lesions of the brainstem, usually hemorrhagic or ischemic, cause an abrupt onset of coma and are associated with abnormal neuro-ophthalmologic findings. Pupils are pinpoint due to the disruption of pontine sympathetic pathways or are dilated due to the destruction of the third cranial nerve nuclei or intraaxial exiting fibers. Disconjugate eye movements and nystagmus often occur while vertical eye movements are relatively spared. Ocular bobbing signifies pontine damage. Upper motor neuron

signs develop, and patients can become quadriplegic; flaccidity in the upper extremities and flexor withdrawal responses in the lower extremities often accompany midbrain-pontine damage.

Pathologically, basilar artery occlusion leads to asymmetric ischemia of the brainstem, with the involvement of the ARAS, the neighboring densely packed neuropil, as well as the descending and ascending motor and sensory tracts. Thrombosis of the rostral basilar artery leads to an infarction of the midline thalamic nuclei and brief coma without other obvious brainstem signs. A hemorrhage into the ventral pons occasionally spares consciousness but produces neuro-ophthalmologic signs and motor dysfunction. Extension of hemorrhage into the rostral pontine tegmentum results in a stupor, coma, or death. Basilar artery migraine can produce altered consciousness, possibly by interfering with blood flow in the basilar artery system. Rapidly developing extensive central pontine myelinolysis may cause a coma by extension into the pontine tegmentum. Other intrinsic brainstem lesions (e.g., tumor, abscess, granuloma, and demyelination) tend to progress slowly and usually spare arousal mechanisms. However, they may reduce attention and other cognitive functions, leading to severe psychomotor retardation.

Posterior extraaxial fossa lesions cause comas by the direct compression of the ARAS in the brainstem and in the diencephalon by upward transtentorial herniation. Compression of the pons may be difficult to distinguish from intrinsic lesions but is often accompanied by a headache, vomiting, and hypertension due to a Cushing reflex. Upward herniation at the midbrain level is initially characterized by a coma, reactive miotic pupils, asymmetric or absent caloric eye responses, and decerebrate posturing; caudal-rostral brainstem dysfunction then occurs, with midbrain failure and midposition fixed pupils.¹⁰ Causes of brainstem compression include cerebellar hemorrhage, infarction, and abscess, rapidly expanding cerebellar or fourth ventricle tumors, or less commonly, infratentorial epidural or subdural hematomas. The drainage of the lateral ventricles to relieve obstructive hydrocephalus due to posterior fossa masses can potentially precipitate upward acute transtentorial herniation.^{11,12}

Downward herniation of the cerebellar tonsils through the foramen magnum causes acute medullary dysfunction, as well as abrupt respiratory and circulatory collapse. Less severe impaction of the tonsils in the foramen magnum can lead to obstructive hydrocephalus and consequent bihemispheric dysfunction with altered arousal. Clinical manifestations include headache, nausea, vomiting, lower cranial nerve signs, vertical nystagmus, ataxia, and irregular breathing. Moreover, a lumbar puncture in this context carries the risk of catastrophic consequences.¹¹

Nonstructural Causes of Coma

Nonstructural disorders (e.g., metabolic or toxic disturbances) produce comas by diffusely depressing the function of the brainstem and cerebral arousal mechanisms. The anatomic locus of metabolic brain diseases has not been clearly defined. The onset of coma can be abrupt, as with toxic drug ingestion, general anesthesia, or cardiac arrest, or it may evolve slowly after a period of confusion and inattention. The chief manifestations of metabolic encephalopathy are disturbances in arousal and cognitive function. Other findings include abnormalities of the sleep/wake cycle, autonomic disturbances, and abnormal breathing variations.

A helpful distinguishing clinical feature of diffuse encephalopathy is the preservation of the pupillary light response; the only exceptions are an overdose of anticholinergic agents, near-fatal anoxia, or self-initiated malingering. Typically, a lack of pupillary reactivity requires a search for an underlying structural lesion. Neurologic examination reveals a decreased level of arousal and widespread cognitive decline. Deeply comatose patients without brainstem or hemisphere function and no known cause for a coma must be assumed to have suffered accidental or intentional poisoning. Metabolic disturbances of arousal and cognition particularly affect elderly patients who suffer from serious systemic illnesses or have undergone complicated surgery.

Multilevel CNS dysfunction characterizes metabolic encephalopathy. At the onset, abnormalities in cognition are at least as severe as the disturbance of arousal. Misperception, disorientation, hallucinations, concentration and memory deficits, and occasionally hypervigilance may progress to profound stupor and coma. The patient's level of arousal and consciousness often fluctuates. Motor abnormalities, if present, are usually symmetric, and patients often suffer from tremors, asterixis, and myoclonus. Spontaneous motor activity may range from hypoactivity (e.g., in cases of sedating drug or endogenous metabolic disturbances) to hyperactivity (e.g., after drug withdrawal or overdose of stimulants). Seizures can occur in cases of alcohol or drug withdrawal and in patients with established cortical pathology. Focal seizures may occur even without structural disease during hypoglycemia, hepatic encephalopathy, uremia, abnormal calcium levels, or toxin ingestion. Autonomic dysfunction can manifest as hypothermia with hypoglycemia, myxedema, or sedative drug overdose. Hyperthermia can occur in withdrawal states, particularly delirium tremens, anticholinergic drug overdose, infection, neuroleptic malignant syndrome, or malignant hyperthermia.

The metabolic need of the brain largely depends on the oxidation of glucose. Certain fatty acids and ketone bodies can supply part of the metabolic needs in emergency circumstances but fail to meet energy requirements. Normal cerebral blood flow (CBF) is around 55 mL/100 g tissue/min. At CBF < 20 mL/100 g/min, oxygen delivery becomes insufficient for normal levels of oxidative metabolism, and the cerebral glycolytic rate increases. Patients lose consciousness, and the electroencephalogram (EEG) is suppressed secondary to synaptic failure at CBF levels between 16 and 20 mL/100 g/min. The cortical evoked response is abolished below about 15 mL/100 g/min. At a CBF around 8 mL/100 g/min, the energy-dependent membrane pump fails, and the membrane potential collapses. Unless the CBF is restored promptly, irreversible neuronal injury will ensue. However, the threshold for ischemic neuronal injury is time-dependent. The complete cessation of CBF leads to a loss of consciousness in 8 seconds, and EEG suppression occurs between 10 and 12 seconds. ATP exhaustion and ionic pump failure occurs in 120 seconds. Selective neuronal damage starts after periods as brief as 5 minutes, and severe neuronal damage occurs after 20 to 30 minutes. Brain necrosis or infarction begins after 1 to 2 hours.

Under physiologic conditions, glucose is the brain's only substrate and crosses the blood-brain barrier by facilitated transport. The normal brain uses about 55 mg glucose/100 g/min. In adults, hypoglycemia (a blood glucose level <40 mg/dL) produces signs and symptoms of encephalopathy resulting from dysfunction of the cerebral cortex, before the brainstem. Neurologic presentation of hypoglycemia can vary from the focal motor or sensory deficits to a coma. Acute symptoms of hypoglycemia are better correlated with the rate at which the blood glucose levels decrease than with the degree of hypoglycemia. The blood glucose level at which cerebral metabolism fails and symptoms develop varies among individuals, but in general, confusion occurs at levels <30 mg/dL and a coma at <10 mg/dL. The brain stores about 2 g of glucose and glycogen, so a patient in a hypoglycemic coma may survive 90 minutes without suffering irreversible brain damage. The pathophysiology of coma from hypoglycemia is not well understood. The disorder cannot solely be attributed to glucose starvation of the neurons. Rather than such an internal catabolic death, evidence suggests that neurons are killed by external factors. Around the time the EEG becomes isoelectric, endogenous neurotoxins are produced and released by the brain into tissue and CSF. The distribution of necrotic neurons is unlike that of ischemia and is related to white matter and CSF pathways. The toxins first disrupt the dendritic trees, sparing the intermediate axons, an indication of excitotoxic neuronal injury. The exact mechanism of excitotoxic neuronal necrosis may involve hyperexcitation and culminates in the rupture of the cell membrane.

The pathophysiology of other metabolic encephalopathies is less well established and is discussed elsewhere.¹ Hepatic encephalopathy is caused not merely by ammonia intoxication but also involves the

accumulation of neurotoxins, such as short-chain and medium-chain fatty acids, mercaptans, and phenols. Altered neurotransmission may play a role in the accumulation of benzodiazepine-like substances, the imbalance of serotonergic and glutaminergic neurotransmission, and the accumulation of false neurotransmitters. The identity of the neurotoxins involved in uremic encephalopathy is uncertain and includes urea itself, guanidine and related compounds, phenols, aromatic hydroxyacids, amines, various peptide "middle molecules," myoinositol, parathormone, and amino acid imbalance. The cause of the disequilibrium syndrome may entail more than osmotic water shifts. The pathogenesis of pancreatic encephalopathy may involve demyelination of brain white matter due to liberated enzymes from a damaged pancreas, disseminated intravascular coagulation, or fat embolism.

The mechanism of action of exogenous toxins or drugs depends partially on both the structure and the dose. It should also be determined that none of the sedatives taken acutely produces permanent damage to the nervous system, making prompt diagnosis and effective treatment essential.

DIFFERENTIAL DIAGNOSIS

Several different behavioral states appear similar to, and can be confused with, coma. Differentiation of such states from a true coma has important diagnostic, therapeutic, and prognostic implications. Moreover, a coma is not a permanent state; patients who survive an initial coma may evolve through and into these altered behavioral states. All patients who survive beyond the stage of acute systemic complications reawaken and either proceed to recovery (with none or varying degrees of disability) or remain in a vegetative state.

The *vegetative state* can be defined as wakefulness without awareness and is the consequence of various diffuse brain insults.^{1,13} It may be a transient phase through which patients in a coma pass as the cerebral cortex recovers more slowly than the brainstem. Vegetative patients appear to be awake and to have cyclical sleep patterns; however, they do not exhibit evidence of cognitive function or learned behavioral responses to external stimuli. They may exhibit spontaneous eye opening, eye movements, and stereotypic facial and limb movements but are unable to demonstrate speech or comprehension and lack purposeful activity. They generate a normal body temperature and usually have functional cardiovascular, respiratory, and digestive systems but are doubly incontinent. The vegetative state should be termed *persistent* at 1 month after injury and *permanent* at 3 months after nontraumatic injury or 12 months after traumatic injury.^{14,15} Extended observation is required to assess any behavioral responses to external stimulation and demonstrate cognitive unawareness. The EEG is never isoelectric but shows various patterns of rhythm and amplitude, inconsistent from one patient to the next. Normal EEG sleep/wake patterns are absent.

In the *locked-in syndrome*, patients retain or regain arousability and self-awareness, but because of extensive bilateral paralysis (i.e., deafferentation) can no longer communicate except in severely limited ways. Such patients suffer bilateral ventral pontine lesions with quadriplegia, horizontal gaze palsies, and lower cranial nerve palsies. Voluntarily, they are capable only of vertical eye movements and/or blinking.¹ Sleep may be abnormal, with a marked reduction in non-REM and REM phases. The most common etiology is pontine infarction due to basilar artery thrombosis, but others include pontine hemorrhage, central pontine myelinolysis, and mass brainstem lesions. Neuromuscular causes of the locked-in syndrome include severe acute inflammatory demyelinating polyradiculoneuropathies, myasthenia, botulism, and neuromuscular blocking agents. In these peripheral disorders, the upward gaze is not selectively spared.

Akinetic mutism describes a rare subacute or chronic state of altered behavior, in which a patient who appears alert is both silent and immobile but not paralyzed.¹⁶ External evidence of mental activity is unobtainable. The patient usually lies with eyes opened and retains cycles of self-sustained arousal, giving the appearance of vigilance. Skeletal muscle tone can be normal or hypertonic but is usually not spastic.

Movements are rudimentary even in response to unpleasant stimuli. Affected patients are usually doubly incontinent. Lesions that cause akinetic mutism vary widely. One pattern consists of bilateral damage to the frontal lobe or limbic-cortical integration with relative sparing of the motor pathways, and vulnerable areas involve both basal and medial frontal areas. Similar behavior can also follow incomplete lesions of the deep gray matter (paramedian reticular formation of the posterior diencephalon and adjacent midbrain), but such patients usually suffer double hemiplegia and act slowly yet are not completely akinetic or noncommunicative.

Catatonia is a symptom complex associated most often with psychiatric disease. This behavioral disturbance is characterized by stupor or excitement and variable mutism, posturing, rigidity, grimacing, and catalepsy. It can be caused by a variety of illnesses, both psychiatric (affective more than psychotic) disorders, as well as structural or metabolic diseases (e.g., toxic and drug-induced psychosis, encephalitis, and alcoholic degeneration). Psychiatric catatonia may be difficult to distinguish from organic disease because patients often appear lethargic or stuporous rather than totally unresponsive. Such patients also may have a variety of endocrine or autonomic abnormalities. Patients in a catatonic stupor do not move spontaneously and appear unresponsive to the environment despite what appears to be a normal level of arousal and consciousness. This impression is supported by a normal neurologic exam and the subsequent recall of most events that took place during the unresponsive period. Patients usually lie with their eyes opened, may not blink in response to visual threats, but one can usually elicit optokinetic responses. The pupils are semidilated and reactive to light, the oculocephalic reflexes are absent, and vestibulo-ocular testing evokes normal nystagmus. Patients may hypersalivate and be doubly incontinent. Passive movement of the limbs meets with waxy flexibility, and catalepsy is seen in 30% of patients. Choreiform jerks of the extremities and facial grimaces are common. The EEG, both of catatonic excitement and stupor, often shows a reactive, low-voltage, fast-normal record rather than the slow record of a comatose patient.

■ APPROACH TO COMA

The initial approach to stupor and coma is based on the principle that all alterations in arousal are acute, life-threatening emergencies. Urgent steps are required to prevent or minimize permanent brain damage from reversible causes, often before the cause of the coma is established. Patient evaluation and treatment must necessarily occur simultaneously. Serial examinations are needed with accurate documentation, to determine a change in state of the patient. Accordingly, management decisions (therapeutic and diagnostic) must be made. The clinical approach to an unconscious patient logically entails the following steps: (1) emergency treatment; (2) history (e.g., from relatives, friends, and emergency medical personnel); (3) general physical examination; (4) neurologic profile, the key to categorizing the nature of coma; and (5) specific management.

Emergency Management

The initial assessment must focus on the vital signs to determine the appropriate resuscitation measures; the diagnostic process begins later. Urgent, and sometimes empiric, therapy must be administered to avoid additional brain insult.

Oxygenation must be ensured by establishing an airway and ventilating the lungs. The threshold for intubation should be low in the comatose patient, even if the respiratory function is sufficient for proper ventilation and oxygenation: the level of consciousness may deteriorate, and breathing may decompensate suddenly and unexpectedly. An open airway must be maintained and protected from aspiration. While preparing for intubation, maximal oxygenation can be ensured by suctioning the upper airway and manually ventilating with oxygen using a mask and bag. Bag-valve-mask ventilation with 100% oxygen and 1 mg of intravenous (IV) atropine may help prevent cardiac dysrhythmias.

If cervical spine injury is a possibility or has not been excluded, intubation should be performed by the most skilled practitioner available, with cervical spine precautions. A brief neurologic examination is performed before sedation required for intubation.

The key points of the *rapid neurologic exam* are hand drop from over the head (to assess for malingering or hysterical loss of consciousness); pupillary size and response to light; abnormal eye movements (i.e., active disconjugate, unilaterally paralytic, passively induced, or absent); grimacing/withdrawal from noxious stimulation; and abnormal plantar response (unilateral or bilateral Babinski sign).¹⁷ Assisted ventilation should continue during the examination if necessary. Neuromuscular blockade required for patient management and care should be deferred if possible until the neurologic examination is completed (3-5 minutes). Signs of arousal or inadequate sedation include dilated reactive pupils, copious tears, diaphoresis, tachycardia, systemic hypertension, and increased pulmonary artery pressure. Thereafter, head computed tomography (CT) may be required.

Evaluate respiratory excursions: Arterial blood gas measurement is the only certain method to determine adequate ventilation and oxygenation. Pulse oximetry is useful, however, because it provides immediate, continuous information regarding arterial oxygen saturation. The comatose patient ideally should maintain a $\text{PaO}_2 > 100$ mm Hg and a PaCO_2 between 34 and 37 mm Hg. Hyperventilation ($\text{PaCO}_2 < 35$ mm Hg) should be avoided unless herniation is suspected. Unless contraindicated, place a nasogastric tube to facilitate gastric lavage and prevent regurgitation.

Maintain circulation to assure adequate cerebral perfusion. Appropriate resuscitation fluid is normal saline and a mean arterial pressure around 100 mm Hg is adequate and safe for most patients. While obtaining venous access, collect blood samples for anticipated tests (Box 48-1). Treat hypotension by replacing any blood volume loss, and use vasoactive agents. Judiciously manage systemic hypertension with hypotensive agents that do not substantially raise ICP by their vasodilating effect (e.g., labetalol, hydralazine, or a titrated nitroprusside infusion are the favored agents for managing uncontrollable hypertension). For most situations, the systolic blood pressure should not be treated unless it is >160 mm Hg. Maintain the urine output at a minimum of 0.5 mL/kg/h; an accurate measurement requires bladder catheterization.

Glucose and thiamine: Hypoglycemia is a frequent cause of altered consciousness; administer glucose (25 g as a 50% solution, IV) immediately after drawing blood for baseline values. Empiric glucose treatment will prevent hypoglycemic brain damage and outweighs the theoretical risks of additional harm to the brain in hyperglycemic, hyperosmolar, or anoxic coma. Thiamine (100 mg) must be administered with the glucose infusion to prevent precipitation of Wernicke encephalopathy in malnourished, thiamine-depleted patients. Rarely, an established thiamine deficiency can cause a coma.

Repeated generalized seizures damage the brain and *must be stopped*. Initial treatment should include IV benzodiazepines, lorazepam (2-4 mg), or diazepam (5-10 mg). Seizure control can be maintained with phenytoin (18 mg/kg IV at a rate of 25 mg/min) (also see Chapter 54). Seizure breakthrough requires additional benzodiazepines.

Careful and mild sedation should be given to the agitated, hyperactive patient to prevent self-injury. Sedation facilitates ventilator support and diagnostic procedures. Small doses of IV benzodiazepines, intramuscular haloperidol (1 mg as often as hourly until the desired effect), or morphine (2-4 mg IV) are appropriate.

Consider specific antidotes: Drug overdose is the largest single cause (30%) of coma in the emergency room. Most drug overdoses can be treated by supportive measures alone. However, certain antagonists specifically reverse the effects of coma-producing drugs. Naloxone (0.4-2 mg, IV) is the antidote for opiate coma. The reversal of narcotic effect, however, may precipitate acute withdrawal in an opiate addict. In a suspected opiate coma, the minimum amount of naloxone should be given to establish the diagnosis by pupillary dilatation and to reverse respiratory depression and coma. Do not attempt to completely reverse all drug effects with the first dose. IV flumazenil reverses all

BOX 48-1**Emergency Laboratory Tests of Metabolic Coma****IMMEDIATE TESTS****Venous Blood**

Glucose
Electrolytes (Na, K, Cl, CO₂, PO₄)
Urea and creatinine
Osmolality

Arterial Blood (Check Color)

pH
PO₂
PCO₂
HCO₃
HbCO (if available)

Cerebrospinal Fluid

Gram stain
Cell count
Glucose
Electrocardiogram

DEFERRED TESTS (INITIAL SAMPLE, PROCESS LATER)**Venous Blood**

Sedative and toxic drugs
Liver function tests
Coagulation studies
Thyroid and adrenal function
Blood cultures
Viral titers

Urine

Sedative and toxic drugs
Culture

Cerebrospinal Fluid

Protein
Culture
Viral and fungal titers

benzodiazepine-induced coma, and a coma unresponsive to 5 mg flumazenil in divided doses given over 5 minutes is not due to a benzodiazepine overdose. Recurrent sedation can be prevented with flumazenil (1 mg IV) every 20 minutes.¹⁸ The sedative effects of drugs with anticholinergic properties, particularly tricyclic antidepressants, can be reversed with physostigmine (1-2 mg IV). Pretreatment with 0.5 mg atropine will prevent bradycardia. Only full awakening is characteristic of an anticholinergic drug overdose, as physostigmine has nonspecific arousal properties. Physostigmine has a short duration of action (45-60 minutes), and doses may need to be repeated.

Adjust body temperature: hyperthermia is dangerous because it increases the brain metabolic demand and, at extreme levels, denatures brain proteins.¹⁹ Hyperthermia above 40°C requires nonspecific cooling measures even before the underlying etiology is determined and treated. Hyperthermia most often indicates an infection but may be due to intracranial hemorrhage, anticholinergic drug intoxication, or heat exposure. A body temperature of below 34°C should be *slowly* increased to above 35°C to prevent cardiac dysrhythmia. Hypothermia accompanies profound sepsis, sedative-hypnotic drug overdose, drowning, hypoglycemia, or Wernicke encephalopathy.

History

Once vital functions have been protected and the patient's condition is stable, clues to the cause of the coma must be sought by interviewing relatives, friends, bystanders, or medical personnel who may have observed the patient before or during the decline in consciousness. The history should include:

- Witnessed events: Head injury (see Chapter 56), seizure, details of a motor vehicle accident, circumstances under which the patient was found.

- Evolution of a coma: Abrupt or gradual, headache, progressive or recurrent weakness, vertigo, nausea, and vomiting.
- Recent medical history: Surgical procedures, infections, and current medication.
- Past medical history: Epilepsy, head injury, drug or alcohol abuse, stroke, hypertension, diabetes, heart disease, cancer, and uremia.
- Previous psychiatric history: Depression, suicide attempts, and social stresses.
- Access to drugs: Sedatives, psychotropic drugs, narcotics, illicit drugs, drug paraphernalia, empty medicine bottles.

General Physical Examination

A systematic, detailed examination is helpful and necessary in the approach to the comatose patient, who is in no condition to describe prior or current medical problems. This examination is an extension of the rapid initial evaluation and should look for:

- Efficacy of resuscitation measures, determined by repeated assessment of vital signs.
- External evidence of trauma.
- Evidence of acute or chronic medical illnesses.
- Evidence of ingestion or self-administration of drugs (e.g., needle marks, alcohol on breath).
- Evidence of nuchal rigidity. Caution is required if severe neck injury is possible or has not been excluded. Nuchal rigidity may disappear in deeply comatose patients with meningeal infection/inflammation.

Neurologic Profile

Establishing the nature of the coma is critical for appropriate management and requires:

- Correct interpretation of neurologic signs that reflect either the integrity or impairment of various functional levels of the brain.
- Determining whether the pattern and evolution of these signs are best explained by a supratentorial or infratentorial structural lesion, a metabolic-toxic encephalopathy, or a psychiatric cause (Box 48-2 and Table 48-1).

The clinical neurologic functions that provide the most useful information in making a categorical diagnosis are outlined in Box 48-3. These indices are easily and quickly obtained. Furthermore, they have a high degree of interexaminer consistency, and when applied serially, they accurately reflect the patient's clinical course. Once the cause of coma can be assigned to one of these categories, specific radiographic, electrophysiologic, or chemical laboratory studies can be used to make a disease-specific diagnosis and detect existing or potential complications.

Specific Management**Supratentorial Mass Lesions**

If the cause of the coma is a presumed supratentorial mass, the severity and rate of evolution of signs should be determined. A stabilized patient next requires an emergency head CT or magnetic resonance imaging (MRI). Carotid angiography is less informative, and a skull x-ray is not helpful. The priority in a deep coma or established/threatening transtentorial herniation is to apply a medical treatment for intracranial hypertension successfully. Brief hyperventilation to a PaCO₂ between 25 and 30 mm Hg on an Fio₂ of 1.0 is the most rapid method to reduce intracranial hypertension. This is usually achieved by adjusting the ventilation rate to 10 to 16/min and tidal volume to 12 to 14 mL/kg. An osmotic agent must be given concurrently. The preferred osmotic agent is a 20% mannitol solution as a 1-g/kg body weight IV bolus. Maximum ICP reduction occurs within 20 to 60 minutes, and the effect of a single bolus lasts about 6 hours. Corticosteroids are not indicated in the emergent empirical management of increased ICP. Furthermore, since steroids are effective only for certain lesions (e.g., edema around a brain tumor or abscess), use can be delayed until a diagnosis has been made by a head CT. After the initial

BOX 48-2**Neurologic Profile (Modified Glasgow Coma Scale)****VERBAL RESPONSE**

Oriented speech
 Confused conversation
 Inappropriate speech
 Incomprehensible speech
 No speech

EYE OPENING

Spontaneous
 Response to verbal stimuli
 Response to noxious stimuli
 None

MOTOR RESPONSE

Obeys
 Localizes
 Withdraws (flexion)
 Abnormal flexion
 Abnormal extension
 None

PUPILLARY REACTION

Present
 Absent

SPONTANEOUS EYE MOVEMENT

Orienting
 Roving conjugate
 Roving disconjugate
 Miscellaneous abnormal movements
 None

OCULOCEPHALIC RESPONSE

Normal (unpredictable)
 Full
 Minimal
 None

OCULOVESTIBULAR RESPONSE

Normal (nystagmus)
 Tonic conjugate
 Minimal or disconjugate
 None
 Deep tendon reflexes
 Normal
 Increased
 Absent

TABLE 48-1**Correlation Between Levels of Brain Function and Clinical Signs**

| STRUCTURE | FUNCTION | CLINICAL SIGN |
|---|---|--|
| Cerebral cortex | Conscious behavior | Speech (including any sounds) Purposeful movement Spontaneous To command To pain |
| Brainstem activating and sensory pathways (reticular activating system) | Sleep/wake cycle | Eye opening Spontaneous To command To pain |
| Brainstem motor pathways | Reflex limb movements | Flexor posturing (decorticate) Extensor posturing (decerebrate) |
| Midbrain CN III | Innervation of ciliary muscle and certain extraocular muscles | Pupillary reactivity |
| Pontomesencephalic MLF | Connects pontine gaze center with CN III nucleus | Internuclear ophthalmoplegia |
| Upper pons | | |
| CN V | Facial and corneal | Corneal reflex—sensory |
| CN VII | Facial muscle innervation | Corneal reflex—motor response Blink Grimace |
| Lower pons | | |
| CN VIII (vestibular portion) connects by brainstem pathways with CN III, IV, VI | Reflex eye movements | Doll's eyes Caloric responses |
| Pontomedullary junction | Spontaneous breathing Maintained BP | Breathing and BP do not require mechanical or chemical support |
| Spinal cord | Primitive protective responses | Deep tendon reflexes Babinski response |

BP, Blood pressure; CN, cranial nerve; MLF, medial longitudinal fasciculus.

ICP management, a head CT or MRI is required. The scan will reveal the nature of the supratentorial lesion and associated mass effect. Arrangements must be made to evacuate an epidural or subdural hematoma promptly. Intraparenchymal masses that acutely produce deep stupor or coma initially are best managed nonsurgically. When steroids are indicated, a dexamethasone bolus should be given (up to 100 mg IV), followed by 6 to 24 mg every 6 hours. Once signs of herniation have abated, the ventilator rate should be carefully reduced to achieve a $Paco_2$ of 34 to 37 mm Hg and additional ICP-induced therapy used to manage intracranial hypertension as necessary (see below).

The patient's vital signs and neurologic condition require repeated examination. The head should be kept slightly elevated (15 degrees). Mannitol may be repeated if necessary every 4 to 6 hours and/or hypertonic saline can be used either as bolus or infusion; serum electrolytes and fluid balance must be monitored. When patients with presumed increased ICP do not respond clinically as expected to medical management or when obstructive hydrocephalus complicates a supratentorial mass lesion, we favor the placement of a ventriculostomy into the lateral ventricle. The ventriculostomy allows for the accurate measurement of ICP and provides a method for CSF drainage if necessary (also see Chapter 56). The placement of a ventriculostomy

allows the calculation of CPP (mean systemic arterial pressure minus ICP), a critical determinant of CBF and therefore, of oxygen and substrate delivery. Monitoring ICP also allows for the titration of therapies. Drainage of CSF aims to reduce ICP to maintain CPP (>60 mm Hg) and improve intracranial compliance. After increased ICP has responded to emergency management and the patient's condition has stabilized, definitive treatment of the lesion mass is required as deemed appropriate.

Infratentorial Lesions

The evolution of neurologic symptoms and signs, as well as the neurologic exam, generally give sufficient information to localize the lesion to the posterior fossa; the lesions themselves may be intrinsic or extrinsic to the brainstem. Rapid neurologic deterioration of a patient suspected of harboring an infratentorial lesion can demand emergency treatment before a head CT scan is performed. Treatment of a presumed extrinsic compressive lesion of the brainstem entails measures that decrease ICP as outlined earlier. Patients in a stupor or showing signs of progressive brainstem compression from a cerebellar hemorrhage or infarction require urgent evacuation. Intrinsic brainstem lesions are best treated conservatively; an incomplete stroke may benefit from thrombolysis and/or heparin anticoagulation. Posterior

BOX 48-3 Characteristics of Categories of Coma**SUPRATENTORIAL MASS LESION AFFECTING DIENCEPHALON/BRAINSTEM**

Initial focal cerebral dysfunction
Dysfunction progresses rostral to caudal
Signs reflect dysfunction at one level
Signs often asymmetric

SUBTENTORIAL STRUCTURAL LESION

Symptoms of brainstem dysfunction or sudden-onset coma
Brainstem signs precede or accompany the coma
Cranial nerve and oculovestibular dysfunction
Early onset of abnormal respiratory patterns

METABOLIC-TOXIC COMA

Confusion or stupor precede motor signs
Motor signs usually symmetric
Pupil responses generally preserved
Myoclonus, asterixis, tremulousness, and generalized seizures common
Acid-base imbalance common, with compensatory ventilatory changes

PSYCHOGENIC COMA

Eyelids squeezed shut
Pupils reactive or dilated, unreactive (cycloplegics)
Oculocephalic reflex unpredictable, nystagmus on caloric tests
Motor tone normal or inconsistent
No pathologic reflexes
Awake-pattern EEG

fossa tumors are managed initially with osmotic agents and steroids; definitive treatment includes surgery and/or radiation. Placement of a ventricular catheter for acute hydrocephalus must be considered cautiously and in consultation with a neurosurgeon; the danger exists of potentially fatal upward transtentorial herniation.¹²

Metabolic Toxic Coma

The task of the physician in the first contact with the patient in a metabolic coma is to preserve and protect the brain from permanent damage. Metabolic and toxicologic studies must be performed on the first blood that is drawn (see Box 48-1). Treatable conditions that quickly, irreversibly damage the brain include the following.

Hypoglycemia. Glucose (50 mL of a 50% solution IV) should be given during emergency treatment before the blood results return. Prolonged hypoglycemic coma that has considerably damaged the brain will not be reversed by a glucose load; a glucose bolus may transiently worsen hyperglycemic hyperosmolar coma. In contrast, the osmolar load of IV glucose may transiently decrease the elevated ICP and lighten non-hypoglycemic coma. A glucose infusion is needed to prevent recurrent hypoglycemia.

Acid-Base Imbalance. The hyperventilating comatose patient with acute severe metabolic acidosis and threatening cardiovascular collapse requires emergency treatment. For an accurate assessment, an arterial blood gas measurement is mandatory. Administration of NaHCO₃ (1 mEq/kg body weight IV) can be life saving. Simultaneously, a search for and specific treatment of the cause must be conducted.

Hypoxia. Carbon monoxide poisoning requires hyperoxygenation with 100% oxygen to facilitate the excretion of this toxin. Closely monitor and correct blood pressure and cardiac rhythm abnormalities. Idiopathic and drug-induced methemoglobinemia is treated with methylene blue (1–2 mg/kg IV over a few minutes; repeat dose after 1 hour if needed). Anemia alone does not cause coma but exacerbates other forms of hypoxemia. Transfusion of packed red blood cells is appropriate for severe anemia (hematocrit < 25%). Cyanide poisoning causes histotoxic hypoxia of the brain. Treatment entails amyl nitrite (vapor or crushed ampule inhaled every minute), sodium nitrite (300 mg IV), followed by sodium thiosulfate (12.5 g IV).

Acute Bacterial Meningitis. A lumbar puncture must be considered in any unconscious patient with fever and/or signs of meningeal irritation. If possible, an emergency head CT should be performed before a lumbar puncture on a comatose patient to rule out unexpected mass lesions. Increased ICP is present in all cases of bacterial meningitis, but a lumbar puncture is not contraindicated when this diagnosis is suspected. Cerebral herniation seldom, if ever, occurs except in small children.²⁰ Clinical correlates of impending herniation demanding a more cautious approach to lumbar puncture including a coma or rapidly deteriorating level of arousal, focal neurologic signs, and tonic or prolonged seizures. Papilledema is rare in acute bacterial meningitis. Should unexpected herniation occur after a lumbar puncture, treatment with hyperventilation and IV mannitol is indicated. Appropriate antibiotic treatment can usually await the results of spinal fluid Gram stain. If the Gram stain is negative, yet a bacterial etiology is suspected, empiric broad-spectrum antibiotic treatment with a third-generation cephalosporin and vancomycin is appropriate.

Drug Overdose. Certain general principles apply to all patients suspected of having ingested sedatives.^{21,22} Most drug overdoses are treated by emergent and supportive measures (Table 48-2). Once vital signs are stable, attempts should be made to remove, neutralize, or reverse the effects of the drug. Patients in a coma from recent drug ingestion require gastric lavage after tracheal intubation. A large (preferably double-lumen) gastric tube must be placed orally. Lavage is performed in the head-down position on the left side, using a 200- to 300-mL bolus of tap water or 0.45% saline and continued until the return is clear. After lavage, 1 or 2 tablespoons of activated charcoal are passed down the lavage tube. With meticulous support, patients with uncomplicated drug-induced coma should recover without neurologic deficit. Hemodialysis can hasten the recovery from coma due to massive doses of barbiturates or glutethimide.

Constant vigilance and attention to the patient's condition, with timely and appropriate diagnostic and therapeutic evaluation, assures the best possible outcome of metabolic coma. Effective care demands meticulous attention to the maintenance of tissue perfusion and oxygenation, documentation, and the anticipation of acute neurologic events (particularly diminished cerebral perfusion, herniation, or seizures), aggressive, rapid treatment of initial or subsequent infections, and prevention of agitation. Deep venous thrombosis can be prevented with either subcutaneous heparin (5000 units every 12 hours) or full-length leg pneumatic compression boots. Enteral or parenteral feeding within 36 to 48 hours is required to satisfy nutritional needs. Corneal injury can be prevented by protecting the eyes with lubricants and taping the lids shut.

THE ROLE OF SPECIAL INVESTIGATIONS**Neurodiagnostic Imaging**

Once the patient with an altered mental status is resuscitated and stabilized, further investigation may be necessary to document the location and type of the lesion, as well as direct therapy. CT and MRI provide an anatomic and/or functional assessment of the CNS and helpful information for defining the localization of lesions that produce a coma.

A cranial CT scan is the most expedient imaging technique for evaluating the comatose patient and gives the most rapid information about possible structural lesions with the least risk. The value of CT in defining mass lesions, hemorrhage, and hydrocephalus is established. The CT scan shows tissue shifts due to intracranial intercompartmental pressure gradients, but compared to MRI may underestimate the anatomy of the herniation.¹¹ Certain lesions, such as early infarction (<12 hours' duration), encephalitis, and isodense subdural hemorrhage may be difficult to visualize. Posterior fossa pathology may be obscured by bone artifacts inherent in the CT technique. Raised ICP is suggested by effacement of cortical sulci, a narrow third ventricle, and obliteration of the suprasellar or quadrigeminal cisterns but cannot be otherwise quantified.

TABLE 48-2 Neurologic Manifestations of Common Drug Poisoning

| DRUG | SIGNS & SYMPTOMS | DIAGNOSTIC TEST | TREATMENT |
|--|---|--|--|
| Carbon monoxide | Confusion, agitation, headache, convulsions, coma, respiratory failure, cardiovascular collapse | History Carboxyhemoglobin level | Remove patient from area, 100% oxygen until carboxyhemoglobin levels fall to <5% Hyperbaric oxygen if central nervous system affected Treat cerebral edema with hyperventilation, diuretics, and cerebrospinal fluid drainage if necessary |
| Salicylate | Tinnitus, hyperpnea, confusion, convulsions, coma, hyperthermia | Blood | Supportive care, gastric lavage, charcoal, systemic alkalinization, hemodialysis for coma or seizures |
| Cyanide | Agitation, confusion, headache, vertigo, hypertension, hypotension, seizures, paralysis, apnea, coma | Blood | Amyl nitrate, sodium nitrate, sodium thiosulfate, 100% oxygen, hyperbaric oxygen for refractory signs Vitamin B ₁₂ injection |
| ANTICONVULSANTS | | | |
| Phenytoin | Drowsiness, ataxia, nystagmus, tremulousness, coma | Blood | Supportive care, gastric lavage, charcoal |
| Carbamazepine | Dysrhythmias with carbamazepine or phenytoin overdose | Ammonia level in patients taking valproic acid | Watch for withdrawal seizures |
| Phenobarbital (see barbiturates) | | | |
| Valproic acid | | | |
| Primidone | | | |
| Ethosuximide | | | |
| Felbamate | | | |
| Clonazepam (see benzodiazepines) | | | |
| SEDATIVE HYPNOTICS | | | |
| Benzodiazepines | Confusion, lethargy, ataxia, nystagmus, hypothermia, dysarthria, respiratory depression, coma | Blood | Supportive care, gastric lavage, flumazenil for benzodiazepine overdose, hemoperfusion for extreme barbiturate intoxication |
| Barbiturates | | | |
| Chloral hydrate | Pupillary reactions preserved except in instances of deep barbiturate coma | | |
| Meprobamate | Possible withdrawal seizures | | |
| Ethchlorvynol | Agitation, hypertonic hyperreflexia, ataxia, hallucinations, convulsions | Blood | As above |
| Methaqualone | | | |
| Ethanol | Confusion, agitation, delirium, ataxia, nystagmus, dysarthria, coma | Blood, breath | Supportive care, lavage if within 1 hour of ingestion, thiamine, glucose |
| Opioids | Lethargy, small reactive pupils, hypothermia, hypotension, urinary retention, shallow irregular respirations, convulsions | Urine Response to naloxone | Naloxone, 0.4 mg IV or IM; continuous naloxone infusion if necessary Supportive care with intubation as necessary Lavage if overdose is by ingestion |
| STIMULANTS | | | |
| Amphetamine | Hypervigilance, paranoia, violent behavior, tremulousness, dilated pupils, hyperthermia, tachycardia or arrhythmia, focal neurologic signs secondary to CNS stroke or hemorrhage, seizures | Blood, urine | Supportive care, sedation with benzodiazepines Treat hypertensive crisis with sodium nitroprusside or labetalol Watch for rhabdomyolysis |
| Methylphenidate | | | Gastric lavage, charcoal |
| Cocaine | | | Benzodiazepines and haloperidol for sedation |
| Psychedelics (e.g., LSD, mescaline, phencyclidine) | Delirium, delusions, marked agitation, hallucinations, hyperactivity, dilated pupils, hyperreflexia, nystagmus | Blood Measure phencyclidine levels in gastric juice | |
| ANTIDEPRESSANTS | | | |
| Tricyclic antidepressants | Anticholinergic effects: dry mouth, agitation, restlessness, ataxia, tachycardia or arrhythmias, hyperthermia, hysteria, convulsions, mydriasis | Blood, urine | Cardiac monitoring, gastric lavage, charcoal, mild systemic alkalinization Physostigmine for refractory arrhythmias Anticonvulsants for seizures Symptomatic care, gastric lavage, avoid narcotics |
| Monoamine oxidase inhibitors | Drowsiness, ataxia, seizures, hypertensive crisis Hypotension with severe overdose | | Gastric lavage |
| Neuroleptics | Dystonia, drowsiness, coma, convulsions, hypotension, miosis, tremor, hypothermia, neuroleptic malignant syndrome | Urine | Treat extrapyramidal signs with diphenhydramine or benztropine mesylate Treat neuroleptic malignant syndrome with dantrolene or bromocriptine |
| Lithium | Lethargy, tremulousness, weakness, polyuria, polydipsia, ataxia, seizures, coma | Blood | Hemodialysis for delirium, seizures, or coma |
| Methanol, ethylene glycol | Drunkness, hyperventilation, stupor, convulsions, coma | Blood | Symptomatic care, gastric lavage, ethanol infusion, hemodialysis |
| Antihistamines | Blindness with methanol use Anticholinergic effects: dry mucosa, flushed skin, hyperthermia, dilated pupils, delirium, hallucinations, seizures, coma | | For methanol intoxication, 4-methylpyrazole Supportive care, gastric lavage, control of seizures with benzodiazepines, physostigmine for life-threatening anticholinergic effects |
| Organophosphates | Cholinergic crisis: cramps, excessive secretions, diarrhea, bronchoconstriction Later: tremulousness, fasciculations, weakness, convulsions, hypertension, tachycardia, confusion, anxiety, coma | RBC cholinesterase level | Symptomatic care, decontamination, atropine, pralidoxime |

An MRI can be performed depending on the clinical setting and stability of the patient's condition. It is limited in the urgent setting of coma evaluation because of the length of time required to perform the imaging, image degradation can occur even by a slight movement of the patient, and the relative inaccessibility of the patient for emergencies that may occur during imaging. Nevertheless, an MRI provides superb visualization of posterior fossa structures, which is useful when intrinsic brainstem lesions are suspected as the cause of a coma.¹¹ MRI images of anatomic lesions (e.g., those resulting from acute stroke, encephalitis, central pontine myelinolysis, and TBI) are associated with a greater resolution and at an earlier time than CT scanning. Injection of gadolinium helps delineate the areas of blood-brain barrier breakdown and may augment the sensitivity of this technique. Moreover, diffusion imaging can almost immediately reveal ischemic brain. Sagittal MRI views are useful in documenting the degree of supratentorial or infratentorial herniations and may enable intervention before clinical deterioration (Fig. 48-1).¹¹ Newer MRI techniques allow functional imaging of the CNS by the measurement of CBF to a particular region. The future application of this technique may allow rapid determination of diminished CBF (e.g., in stroke or vasospasm) and may be useful in assessing the effect of therapeutic interventions.

Electroencephalogram

The EEG can provide useful information in the evaluation of the unresponsive patient. With metabolic and toxic disorders, EEG changes reflect the degree and severity of the altered arousal or delirium, characterized by decreased frequency of the background rhythm and the appearance of diffuse slow activity in the theta (4-7 Hz) and/or delta (1-3 Hz) range. Bilaterally synchronous and symmetric medium- to high-voltage broad triphasic waves are observed in various metabolic encephalopathies, most often in hepatic coma. Rapid beta activity (>13 Hz) suggests the ingestion of sedative hypnotics, such as barbiturates and benzodiazepines. Acute focally destructive lesions show focal slow activity. When periodic lateralized epileptiform discharges appear

acutely in one or both temporal lobes, herpes simplex encephalitis must be strongly considered. A nonreactive diffuse alpha pattern in a comatose patient usually implies a poor prognosis and is most often seen after anoxic insults to the brain or after acute destructive pontine tegmentum damage.^{23,24} A normally reactive EEG in an unresponsive patient suggests psychiatric disease, but a relatively normal EEG can accompany the locked-in syndrome, some examples of akinetic mutism, and catatonia, all of which can be caused by structural brain lesions. Attempts to correlate the pattern and frequency spectra of a post-resuscitative EEG with neurologic outcome have been unsatisfactory since its predictive value is at best 88% accurate.²⁵

Nonconvulsive generalized status epilepticus and repeated complex partial seizures may produce altered levels of awareness or arousal. Thus, the EEG is an indispensable tool for the diagnosis and management of both these disorders. Continuous EEG monitoring optimizes the management of status epilepticus, as clinical assessment is insufficiently sensitive to detect continued electrographic seizures. Furthermore, continuous EEG monitoring in the ICU has shown an unsuspected high incidence of electrographic seizure activity in critically ill neurologic patients.^{26,27}

Jugular Venous Oximetry

Changes in jugular venous oxygen saturation measures the relationship between cerebral metabolic rate and CBF.²⁸ This form of monitoring offers the potential to minimize secondary insults after traumatic brain injury (TBI) by providing a warning of cerebral ischemia. It should be considered in comatose patients in conjunction with ICP monitoring (discussed later) to optimize treatment.

Transcranial Doppler Ultrasonography

Transcranial Doppler ultrasonography allows for the noninvasive measurement of blood flow velocity in basal cerebral arteries.²⁹ The dynamic high resolution provided and confirmed correlation with

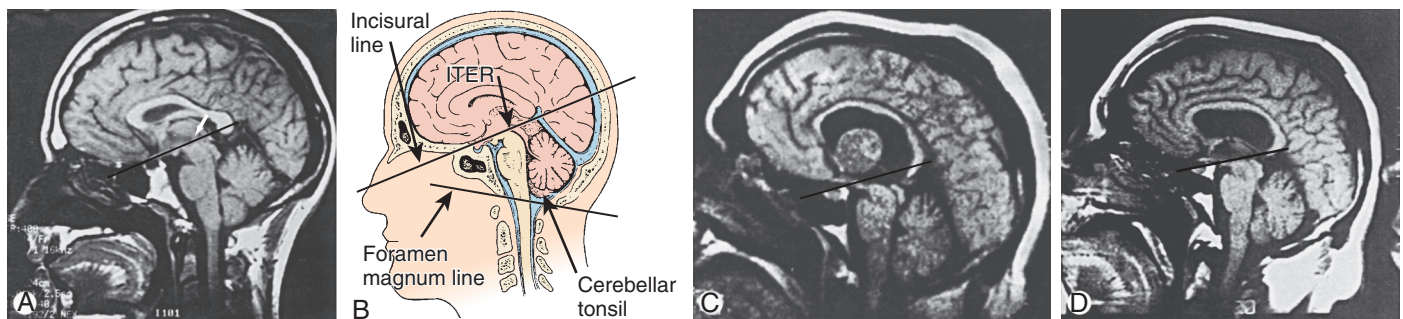


FIGURE 48-1 ■ Midsagittal magnetic resonance imaging (MRI) views of a normal adult brain and a brain with reversible downward transtentorial herniation. **A**, MRI view of the normal adult male brain. **B**, Schematic representation. The opening of tentorium of the cerebellum or anterior cerebellar notch lies along a line (incisural line) defined anteriorly by anterior tubercle of sella turcica and posteriorly by the junction of Galen's vein, inferior sagittal sinus, and the confluence of the straight sinus. The proximal opening of aqueduct of Sylvius, the iter ad infundibulum (*top arrow*), lies within 2 mm of incisural line. The foramen magnum line is defined between the inferior tip of clivus anteriorly and the bony base of posterior lip of the foramen magnum. **C**, A 47-year-old man who experienced 1 week of a headache, nausea, vomiting, and gait ataxia presented with an abrupt-onset coma, palsy of cranial nerve III, hyperreflexia, and bilateral extensor plantar responses. The MRI revealed third ventricular mass, obstructive hydrocephalus, and the displacement of iter ad infundibulum inferiorly by 6.5 mm. Cerebellar tonsils were not displaced. **D**, Subsequent MRI view in the same patient 2 weeks after surgical removal of a colloid cyst. Iter ad infundibulum is 1.2 mm below the incisural line. The patient had a full neurologic recovery. (**A**, **C**, and **D** from Reich JB, Sierra J, Camp W, et al. Magnetic resonance imaging measurements and clinical changes accompanying transtentorial and foramen magnum brain herniation. *Ann Neurol* 1993;33:159-70.)

other hemodynamic modalities encourages increasing numbers of neurointensivists to adopt the technique. Its importance in a coma is in the early detection of vasospasm in subarachnoid hemorrhage and at the time of brain death,³⁰ where an oscillating reverberatory movement has been noted in flow-velocity waveforms.

Evoked Potentials

Evoked potentials (EPs) are used to follow the level of CNS function in comatose patients.³¹ The clinical use of brainstem auditory evoked potential (BAEP) and short latency somatosensory evoked potential (SEP) responses stems from the correlation between EP waveform and presumed generators within certain CNS structures. The SEP shows special promise in the ICU field because EP components generated supratentorially in the thalamus and primary sensory cortex can be identified and followed over time. Shifts of intracranial structures that lead to herniation syndromes are reflected in abnormalities in SEPs, whereas BAEPs are generated entirely at or below the lower midbrain and are less often affected. EPs are less affected than EEG readings by sedatives and septic or metabolic encephalopathies, factors that often confound interpretations in comatose patients. Anatomic specificity and physiologic and metabolic immutability are the basis of clinical utility of EPs. Abnormal test results, however, are etiologically nonspecific and must be carefully integrated into the clinical situation by a physician familiar with their use. Caution is needed in the interpretation of SEPs to ensure that absent responses are not due to technical problems. Repeat SEPs are useful in the following progress. A progressive decline in response amplitude appears to be associated with a worsening prognosis. Studies have shown that all patients with anoxic coma and bilaterally absent SEPs had died or remained in the persistent vegetative state.³² In a traumatic coma, absent SEPs may be a less definitive prognostic indicator as recovery of consciousness has been reported in some patients.³³ Furthermore, comatose patients, especially those with the motor response of flexor posture or better, with an initial poor prognostic EEG pattern but normal SEPs, may have the potential for recovery and should be supported until their condition has changed to a more prognostically definitive category.³⁴ BAEPs and median SEPs obtained within 24 hours of coma onset had a 3-month predictive outcome (compared to Glasgow Outcome Scale [GOS]) in patients with TBI, brain hemorrhage, or neoplasm.³⁵ Diagnostic sensitivity for an unfavorable outcome was low for both parameters, although the specificity and positive predictive values were equally high for the abnormal wave VI of BAEPs and median SEPs.

Intracranial Pressure Monitoring

A review of published randomized controlled studies of real-time ICP monitoring by invasive or semi-invasive means in an acute coma (traumatic or nontraumatic etiology) versus no ICP monitoring (i.e., clinical assessment of ICP) examined the outcome measures of all-cause mortality and severe disability at the end of a given follow-up period.³⁶ The conclusion drawn is that there are insufficient data to clarify the role of routine ICP monitoring in all severe cases of acute coma. However, it is of value in TBI and should be considered on a case-by-case basis in other cases of coma.

Positron Emission Tomography

Recent studies comparing patients in a minimally conscious state and controls, using oxygen-15 positron emission tomography (PET), revealed activation patterns in key brain regions linked to pain processing that were distinguishable from patterns in patients in a persistent vegetative state. These observations suggest the need for analgesic treatment in a minimally conscious state but not for patients in the persistent vegetative state.³⁷ Additional use of brain PET as a research tool to study patients in comatose states will provide further important insight into this condition.

PROGNOSIS

A complete evaluation of the comatose patient must include an estimate of prognosis. The outcome in a given comatose patient cannot be predicted with absolute certainty. Available serial data are not sufficiently specific or selective to help in establishing the prognosis in an individual patient. Guidelines on the outcome of coma have been compiled based on serial examinations. Although the status of the comatose patient on admission is valuable in providing early informed discussion with relatives of patients and medical colleagues, that moment in most instances does not provide sufficient information to withhold immediate therapy. However, the early establishment of a highly probable poor outcome should ideally be made within 24 hours after hospital admission to protect families from false hope in futile cases. A logical and sensible approach to prognostication includes an etiologic subcategorization into a medical, drug-induced, and traumatic coma.

Numerous descriptive scoring systems, both pre- and in-hospital, are used in an attempt to assess the severity of the illness and predict patient outcome. A 2-year prospective study compared the severity-of-illness scoring systems (Acute Physiology and Chronic Health Evaluation [APACHE] II and Mainz Emergency Evaluation System [MEES]) to mental status measurement (Glasgow Coma Scale [GCS]) in predicting outcome of 286 consecutive adult patients hospitalized for nontraumatic coma.³⁸ There were no statistically significant differences among the scoring systems to correctly predict outcome. APACHE II and MEES should not replace GCS. For prediction of mortality, the GCS score also provides the best indicator in nontraumatic comatose patients (simple, less time consuming, and accurate in an emergency situations). Useful factors in determining the outcome of medical coma include cause, depth, and duration of coma. Clinical signs reflecting brainstem, motor, and verbal function are the most helpful and best validated predictors (95% confidence interval).³⁹⁻⁴² Overall, only 15% of patients in an established medical coma for 6 hours will make a good or moderate recovery; others will die (61%), remain vegetative (12%), or become permanently dependent on others for daily living (11%). Prognosis depends largely on the etiology of the medical coma. Patients in a coma due to a stroke, subarachnoid hemorrhage, or cardiorespiratory arrest have only about a 10% chance of achieving independent function. Some 35% of patients will achieve moderate to good recovery if the coma is due to other metabolic reasons including infection, organ failure, and biochemical disturbances. Almost all patients who reach the hospital after sedative overdose or other exogenous agents will recover moderately or completely. The depth of the coma affects individual prognosis. Patients who open their eyes in response to noxious stimuli after 6 hours of coma have a 20% chance of making a good recovery, versus 10% if eyes remain closed. The longer the coma persists, the less likely the chances for recovery; 15% of patients in a coma for 6 hours make a good or moderate recovery compared with only 3% who remain unconscious at 1 week.^{39,40} Coma following TBI has a somewhat better prognosis (see later discussion).

The severity of signs of brainstem dysfunction on admission inversely correlates with the chance of a good recovery from a medical coma. Absent pupillary responses at any time after onset and, except in barbiturate or phenytoin poisoning, absent caloric-vestibular reflexes 1 day after onset indicate a poor prognosis (<2% recovery). Except for sedative drug poisoning, no patient with absent pupillary light reflexes, corneal reflexes, oculocephalic or caloric responses, or lack of a motor response to noxious stimulation at 3 days after onset is likely to regain independent function. In a prospective study of 500 patients in a medical coma, a uniform group of 210 patients suffered anoxic injury: 52 had no pupillary reflex at 24 hours, all of whom died. By the third day, 70 were left with a motor response worse than withdrawal and all died. By the seventh day, the absence of roving eye movements was seen in 16 patients, all of whom died.^{39,40}

Patients likely to recover to functional independence will within 1 to 3 days speak words, open their eyes to noise, show nystagmus

on caloric testing, or have spontaneous eye movements. More than 25% of patients with an anoxic injury who show roving conjugate eye movements within 6 hours of the onset of coma or who show withdrawal responses to pain or eye opening to pain will recover independence and make a moderate or good recovery. The use of the combination of clinical signs helps to improve the accuracy of prognosis: at 24 hours, the absence of a corneal response, pupillary light reaction, or caloric or doll's-eye response is not compatible with recovery to independence.

Postanoxic convulsive status epilepticus and/or myoclonic status epilepticus reflect a poor prognosis. Occasionally, patients recover consciousness but remain handicapped; however, most die or become vegetative.^{43,44} Associated clinical findings (e.g., a loss of brainstem reflexes or eye opening at the onset of myoclonic jerks) and sinister EEG patterns (e.g., suppression or burst-suppression) confirm the grim neurologic outcome in this group. Autopsy studies show that cerebral and cerebellar damage can be ascribed to the initial ischemic hypoxic event; although there is no evidence that status epilepticus further contributes to this damage. Please see Chapter 54 for further details of therapy.

A meta-analysis of prognostic studies in anoxic-ischemic coma examined the value of biochemical markers of brain damage in CSF or serum.⁴⁵ Only levels of CSF markers (i.e., creatine kinase brain isoenzyme, neuron-specific enolase) reached the 0% false-positive rate. Since small numbers of patients are involved in studies and methodological limitations, the results are not sufficient to provide a solid basis for management decisions of patients in a coma.

The most accurate prediction of outcome in a patient in a medical coma is obtained from the use of a combination of clinical signs, and there is little to be added by more sophisticated testing, other than identifying the cause of the coma.^{39,40} Within the first week, it is hard to justify the withdrawal of therapy from patients in a medical coma unless they are already brain dead or lack all signs of brainstem function. After that, the probability of being able to predict the quality of life increases steadily. A multisociety task force of neurologists and neurosurgeons obtained a large amount of data concerning the persistent vegetative state that provides guidelines to outcomes in patients remaining vegetative 1 month following severe TBI or coma-producing medical illness (mostly anoxic).¹⁵

The recent and widespread application of mild therapeutic hypothermia after cardiac arrest has raised concern about the reduced or altered ability to prognosticate outcome. Clinical variables, such as brainstem reflex recovery, myoclonus, and absent motor response to pain, showed higher false-positive mortality predictions in comatose survivors of cardiac arrest compared to predictions by the American Academy of Neurology guidelines at 72 hours.⁴⁶ Greater use of higher doses of sedatives related to hypothermia therapy or the direct effects of hypothermia may play a role.^{47,48} Therefore, caution in prognostication is advised until a better understanding of the effects of this important new therapy emerges.

Among adults with TBI who were in a vegetative state at 1 month ($n = 434$), 33% died, 15% remained vegetative, and 28% suffered a severe disability at 1 year. Among children vegetative for 1 month post trauma ($n = 106$), 9% died, 29% remained in a persistent vegetative state, and 35% were severely disabled at 1 year; only 27% attained moderate/good recovery.

Nontraumatic (medical) coma results were even worse. Among 169 adults with nontraumatic brain injury who were vegetative at 1 month, 53% died within 1 year, 32% remained vegetative, and only 14% made a moderate/good recovery. The outcome of 45 children in similar circumstances was associated with 22% dead, 65% still vegetative, and only 6% with a moderate/good recovery at 1 year.

It is possible in a fraction of patients to predict within the first week those who will recover, those who will die in a coma or enter a vegetative state, and those who will survive with a severe disability. It is well established that patients in an anoxic coma who are in a vegetative state for 1 month will never recover their full preanoxic physical or cognitive function.

Patients in a coma due to exogenous agents (except carbon monoxide poisoning) carry an overall good prognosis, provided that circulation and respiration are protected by avoiding or correcting cardiac dysrhythmia, aspiration pneumonia, and respiratory arrest. Despite absent brainstem reflexes (i.e., electrocerebral silence on EEG), patients with deep sedative drug intoxication have the potential for a complete recovery. Therefore, in the emergent situation, patients in a coma of uncertain etiology should be supported vigorously until the precise cause of the coma has been fully established.

The outcome of a traumatic coma is better than a medical coma, and the prognostic criteria are somewhat different.^{15,33,49} Many patients with TBI are young; posttraumatic prolonged unconsciousness of up to several months does not always preclude a satisfactory outcome; and compared to the initial degree of neurologic abnormality, patients in a traumatic coma improve more than patients in medical coma. Patients in a coma for longer than 6 hours after TBI have a 40% chance to recover to moderate disability or better at 6 months. The most reliable predictors of outcome at 6 months are:

1. Patient age (worse outcome especially after 60 years).
2. Depth and duration of coma (an inverse correlation with GCS).
3. Pupil reaction and eye movements (absence at 24 hours predicts death or a vegetative state in 90%).
4. The motor response during the first week of injury (Table 48-3).

An independent poor prognostic indicator is sustained, uncontrollably increased ICP (>20 mm Hg). Additional factors play a role in the eventual outcome from a traumatic coma. Specific lesions (e.g., subdural hematoma) that result in a coma can have $<10\%$ recovery rate.⁵⁰ In studies with blunt trauma, comatose patients with increased plasma glucose, hypokalemia, or elevated blood leukocyte counts were associated with lower GCS scores and increased probability of death.⁵¹ There are some reports of patients who have suffered coma as a result of TBI in whom an improvement from the vegetative state has been recognized after months, but these anecdotal cases of recovery are difficult to validate. It seems possible that such patients were not truly vegetative but rather in a state of profound disability with minimal cognition at the beginning of observation.⁵² In one case report, however, patient

TABLE 48-3 Trauma Scale

GLASGOW COMA SCALE TOTAL

| | |
|-------|---|
| 14-15 | 5 |
| 11-13 | 4 |
| 8-10 | 3 |
| 5-7 | 2 |
| 3-4 | 1 |

RESPIRATORY RATE

| | |
|------------|---|
| 10-24/min | 4 |
| 25-35/min | 3 |
| >35 /min | 2 |
| 1-9/min | 1 |
| None | 0 |

RESPIRATORY EXPANSION

| | |
|--------|---|
| Normal | 1 |
| None | 0 |

SYSTOLIC BLOOD PRESSURE

| | |
|-------------|---|
| >89 mm Hg | 4 |
| 70-89 mm Hg | 3 |
| 50-69 mm Hg | 2 |
| 0-49 mm Hg | 1 |
| No pulse | 0 |

PERIPHERAL PERFUSION (CAPILLARY REFILL)

| | |
|---------|---|
| Normal | 2 |
| Delayed | 1 |
| None | 0 |

TOTAL TRAUMA SCORE (SUM OF INDIVIDUAL SCORES)*

*Scores <10 represent $<60\%$ chance of survival.

recovery from a 19-year-duration TBI-induced minimally conscious state was associated with improvements in white matter tracts, demonstrated with MRI diffusion tensor technique.⁵³ Novel MRI technology may thus aid in explaining these unusual recoveries; however, additional studies are warranted.

A systematic review of the trials reporting on multisensory stimulation programs in TBI patients in a coma or the vegetative state found no reliable evidence of the effectiveness of such techniques when compared to standard rehabilitation.⁵⁴ Outcome measures included the duration of unconsciousness (time between injury and response to verbal commands), the level of consciousness (GCS), the level of cognitive functioning, functional outcomes (GOS), or the disability rating scale. The overall methodologic quality was poor, and studies differed widely in design and conduct. Owing to the diversity in reporting of outcome measures, a meta-analysis was not possible. Continuous subcutaneous apomorphine infusion (to stimulate dopaminergic neurotransmission) has been suggested to facilitate awakening, specifically in a traumatic coma.⁵⁵ Consistent with this concept of dopaminergic stimulation, treatment with amantadine may also facilitate the emergence from a coma or states of profound disability after TBI as shown in a randomized trial.⁵⁶ Similarly, other work has suggested possible arousal effects from either a prolonged coma or minimally conscious state with zolpidem administration.⁵⁷ Therefore, further study is warranted.⁵⁸

Prognostic guidelines for medical and traumatic coma should be applied with care. One must be sure that the evaluation and interpretation of clinical signs are correct. The prognostic signs, however, predict general outcomes in large patient groups and cannot be applied with absolute precision to every individual comatose patient. One must selectively exclude the effects of anticholinergic agents (used during resuscitation) on pupillary reactivity and paralytic agents on the motor response.

The ability to predict prognosis following a coma can benefit the patient, family, and physician. Families can be spared both the emotional and financial burdens of caring for individuals with an insignificant chance of independent function and quality of life. Physicians can then properly allocate limited resources to patients with the potential to benefit from advanced medical care. There are recognized difficulties in interpreting outcome studies of coma prognosis: lack of prospective studies, failure to state confidence intervals, and the fact that patients in a coma may die of a nonneurologic disease. The self-fulfilling nature of a poor prognosis is difficult to eliminate: the care of a patient will reflect the treating physicians' impressions and opinions on patient outcome. Ideally, prognostic studies should only be performed on patients who will receive maximal life support for as long as possible, but this is inconsistent with the humane and sensitive management of patients and their relatives.

Analysis of the SUPPORT (Study to Understand the Prognoses and Preferences for Outcomes and Risks of Treatments) trial was used to estimate the cost-effectiveness of aggressive care for patients with non-traumatic coma.^{59,60} Patients with reversible metabolic causes of coma were excluded. The incremental cost-effectiveness was calculated for aggressive care versus withholding cardiopulmonary resuscitation and ventilatory support after day 3 of coma. The incremental cost-effectiveness of the more aggressive strategy was \$140,000 (1998 dollars) per quality-adjusted life year for high-risk patients and \$87,000 per quality-adjusted life year for low-risk patients (five risk factors were age older than 70 years, absent verbal response, absent withdrawal to pain, abnormal brainstem response, and serum creatinine > 1.5 mg/dL). From a purely economic standpoint, making earlier decisions to withhold life-sustaining treatments for patients with very poor prognoses may yield considerable cost savings. On moral and ethical

grounds, however, many physicians object to having to consider the cost factor when it comes to making treatment decisions for more or less sick patients. However, growing financial constraints now imposed on the medical community from the top down by politicians and the business culture may no longer afford such luxury, even in a country like the United States.

KEY POINTS

1. Altered arousal is due to an acute or subacute brain insult and reflects either diffuse and bilateral cerebral dysfunction, failure of the brainstem-thalamic ascending reticular activating system, or both.
2. Coma is not a permanent state. Patients who survive evolve through and into altered behavioral states that reflect various degrees of recovery.
3. Urgent steps are required to minimize additional brain damage, often before the cause of coma is definitely established.
4. The initial assessment must focus on vital signs to determine the appropriate resuscitation measures (Airway-Breathing-Circulation).
5. When the patient is stable, clues to the cause of coma must be sought from informative sources.
6. A systematic, detailed examination is necessary for the comatose patient, who is in no condition to describe the past or current medical history.
7. To determine the cause and evolution of coma, the correct interpretation of neurologic signs that reflect the integrity or impairment of brain functional levels is required.
8. Categorization of coma (supra- or infratentorial structural lesions, metabolic-toxic encephalopathy, or psychogenic unresponsiveness) is important in deciding the sequence of diagnostic and therapeutic steps that ensure the best possible patient outcome.
9. The CT scan is the most expedient imaging technique to provide rapid information about a structural brain lesion and its consequences.
10. Although the outcome of a comatose patient cannot be absolutely predicted, a highly probable poor prognosis should ideally be made within 24 hours after admission to direct the use of intensive care services and protect families from false hope.
11. As a rule, patients in a coma due to exogenous agents carry a favorable prognosis, and patients in posttraumatic coma fare better than a medical coma.
12. With the recent advent of mild hypothermia therapy after cardiac arrest, caution in prognostication is advised because compared to present published guidelines, clinical variables at 72 hours after arrest can show higher false-positive mortality predictors in treated comatose survivors.
13. Therapy with amantadine may afford benefit in some cases of traumatic coma.

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■ References for this chapter can be found at expertconsult.com.

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Biofluid-based biomarkers of brain injury have great potential for aiding in diagnostic, monitoring, and therapeutic applications in neurointensive care. Brain injury biomarkers such as neuron-specific enolase (NSE) have already demonstrated some prognostic utility in patients after cardiac arrest¹ and also have potential uses in a variety of intensive care unit (ICU)-relevant central nervous system (CNS) insults such as traumatic brain injury (TBI) and stroke. In this chapter we will use TBI as a prototype disease to demonstrate how brain injury biomarkers could complement conventional diagnostic and monitoring tools in ICU management.

BIOFLUID-BASED BIOMARKERS FOR DETECTING BRAIN INJURY IN THE ICU

A biomarker is defined as a “biologically based parameter that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”^{1a} During brain injury, a variety of cellular changes can occur, including degeneration, protease activation, oxidative stress, and metabolic disturbances. These changes result in the shedding of specific proteins into the cerebrospinal fluid (CSF) or serum that can be identified and studied for their association with disease presence, outcome, and progression. These biofluid-based biomarkers reflect the earliest changes that occur in the cells before the evidence of injury appears on images. Therefore, the use of biomarkers could offer a rapid, noninvasive, and cost-effective tool for the diagnosis of brain injury and determination of the subsequent need for additional diagnostic testing, monitoring, or therapeutic intervention.

Most biofluid-based markers of CNS injury to date are proteins or protein fragments. In the content of basic research, several brain injury biomarkers including NSE, glial protein S-100 β , glial fibrillary acidic protein (GFAP), and myelin basic protein (MBP) have been shown to have great utility in TBI specifically. Alpha-II spectrin protein and its breakdown products (SBDPs) are potential biomarkers of necrosis and apoptosis following TBI. The cleaved form of the axonally located microtubule binding protein tau (c-tau) has been identified as a new biomarker in mouse and rat TBI models. In addition, inflammation markers such as neurofilament-H are promising axonal injury biomarkers of various forms of acute brain damage in experimental TBI models.

Proteomics is the large-scale study of proteins, particularly their structures and functions. This field includes the study of changes in protein expression patterns as related to diseases and environmental conditions. The search for biomarkers of TBI has been approached by integrating biofluid and tissue information. This new approach takes advantage of functional synergy between certain biofluids and tissues with the potential for clinically significant findings. Using differential neuroproteomic methods, a systematic assessment has successfully identified additional protein biomarkers for TBI, such as ubiquitin C terminal hydrolase-L1 (UCH-L1) and microtubule-associated protein 2 (MAP2), with relevant animal models.²

The application of basic scientific discoveries to the clinical setting remains a challenge. Systems biology—the computational and mathematical modeling of complex biological systems—is an approach to building a holistic, systematic, and unbiased understanding of the

structural and behavioral elements of biological networks. Translating these findings into the clinical, data-driven development cycle, data-mining steps for discovery, qualification, verification, and clinical validation are needed. Data mining techniques used in this field extend beyond the level of data collection data to an integrated scheme of animal modeling, instrumentation, and functional data analysis. In the context of TBI proteomics, systems biology tools can be incorporated in several ways to overcome many of the limitations of simple proteomics.³

Current Biomarker Candidates and Their Properties

Although no biomarkers are yet FDA-approved for clinical use, considerable research into protein biomarkers for TBI has produced several putative diagnostic and prognostic markers. Table 49-1 describes the most studied potential TBI biomarkers.

GFAP is an astrocyte-specific intermediate filament protein known as a marker of astrocyte activation. Eight different isoforms of this protein are expressed across numerous subsets of astrocytes. Measurements of GFAP and its breakdown products have provided promising data on injury pathways, focal versus diffuse injuries, and prediction of morbidity and mortality. GFAP was studied in both CSF and serum of patients with severe TBI.⁴⁻⁹ Serum GFAP levels in severe and moderate TBI with GCS <12 are associated with unfavorable outcome at 6 months.¹⁰ New ELISA for GFAP and its breakdown products detected both mild-moderate TBI¹¹ and the full spectrum of TBI (TRACK-TBI cohort)¹² in two independent studies. Similarly, Metting et al. demonstrated that serum GFAP was increased in patients with an abnormal CT after mild TBI.¹³ Another follow-up study using the TRACK-TBI cohort shows that the combination of UCH-L1 with GFAP/BDP further improves its diagnostic utility.¹⁴

UCH-L1 is a deubiquitinating enzyme highly expressed in neuronal cells. It is one of the few markers identified using proteomic methods. In addition, its high brain specificity and abundance in brain tissue make it an attractive candidate marker. CSF and serum UCH-L1 levels were found to be elevated in patients with severe TBI, correlating with the severity and outcome of injury.^{15,16} Increased levels of UCH-L1 post-TBI is proposed to be secondary to blood-brain barrier (BBB) dysfunction.¹⁷ Several other studies also report the detectability of UCH-L1 in blood following mild TBI and with UCH-L1 levels correlating with traditional clinical assessments.^{11,18} However, the utility of UCH-L1 in mTBI with respect to its sensitivity and specificity requires further clinical assessment.

Tau is an intracellular, microtubule-associated protein with a molecular mass of 48 to 67 kDa that is highly enriched in axons. TBI was found to cause the cleavage of tau protein, with elevated levels of c-tau in CSF and serum. c-tau possesses many desirable characteristics of a biochemical marker and is associated with both disruption of the BBB and postinjury cleavage of tau protein.¹⁹ Other studies from two groups have demonstrated the significance of Tau/c-tau in predicting outcome in severe TBI patients.^{20,21} Similarly, several studies report the utility of Tau or c-tau in the prediction of outcome in mTBI.^{22,23} However, other studies have reported the poor ability of tau protein to predict outcome and postconcussion syndrome in mTBI.²⁴ Recently, two ultra-sensitive assay platforms were developed to enable the robust detection

TABLE 49-1 Potential TBI Protein Biomarkers That Could Have Critical Care Utilities

| TBI PROTEIN BIOMARKER | FULL PROTEIN NAME | ORIGIN | HUMAN SEVERE TBI DATA | HUMAN MODERATE-MILD TBI OR CONCUSSION DATA |
|-------------------------------|--|--|-----------------------|--|
| GFAP (and BDPs) | Glial fibrillary acidic protein (and its breakdown products) | Glial injury | Yes | Yes |
| UCH-L1 | Ubiquitin C-terminal hydrolase-L1 | Neural injury | Yes | Yes |
| Tau (P-Tau) | Microtubule-associated Tau protein (phosphorylated Tau protein) | Axonal injury | Yes | Yes |
| S100b | S100b protein | Glia/BBB | Yes | Yes |
| SBDPs (SBDP150, 145, and 120) | α II-spectrin breakdown products of 150, 145, and 120 kDa | Axonal injury; brain cell necrosis-apoptosis | Yes | ? |
| MBP | Myelin basic protein | Demyelination | Yes | — |
| NSE | Neuron-specific enolase | Neural | Yes | — |
| NF-H, NF-L | Neurofilament protein-light and -heavy | Axonal | Yes | — |

The above list of markers is not exhaustive but reflects the current state of the art. Other possible markers include neurofilament proteins MAP2 (microtubule-associated protein 2A,2B), fatty acid binding protein-H (H-FABP), and BDNF (brain-derived neurotrophic factor) and autoantibodies to brain antigens. But more studies are required for further clinical utility verification and biomarker characterization.

of Tau (and a phosphorylated form of Tau) in serum from acute-phase TBI patients with various levels of TBI severity.²⁵

S100B is a glia-specific calcium-binding protein. Elevated *S100B* levels accurately reflect the presence of neuropathologic conditions including TBI or neurodegenerative diseases linked to astroglial injury. More important, *S100B* levels are reported to rise before any detectable changes in intracranial pressure, neuroimaging, or neurologic examination findings. *S100B* is considered a prognostic biomarker of BBB permeability and CNS injury. Several studies have reported that *S100B* protein might detect brain death after severe TBI.^{26,27} Another study showed that serum and urine levels of *S100B* after TBIs have prognostic significance for survival and disability.²⁸ A similar study on serum *S100B* measured 24 hours after injury reported that it predicts unfavorable outcome—that is, Glasgow Outcome Scale (GOS) score <4 or death at 3 months after injury in severe TBI patients.²⁹ *S100b* elevation has also been found after mTBI.³⁰ Although *S100β* remains promising as an adjunctive marker, the main limitation toward its use is the lack of specificity to brain trauma, especially given that *S100B* can be released by cells other than astrocytes.

α II-spectrin is a cytoskeletal protein enriched in neuronal axons and presynaptic terminals. *α II-spectrin breakdown products (SBDPs)* are produced by the breakdown of α II-spectrin by calpain and caspase, which are activated in the brain after TBI. SBDPs thus reflect axonal damage. SBDP150 and SBDP145 are indicative of calpain activation, often associated with acute necrotic neuronal cell death, while SBDP120 is generated by the action of caspase-3 and is associated with delayed apoptotic neuronal death. α II-spectrin has been studied primarily in the context of severe TBI. Elevation of SBDP150 and/or SBDP145 levels in CSF was reported as a possible outcome predictor in patients with severe TBI versus initial CT diagnosis with Marshall grade. SBDPs, especially CSF SBDP150, may be useful as a differential diagnostic biomarker for its ability to distinguish between focal and diffuse injury in the acute phase of TBI.^{31,32} Whereas α II-spectrin is present in various nucleated cells and most tissues, its high abundance and enrichment in brain and the fact that SBDPs are injury-generated make SBDPs potentially useful TBI biomarkers, especially in combination with other more brain-specific markers.

Myelin basic protein (MBP) is one of the most abundant proteins in white matter, composing 30% of the myelin protein. MBP is important in the myelination of nerves. As a constituent of the sheath, MBP is essential for normal myelination and axonal signal conduction. Several studies on severe TBI patients have reported that MBP levels could

track the occurrence of post-TBI hypoxia, predict the outcome, and prompt adequate treatment.^{7,33} Serum MBP is elevated in the majority of children with acute TBI, including well-appearing children with TBI from child abuse in whom the diagnosis might otherwise have been missed.³⁴ Most recently, a review by Kochanek et al. suggests that MBP is a potential biomarker for pediatric TBI.³⁵ Because TBI lacks clinical sensitivity, the interest in MBP as a biomarker for TBI is lower than that of *S100B*, NSE, and GFAP. One possible explanation for this lack of sensitivity is that MBP undergoes extensive fragmentation/degradation following TBI, thus complicating its robust detection by traditional sandwich ELISA.

NSE is a glycolytic enzyme that is present in central and peripheral neurons and neuroendocrine cells, with serum levels rising after cell injury. NSE is passively released into the extracellular space only under pathologic conditions during cell destruction. Acute post-TBI levels of NSE and MBP were correlated with outcome in children, particularly those under 4 years of age.^{36,37} In the setting of diffuse axonal injury in severe TBI, levels of NSE at 72 hours after injury have shown an association with unfavorable outcome.³⁸ However, in very early studies, serum or CSF NSE were considered of limited utility as markers of neuronal damage.^{39,40} A limitation of NSE is the occurrence of false-positive results that occur because NSE is also present at high levels in red blood cells.

Neurofilament (NF) proteins are the key intermediate filaments in neurons and a major component of the axonal cytoskeleton. The major neuronal filaments in the CNS are those assembled from NF triplet proteins: neurofilament light (NF-L; 61 kDa), medium (NF-M; 90 kDa), and heavy (NF-H; 115 kDa). Following TBI, calcium influx into the cell contributes to a cascade of events that activates calcineurin, a calcium-dependent phosphatase that dephosphorylates neurofilament side-arms, presumably contributing to axonal injury. Phosphorylated NF-H (pNF-H) was found to be elevated in the CSF of adult patients with severe TBI compared to controls.⁴¹ Similarly, hyperphosphorylated NF-H has also been shown to significantly correlate with neurologic deficit in severe TBI children.⁴² More recently, phosphorylated NF-H was shown to stratify lower grades of injury, with significant rises in pNF-H seen up to 3 days after mild TBI. pNF-H levels in CSF are also elevated in amateur boxers. Although pNF-H is showing promise as both a sensitive and specific marker of axonal injury after TBI, consideration of other NF isoforms is needed to stratify injury severity in TBI patients. For example, amateur boxers also have elevated CSF levels of NF-L.²³

TBI is a complex injury: primary injury occurs at the moment of trauma, when tissues and blood vessels are stretched, compressed, and torn; secondary injury then follows. Secondary injury events include damage to the BBB, release of factors that cause inflammation, free radical overload, excessive release of the neurotransmitter glutamate (excitotoxicity), influx of calcium and sodium ions into neurons, and dysfunction of mitochondria. We thus anticipate a growing list of putative TBI biomarkers with different cell or subcellular origins and different diagnostic and prognostic properties. Such findings are also very likely for other relevant CNS insults in neurocritical care. Preclinical and clinical studies suggest the potential alteration of the following proteins in some cases of TBI: neurite degeneration markers, MAP2, amyloid β peptide (A β 1-40, A β 1-42), neuroinflammatory markers (microglial ionized calcium-binding adapter molecule 1, inflammatory proteins-caspase-1, NALP-1, ACS),^{43,44} biofluid levels of neurotropic markers (brain-derived neurotrophic factor, nerve and growth factor, and heart-type fatty acid binding protein).⁴⁵⁻⁴⁷ Last, autoimmune markers (autoantibodies to brain antigens such as GFAP) have also been reported as potential biomarkers for subacute or chronic phases of TBI.⁴⁸ However, future work is required for their clinical utility verification and biomarker characterization.

POTENTIAL USES OF BRAIN BIOMARKERS FOR TBI PATIENT MANAGEMENT

Severe TBI

TBI severity is assessed immediately or serially monitored using GCS cranial CT scan, which is also useful for identifying hemorrhage, swelling, or skull fracture. CT scans can also provide direct localization information that helps guide possible surgical intervention. Lesions contributing to increased intracranial pressure or intracranial hemorrhage frequently require decompressive craniectomy, ventriculostomy, or treatment to increase cerebral perfusion pressure with the objective of restoring energy and oxygen supply. During the acute phase of severe

TBI, protein biomarkers are thought to be released into the CSF and/or into the circulation by passing through the disrupted BBB. These body fluid-based biomarkers represent the extent of damage to neurons or astrocytes and reflect a great diversity in outcomes, ranging from immediate death to full recovery. Thus far, no single protein biomarker can describe the complete profile of TBI pathology, which involves a complex cascade of pathophysiologic events, subsequent degeneration of various brain cell types (neurons, glia, oligodendrocytes), and deterioration of brain micro- and macro-structures and functions. Brain function relies not only on intact neurons and astrocytes but also on intact network connectivity. Thus, ideally, we should use a combination of complementary TBI biomarkers that originate from different cell types or subcellular structures that are vulnerable to TBI (see Table 49-1). This approach will likely allow us to assess the extent of cellular and structural damage and, eventually, the recovery process of the brain as a whole at different stages after the initial TBI event (Fig. 49-1). Thus, by serial monitoring of biofluid levels (CSF, blood) for a panel of protein biomarkers, we can gain information regarding the severity of the injury, the progression of the injury, possible occurrence of secondary insult, and prognosis of TBI patients and may even be able to formulate personalized therapeutic strategies (Fig. 49-2).

In conclusion, we have described the importance of biofluid-based protein biomarker detection following severe TBI germane to neurocritical care. We also propose a possible logistic workflow where such TBI biomarkers tests can be integrated into common clinical practice for acute TBI patients in the critical care setting. We also covered a number of TBI protein biomarkers with potential uses in TBI. However, a limitation at present is the lack of an established point-of-care device (POC platform) that can readily provide biomarker readouts within 20 to 30 minutes. Another challenge is to determine whether we already have the optimal biomarkers for formulating the best possible biomarker panel for TBI or if we need to continue to search for more ideal candidates. The next 5 to 10 years promise to be an exciting time for witnessing how the implementation of TBI biomarker-based diagnostics will change medical practice regarding critical care TBI patient management and, ultimately, for the full spectrum of patients in the neurocritical care setting.

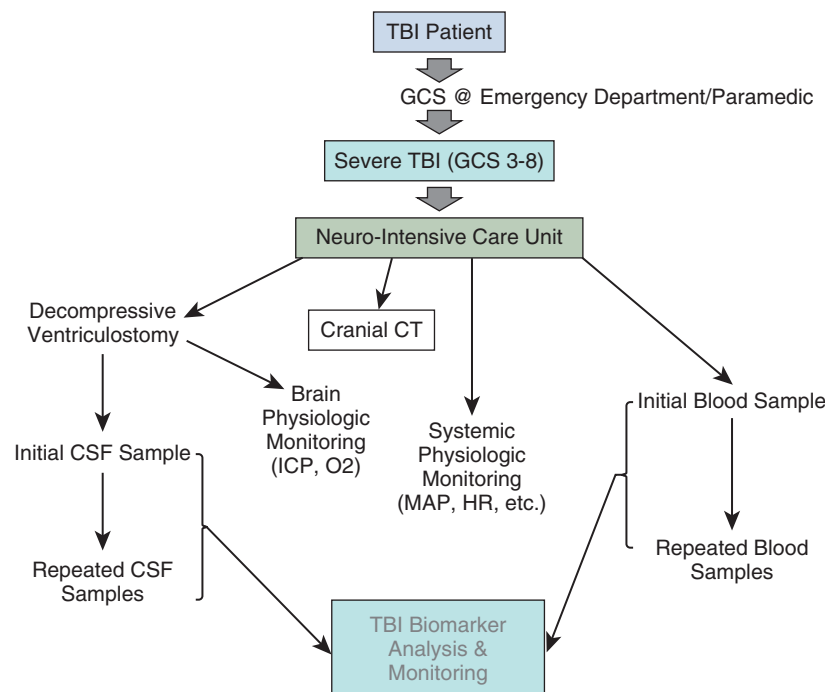


FIGURE 49-1 ■ Envisioned uses of brain biomarkers for severe traumatic brain injury (TBI) patient management. CSF, cerebrospinal fluid; CT, computed tomography; GCS, Glasgow Coma Scale; HR, heart rate; ICP, intracranial pressure; MAP, mean arterial blood pressure.

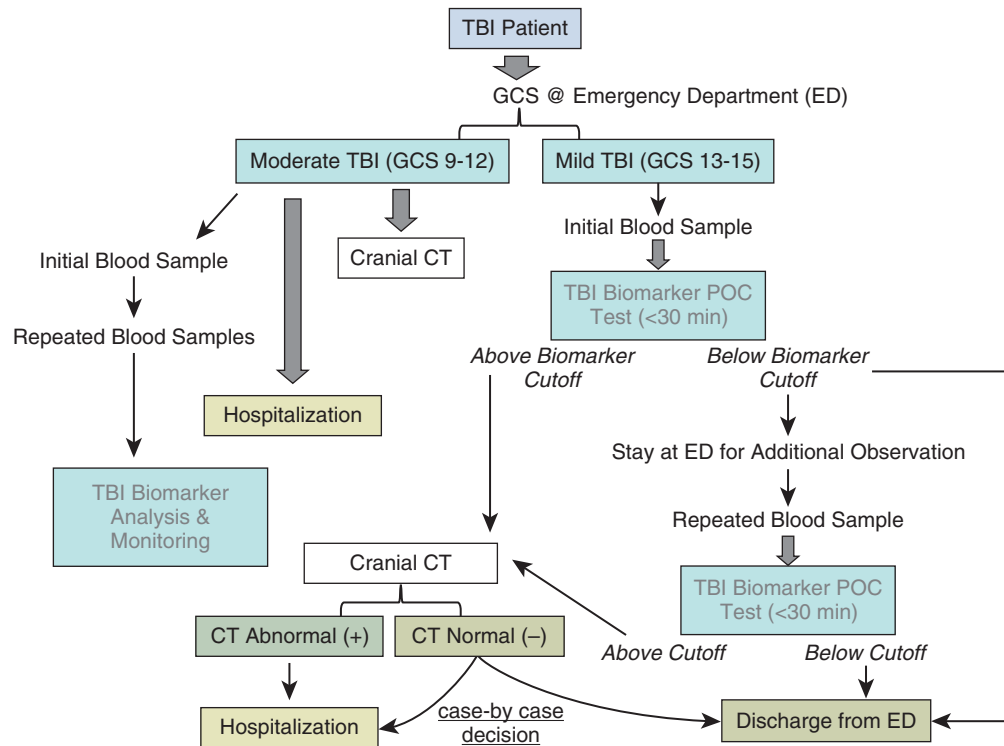


FIGURE 49-2 ■ Envisioned uses of brain biomarkers for mild-moderate traumatic brain injury (TBI) patient management.

KEY POINTS

1. Serum biomarkers of brain injury are being developed for multiple purposes and applications in a wide variety of patients in the neurocritical care setting including (a) prognostication, (b) to categorize injury severity, (c) to help identify otherwise unrecognized brain injury in ICU patients, and (d) to monitor treatment effects.
2. Glial fibrillary acidic protein (GFAP) is a marker of brain injury derived from astrocytes and is showing promise for clinical translation.
3. Two neuronal markers, namely ubiquitin C terminal hydrolase-L1 (UCH-L1) and neuron-specific enolase (NSE), also have potential to identify brain injury. NSE is currently used in some centers for prognostication after cardiac arrest.
4. Myelin basic protein is an emerging marker of white matter damage that is being assessed in clinical studies.
5. The microtubule associated protein Tau is an emerging biomarker that is implicated as an initiator of chronic neurodegenerative disease including chronic traumatic encephalopathy.

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Cardiopulmonary arrest may occur as the endpoint or consequence of many diseases. Often when treatment is initiated the mechanism is unknown, and an algorithmic approach titrated to real-time monitoring is used. When the cause is known or suspected, therapy can be individualized and directed at that cause. In all cases, management has two priorities: (1) rapid restoration of cardiopulmonary function and (2) minimization of ischemic damage to end organs, especially the brain. Restoration of circulation is comprised largely of mechanical and electrical treatment. In contrast, treatment of brain and other organ injury primarily involves prevention of secondary cellular and molecular events using specific and detailed intensive care. Meaningful survival is unlikely without attention to both the heart and brain.

From the first introduction of closed-chest compressions until 2000, there was little change in long-term survival after cardiac arrest.^{1,2} However, subsequent regional efforts to improve resuscitation practices at multiple levels, including emergency response and post-cardiac arrest care, have yielded significant improvements in meaningful survival.^{3,4} Specific patterns of physiologic changes after cardiac arrest have been described, and there is accumulating evidence about which aspects of post-cardiac arrest management influence final outcomes.⁵⁻⁷ Improving outcomes further requires an integrated approach to immediate resuscitation, subsequent intensive care management, and post-intensive care recovery. This chapter will review the epidemiology of cardiac arrest, the initial approach for reversing cardiopulmonary arrest, modifications of this approach appropriate for specific disease states, and post-cardiac arrest care designed to minimize brain injury.

■ EPIDEMIOLOGY

In industrialized countries, heart disease is the overall leading cause of death, with an incidence of cardiopulmonary arrest outside the hospital ranging from 55 to 120 events per 100,000 people per year.⁸⁻¹¹ Median survival after out-of-hospital cardiac arrest is estimated at 10.6%,⁸ but the range varies regionally from less than 2%^{12,13} to 16% in certain exemplary systems.¹¹ The incidence of cardiac arrest in hospitals is about 0.17 events per hospital bed per year.¹⁴ For inpatients experiencing cardiac arrest, median survival to hospital discharge is about 20%.¹⁵ Almost half of in-hospital cardiac arrests occur in an intensive care unit (ICU) setting, where survival is higher than that in an unmonitored unit.¹⁵ Respiratory insufficiency is the most common preexisting condition for in-hospital cardiac arrest,¹⁵ and as many as 17% of episodes of respiratory compromise in hospitals progress to cardiac arrest.¹⁶

While out-of-hospital cardiac arrest is more common in men than in women both outside¹⁰ and inside hospitals,¹⁴ the incidence of cardiac arrest is higher in women (6%) than in men (4.4%) who are admitted to a hospital for acute myocardial infarction (MI).¹⁷ Cardiac arrest outside a hospital affects Blacks and Latinos more than Whites Caucasians or Asians,^{10,12,18} and rates are higher in neighborhoods composed of minority and lower socioeconomic status populations. These groups are also more likely to have a cardiac arrest, less likely to have bystander CPR, and less likely to survive.^{19,20} While sudden death can affect patients of all ages, the mean age for sudden cardiac arrest is between 65 and 70 years in most studies.^{10,11,14}

Most mortality after cardiac arrest is attributable to cardiopulmonary collapse or brain injury. Only one-third to one-half of patients who collapse outside a hospital and only 44% of patients who collapse in a hospital have restoration of circulation long enough to be admitted to the ICU.¹⁴ Two-thirds of patients who are admitted to a hospital after an out-of-hospital collapse²¹ and 60% of patients who are resuscitated from cardiac arrest in a hospital¹⁴ die prior to discharge from the hospital. Postischemic brain injury is the most common reason for in-hospital death after out-of-hospital cardiac arrest,^{14,22} whereas multiple organ failure is more common after in-hospital cardiac arrest.²³ Failure to awaken contributes to withdrawal of life-sustaining treatment for about 61% of out-of-hospital cardiac arrest patients.

■ RESTORING CIRCULATION

Acute treatment of cardiac arrest consists of two concurrent, goal-directed activities: (1) artificial circulation of oxygenated blood to heart and brain and (2) electric shock to terminate ventricular fibrillation (VF) and unstable tachydysrhythmias (Fig. 50-1). Continuous, uninterrupted, high-quality chest compressions are the cornerstone of resuscitation,²⁴ whereas electrical rescue shocks are used only when appropriate.²⁵ The organization of an electrocardiogram (ECG) and the presence of a pulse will prompt appropriate selection of therapy. The recommended division of time and prioritization of activities to accomplish these goals is depicted in Figure 50-2. All other activities, including medications and advanced airway maneuvers, are designed to supplement these two core activities, and optimization requires minimal interruption in the two core activities. Focused bedside ultrasound can aid in the assessment of critically ill patients and identify reversible causes only if performed without interrupting resuscitation.²⁶ The American Heart Association and European Resuscitation Council provide consensus scientific statements about the acute management of cardiac arrest, including a detailed review of specific drugs and procedures.²⁷ The following section provides an overview of airway management, circulation support, rescue shock for defibrillation, and drug therapy.

Airway and Ventilation

Obstruction of the airway occurs in patients with impaired consciousness, including cardiac arrest preventing oxygenation and ventilation.²⁸ Agonal respiration occurs after acute cardiac arrest for an additional 1 to 2 minutes,²⁹ which may confuse lay people and delay the recognition of cardiac arrest. While associated with survival, it is unclear whether agonal respiration generates sufficient ventilation to support life.³⁰ Regardless, artificial ventilation is required for patients requiring more than momentary resuscitation efforts.

Simple maneuvers to open the airway include extension of the neck (head tilt) and forward displacement of the mandible (chin lift). Insertion of an oropharyngeal or nasopharyngeal airway can displace the tongue from the posterior pharynx. Positive pressure ventilation using mouth-to-mouth or bag-valve-mask (BVM) ventilation with as little as 400 mL in adults (6-7 mL/kg) delivered over 2 to 3 seconds will cause the chest to rise.³¹ Minute ventilations smaller than those required for long-term support probably provide adequate gas exchange during cardiac arrest. Conversely, hyperventilation or hyperexpansion of

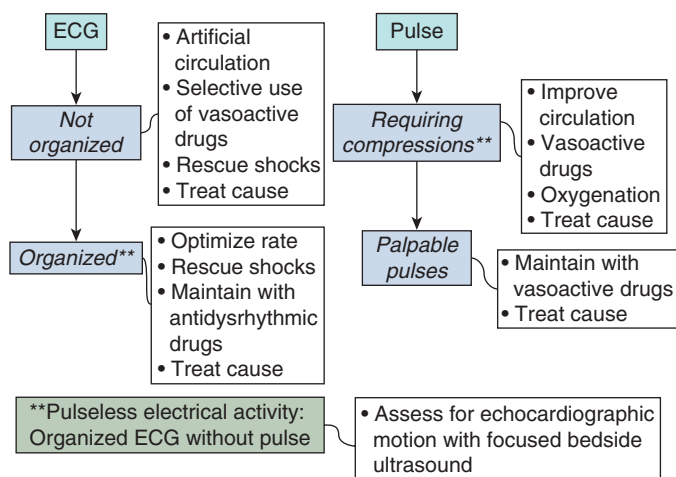


FIGURE 50-1 ■ Continuous reassessment of the patient during cardiac resuscitation relies on an ECG and on the presence of cardiac mechanical activity (pulses). If an organized ECG is not present, interventions should be undertaken to restore an organized ECG. If mechanical cardiac activity is not present, interventions should be undertaken to improve mechanical cardiac activity. Achieving both goals results in return of circulation.

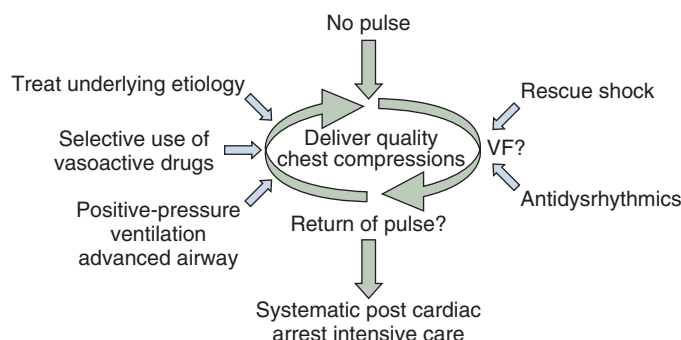


FIGURE 50-2 ■ Prioritization of activities must occur during cardiac resuscitation. Central circle emphasizes that core activity of chest compression should be interrupted only to provide rescue shocks when appropriate or when restoration of circulation occurs. All drugs, airway devices, and other interventions are designed to augment either artificial circulation or defibrillation. None of these adjuncts should interrupt or detract from providing artificial circulation. VF, ventricular fibrillation.

the chest impairs venous return and decreases circulation during resuscitation.³²

The need for gas exchange must be balanced against the fact that even brief interruptions in chest compressions reduces coronary perfusion pressure (CPP) (Fig. 50-3).³³ In swines, comparison of different chest compressions to ventilation ratios suggests that 2 breaths per 50 or more chest compressions are optimal for resuscitation.³⁴ An innovative practice to reduce interruptions in compressions is to provide chest compressions without any artificial ventilation³⁵ or with passive insufflation of oxygen.³⁶ Chest compressions alone probably do not generate significant ventilation in humans.^{28,37} As a compromise, some systems deliver uninterrupted chest compressions and asynchronous positive pressure breaths. Regardless of ratio, the duration of any pause to deliver breaths must be minimized.

Waveform capnography can confirm ventilation and monitor adequacy of circulation. During cardiac arrest, end-tidal CO₂ is related to

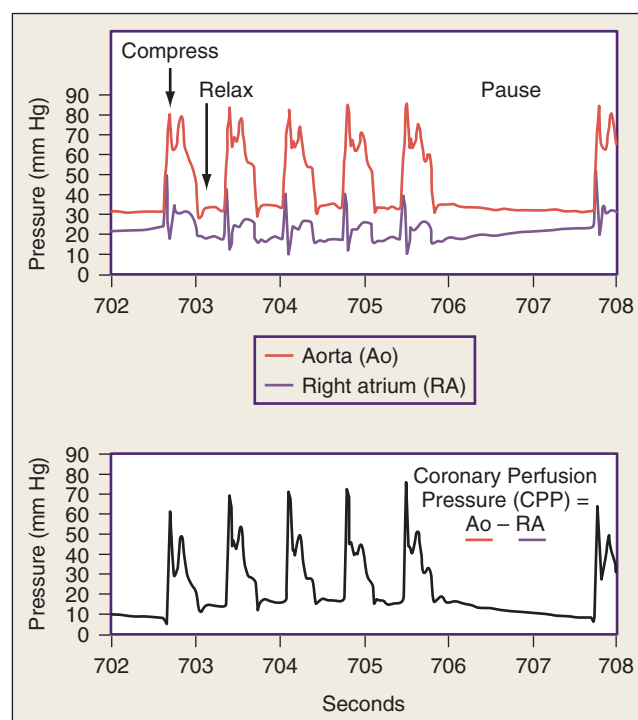


FIGURE 50-3 ■ Chest compressions provide coronary perfusion by creating a pressure gradient between the aorta (Ao) and the inside of ventricles (approximated by right atrium [RA]). Gradient between sites is the coronary perfusion pressure (CPP). During chest compression, pressure increases in both Ao and RA. During relaxation, pressure persists in Ao more than RA. Thus, myocardial blood flow is most related to CPP during relaxation phase of chest compressions. Note that CPP declines within 1 to 2 seconds when compressions pause for ventilation. (Unpublished laboratory data.)

cardiac output and pulmonary blood flow.³⁸ Therefore, CO₂ levels may be very low (<10 mm Hg) at the onset of resuscitation. Adequate artificial circulation will cause CO₂ levels to increase, and these levels may be used as a feedback to improve or modify chest compressions. An end-tidal CO₂ level greater than 15 to 16 mm Hg is associated with successful cardiac resuscitation.^{39,40} Conversely, end-tidal CO₂ less than 10 mm Hg after 20 minutes of resuscitative efforts can confirm failure of resuscitation.⁴¹ Common resuscitation drugs disrupt the association between capnography readings and pulmonary blood flow: epinephrine infusion reduces CO₂ levels, and sodium bicarbonate infusion produces a transient elevation of CO₂ levels. An abrupt increase in end-tidal CO₂ levels, usually to levels over 35 mm Hg, may be useful in recognizing the return of circulation, without interrupting chest compressions for pulse checks (Fig. 50-4).

Airway Devices

The most common ventilation device used by rescue personnel, paramedics, and other healthcare providers is a self-inflating bag attached to a face mask (BVM), which requires adequate training and practice for ventilation success by a single provider. Two providers achieve more reliable airway management. BVM ventilation also pushes air into the stomach.⁴² This can promote emesis and abdominal distention, impair venous return, and reduce lung compliance.⁴³ Normal esophageal resistance to air entry into the stomach (15 to 20 cm H₂O)⁴⁴ declines with loss of muscle tone during cardiac arrest (5–8 cm H₂O).⁴⁵

Tracheal intubation with a cuffed tracheal tube secures the airway definitively and protects from emesis. However, laryngoscopy requires an interruption in chest compressions. Observational studies found

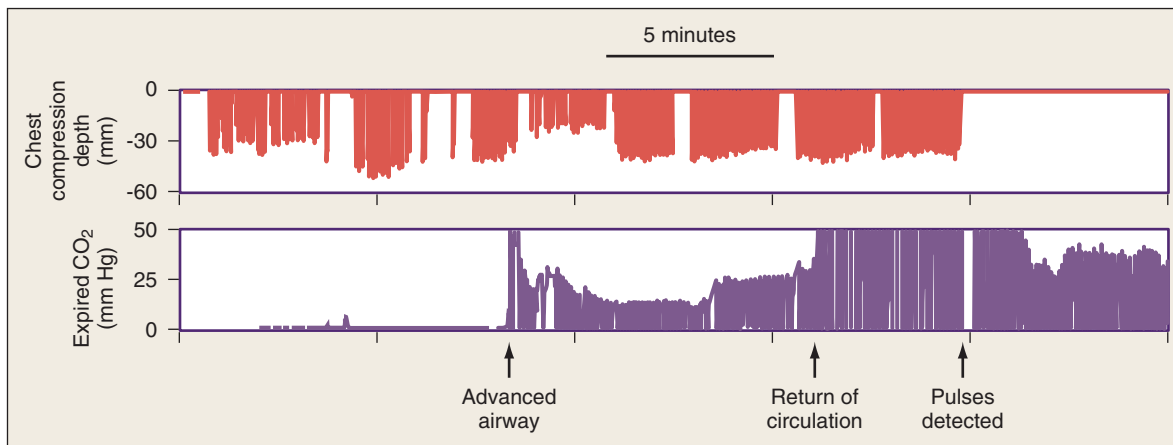


FIGURE 50-4 ■ End-tidal CO₂ changes during resuscitation. Tracings from monitor-defibrillator with an accelerometer to measure chest compression depth (*top trace*) and waveform capnography to measure exhaled CO₂ (*bottom trace*). Exhaled CO₂ confirms correct placement of an advanced airway. Note frequent interruptions in chest compressions prior to placing advanced airway. More continuous chest compressions are followed by an abrupt rise in exhaled CO₂, corresponding to return of circulation, including pulmonary circulation. Chest compressions continue for 2 to 3 minutes until providers detect a palpable pulse.

extremely long interruptions in chest compressions during “uncomplicated” tracheal intubation.⁴⁶ Therefore, consider delaying tracheal intubation until after other life-saving interventions. Ultimately, patients in coma or with continued respiratory failure will require tracheal intubation.

Supraglottic airway adjuncts such as double-lumen combination tracheal-esophageal tubes (e.g., Combitube), laryngeal tubes (e.g., King-LT), or laryngeal mask airways can temporarily secure the airway during resuscitation.^{47,48} These devices have the advantage of blind insertion within seconds without laryngoscopy or interruptions in chest compressions.⁴² Clinicians should strongly consider using these supraglottic airways as the first advanced airway during resuscitation.

Artificial Circulation

In patients without a pulse, compression of the heart and chest by repetitive depression and release of the sternum circulates blood. The critical parameter for restoring myocardial energy stores and thus spontaneous circulation is the development of adequate CPP. CPP is the pressure gradient between the aorta and the inside of the ventricles at the end of diastole or during the relaxation phase of chest compressions. Most blood flows through the ventricular walls during diastole or during the relaxation phase of chest compressions, when ventricular pressure is the lowest (see Fig. 50-3). CPP is highly correlated with myocardial perfusion and consequently with the likelihood of resuscitation.⁴⁹ In humans, return of circulation requires that the developed CPP exceeds 15 to 20 mm Hg.

Peak arterial pressure or palpable pulses measured during chest compressions do not necessarily represent CPP because ventricular pressures are simultaneously elevated. Consequently, palpation of pulses and systolic pressures developed by chest compressions may be misleading. It is most useful to follow the “diastolic” or relaxation-phase arterial pressure. If unable to follow any of these pressures, the clinician must rely on indirect evidence of myocardial perfusion, such as improved electrical and mechanical activity or increased pulmonary CO₂ excretion.

Even brief interruptions in chest compressions decrease CPP, and interruptions are inversely associated with restoring circulation and survival.²⁴ When chest compressions are measured during actual resuscitations by paramedics or hospital providers, interruptions and

pauses are frequent.^{50,51} Some monitor-defibrillators now have features to measure and record chest compressions and to provide real-time feedback about depth and rate to providers.⁵² These features have no detectable effect on survival.⁵³ The chest compression fraction is one metric of compression continuity that is emphasized as a component of high-quality resuscitation²⁴ (Fig. 50-5), and many clinicians feel that the real-time and automated feedback is a useful safety and quality improvement mechanism to enhance total system performance.

Direct cardiac compression via thoracotomy is more effective than external chest compressions, producing roughly a three-fold increase in CPP.^{54,55} This approach also allows recognition of cardiac tamponade, treatment by pericardiectomy, direct visualization of mechanical activity and fibrillation, and direct electrical defibrillation or pacing. In the setting of cardiopulmonary collapse due to exsanguination, thoracotomy also allows for aortic compression to shunt blood to the heart and brain as well as direct control of intrathoracic bleeding. Until the 1960s, thoracotomy was the standard approach for treatment of sudden cardiac arrest, but this procedure has now been supplanted by closed-chest compressions. A cases series has described how this technique continues to be successful, and its use should be considered when closed-chest compressions are ineffective.⁵⁴ Open-chest cardiac massage is most likely to succeed if initiated early during resuscitation.⁵⁶

To improve delivery of uninterrupted chest compressions, a variety of mechanical devices have been developed.^{24,33,57,58,59} Some of these devices exploit circumferential compression or active compression/decompression of the chest. A Cochrane Review of mechanical versus manual chest compressions for cardiac arrest found no evidence of benefit of mechanical compressions in the return of spontaneous circulation or survival to hospital admission, and a subsequent pragmatic randomized trial found no improvement in 30-day survival.^{59,60} While no current device is superior to well-conducted manual compressions, these devices may play a role in providing chest compressions in settings where manual compressions are difficult or impossible (e.g., during ambulance transport, under the fluoroscopy arm, or when multiple providers are not available).

Extracorporeal Circulation

Extracorporeal perfusion for restoration of circulation (E-CPR) can be used to resuscitate subjects for whom chest compressions have

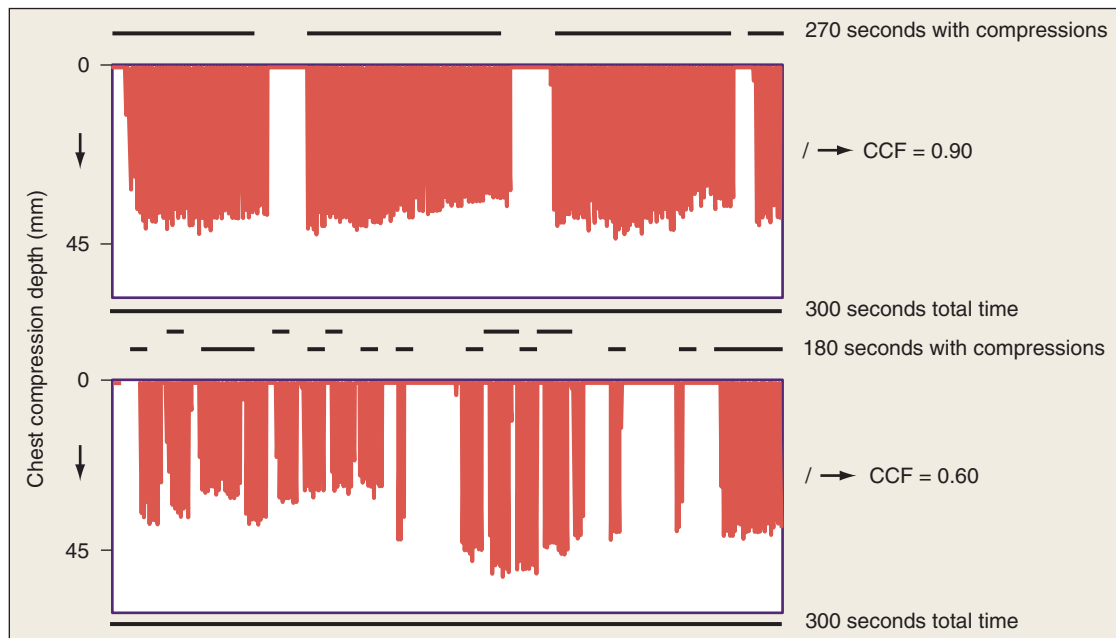


FIGURE 50-5 ■ Chest compression fraction (CCF) describes the continuity of chest compressions during resuscitation. Tracings of chest compressions detected by the accelerometer of a monitor-defibrillator can be used to calculate the proportion of time when chest compressions are occurring. In top tracing, there are few pauses, and CCF is 0.90. In lower tracing, frequent interruptions for breaths or procedures results in CCF of 0.60.

TABLE 50-1 Sample Selection Criteria for Extracorporeal Perfusion for Restoration of Circulation (E-CPR)

| | SURUGADAI NIHON UNIVERSITY HOSPITAL TOKYO, JAPAN | SHARP MEMORIAL HOSPITAL SAN DIEGO, CA | ALFRED HOSPITAL MELBOURNE, VICTORIA, AUSTRALIA |
|-------------------------------|--|--|--|
| INCLUSION CRITERIA | Age 18 to 74 Witnessed cardiac arrest Presumed cardiac etiology EMS arrival ≤15 minutes Defibrillation by AED or EMS personnel Persistent cardiac arrest on arrival to ED | Persistent cardiac arrest Shock refractory to standard therapies | Age 18 to 65 Suspected cardiac etiology Any CPR within 10 minutes of collapse Initial rhythm of ventricular fibrillation 30 minutes of persistent cardiac arrest |
| EXCLUSION CRITERIA | Presumed noncardiac etiology Successful ROSC ≤10 minutes of arrival to ED Core body temperature <30°C on arrival to ED Pregnancy | Initial rhythm of asystole Any CPR not initiated ≤10 minutes of cardiac arrest Estimated EMS transport time >10 minutes Total arrest time >60 minutes Suspicion of sepsis or hemorrhage Preexisting severe neurologic disease | Known preexisting significant neurologic disability Known significant end-stage comorbidities Terminal illness due to malignancy |

Sample selection criteria for extracorporeal life support (ECLS) in out-of-hospital cardiac arrest (OHCA).

AED, automatic external defibrillator; ED, emergency department; ROSC, return of spontaneous circulation.

failed.^{61,62,63} However, this approach requires specialized technical skill, system commitment, and increased costs and risks. Logistical issues include limited availability of perfusion equipment, setup time for circuit priming, and delays in establishing adequate venous and arterial access. Portable cardiopulmonary bypass devices that can be primed quickly, along with improved techniques for rapid vascular access, have broadened the use of E-CPR.

It is critical that E-CPR be used for appropriately selected patients. The ideal candidate is young with a witnessed cardiac arrest from a shockable rhythm, with a presumed cardiac etiology, who receives immediate CPR, and who has a brief interval until successful

cannulation and commencement of extracorporeal resuscitation. Examples of selection criteria from three centers are given in Table 50-1.

The timing of E-CPR is equally important because irreversible myocardial and neurologic injury can preclude survival despite restoring flow. Conventional resuscitation is clearly preferred when patients have early recognition, early high-quality chest compressions, and early defibrillation. However, increasing the duration of treated cardiac arrest decreases the odds of functionally favorable survival (perhaps as low as 1% after 16 minutes of professional resuscitation).⁶⁴ After failing rapid resuscitation, E-CPR should be considered for suitable

candidates. One successful E-CPR program found that 85% of E-CPR survivors had perfusion started less than 55 minutes after collapse. Longer initiation times were rarely associated with favorable neurologic recovery.⁵⁸

Electrocardiogram Monitoring

Continuous three-lead ECG monitoring is essential for guiding resuscitation. A practical approach is to divide rhythms into organized and not organized. Organized rhythms include supraventricular rhythms or ventricular tachycardia (VT). Not-organized rhythms include VF and asystole. Not-organized rhythms cannot support the pumping of blood, regardless of volume status, cardiac muscle state, and vascular integrity. Therefore, restoring cardiac electrical activity to an organized rhythm is an essential step in resuscitation. Organized rhythms can support pumping of blood unless they are too slow (<30-40 complexes/min) or too fast (>170-180 complexes/min). An organized rhythm in the absence of a pulse is termed *pulseless electrical activity* (PEA).

As the incidence of PEA as initial cardiac rhythm increases, with a relative decrease in the incidence of initial VF,^{10,65-67} PEA is an area of increased study and focus. Point-of-care cardiac ultrasound during resuscitation allows for more nuanced assessment of PEA. PEA may be subdivided into an organized rhythm in the absence of pulse with or without echocardiographic motion ("true PEA" vs. "pseudo-PEA"). In pseudo-PEA, pausing compressions and administering vasopressors may restore circulation.⁶⁸ Perfusion may be so poor that the pulse is absent in VT, supraventricular tachycardia, and atrial fibrillation, even with rapid ventricular response, and is also unresponsive to the filling of the heart. These tachydysrhythmias should be corrected by rescue shock.

The absence of perfusion with slow organized electrical activity may result from damage to the heart muscle (as in massive MI) or from uncoupling of electrical and mechanical activity (as in prolonged circulatory arrest). The rate of complexes may be used to monitor resuscitation efforts. With increasing ischemia, energy depletion will occur in the electrical system, and the rate of PEA will slow down. If resuscitation improves the energy state of the heart, the rate of PEA will accelerate. Narrow complexes reaching rates of 80 to 100 beats per minute often herald the return of a pulse. Falling rates reflect unsuccessful resuscitation efforts. The morphology of complexes in PEA may also point toward a simplified approach to this rhythm. Narrow complexes tend to indicate a mechanical issue, whereas wide complexes tend to indicate a metabolic derangement or agonal rhythm.⁶⁹

VF and asystole lie along a continuum of not-organized ECG. Arbitrary peak-to-peak amplitude of the ECG is usually used to distinguish asystole (amplitude <0.1-0.2 mV) from VF (amplitude >0.2 mV).⁷⁰ However, VF also exhibits temporal structures that may be absent in asystole.⁷¹ VF is a chaotic electrical activity formed by multiple interacting waves of activation within the heart.⁷² VF emerges from broken wavefronts that result from areas of ischemia (as in MI), areas of prolonged refractoriness (as in drug-induced or inherited prolonged QT intervals), or too-rapid succession of activation potentials (as in tachycardia or an "R on T" premature beat). As the organization and amplitude of these waves decline due to ischemia or hypoxemia, the amplitude of the ECG also declines. Reperfusion of the heart in asystole may restore VF. Furthermore, the amplitude and organization of the VF increases with reperfusion, providing a marker of adequate artificial perfusion.

Rational Use of Rescue Shocks for Defibrillation

Delivery of immediate transthoracic electric rescue shocks to patients in VF can convert VF into an organized cardiac rhythm. Rescue shocks are highly effective when VF is for a very brief duration (<1-2 minutes). These shocks may work by depolarizing the heart, canceling the

original wavefronts, or prolonging the refractory periods.⁷² Although rescue shocks can successfully restore an organized rhythm, repeated shocks may directly damage the myocardium.⁷³ Optimal therapy should provide rescue shocks at the lowest effective energy while minimizing the number of unsuccessful rescue shocks.

In the out-of-hospital setting when the collapse is not witnessed by paramedics, only 9% to 12% of rescue shocks restore an organized ECG,^{74,75} and most shocks convert VF into asystole.⁷⁶ Even after successful defibrillation, VF may recur because of incomplete depolarization by the shock, heterogeneous areas of refractoriness, or persistent foci of chaotic activity.⁷⁷ Multiphasic shock waveforms are more effective for depolarization of individual myocytes and require less energy than monophasic waveforms.⁷² Consequently, most available defibrillators deliver biphasic waveforms. Increasing pressure of paddles from 0.5 kg to 8 kg on the chest decreases transthoracic impedance by as much as 14% and increases delivery of current to the heart.^{78,79} This advantage of paddles must be weighed against the increased safety and convenience afforded by hands-free self-adhesive defibrillation pads, which are now used in most settings. In the past, multiple shocks would be delivered in rapid succession to decrease chest impedance. However, repetitive shocks decrease chest impedance by about 8% or less in actual patients,^{78,80,81} which does not justify the interruption of artificial circulation to deliver "stacked" shocks. Reducing the interruption in chest compressions before and after a rescue shock is associated with greater resuscitation success,⁸² which led to the coining of the term *perishock pause*. Duration of the perishock pause is inversely associated with survival to hospital discharge.⁸³ Specific techniques to reduce the perishock pause include continuing chest compressions while the defibrillator is charging, only stopping at the last moment prior to shock, and eliminating the postshock pulse check. Using gloves and modern self-adhesive defibrillation pads, the risk of shock to rescuers from touching a patient during defibrillation is small.²⁵ Manual compressions may be continued during rescue shocks, or even while using mechanical chest compression devices.

For VF that has lasted more than 3 to 4 minutes, preclinical data suggest that delaying rescue shocks until after a few minutes of chest compressions will improve success.⁸⁴⁻⁸⁷ To date, two clinical studies in out-of-hospital cardiac arrest patients have found that either 90 seconds or 3 minutes of chest compressions prior to delivery of the initial rescue shock improved resuscitation rates for subjects with VF outside a hospital, particularly when rescuer response intervals were longer than 4 minutes.^{2,88} However, a third study found no difference in outcome with 5 minutes of chest compressions prior to shock,⁸⁹ while a fourth study found no difference in outcome with 3 minutes of chest compressions prior to shock.⁹⁰ Finally, a large multicenter trial comparing immediate rescue shock to 3 minutes of chest compressions prior to rescue shock recently stopped enrollment, finding no difference between groups.⁹¹ Taken together, the clinical data suggest that the first rescue shock for VF should be delivered as soon as possible within 3 to 5 minutes as long as chest compressions are started immediately but that there is no reason to intentionally delay the rescue shock.

Quantitative analysis of the VF waveform can distinguish early VF from late VF and may be useful in estimating the likelihood of rescue shock success.⁹² Larger amplitude of VF⁹³ as well as frequency-based measures and nonlinear dynamic measures of VF organization⁹⁴⁻⁹⁷ are associated with a higher probability of rescue shock success. Future generations of defibrillators may provide real-time, semiquantitative estimates of the probability that a rescue shock will succeed in restoring an organized rhythm. It is unknown if these quantitative measures will be clinically useful for titrating resuscitation.

Beta-blockade with a short-acting agent such as esmolol represents another therapeutic option for VF. Beta-activation increases myocardial oxygen requirements, worsens ischemic injury, lowers the VF threshold, and worsens postresuscitation myocardial function.⁹⁸⁻¹⁰⁰ Blocking beta receptors may terminate the electrical storm responsible for refractory VF.⁹⁸⁻¹⁰² Esmolol is a favorable agent given its ultra-short half-life.¹⁰³

Drug Therapy

No drug therapy has been demonstrated to improve long-term survival.¹⁰⁴ Nonetheless, drug therapy in cardiac arrest can be divided into three categories: pressors, antidysrhythmics, and metabolic drugs. Pressors are used during resuscitation and include epinephrine and vasopressin. Both these drugs can increase CPP via the α -adrenergic (epinephrine) or vasopressin receptors (Fig. 50-6).^{105,106} Epinephrine is usually administered in 1-mg (~ 0.015 mg/kg) increments. In laboratory studies, the pressor effects of epinephrine during cardiac arrest were brief (~ 5 minutes). Vasopressin is administered as 40-unit boluses (~ 0.5 units/kg) and produces a longer lasting increase in CPP (~ 10 minutes). Both drugs should be titrated to improvement in clinical indicators (ECG waveform, mechanical activity, changes in end-tidal CO_2 or diastolic arterial pressure as a surrogate for CPP). Rote, repeated administration is unlikely to result in meaningful outcome improvements. This concept of goal-directed cardiac arrest resuscitation is an emerging paradigm within resuscitation science supported by preclinical¹⁰⁷ and preliminary clinical work.¹⁰⁸

Older clinical trials comparing higher initial boluses of epinephrine (15 mg vs. 1 mg) found a higher rate of pulse restoration (13% vs. 8%) and higher rate of admission to a hospital (18% vs. 10%),¹⁰⁹ but the overall survival was not significantly different. Comparison of moderate doses (7 mg vs. 1 mg) of epinephrine in both in-hospital and out-of-hospital cardiac arrest found no change in pulse restoration or survival.¹¹⁰ Likewise, comparison of 0.02 mg/kg versus 0.2 mg/kg epinephrine found no change in pulse restoration or survival.¹¹¹ It is possible that the β -adrenergic effect of these higher doses of epinephrine produces toxicity that limits long-term survival. Postarrest impairment of cardiac index and oxygen delivery has been related to epinephrine dose.¹¹² Likewise, neurologic impairment has also been related to epinephrine dose.¹¹³ Increasingly, it is recognized that higher doses of epinephrine may impair cerebral circulation, a detrimental effect that may offset any benefit from increasing rates of restoration of circulation.¹¹⁴ Titrated epinephrine infusions may balance these

positive and negative effects, but this approach has not yet been explored clinically.

Vasopressin can increase CPP without complicating β -adrenergic effects. Resuscitation rates and survival are identical for patients resuscitated with vasopressin and standard doses of epinephrine after in-hospital¹¹⁵ or out-of-hospital cardiac arrest.¹¹⁶ However, post hoc analyses suggest vasopressin may be superior for resuscitation and survival of patients whose first ECG rhythm is asystole and for those subjects requiring multiple doses of vasopressors.¹¹⁶ Subsequent studies examined the combination of epinephrine with vasopressin versus epinephrine alone for treatment of cardiac arrest.^{117,118} These studies found no difference in outcome with the different combinations of drugs. Therefore, use of either vasopressin or epinephrine is reasonable in the setting of a cardiac arrest, but vasopressin is not recommended instead of epinephrine in general practice.

Although preclinical and existing clinical data support the conclusion that vasoactive drugs during CPR can increase the probability of restoring spontaneous circulation, it is unclear whether these drugs actually improve overall survival. One trial in out-of-hospital cardiac arrest patients compared resuscitation without intravenous (IV) drugs to resuscitation with IV drugs.¹⁰⁴ In this study, IV drugs increased the rate at which the pulse was restored (32% vs. 21%) but not the rate of neurologic survival (9.8% vs. 8.1%). Likewise, a massive, population-based, matched cohort study found that prehospital epinephrine was associated with restoration of circulation but with lower probability of 1-month survival and favorable functional outcome.¹¹⁹ These data raise the worrisome possibilities that when IV drugs are required to restore cardiac activity, severe brain injury has already occurred, or that the drugs used have added to the brain injury.¹¹³

The role of antidysrhythmic drugs during cardiac arrest is equivocal.^{120,121} Atropine may relieve bradycardia when it is vagally mediated. However, nervous system influences on the heart are largely eliminated after more than 1 to 2 minutes of circulatory arrest. Therefore, there is little expectation that atropine will improve resuscitation from asystole or PEA. Lidocaine, procainamide, and bretylium have a

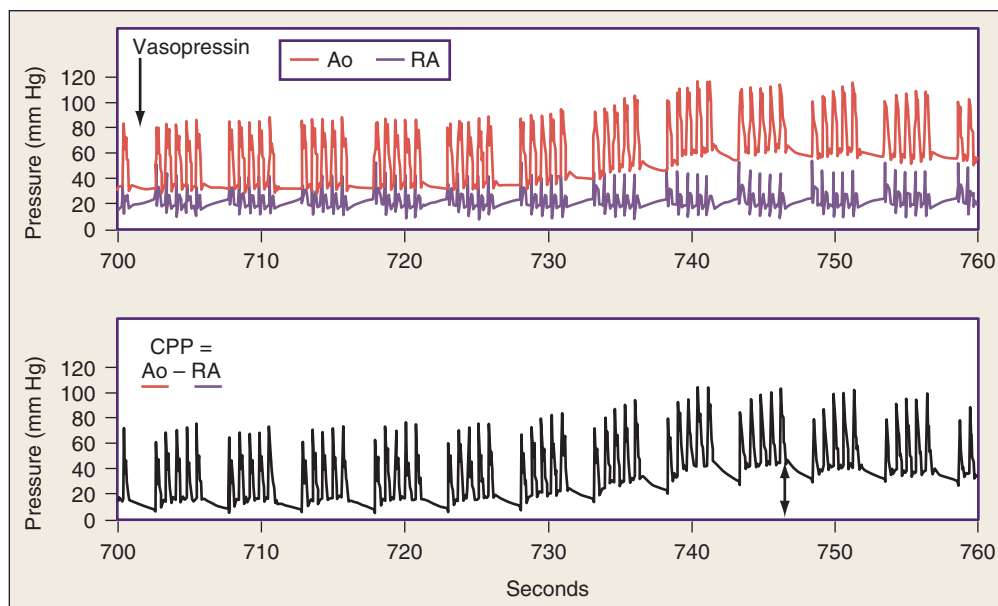


FIGURE 50-6 ■ Administration of a vasoactive drug, in this case vasopressin, can increase coronary perfusion pressure (CPP) produced by chest compressions. Note that CPP generated by chest compressions alone is below the 15 to 20 mm Hg believed necessary for restoration of circulation. However, aortic pressure (Ao) and thus CPP increase above this threshold 40 to 60 seconds after drug administration (arrow), while right atrial (RA) pressure remains unchanged. When treating cardiac arrest, it is reasonable to expect the vasoactive drug will act after 60 more seconds of chest compressions. (Unpublished laboratory data.)

long history of use in the treatment of VF. Once VF is established, lidocaine can increase the electrical energy required to defibrillate by more than 50%.¹²² Other classes of antidysrhythmics without sodium channel blockade do not alter defibrillation energy requirements. For example, amiodarone (5 mg/kg) is superior to placebo¹²³ and to lidocaine¹²⁴ in terms of restoring the pulse in out-of-hospital patients with VF that is not terminated by three rescue shocks. A large clinical trial comparing amiodarone, lidocaine, or placebo for shock-refractory VF found no overall difference in survival.¹²⁵ However, both lidocaine and amiodarone were superior to placebo in the subgroup of witnessed VF.

Empiric treatments of metabolic disturbances with bicarbonate or other buffers may improve acidemia resulting from ischemia. While systems with increased use of bicarbonate report higher rates of successful resuscitation,¹²⁶ no trial has demonstrated that sodium bicarbonate administration improves outcome.¹²⁷ Aminophylline has been proposed as an antagonist of adenosine released during ischemia. Two prospective studies of aminophylline administration to subjects with PEA or asystole found no improvement in resuscitation.^{128,129} Use of dextrose-containing fluids versus dextrose-free fluids did not alter outcome for out-of-hospital cardiac arrest patients.¹³⁰ Other metabolic therapies including calcium and magnesium also lack supporting data.^{131,132} However, it is appropriate to consider specific use of these agents to correct known abnormalities that are contributing to cardiac arrest, such as known hyperkalemia, calcium channel blocker overdose, torsades, or hypomagnesemia.

Taken together, the data support a simple pharmacologic approach to the treatment of cardiac arrest: vasopressors, epinephrine, or vasopressin can augment CPP generated during chest compressions, antidysrhythmic drugs may be useful for maintaining organized rhythms in witnessed shock-refractory VF, and all other drug therapies should be based on the clinical situation and the response of the patient.

ASPECTS OF CARDIAC ARREST IN SPECIFIC SITUATIONS

If the original etiology of cardiac arrest is available, treatment and prognosis can be individualized to the specific patient. Among out-of-hospital patients, as many as 66% have primary cardiac disturbances.¹³³ For in-hospital patients experiencing cardiac arrest, dysrhythmia and cardiac ischemia account for 59% of events.¹⁴ This section reviews unique features of cardiac arrest resulting from both cardiac and noncardiac causes.

Primary Cardiac Events

Primary dysrhythmia or cardiogenic shock is the most common proximate cause of cardiac arrest.^{133,134} Patients undergoing angioplasty have a 1.3% incidence of cardiac arrest, and survival in these patients resembles survival in other populations.¹³⁵ Among patients admitted to a hospital with acute MI, cardiac arrest occurs in 4.8%.¹⁷ Dysrhythmias are common during the hours after reperfusion therapy,¹³⁵ although reperfusion therapy reduces the overall risk of cardiac arrest.¹³⁶ During acute MI, cardiac arrest is most likely to occur in patients with lower serum potassium levels, more than 20 mm of total ST elevation, and a prolonged QTc interval during the first 2 hours of their event.¹³⁶ Some 3.3% of subjects surviving acute MI suffered sudden cardiac death.¹³⁷ Abnormalities of the heart are present in most cases of cardiac arrest, with coronary artery disease present in at least 65% of autopsies.¹³⁸ Taken together, these data suggest that most patients with cardiac arrest will have contributing cardiovascular disease.

When angiography was performed on consecutive patients resuscitated from cardiac arrest, acute coronary artery occlusion was identified in 48% to 58% of the patients.^{139,140} Similarly, 51% of initially resuscitated outpatients exhibited an elevation in cardiac enzymes or

ECG evidence of acute MI.¹⁴¹ In one series, troponin T was elevated in 40% of out-of-hospital patients undergoing CPR.¹⁴² The direct myocardial injury from defibrillation and CPR may cause spurious elevations of creatine kinase that are unrelated to cardiovascular disease.¹⁴³ However, elevation in cardiac troponin levels are believed to reflect acute MI rather than injury from electric shocks.¹⁴⁴ Thus, the 40% of subjects undergoing CPR with elevated troponin probably suffered myocardial injury prior to collapse.

Unless a clearly noncardiac etiology for cardiac arrest is evident, acute coronary angiography may reveal an indication for angioplasty, thrombolysis, or other reperfusion therapy. Early reperfusion therapy is associated with improved survival and outcome.^{17,139,145,146} Primary revascularization is safe in comatose patients undergoing hypothermia treatment, and good outcomes have been reported.^{147,148} Therefore, coma and its treatment should not delay emergent treatment of acute coronary syndrome if suspected.

Primary ventricular tachydysrhythmias are rapidly reversible and are the initially recorded rhythm in 23% to 41% of out-of-hospital cardiac arrest patients^{10,11,149} and in 25% of in-hospital cardiac arrest patients.¹⁴ Long-term antidysrhythmia treatment should be considered for patients who survive sudden cardiac arrest. At a minimum, treatment should be considered for patients with decreased left ventricular function or primary dysrhythmia without a reversible cause.¹⁵⁰ Importantly, subjects surviving a life-threatening ventricular dysrhythmia have a 15% to 20% risk of death during a mean of 16 months of follow-up, even when a reversible cause of the dysrhythmia such as electrolyte disturbance or hypoxia is identified.¹⁵¹ Implantable defibrillators are superior to antidysrhythmic drugs for reducing the risk of subsequent death.¹⁵² This benefit is primarily in subjects with a left ventricular ejection fraction (LVEF) less than 0.35.¹⁵³ Implantable defibrillators were not better than antidysrhythmic drugs in a European trial that enrolled subjects resuscitated from cardiac arrest secondary to ventricular dysrhythmia without regard to LVEF.¹⁵⁴ Nevertheless, these devices offer significant hope of preventing sudden cardiac death, and identification of patients that they may benefit is an active area of research. At present, implantable defibrillators should be discussed for patients who recover from coma with LVEF less than 0.35 or who survive a ventricular arrhythmia in the absence of clearly reversible causes.

Asphyxia

Asphyxia causes transient tachycardia and hypertension, followed by bradycardia and hypotension, progressing to PEA or asystole. This period of blood flow with severe hypoxemia prior to cardiac arrest may make asphyxiation a more severe injury than VF or other rapid causes of circulatory arrest.¹⁵⁵ Brain edema is more common on CT scans after resuscitation when cardiac arrest is caused by pulmonary rather than cardiac etiologies.¹⁵⁶ During cardiac arrest, pulmonary edema develops from redistribution of blood into the pulmonary vasculature,¹⁵⁷ worsening oxygenation in the asphyxiated patient. Attention to the primary cause of asphyxia, as well as to maneuvers that will increase oxygenation, may be necessary.

Pulmonary Embolism

Pulmonary emboli may occur in postsurgical patients, as well as in medical patients with impaired mobility.¹⁵⁸ In two series, pulmonary emboli were present in 10% of both in-hospital deaths¹⁵⁹ and out-of-hospital deaths.¹⁶⁰ Pulmonary emboli can result in rapid cardiopulmonary collapse and should be considered as a possible etiology of cardiac arrest in the proper clinical setting or when collapse is preceded by sudden shortness of breath, hypoxemia, and/or pleuritic chest pain.

Pulmonary emboli cause cardiac arrest from hypoxemia or when a large thrombus obstructs right ventricular outflow into the pulmonary arteries. This situation results in a dilated, distended right ventricle and an empty left ventricle, which can be seen on a transthoracic

echocardiogram. Circulation cannot be restored unless this obstruction is relieved. Because the primary disturbance is hypoxemia and decreased cardiac output, cardiac arrest from pulmonary embolism often presents with an initial rhythm of PEA or asystole.

Administration of a bolus of fibrinolytic drugs such as tenecteplase has been used with reported success in nonrandomized trials during resuscitation of undifferentiated patients,¹⁶¹ but it failed to demonstrate benefit in a larger randomized trial of undifferentiated patients in cardiac arrest.¹⁶² Likewise, a randomized trial of tissue plasminogen activator to patients for out-of-hospital cardiac arrest with an initial rhythm of PEA failed to demonstrate any benefit.¹⁶³ There are few data on the treatment of cardiac arrest resulting from massive pulmonary emboli, and individual decisions to use fibrinolytics in this setting must be tempered by the low probability of success.

Electrolyte Disturbances

Potassium disturbance is the most likely electrolyte disturbance to result in cardiac arrest. In cardiac patients, hypokalemia has been linked to the incidence of VF after MI.^{136,164} Hypokalemia may also account for the increased incidence of sudden death in patients taking large doses of diuretics. VF is rare in patients where serum potassium is maintained over 4.5 mEq/L. Conversely, hyperkalemia can prolong repolarization, increasing the likelihood of VF initiation. Hyperkalemia may also suppress automaticity in the myocardial electrical system, leading to bradycardic PEA or asystole. Interestingly, cardiac arrest occurring during hemodialysis is not associated with high or low potassium levels but is more common after patients are dialyzed against a low (0 or 1 mEq/L) potassium dialysate.¹⁶⁵ These data suggest that rapid changes in potassium rather than the absolute value are important triggers of cardiac arrest in this population. Derangements of calcium and magnesium may produce similar or synergistic changes in cardiac conduction.

The clinical setting of cardiac arrest or widened ventricular complexes with repolarization abnormalities on ECG may suggest a primary electrolyte disturbance. If hyperkalemia is suspected, the usual acute resuscitation maneuvers can be supplemented by a bolus injection of calcium carbonate (1 g), bicarbonate (1 mEq/kg), and perhaps insulin (0.1 units/kg) with glucose (0.5 to 1 gm/kg). These drugs may improve cardiac electrical stability, facilitating restoration of circulation.

Poisoning

Cardiac arrest can result from drug overdose. Therapy does not change except when specific antidotes or countermeasures to the poison are available. For example, calcium channel blocker overdose may be countered by administration of IV calcium.¹⁶⁶ Beta-blocker toxicity may require large doses of inotropic agents¹⁶⁷ or may respond to glucagon.¹⁶⁸ Digoxin overdose may respond to digoxin-binding antibodies.¹⁶⁹ In the case of narcotic-induced respiratory depression, subsequent cardiac arrest is usually a specific case of asphyxia rather than specific cardiotoxic effects. Case reports have suggested treating local anesthetic toxicity with 1 to 3 mL/kg of Intralipid.¹⁷⁰ This intervention is likely to be explored for other lipid-soluble poisonings.¹⁷¹ Poisoned patients are often younger with few comorbidities and may recover well once the poison is eliminated. This potential for a better outcome may justify longer and more aggressive efforts at resuscitation. A recent cohort study of recreational drug overdose-related cardiac arrest found that overdose-related patients who survived to hospital discharge were more likely than other cardiac arrest patients to have a favorable discharge disposition.¹⁷²

Sepsis

Cardiac arrest developing from sepsis may involve direct myocardial depression from humoral factors.^{173,174} Vasodilation also results in apparent hypovolemia. Finally, impaired oxygen extraction, shunting,

and mitochondrial depression can produce cellular hypoxia. Because pump and vascular failure are the principal physiologic derangements, the most common initial ECG rhythm would be expected to be a rapid PEA that slows to asystole with ischemia. Large doses of inotropes, vasoconstrictors, and volume may be needed to restore circulation. Acute volume resuscitation may require 100 mL/kg of isotonic fluids or more and must be titrated to physiologic endpoints (for example, central venous oxygen saturation, CVP, or urine output). Because the underlying sepsis physiology will still be present when the pulse is restored, these patients may prove exceedingly unstable during the subacute recovery period and have a reduced chance of survival.^{30,175-177}

Trauma/Hemorrhage

Hypovolemic cardiac arrest occurs after severe trauma, gastrointestinal hemorrhage, or other blood loss. Absence of venous return results in an empty heart that cannot produce cardiac output despite a normal inotropic state and vascular tone. As with sepsis, this situation would most likely present with a rapid PEA that slows to asystole, but VF can develop in response to global ischemia. Because cardiac function and vascular function are initially normal, inotropes and vasoconstrictors are unlikely to benefit hypovolemic cardiac arrest. Likewise, during hypovolemic cardiac arrest, the empty cardiac ventricles render external chest compressions ineffective. As such, there is no physiologic justification to employ the same resuscitation measures that are used for more traditional cases of cardiac arrest. Instead, attention should be turned toward emergent procedures to control hemorrhage, intravascular volume expansion with crystalloid fluids or blood products,¹⁷⁸ and mobilization toward definite surgical repair. After restoration of circulation, patients with hemorrhagic cardiac arrest are likely to develop multisystem organ failure.¹⁷⁸

If blood loss is ongoing or if massive volume replacement cannot be rapidly instituted, thoracotomy allows clamping or compression of the aorta, perhaps retaining sufficient blood in the proximal aorta to perfuse the coronary and cerebral arteries. This procedure has reported success in the treatment of penetrating traumatic injuries¹⁷⁹ but not in blunt trauma.¹⁸⁰ Survival is better if thoracotomy occurs in the operating room after a brief loss of pulse and best if the penetrating injury has created a cardiac tamponade that is directly relieved by pericardiectomy. Clearly, restoration of circulation must be accompanied by repair of the site of hemorrhage.

Hypothermia

Hypothermia represents an important situation where prolonged resuscitative efforts are justified by the greater tolerance of the cold heart and brain to ischemia. Survival with favorable neurologic recovery has been reported after cold water submersion or exposure, with cardiac arrest, and resuscitation efforts lasting several hours.^{181,182} Subjects in whom circulatory arrest occurs because of hypothermia appear to be more salvageable than subjects who asphyxiate or have circulatory arrest prior to becoming cold.¹⁸³

Treatment should be based upon the initial temperature of the patient. For temperatures between 32°C and 37°C, no change in drug or electrical treatment is required, and this level of hypothermia may be beneficial for resuscitation of both brain and heart.^{184,185} For temperatures between 29°C and 32°C, cardiac activity may be preserved, and external warming (warm air, heating lights, warm blankets) and warm IV fluids should accompany usual resuscitation efforts. The likelihood of generating sufficient perfusion to rewarm the body declines as temperatures decrease from 32°C to 29°C, and more invasive warming should be considered if external warming fails to elicit a rapid response. Mechanical and electrical activity of the heart is disrupted at temperatures below 28°C, and patients may exhibit PEA, VF that is refractory to defibrillation attempts, or asystole. Repetitive rescue shocks in such patients are not justified and may be detrimental; instead, rescue shocks should

be reserved until the patient has been rewarmed in the setting of ongoing circulatory support. Efficacy of most resuscitation drugs may be impaired.

Active rewarming during resuscitation of victims of severe hypothermia can include arterial and venous access for partial or complete cardiopulmonary bypass. Extracorporeal circulation is particularly useful because it can provide artificial circulation and warming, simultaneously.^{183,186,187} Another option is the placement of thoracostomy tubes and lavage of the chest with warm fluids.¹⁸⁸ Thoracostomy is intuitively preferable to peritoneal lavage because the heart is directly warmed. Warm air forced over the body surface provides the least heat exchange.¹⁸⁹ In any case, it is difficult to determine whether or not circulation can be reestablished in profoundly hypothermic patients until near physiologic core temperatures (32°C to 36°C) are restored.

Other Medical Conditions

Comorbidities have a tremendous influence on the outcome of patients with cardiac arrest.^{134,190,191} In some cases, cardiac arrest may be an expected progression of the patient's disease. For example, no survivors were reported among cancer patients with expected cardiac arrest.¹⁹¹ Therefore, it may be appropriate to set limits on resuscitation efforts in certain medical conditions prior to cardiopulmonary collapse. Ideally, discussion about the expectations for resuscitative efforts should be held with the patient, his or her family, or the patient's representatives prior to cardiac arrest. If those discussions did not occur prior to the first cardiac arrest, they should promptly follow any initially successful resuscitation.

POSTCARDIAC ARREST CARE TO MINIMIZE BRAIN INJURY

Postcardiac arrest syndrome is a defined clinical entity, consisting of brain injury, myocardial dysfunction, systemic ischemia/reperfusion, and the persistent precipitating pathology that caused the cardiac arrest. Management of this syndrome in patients after restoration of circulation directly affects their ultimate outcome. For example, survival varies for comparable patients treated by a single ambulance service who are delivered to different hospitals with institutional differences in in-hospital management.^{5,6} The American Heart Association and European Resuscitation Council now incorporate guidelines for the treatment of post-cardiac arrest syndrome into their consensus scientific statement. This section will highlight a bundled post-cardiac arrest care package, designed to mitigate primary injury and prevent secondary brain injury.

Brain injury after ischemia is an active process that develops over hours to days after resuscitation. Multiple cellular and molecular mechanisms contribute to this brain injury.¹⁹² Mechanisms include increased release of excitatory amino acids, free radicals, and energy failure. Protein synthesis is inhibited at the level of translation initiation for several hours.¹⁹³ There are focal disturbances of cerebral blood flow.¹⁹⁴ Specific intracellular and extracellular signaling pathways are activated for several hours after brain ischemia,^{195,196} which may lead to specific changes in gene transcription. Finally, activation of specific proteases between 24 and 72 hours after reperfusion is associated with the appearance of histologic signs of neuronal death.¹⁹⁷ The relative contribution of each of these processes to neuronal injury and their potential as targets for therapeutic intervention are unknown.

Despite detailed knowledge of the mechanisms involved with brain ischemia, no drug to date has demonstrated a clear benefit in human trials. Randomized trials have examined thiopental, the calcium channel blocker lidoflazine, magnesium, and diazepam.¹⁹⁸⁻²⁰⁰ One explanation for this failure is that multiple mechanisms contribute simultaneously to the process of ischemic neuronal death. Antagonizing one pathway leading to neuronal death may leave

other backup mechanisms unaffected. Less specific therapies may prove more effective. For example, two prospective randomized clinical trials found that induction of whole-body mild hypothermia (32°C to 34°C) for 12 to 24 hours after resuscitation improved survival and neurologic recovery.^{184,201} Whether this type of temperature management itself conferred an actual benefit or just served to prevent deleterious hyperthermia, it is important to note the success of this type of systemic therapy. Observational data also support coronary revascularization and meticulous avoidance of hyperthermia, hypotension, hypocarbia, hypoxia, and hyperglycemia.^{5,202-204} Taken together, systematic brain-oriented intensive care, rather than a single therapeutic drug or intervention, is required to improve outcome (Table 50-2).

Coronary Revascularization

Given the prevalence of acute coronary occlusions and high-risk coronary artery disease in this population, appropriate treatment of acute coronary syndrome or ST elevation MI (STEMI) should be promptly

TABLE 50-2 Postcardiac Arrest Intensive Care

| | |
|----------------------------|---|
| TEMPERATURE | Targeted temperature management 33°C to 36°C for 24 hours or longer Rewarm slowly (<0.25°C/h) Avoid fever for 48 hours or until awake |
| CARDIOVASCULAR | Mean arterial pressure >80 mm Hg during first day (inotropic and vasopressor support as needed; invasive monitoring as needed) Reperfusion therapy for acute myocardial infarction, regardless of concurrent coma or treatment with hypothermia Medical management for acute coronary syndromes (antiplatelet drugs, anticoagulation) |
| PULMONARY | Avoid hyperventilation Avoid hypoxia or unnecessary hyperoxia Pneumonitis is common |
| GASTROINTESTINAL | Usual care Consider early refeeding (after hypothermia) to reduce translocation |
| FLUIDS/ELECTROLYTES | Monitor CVP and urine output with hypothermia/rewarming Monitor potassium/electrolytes during temperature changes Keep potassium ≥4.5 mEq/L Monitor glucose frequently, normal treatment of hyperglycemia >180 mg/dL |
| INFECTION | Pneumonia is common Prophylactic antibiotics are of unproven benefit Antipyretics are reasonable |
| NEUROLOGIC | CT scan to exclude intracranial lesions Sedation and muscle relaxation as needed for targeted temperature management Monitor for seizures with continuous EEG Suppress malignant EEG patterns with antiepileptic therapy Serial clinical examinations for prognosis Examinations may change dramatically over first 72 hours (or longer with hypothermia treatment) EEG, SSEP, and MRI with DWI can supplement clinical examination for prognosis in selected patients Consider pharmacologic stimulation in patients with intact SSEP but persistent coma |

CT, computed tomography; CVP, central venous pressure; DWI, diffusion-weighted imaging; EEG, electroencephalogram; MRI, magnetic resonance imaging; SSEP, somatosensory evoked potential.

initiated, regardless of initial level of consciousness.²⁰⁵ Furthermore, emergent coronary angiography is reasonable even in the absence of STEMI because acute coronary ischemia is such a common precipitant of cardiac arrest. Repeated observational studies have highlighted immediate coronary angiography with concomitant coronary intervention as an independent predictor of survival and favorable neurologic outcome, irrespective of the presence or absence of STEMI on the initial ECG.^{139,140,146,206,207} There has been no randomized trial of this therapy to date.

Targeted Temperature Management

Meticulous temperature control is important during the first 24 to 48 hours after ischemic brain injury. Bacteremia and spontaneous fever are common in resuscitated patients, making active prevention of hyperthermia mandatory.^{208,209} Fever prevention is beneficial to the injured brain after traumatic brain injury, stroke, and cardiac arrest.^{202,210,211} Mechanistically, temperature probably affects more than the brain metabolic rate (manipulations of temperature that improve neurologic recovery in laboratory studies produce no effect on jugular venous lactate or oxygen uptake).²¹² Instead, a variety of signaling pathways and cellular responses are sensitive to relatively small (1°C to 2°C) changes in brain temperature.^{195,196} Also, lowering brain temperature can reduce intracranial pressure,²¹³ as well as vulnerability to seizures.²¹⁴

For more than a decade, mild induced hypothermia (32°C to 34°C) for 12 or 24 hours has been the cornerstone of post-cardiac arrest intensive care. Two randomized trials published in 2002 found a 24% to 30% reduction in relative risk for death or poor neurologic outcome²¹⁵ and significant improvement in the odds of survival and good neurologic outcome for subjects resuscitated from VF cardiac arrests.^{184,201} More recently, a large, prospective, randomized trial comparing a targeted temperature of 33°C with 36°C found that both groups had similar mortality and neurologic outcome at 180 days.²¹⁶ The most notable difference between the 2002 trials compared with the more recent trial was that the earlier studies did not adequately control temperature in the control arm. Temperatures greater than 37°C occurred in subjects for both control groups, whereas tight control at 36°C was followed in the more recent trial. Additionally, the recent trial used a blinded neurologic assessment along with regimented decisions about prognosis. While controlling temperature at 36°C is not superior to a strict temperature control at 33°C, it is not clear what temperature is best for patients who differ from the study population. Patients in the 33°C versus 36°C trial had very high rates of witnessed cardiac arrest, bystander CPR, initial shockable rhythm, and very brief intervals from collapse until start of basic life support. It is possible that unidentified subgroups of patients may benefit from a specific target temperature or from titrated use of temperature.

Current recommendations are to keep all comatose post-cardiac arrest patients at a constant target temperature ranging between 32°C and 26°C. This is different from reactive treatment of fever, which has not been studied in clinical trials. It is erroneous to assume that selection of 36°C as a target temperature is synonymous with not managing temperature or fever prevention without active controls. Active measures require thermostatically controlled devices, of which there are many. Importantly, there is no clinical situation where control of temperature in this range is contraindicated; even bleeding does not increase at 36°C.

There is no biological basis to believe that the neurologic benefit of temperature management is specific to patients with one type of cardiac rhythm. Patients with all rhythms were included in the largest clinical trial.²¹⁶ Multiple case series report successful application of induced hypothermia for patients after out-of-hospital and in-hospital cardiac arrest with all initial rhythms.^{3,217,218} At the time of resuscitation, many patients were already mildly hypothermic, with core temperatures between 35°C and 35.5°C.^{184,201,219} This spontaneous cooling may result from the mixing of core and peripheral blood

compartments during circulatory arrest, but patients typically rewarm within a few hours unless specific interventions are instituted.^{202,220}

The optimal duration of temperature management, the maximum delay in achieving target temperatures, the optimal target temperature, and the preferred rate of rewarming are unknown. Laboratory studies suggest that cooling to a range from 32°C and 35°C for 12 to 24 hours is beneficial, particularly if cooling is achieved within 6 hours after resuscitation. These studies also suggest that rewarming should be performed slowly (<0.25°C/hour). A regimen similar to the largest clinical trial (24 to 28 hours, followed by meticulous fever suppression for at least 3 days) is reasonable.²¹⁶

After cardiac arrest, temperature management can be achieved by a variety of techniques including surface cooling with ice packs, cooling blankets or endovascular devices.^{185,201,221} Initial studies using surface cooling alone suggested that it is slow and may require 4 to 6 hours to reach 34°C.^{184,210,222} However, neuromuscular blockade and sedation to prevent shivering greatly accelerate surface cooling.²²³ There are few direct comparisons of surface cooling and endovascular cooling; however, endovascular catheters may provide more stable control of temperature over time.^{224,225} Local cooling of the head is unlikely to produce brain hypothermia when there is adequate perfusion by warm core blood,²¹⁹ although the head can be an effective site for removing heat from the body.²²⁶

Rapid infusion of 30 mL/kg cold (4°C) crystalloid fluid produces a rapid decrease in core temperature in post-cardiac arrest patients.^{220,227-229} Cold fluid boluses must be administered quickly into the central circulation (via a central line or under pressure infusion via a peripheral line). The volume required may limit this intervention in some patients. Recent clinical trials show no beneficial outcome when paramedics use cold intravenous fluids for undifferentiated cardiac arrest patients prior to hospital arrival and instead observe an increase in complications.²³⁰⁻²³² Therefore, this intervention is best used in a hospital critical care setting with adequate monitoring and resources. Cold IV fluids only produce a transient decrease in core temperature, requiring that a maintenance technique (endovascular or surface cooling device) be in place after the infusion.^{220,229}

Induction of cooling can result in peripheral vasoconstriction, with an apparent reduction in vascular volume, rise in CVP, and diuresis.²³³ Rewarming causes vessels to dilate, CVP to fall, and the patient to appear relatively hypovolemic. Inattention to these fluid shifts was cited as a pitfall in trials of therapeutic hypothermia for traumatic brain injury.²³³ Hypokalemia, hypophosphatemia, and hypomagnesemia also occur during cooling, followed by hyperkalemia during rewarming.^{234,235} Frequent monitoring and correction of electrolytes are warranted.

Primary angioplasty is safe in patients undergoing hypothermia treatment.^{147,148,185} Mild hypothermia greater than 30°C does not interfere with defibrillation. Cooling from 37°C to 31°C has a positive inotropic effect, increasing stroke volume to a greater extent than it decreases heart rate.²³⁶ Clinical data report a transient 18% decline in cardiac index with cooling to 33°C.²³⁷

Infections may become more common when patients are cooled for 24 hours or longer.^{184,201} Although mild hypothermia can inhibit platelet function and coagulation,²³⁸ these changes are of a smaller magnitude, leading to few bleeding complications, even in subjects with concurrent trauma or administration of heparinoids and glycoprotein IIb/IIIa inhibitors.^{185,210} Bleeding after hypothermia and cardiac catheterization was reported in 6.2% of post-cardiac arrest patients.²³⁹ Elevation in pancreatic enzymes has been reported in cooled patients, but these changes resolve with rewarming.^{184,237} Creatinine clearance and platelet count may fall during cooling, but both parameters normalize with rewarming.²³⁷

Hemodynamic Management

Myocardial function declines transiently after cardiac arrest.²⁴⁰ Oxidative stress or other triggers can lead to myocyte damage after reperfusion.²⁴¹ Clinically, some vasoactive and/or inotropic drug support is

necessary in a large proportion of patients resuscitated from cardiac arrest, with expected recovery over the subsequent 24 to 48 hours.

During the first day after resuscitation from cardiac arrest, patients exhibit increased cerebral vascular resistance²⁴² and impaired cerebral autoregulation.^{243,244} When autoregulation is present, it is right-shifted such that brain perfusion declines when mean arterial pressure (MAP) declines below 80 to 120 mm Hg. When blood pressure is maintained, clinical positron emission tomography (PET) studies suggest that regional perfusion remains matched to metabolic activity after cardiac arrest.^{245,246} Thus, available data indicate that perfusion of the brain requires a higher MAP than normal during the first hours to days after cardiac arrest. Periods of hypotension after the pulse is restored may add significant secondary ischemic brain injury.

If tolerated by the heart, relative hypertension (MAP of 80 to 100 mm Hg) should be considered using inotropes and/or pressors to prevent brain hypoperfusion. Episodes of hypotension after resuscitation are associated with death and poor neurologic recovery in postarrest patients.^{203,247} Conversely, higher MAP is associated with survival and better neurologic recovery.^{248,249} Hemodynamic management strategies are not well defined in most postarrest care implementation studies,²⁵⁰ and no specific choice of pressors has been demonstrated to be superior. Dopamine (5–20 µg/kg/min), norepinephrine (0.01–1 µg/kg/min), and/or epinephrine (0.01–1 µg/min) are all potential agents. Dopamine has the disadvantage of inducing tachydysrhythmias. Conversely, epinephrine has more positive inotropy than norepinephrine but can prolong lactic acidosis. Therefore, the choice and doses of these agents must be titrated to individual patients.

Oxygenation and Ventilation

Postcardiac arrest hyperoxia ($\text{PaO}_2 \geq 300$ mm Hg) was associated with higher inpatient mortality than normoxia.^{251,252} These studies speculate that high oxygen concentration increases oxidative free radical damage. One multicenter cohort study found a linear, dose-dependent relationship between levels of oxygen tension and inpatient mortality but could not identify a single threshold for harm.²⁵³ In the absence of evidence to support a specific PaO_2 goal for patients, it is reasonable to titrate FiO_2 to the lowest values sufficient to maintain a normal arterial oxygen-hemoglobin saturation (94% to 98%).

Although the post-cardiac arrest brain suffers from impaired cerebral autoregulation, it tends to preserve CO_2 reactivity.²⁴⁴ Both hypocapnia ($\text{PaCO}_2 \leq 30$ mm Hg) and hypercapnia ($\text{PaCO}_2 \geq 50$ mm Hg) are independently associated with poor neurologic outcome.²⁵⁴ As in traumatic brain injury, hypo- and hyperventilation result in dysfunctional cerebral perfusion, so it is best to ventilate with a goal of normocarbia (PaCO_2 35 to 45 mm Hg).

Glucose Control

Elevated serum glucose is common after cardiac arrest and is associated with poor outcome,^{130,255} but hyperglycemia may simply be a marker of greater illness severity. Both epinephrine and physiologic stress can elevate serum glucose, and mild hypothermia may reduce insulin sensitivity.²⁵⁶ However, multivariate models that account for resuscitation time and medication usage show an effect of serum glucose on admission and the first 48 hours of intensive care on long-term outcome.^{5,257} Monitoring of glucose and treatment of hyperglycemia are reasonable.

Intensive glycemic control with a low target range (72–108 mg/dL, 4–6 mmol/L) has not proven beneficial outside of the surgical population where it was first studied¹²⁵⁸ and may be harmful in medical intensive care.^{259,260} After cardiac arrest, there was no difference in outcome when a moderate glucose range was targeted (108–144 mg/dL; 6–8 mmol/L) versus a strict lower range (72–108 mg/dL; 4–6 mmol/L).²⁶¹ However, the incidence of hypoglycemic events was higher in the strict versus moderate control group (18% vs. 2% of patients). Given the available data, treatment of glucose levels above 180 mg/dL (10 mmol/L) is reasonable.

Hematologic Changes

Cardiac arrest is associated with activation of coagulation that is not balanced by fibrinolysis and is perhaps related to ischemic injury to the endothelium. This hematologic profile is reminiscent of disseminated intravascular coagulation and may contribute to subsequent end organ dysfunction. Markers of thrombogenesis that have been reported include increased thrombin-antithrombin complexes and fibrinopeptide A.^{262,263} These increases are not balanced by fibrinolytic factors for at least 24 hours.

At present, use of anticoagulation is variable, and there are no prospective trials evaluating the effect of empiric anticoagulation after resuscitation. Anticoagulation and even fibrinolytic drugs are safe after CPR.^{162,263–265} A retrospective series noted a univariate relationship between anticoagulation and 6-month survival that was not significant in a multivariate model.²⁵⁷ Given the hematologic evidence of active thrombogenesis, anticoagulation should be considered whenever there is a possibility of a thrombotic etiology.

Infection

Both ischemia-triggered systemic inflammatory responses and infections are common after cardiac arrest.²⁶⁶ Pneumonia, bloodstream infections, and catheter-related infections are the most common infectious complications.^{266,267} Pneumonia, especially, is associated with the duration of mechanical ventilation and length of ICU stay but does not appear to have an impact on mortality or neurologic outcome.^{266–268} Bacteremia occurs in 39% of patients during the first 12 hours after resuscitation.²⁰⁸ The accurate diagnosis of post-cardiac arrest infections is hampered by an associated increase in inflammatory markers^{269,270} and body temperature control. Despite these observations, the role of prophylactic antibiotics or antipyretics is unknown, and selective treatment of identified infections is reasonable.

PREDICTING NEUROLOGIC RECOVERY

The goal of clinical practice is always to restore the patient to full consciousness and function.²⁷¹ All patients with circulatory arrest of more than 1 or 2 minutes will be comatose at initial presentation, but some of these patients can recover and awaken. Therefore, signs of neurologic activity immediately after restoration of circulation are encouraging, but their absence does not preclude eventual recovery. Unfortunately, many cardiac arrest survivors fail to completely awaken and may meet criteria for a persistent vegetative state.^{272,273} The status of patients who do not quite meet these criteria but are not awake has been described as a minimally conscious state.²⁷⁴ Less than 10% of patients who are hospitalized after cardiac arrest progress to formal brain death.²³

Determining the neurologic prognosis of patients resuscitated from cardiac arrest has been the subject of multiple reviews and guideline statements^{275–278} before and after the setting of modern ICU care. It remains unclear whether the traditional findings associated with poor outcome^{279–281} are still valid in the setting of modern ICU care and targeted temperature management. In fact, good survival has been reported after some situations previously believed to have universally poor outcomes such as post-cardiac arrest status myoclonus and seizures^{282,283} or the absence of cortical responses on evoked potentials.²⁸⁴ Neurologic recovery continues over a longer time period than the 3 days recommended in historical publications.^{275,276} Therefore, longer periods of support and observation are appropriate for many patients. Furthermore, a multimodal approach to determining prognosis that includes imaging and neurophysiologic studies may be useful to sort out difficult cases in which the physical examination is equivocal.²⁸² In a practical approach, the clinician can make an initial estimate of the probability of recovery based on clinical exam. As more information becomes available from clinical progression, imaging studies, and neurophysiologic studies, this estimate can be revised in order to advise families and proxy decision makers. Daily reevaluations are

required to decide if ongoing therapy is consistent with the patient's goals in light of the best estimate of the probability of various outcomes.

Baseline Probability of Recovery

In cohorts of patients admitted to a hospital after in-hospital and out-of-hospital cardiac arrest, approximately 31% to 33% of patients recovered to a favorable functional status.^{22,23} While clinicians could start with an estimate that all patients have about 30% chance of good recovery, it is obvious that some patients have much greater illness severity than others at admission. The expectation of survival should be revised based on this fact. Various prognostic tools or scores can refine the estimated odds of recovery based on initial physiologic status or historical features.^{285,286} One simple score is the Pittsburgh Cardiac Arrest Category (PCAC) (Box 50-1). This score divides patients into four categories based on initial coma examination and degree of cardiopulmonary failure.²⁸⁷ Probability of survival, good functional recovery, and risk of multiple organ failure varies by category. This score has advantages of being fast, easy to communicate, and validated in prospective cohorts.²⁸⁸ Using some initial assessment of illness severity is a reasonable practice for the clinician who wants to provide realistic estimates for families or surrogate decision makers.

Clinical Examination

A classic case series found that pupillary reflexes, corneal reflexes, and motor activity can change over the first 72 hours after resuscitation.²⁸¹ By 72 hours, persistent absence of pupillary light reflex and corneal response is highly predictive of permanent coma,^{277,278} but the motor examination is much less reliable. Specifically, motor response less than flexion at 3 days was reported to have a false-positive rate ([FPR] percentage where tests predict a poor outcome, but patients have a good outcome) of 14% (95% confidence interval [CI], 3%-44%)²⁸⁹ or 8% (95% CI, 2%-25%).²⁸² In contrast, among patients not treated with therapeutic hypothermia, the absence of pupillary light reflex (>72 hours) after cardiac arrest has an FPR 0% (95% CI, 0%-8%) for

predicting death or vegetative state. The presence of myoclonus is not reliable for predicting poor outcome and must be distinguished from status myoclonus (persistent, repetitive myoclonus). Status myoclonus on admission is associated with death or vegetative state with 0% FPR (95% CI, 0%-14%). Status myoclonus at 24 hours after cardiac arrest has a more precise 0% FPR (95% CI, 0%-3%).^{277,278} Similar patterns of findings are true among patients treated with therapeutic hypothermia, though longer periods of observation may be required to clear potential confounding factors by sedation.

Physiologic response to targeted temperature management provides another avenue for insight into the potential for neurologic recovery. The presence of shivering,²⁹⁰ the amount of patient heat generation (derived from the inverse average water temperature of cooling devices),²⁹¹ and the presence of bradycardia (<60 beats/minute)²⁹² during the induction and maintenance of temperature management are each associated with favorable neurologic outcome.

Imaging Studies

Imaging of the brain is important to exclude injury incurred at the time of collapse and to exclude intracranial causes of collapse. A noncontrast cranial computed tomography (CT) scan to exclude hemorrhage is prudent in comatose patients after cardiac arrest and prior to anticoagulation or fibrinolytic therapy.^{293,294} In general, noncontrast CT scan is insufficiently sensitive to determine prognosis after cardiac arrest unless severe changes are present, such as generalized edema that is often associated with loss of brainstem reflexes and may progress to herniation and brain death (Fig. 50-7). The amount of brain edema can be quantified with a ratio of attenuation (Hounsfield units) in select regions of gray matter and white matter. This "gray-to-white ratio" is directly associated with survival and functional outcome.^{295,296} Whether treatment of cerebral edema is worthwhile or futile has not yet been studied.

Magnetic resonance imaging (MRI) can visualize subtler changes in brain after cardiac arrest. For example, increased cortical signals on diffusion-weighted images (DWI) or fluid-attenuated inversion recovery (FLAIR) are associated with poor neurologic outcome.²⁹⁷ For patients who remain comatose for several days and in whom clinical or electrophysiologic testing is indeterminate, MRI can provide additional information about the extent of brain injury. Expectations and enthusiasm for long-term support may be reduced if extensive cortical lesions are present, whereas persistence may be justified if anatomic extent of injury appears limited. An important caveat with interpretation of all brain imaging after global ischemia is the differing clinical impact of lesions in different brain regions. The anatomic complexity of the brain precludes any simple quantitative relationship between the number or size of lesions and outcome. Isolated DWI abnormalities in single anatomic locations are not specific for poor neurologic outcome.²⁹⁸ Furthermore, the existing literature about MRI is limited by indication bias: only a select subgroup of patients who are not improving clinically have this test, potentially inflating the prognostic significance of any findings. Long-term cognitive deficits are associated with global brain volume loss after cardiac arrest.²⁹⁹ MRI should be used as an adjunct for assessing postcardiac arrest brain damage in centers with neurologic or neuroradiologic expertise for interpreting these tests.

Neurophysiology

Electroencephalogram (EEG) patterns after resuscitation change over time.^{300,301} The greatest utility of an EEG is to diagnose seizures and exclude nonconvulsive seizures as an etiology of unresponsiveness. Seizures are diagnosed clinically in 5% to 20% of comatose patients after cardiac arrest,^{184,301} and the true incidence of nonconvulsive electrographic seizures may be higher. Termination of seizures, if possible, is essential to allow untainted assessment of the neurologic examination (Fig. 50-8). Certain malignant EEG patterns have a strong association with poor outcome. Specifically, generalized suppression

BOX 50-1 Post-Cardiac Arrest Category

The category of a patient can be assessed quickly on arrival to better stratify the initial probability of survival and risk of different complications. Precise research definitions of the categories use scoring systems assessed within 6 hours of return of pulses,²⁸⁷ but clinical examination can usually sort patients into categories. Neurologic examination cannot be assessed if drugs or paralytics are confounding.

CATEGORY 1—AWAKE (FOLLOWS COMMANDS)

80% chance of survival; 60% chance of good functional recovery
<5% chance of multiple organ failure

CATEGORY 2—COMA WITH PRESERVED BRAINSTEM REFLEXES*

60% chance of survival; 40% chance of good functional recovery
20% chance of multiple organ failure

CATEGORY 3—COMA WITH PRESERVED BRAINSTEM REFLEXES AND SEVERE CARDIOPULMONARY FAILURE**

40% chance of survival; 20% chance of good functional recovery
40% chance of multiple organ failure

CATEGORY 4—COMA WITH LOSS OF BRAINSTEM REFLEXES

10% chance of survival; 7% chance of good functional recovery
35% chance of multiple organ failure

*Coma with preserved brainstem reflexes = FOUR score Motor + Brainstem scale ≥ 4 ; typically present pupillary light reflex, corneal reflex, and some movement of extremities (at least posturing)

**Severe cardiopulmonary failure = SOFA score cardiac + respiratory subscales ≥ 4 ; typically more than one pressor drug, norepinephrine or equivalent at rates $>0.1 \mu\text{g/kg/min}$ and/or ventilator settings with $\text{PaO}_2/\text{FiO}_2$ ratio <100 .

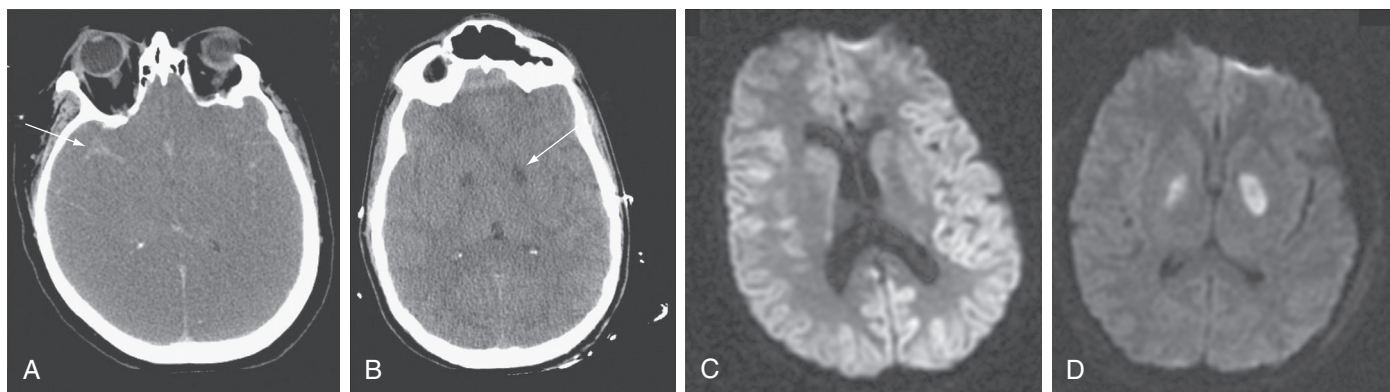


FIGURE 50-7 ■ Imaging of the brain after cardiac arrest. **A**, Severe cerebral ischemia appears as sulcal effacement, with loss of contrast between gray matter and white matter. Congestion of blood in meninges (pseudosubarachnoid hemorrhage [arrow]) sometimes is evident. This pattern on early computed tomography (CT) scan often progresses to herniation and brain death. **B**, Less severe early changes show edema (hypodensity) restricted to basal ganglia (arrow), with sparing of cortex. **C**, Increased magnetic resonance imaging (MRI) signal from extensive areas of cortex on diffusion-weighted images (DWI) of this patient correspond to devastating brain injury with persistent coma. This patient showed no improvement in coma. **D**, DWI for same patient in **B** illustrates high-intensity signal from damaged subcortical areas. In this case, cortex and other structures are normal. After 5 days of coma, this patient awoke, completed rehabilitation, and recovered completely.

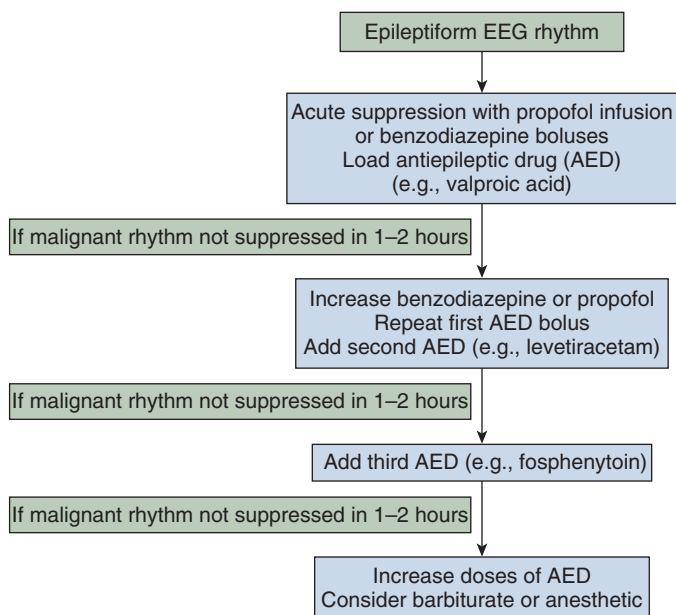


FIGURE 50-8 ■ EEG examination and AED management following resuscitation.

(<20 μ V), burst-suppression pattern associated with generalized epileptic activity, or diffuse periodic complexes on a flat background during the first week after resuscitation are associated with poor neurologic outcome.²⁷⁹ The presence of malignant EEG patterns provides information that is additive with clinical evaluation.³⁰² Thus EEG cannot be used by itself to determine prognosis, but the information provided by EEG can exclude confounders (seizures) and can be integrated into the total clinical picture used to assess prognosis.

Electrophysiologic response to stimuli can also be used to assess whether cortical regions are intact. Recovery of longer latency event-related potentials are associated with awakening.³⁰³⁻³⁰⁵ Conversely, absence of short latency (N20) cortical response to somatosensory evoked potentials (SSEPs) is very specific for poor neurologic outcome

(FPR 0%; 95% CI, 0%-2%) among patients treated with therapeutic hypothermia.^{276,278,279} Like EEG, SSEP responses vary with the elapsed time since resuscitation.³⁰⁰ Recent data suggest that the use of therapeutic hypothermia may increase the time-dependent changes in SSEP. One case series reported two patients treated with hypothermia who had absent N20 responses at 3 days after cardiac arrest but recovered cognition.²⁸³ Therefore, it may be reasonable to repeat SSEPs that show absent N20s several days apart in order to avoid false-negative tests.

Blood Markers

Several peptides appear in the blood after brain injury, including neuron-specific enolase (NSE) and the glia-derived protein, S-100B. After cardiac arrest, NSE reaches a maximum level in serum at 72 hours. High NSE levels at 48 to 72 hours or NSE levels that continue to rise over the first 72 hours after resuscitation are associated with poor outcome.³⁰⁵⁻³⁰⁷ In contrast to NSE, peak levels of S-100B in serum occur during the first 24 hours after resuscitation, and higher S-100B levels are associated with poor neurologic outcome.^{306,308} Hypothermia treatment appears to alter serum NSE levels.³⁰⁹ Use of NSE or S-100B to determine prognosis is limited by the absence of a clear cutoff value that is unsurvivable and the lack of universal standard for laboratory assays. NSE can also be released by injury to nonbrain organs.³¹⁰ These neuronal markers might be considered a tool for following brain injury, analogous to troponin levels for following myocardial injury, but lack the specificity or clarity required to guide therapeutic decisions.

In summary, the determination of neurologic prognosis after cardiac arrest varies from patient to patient. Changes in clinical examination are the cornerstone of prognostication. While the patient is recovering, hypothermia and supportive care may increase the likelihood of recovery. However, electrophysiologic and imaging techniques can add additional useful information to help guide clinicians and families. The approximate timing for each of these studies is depicted in Figure 50-9. New prognostication guidelines from the European Resuscitation Council and European Society of Intensive Care Medicine³¹¹ emphasize the bilateral absence of pupillary and corneal reflexes or N20 wave of SSEPs as the most robust predictors of poor outcome irrespective of temperature management. Early myoclonus, elevated

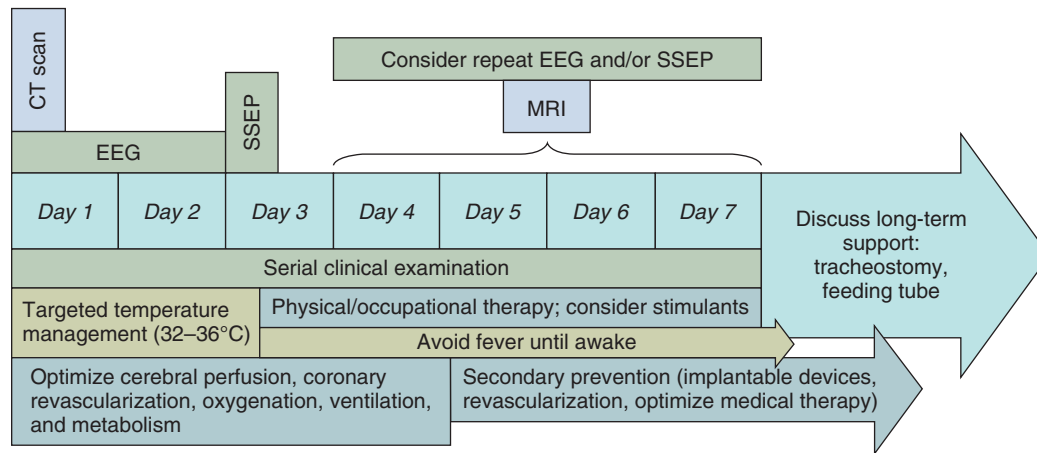


FIGURE 50-9 ■ Rational approach to neurologic treatment, monitoring, and testing after cardiac arrest. For patients remaining in coma, hypothermia treatment followed by therapy and stimulation may improve recovery. Early electroencephalogram (EEG) monitoring is recommended not for prognosis but to allow detection and treatment of seizures. Absence of cortical response on somatosensory evoked potential (SSEP) or malignant EEG patterns after hypothermia treatment may help identify subsets of patients unlikely to ever show improvement. When those tests are indeterminate, and there is no sign of clinical improvement, magnetic resonance imaging (MRI) of the brain may help quantify extent and location of injury, which in turn assists in decisions about continuing long-term support. Most tests are not required when patients exhibit clear clinical improvement. Conversely, patients who progress to brain death should undergo brain death testing once toxicologic confounds, metabolic abnormalities, and shock have been corrected.

values of NSE at 48 to 72 hours from cardiac arrest, unreactive malignant EEG patterns after rewarming, and diffuse signs of anoxic injury on CT or MRI are useful but less robust predictors. Prolonged observation should be considered when the results of initial assessments are inconclusive.

REHABILITATION

The role of rehabilitation or other therapy in recovery from neurologic impairment after cardiac arrest is relatively unstudied. It is clear that both patients and their caregivers have complex needs if neurologic injury is severe.³¹² Older data suggests that long-term improvement is less common when neurologic devastation follows a medical cause like cardiac arrest than when it results from traumatic brain injury.²⁷³ More recent work suggests that rehabilitation can produce similar improvements after global brain ischemia.^{313,314} Nevertheless, early consideration of rehabilitative services including physical therapy and occupational therapy may help promote recovery, just as in acute stroke.³¹⁵ Physical stimulation and maintenance of muscle tone could conceivably promote awakening. When arousal or level of consciousness is impaired after traumatic brain injury, stimulants such as methylphenidate or amantadine have been employed with reduction in total ICU stay or improved final status.^{316,317} While these data are few and indirect, addition of stimulants for postcardiac arrest patients who linger in intermediate coma might be considered, if medically tolerated.³¹⁸

WITHDRAWAL OF LIFE-SUSTAINING TREATMENT

For adults who are neurologically devastated after cardiac arrest in North America, it is more common to die in a hospital than to receive long-term care. An estimated 44% of patients who are initially resuscitated from cardiac arrest in a hospital have withdrawal of care later in their hospitalization.¹⁴ For patients resuscitated from out-of-hospital

cardiac arrest, 61% die after withdrawal of life-sustaining treatments because of predicted neurologic prognosis.²³ Because these decisions are often based on the neurologic prognosis of the patient, withdrawal of life-sustaining treatment limits the number of neurologically impaired individuals who are discharged from the hospital. Consequently, quality of life for those patients who do leave the hospital is generally high.^{21,319,320} Popular reports of awakening after long coma may cause inappropriate optimism for families of patients or surrogate decision makers. Partial awakening of patients into a persistent vegetative state or minimally conscious state can further confuse their expectations. Decision makers should receive information about these syndromes, realistic expectations of recovery, and any specific considerations for the individual patient. Religious, cultural, and personal beliefs will contribute to decisions, and appropriate social service and pastoral support should be provided. Finally, for patients who survive cardiac arrest but who later progress to death or brain death, it is reasonable to evaluate their candidacy to become organ donors: outcomes for transplanted organs from this population are comparable to all other donors.³²¹

SUMMARY

Improvement in outcome after cardiac arrest will require attention both to the reversal of cardiopulmonary arrest and to restoration of consciousness. Isolated attention to only the heart or only the brain is unlikely to improve outcomes for many patients. Appropriate prioritization of the various tools for cardiac resuscitation, along with emphasis on the basic mechanics of artificial circulation, may increase the number of individuals reaching the ICU. Induction of mild hypothermia, management of blood pressure and respiration, along with proper treatment of the root cause of the cardiac arrest may increase the number of initially comatose patients who awaken. Constant reassessment of the likelihood of meaningful recovery, based on clinical examination and ancillary testing, can guarantee that continued care and interventions are appropriate.

KEY POINTS

1. Improvement in outcome after cardiac arrest requires attention both to immediate reversal of cardiopulmonary arrest and promoting recovery of brain function through subsequent intensive care unit (ICU) interventions. Isolated attention to only the heart or only the brain is unlikely to improve outcomes for many patients (see Fig. 50-8).
2. Increased emphasis on the basic mechanics of artificial circulation, specifically uninterrupted vigorous chest compressions, may increase the number of individuals reaching the ICU.
3. It is necessary to prioritize the various adjunct tools for cardiac resuscitation. For example, time devoted to tracheal intubation may delay drug therapy and interrupt chest compressions without altering overall hemodynamics.
4. The cornerstone of drug therapy during resuscitation attempts is the selective administration of vasoactive drugs that will increase coronary perfusion pressure developed by chest compressions. Rote, repeated administration is unlikely to result in favorable neurologic outcome.
5. Induction of targeted temperature management; optimal management of blood pressure, oxygenation, and ventilation; and proper treatment of the root cause of the cardiac arrest may increase the number of initially comatose patients who awaken.
6. Neurologic prognosis is determined using serial clinical examinations supplemented by neurophysiologic or imaging tests. Clinical examination continues to change for many days after cardiac arrest, and even longer periods of observation may be required for patients treated with hypothermia. Constant reassessment of the likelihood of meaningful recovery can guarantee that continued care and interventions are appropriate.

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■ References for this chapter can be found at expertconsult.com.

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Delirium represents a tremendous problem in the ICU. The unpredictable behavior of patients experiencing delirium can be challenging to manage and a risk to both the patient and the hospital staff. Delirium itself can be linked to morbidity while in the ICU. Furthermore, delirium is associated with a significant decline long after the patient is discharged from the hospital.

The incidence of delirium varies based on the specific patient population but has been reported to be as high as 80%.¹ One group found that neurology/neurosurgical patients were at the highest risk, followed by trauma patients, and then medical intensive care patients. Surgical ICU patients were at the lowest risk²; however, this result has not been well validated across multiple institutions.

Delirium is usually associated with agitation (i.e., agitated delirium), but this is not a necessity. Agitated delirium describes a syndrome of excessive motor activity, usually nonpurposeful and associated with internal tension. Delirium can also be a quiet confusion that can be difficult to discern by the examining physician. In contrast, the term *mixed delirium* usually denotes alternating periods of quiet confusion and aggressive, nonpurposeful behavior.

For intensivists, agitation is not so much a diagnosis but a consequence of more fundamental etiologies that, when expressed, result in disquietude. As a result of our high-tech hemodynamic monitoring and support devices, we have conferred new types of stresses upon already hemodynamically unstable patients that we never had to deal with in the past. Modern ICUs now have the potential to return critically ill patients to productivity using technological advances in monitoring and closely titrated care, effectively pinning the patient firmly to the bed with tubes and appliances.

In one large study, mixed delirium was found to be the most common subset (54.9%), with hypoactive somewhat less common (43.5%), and hyperactive agitated delirium was rare (1.6%).³ In this same study, hypoactive delirium was reported more frequently in patients at least 65 years of age (41% vs. 21.6%, $P < 0.001$). Agitation episodes that threaten hemodynamic stability are uncommon but are occurring more frequently as ICUs accept wider ranges of critically ill patients for longer periods of time on complex life support systems.

WHY DOES DELIRIUM OCCUR IN CRITICAL CARE UNITS?

By their nature, critical care units are places that require patience and compliance from patients. Sensitive monitoring systems and indwelling catheters frequently occupy every bodily orifice and require relative patient immobility for long periods. Many patients, especially those over 65 years of age, have a mild underlying dementia that is well controlled in their home environment as pattern recognition suppresses the potential underlying cognitive insufficiency.

Thus, when the same patient is admitted to an ICU for any reason, all the previous pattern recognition is lost, and the patient no longer gets by on habit and routine, and the underlying cognitive insufficiency is freely expressed.

The term *ICU psychosis* was introduced to underline the etiologic significance of psychosocial and psychological factors in understanding the syndrome. ICU activities around the clock may lead to a patient's loss of orientation to time. Monotonous sensory input in the

form of unfamiliar, repetitive, and noisy monitoring equipment; prolonged immobilization; brief but frequently interrupted sleep patterns; social isolation; and unfamiliarity with the ICU personnel (which change frequently) eventually contribute to the pre-delirious state.

The term *ICU psychosis* is not an accurate description of the disorder and leads to misleading conclusions. The term *psychosis*, as used in the psychiatric literature, is characterized by persistent disorders of brain functioning in which no specific organic factors may be causally related. In true delirium, organic causation is not only present but also most often stems from outside of the nervous system. Symptoms of ICU-related delirium are extremely random and purposeless, without systematization, while psychotic symptoms are frequently bizarre but well organized and consistent. The term *ICU stress delirium* would be more applicable for organic brain syndromes occurring in the ICU environment.

Although some causes of delirium are well established, others remain controversial based on the study population and methods of evaluating the data. One systematic review found a strong positive association between delirium and the following risk factors: age, dementia, hypertension, coma, Acute Physiology and Chronic Health Evaluation II (APACHE) score, emergency surgery, mechanical ventilation, polytrauma, and metabolic acidosis.⁴ In contrast, the guidelines published by the Society of Critical Care Medicine only found dementia, hypertension, coma, alcoholism, and the APACHE II score to increase the risk of delirium.⁵ A large prospective study of delirium found that only physical restraints increased the risk of delirium.⁶

There has also been some interest in developing a predictive model for delirium. One large study conducted in the Netherlands with different types of ICU patients resulted in the PREdiction of DELIRium in ICu patients (PRE-DELIRIC) model. PRE-DELIRIC had an area under the receiver operating characteristics curve of 0.87, suggesting good validation with CAM-ICU screening, a type of clinical test used to assess delirium. It included the following factors for analysis: age, APACHE II score, coma, type of ICU, infection, metabolic acidosis, morphine use, sedative use, urea concentration, and urgent admission. This model is a promising method for identifying patients who are at a high risk of delirium and could translate into preemptive therapies to prevent delirium occurrence.

As more research is done in this field, the risk factors will likely be better elucidated.

PATHOPHYSIOLOGY OF DELIRIUM

Numerous theories have been proposed to explain the underlying mechanisms of brain failure that result in delirium.

It is thought by many that a major etiology of integrative brain failure is a hemodynamic or metabolic decompensation elsewhere in the body. The ICU environment provides a repository of typical predisposing factors of a hemodynamic or metabolic nature, including acute or chronic organic brain vascular insufficiency, endocrine insufficiency, acute or chronic cardiopulmonary decompensations, multi-organ system insufficiency, relative hypoxia, poor tissue perfusion, multiple medications, and finally, a sleep/wake cycle disruption caused by immobilization, anxiety, and pain. Clinical signs of agitation are likely to be produced when there is an integrative brain failure plus an intense source of sensory stimuli.

Agitation is a visual clue that disintegration of normal motor axis integration is occurring, with a mischanneling of incoming sensory stimuli. Short circuits into phylogenetically old brain areas (e.g., basal ganglia, reticular formation, vestibular nuclei, and often the red nucleus [extrapyramidal system]) produce the clinical picture of uncoordinated and nonpurposeful movements.

Delirium is characterized by global disorders of cognition and wakefulness, as well as an impairment in psychomotor behavior. Major cognitive functions, such as perception, deductive reasoning, memory, attention, and orientation are all globally disordered. There is a growing consensus that delirium is a manifestation of cerebral insufficiency, both generalized and focal, accompanied by a dysregulation of neurotransmitter systems.

The cholinergic system has been strongly implicated in the development of delirium.⁷ Acetylcholine is an important neurotransmitter for consciousness and the level of arousal. Potential mechanisms for delirium include the reduced production of acetylcholine or decreased acetylcholine transmission. Production of acetylcholine is very sensitive to hypoglycemia, oxidative stresses, and substrate deficiencies. Elevated levels of serum anticholinergic activity are also associated with delirium.⁸ Cholinergic function decreases with age, which may explain why age is a predictive factor for delirium. In addition, anticholinergic medications are associated with an increased incidence of delirium.⁹

Higher than normal dopamine levels have also been correlated with the development of delirium. This may be due to either a reduced reuptake of dopamine or an increased release of this neurotransmitter. Hypoxia can also cause the excessive release of dopamine, and psychosis is known to correlate with elevated dopamine levels. The use of haloperidol for the treatment and prevention of delirium has been suggested in part due to its antagonism of the dopamine receptors.¹⁰ Medications that affect the D2 receptor increase the release of acetylcholine in the prefrontal cortex.¹¹ This interesting finding suggests an interaction between dopamine and acetylcholine levels in the development of delirium.

Inflammation may also be an important pathway. Several studies have found positive associations between inflammatory cytokines and the incidence of delirium.^{12,13} In times of physiologic stress, such as a postoperative state or sepsis, the blood-brain barrier can be compromised. As a result, these inflammatory cytokines can cross the blood-brain barrier and affect brain function. It has been noted that encephalopathy is very common in septic patients. In fact, up to 70% of bacteremic patients have been found to have neurologic derangements.¹⁴

Although a final common pathway for delirium has not yet been elucidated, it is clear that alterations in neurotransmitters, oxidative stress, and inflammation are all related to the development of delirium. As research in this area progresses, hopefully, we will have a better understanding of the pathophysiology of this disorder. This will allow for more selective prevention and treatment of delirium.

It may be that various types of delirium—that is, hyperactive (agitated), hypoactive, or mixed—may be due to different factors in the brain. Perhaps this is why a unifying theory of delirium has not yet been established.

CLINICAL PRESENTATIONS OF DELIRIUM

Disorganized thinking, reduced attentiveness, and rambling, irrelevant, or incoherent thought patterns normally characterize delirium. The delirious patient cannot integrate a coherent stream of thoughts and deduce meaningful information from them. Short-term memory is impaired due to a short attention span and perceptual misregistration of incoming stimuli. Memory retention is also defective. A majority of delirious patients will be amnesic following recovery or will preserve small, random “islands of memory.” Fluctuating levels of arousal over the day’s course is a central hallmark of delirium and a major diagnostic criterion. The manifestations of delirium associated with sleep/wake cycles (e.g., disorganized cognitive and attention pat-

terns) fluctuate in reverse day-night cycles. Poorly organized delusions and hallucinations, as well as the presence of lucid intervals, are virtually diagnostic of stress-induced delirium. This symptomatology effectively differentiates it from dementia, functional psychosis, and dissociative psychogenic states.

During the state of delirium, cognition loses its clarity and goal direction. The patients are unable to reason deductively or solve problems and cannot perceive reality, even with direction from an unaffected onlooker. Since delirious patients cannot re-fit the fragments of cognition, their perceptions are altered, leading to the development of delusions and hallucinations. These delusions tend to be individualized and paranoid (i.e., patients misinterpret the actions and events around them as life threatening and potentially harmful). Hallucinations are characteristically fleeting, changeable, and poorly organized. Patients exhibiting this stress-induced ICU delirium continually resist restraints and treatment modalities, sometimes to the point of exhaustion. Since this psychomotor agitation syndrome usually occurs during the night hours, it has been termed the *sundown syndrome* and is virtually diagnostic of stress-induced delirium.

Organic etiologies for altered mental status, especially sepsis, must be ruled out concurrently with screening for delirium. One of the most common causes of altered mental status in the ICU is sepsis. In fact, encephalopathy from sepsis occurs in 50%-70% of patients.

The gold standard for diagnosing delirium in a patient is not necessarily an evaluation of DSM-5 criteria by a psychiatrist. Psychiatric consults usually deal with psychosis in an outpatient or low-acuity inpatient setting. The experience of psychiatrists with ICU patients may be limited, especially if the patients are intubated or poorly responsive.

Screening for delirium in all patients is helpful for understanding its prevalence and evaluating responses to treatment. The two most validated screening tools for ICU populations are the confusion assessment method for the intensive care unit (CAM-ICU) and the intensive care delirium screening checklist (ICDSC).

The CAM-ICU scale begins with an assessment of the level of consciousness using the Richmond Agitation-Sedation Scale (RASS) or the Riker Sedation-Agitation Scale (SAS)¹⁵ (Box 51-1). Both the SAS and RASS have been validated for use with the CAM-ICU.¹⁶ To examine a patient using the CAM-ICU, the RASS must be greater than -4 or the Riker greater than 2 for the patient to participate in screening.¹⁷ There are then four components to be scored: (1) acute onset or fluctuating course; (2) inattention; (3) disorganized thinking; and (4) an altered level of consciousness. The patient must have the first and second of these features combined with one of the last two (Fig. 51-1). Ideally, this scale would be used more than once during a 24-hour period to screen for delirium both during the day and at night. In the original validation studies, the CAM-ICU had a specificity of 98%-100%, sensitivity of 93%-100%, and good interrater reliability.

BOX 51-1

Richmond Agitation-Sedation Scale (RASS) Versus Riker Sedation Agitation Scale (SAS)

| RASS SCORE | TERM | SAS SCORE | TERM |
|------------|-------------------|-----------|----------------------|
| +4 | Combative | 7 | Dangerous agitation |
| +3 | Very agitated | 6 | Very agitated |
| +2 | Agitated | 5 | Agitated |
| +1 | Restless | 4 | Calm and cooperative |
| 0 | Alert and calm | 3 | Sedated |
| -1 | Drowsy | 2 | Very sedated |
| -2 | Light sedation | 1 | Unable to arouse |
| -3 | Moderate sedation | | |
| -4 | Deep sedation | | |
| -5 | Unarousable | | |

These two scales can be used to assess level of consciousness in an ICU patient.

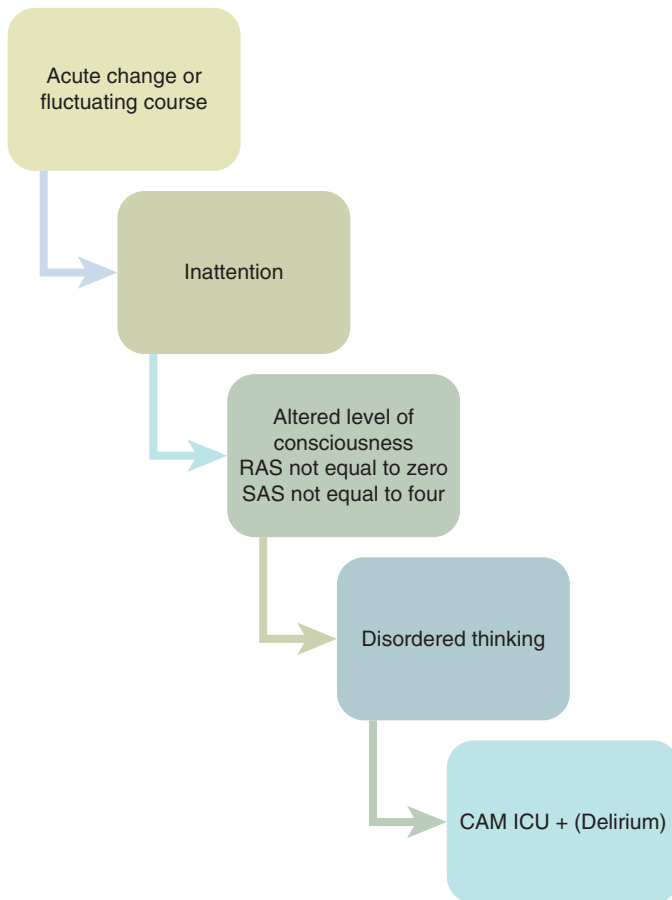


FIGURE 51-1 ■ Confusion Assessment Method for the intensive care unit (CAM-ICU). The CAM ICU screening test has multiple components that must be present to score positive for delirium. Each component has individual questions or assessments that must be positive in order to advance to the next category.

The other commonly used screening test for delirium is the ICDSC. This has eight components, which are evaluated over a 24-hour period (Box 51-2). These are derived from the DSM criteria for delirium. A score of 4 or more is consistent with a diagnosis of delirium. The original validation study demonstrated a specificity of 64% and sensitivity of 99%.¹⁸ One of the chief advantages of the ICDSC is that it evaluates patients over a 24-hour period.

Both the CAM-ICU and ICDSC are effective for the screening of delirium. A meta-analysis of studies involving these methods demonstrates a higher sensitivity and specificity for the CAM-ICU.¹⁹ Regardless of which scale is used, it is important to monitor patients for delirium throughout their ICU stay. Identifying delirious patients allows the clinician to understand the prevalence of delirium in a specific patient population and target appropriate therapeutic strategies.

■ COMORBIDITIES OF DELIRIUM

Factors that exacerbate stress in the ICU shorten the time necessary to produce delirium. These major factors contributing to the development of agitation in the ICU are pain, anxiety, and discomfort.

1. Pain: Most patients who find themselves in the ICU have had an operative or medical procedure that results in pain. The perception of pain exacerbates agitation by stimulating the sympathetic centers in the brain, resulting in catecholamine release. The hormonal

BOX 51-2 Intensive Care Delirium Screening Checklist

COMPONENTS

Altered level of consciousness
Inattention
Disorientation
Hallucination, delusion, or psychosis
Psychomotor agitation or retardation
Inappropriate speech or mood
Sleep/wake cycle disturbance
Symptom fluctuation

Scoring for the ICDSC is performed by the clinician during a 24-hour period of observation. The eight components are individually scored either zero or one. A total of four or greater is necessary to diagnose delirium.

response to pain results in sodium and water retention, due to the secretion of ADH and aldosterone, and hyperglycemia from increased cortisol and epinephrine secretions. In addition, pain also manifests by the easily recognizable triad of tachycardia, tachypnea, and systolic hypertension, all of which are amenable to ICU monitoring.

2. Anxiety: Many factors contribute to the experience of anxiety, including the fear of death or disability, misunderstanding of information provided by staff, discomfort, and the restricted ability to perform daily activities. These factors may also be associated with feelings of helplessness and loss of control. In the ICU environment, anxiety may be characterized by hyperactivity or withdrawal and may not necessarily precipitate a catecholamine response. Anxiety may rapidly progress to delirium, especially in elderly patients who have a decreased ability to cope with unusual stress.
3. Discomfort: Patients forced to lie still for long periods encumbered by indwelling hardware soon become profoundly uncomfortable and seek more comfortable positions. The need to move about and stretch can become an obsession, especially during sleepless nights, which decreases the patient's ability to cope. Sympathetic stimulation does not necessarily occur, but constant musculoskeletal activity may cause physical exhaustion.

DELIRIUM TREMENS AS A MODEL FOR SEVERE AGITATION

Beverages containing the short-acting central nervous system depressant ethanol are commonly imbibed throughout the world. The majority of those enjoying those drinks have a "stop order" switch in their brain that tells them when they have had enough. However, another population of drinkers has no such switch, or it is defective.

This population has the propensity to drink continuously, bathing their brain in a continuous flow of ethanol. This is remarkably separate from "alcoholics," whose addiction commonly presents as social problems rather than the amount of ethanol they imbibe. Alcoholics are the same whether they frequently drink, binge drink, or do not drink at all for long periods.

The brain function of an alcoholic becomes dependent on the depressive effects of ethanol, and the appropriate neuroreceptors are downregulated. Once dependence occurs, the effect extends to other chemical CNS depressants with similar actions to ethanol, particularly benzodiazepines and barbiturates. This is termed *cross-tolerance*. As one becomes dependent on ethanol, one also becomes dependent on other similar drugs.

Withdrawal from ethanol, manifested by the sudden cessation the drug, frequently as a result of trauma and resultant hospitalization, affects the downregulated neuroreceptors. Since ethanol is a short-acting drug, the receptors quickly and sometimes violently upregulate in an unregulated fashion, causing the typical scenario of agitated delirium.

The most aggressive and feared complication of ethanol withdrawal is delirium tremens (DT), a dangerous and potentially lethal syndrome of hyperactive musculoskeletal activity, hypertension, and tachycardia.

Symptoms of DT result from a compensatory increase in the activity of excitatory mechanisms, the neurotransmitters norepinephrine and dopamine, as well as the *N*-methyl-D-aspartate (NMDA) receptor, and diminished activity (downregulation) of the inhibitory receptors γ -aminobutyric acid (GABA)-A and α 2-adrenoceptors after prolonged depression of the CNS by ethanol. It has been hypothesized that physical withdrawal signs (e.g., tremor, hypertension, tachycardia, and autonomic hyperactivity) are determined by the degree of physical dependence developed during the most recent drinking period. In contrast, the psychotic signs (e.g., misperceptions, hallucinations, and seizures) result from accumulated CNS hyperactivity developed over many years of repeated alcohol intoxication and withdrawal.

Once it develops, DT is manifested by an unpredictable and volatile clinical course of agitation. Because of the phenomenon of cross-tolerance, conventional approaches utilizing sedatives (e.g., benzodiazepines and barbiturates) may require a high dosage regimen, which can precipitate hemodynamic and ventilatory depression well before the physiologic manifestations associated with delirium can be brought under control.

Ethanol withdrawal symptoms can be ameliorated with similar, but more predictable, longer acting cross-dependent CNS depressant drugs, restoring brain equanimity. Substituting cross-tolerant drugs to reset neurotransmitters does not proceed quite as effectively as the original drug (ethanol), usually requiring higher doses.

Frequently, hospital house staff choose first-generation benzodiazepines (e.g., chlorthalidoxepoxide and diazepam) for the treatment of ethanol withdrawal because of previous therapeutic recommendations. However, these drugs have been effectively superseded by second- and third-generation sedatives that are more titratable and have fewer long-acting intermediaries.

The first course of action should be the administration of a cross-tolerant sedative, in doses titrated to achieve control of the patient with a minimum of respiratory or hemodynamic side effects. As the severity of DT progresses, titratable medications are required to adjust the levels of sedation to the state of CNS excitation.

Lorazepam is an intermediate to a long-acting benzodiazepine with typical anxiolytic and sedative qualities. The drug has a mild amnesic effect as well. A dose of 4 mg of lorazepam is about equivalent to a dose of 10 mg of diazepam. Intermediary products do not accumulate, and metabolism does not require hepatic oxidation; it only requires glucuronidation, which makes it an attractive drug in liver insufficiency.

Midazolam is relatively water soluble compared with other benzodiazepines, increasing the rapidity of its action. The potency of midazolam is about three to four times that of diazepam, and it has a shorter elimination half-life of 1.5-3.5 h. Sedation following intravenous injection is achieved within 1-5 min, with a duration of less than 2 h.

Clonidine is an α -2 agonist that reduces the heart rate and hypertension, adding to a mild sedative effect. Typically, it is used as a third-line drug for DT because, while readily available in Europe, the IV formulation is not available in the United States.

Dexmedetomidine is an α -2 agonist similar to clonidine but with fewer side effects and is available in an intravenous formulation. Clinical evidence suggests that the use of intravenous dexmedetomidine may exert a beneficial sedative effect and minimal undesirable side effects in selected patients with hypertension and tachycardia as a result of severe agitation syndromes. Cardiac function and hemodynamics may improve as a result of the administration of this drug alone or in combination with attenuated doses of analgesics (e.g., morphine) or sedatives (e.g., midazolam).

There is a risk of bradycardia and/or hypotension during the administration of intravenous dexmedetomidine. However, this is a

small risk for the patients with DT as they are usually hypertensive and tachycardic when treatment commences.

Propofol is a rapid-acting, highly titratable sedative and anesthetic uniquely practical in the ICU environment because its rapid-acting and short-duration properties allow its use as a continuously titrated infusion for severe agitation in intubated patients. Propofol is indicated if the patient is out of control on high-dose benzodiazepines and if the respiratory and hemodynamic effects create hemodynamic and respiratory instability. The patient is intubated, and the treatment with propofol and short-acting beta-blockers is usually effective.

TREATMENT OF DELIRIUM

1. Treatment of stress-induced delirium: Somatosensory stress and confinement can alter delicate brain chemistry. These alterations translate into bizarre and frightening perceptions about one's environment, usually inducing paranoid ideation. From the patient's point of view, the logical course of action in such cases is to escape the perceived harm, but it is difficult to escape the encumbrances of an ICU bed. Therefore, patients exhibiting ICU psychosis continually resist restraints and treatment modalities, sometimes to the point of exhaustion. Appropriate treatment for this state is a neuroleptic medication (e.g., haloperidol), which antagonizes the D2 receptors. Haloperidol also suppresses spontaneous movements and complex behavior that result from disharmonious brain function, with a minimal CNS depressive effect. Haloperidol produces less sedation than phenothiazines, with very little effect on heart rate, blood pressure, and respiration. Despite the widespread clinical use of haloperidol, it has not been shown to reduce delirium length or severity. Atypical antipsychotics may be better at controlling delirium with fewer side effects, but this has not been well established.

Adverse hemodynamic effects are rare in healthy individuals with typical or atypical antipsychotics. Currently, the IV haloperidol dosage is not "approved" by the FDA, but the drug is commonly given by this mode and there has been a broad range of experience with it in the peer-reviewed medical literature. The dose and frequency of administration are dependent on the degree of agitation and, to a lesser extent, the patient's age.

2. Treatment of pain: There have been major advances in the understanding of pain physiology over the past decade. Earlier concepts of a dedicated, simple, spinothalamic pain system are no longer tenable. Much evidence now exists that very complex neural connections involving diverse areas of the nervous system play a part. Pain may be modulated or edited at the spinal cord level, in the periaqueductal gray matter, and brainstem raphe nuclei prior to reaching relays and gating mechanisms in the thalamus on the way to the cerebral cortex. Normally, agitation caused by pain is treated by analgesics or analgesic sedatives (e.g., morphine sulfate). This class of medications ultimately diminishes the stimulus to secrete epinephrine and norepinephrine and so decreases the end organ response to these catecholamines. Agitation syndromes resulting from pain usually resolve when the primary stimulus disappears. Humoral responses of patients in pain (e.g., hypertension and tachypnea) tend to counterbalance the side effects of narcotic analgesics (e.g., hypotension from histamine release and medullary ventilation center depression). The synthetic narcotic fentanyl provides good analgesia and sedation with reduced histamine-related side effects. The parenteral NSAID ketorolac provides pure analgesia with no sedation when the side effects of narcotics are unwelcome.
3. Treatment of anxiety and discomfort: Numerous authors recommend that anxiolytic medications be used routinely in the ICU. Benzodiazepines have been the mainstay of ICU anxiety treatment for many years because they offer a wide margin of safety from unwanted side effects. Their exact mode of action is unknown but appears to be within the limbic system via the neuroinhibitory transmitter gamma aminobutyric acid (GABA). In addition to their

sedative qualities, benzodiazepines have actions that promote anxiolysis, anterograde amnesia, hypnosis, and skeletal muscle relaxation. Patients confined to an ICU bed may not be experiencing much pain but are more likely uncomfortable and seeking a way to relieve muscle cramps and aches. Benzodiazepines are effective as CNS depressants that decrease the perception of discomfort and the resulting anxiety. Benzodiazepines with short half-lives (e.g., midazolam) are especially useful when an hour-to-hour titration is required for patients with unstable hemodynamics. Lorazepam is useful when a longer acting sedative is required for longer term sedation as it has minimal hemodynamic side effects. Lorazepam is also useful in a continuous infusion for long-term sedation. Dexmedetomidine or propofol can also be administered as continuous infusions to assist with anxiety.

Preferred Routes of Administration for Sedatives

The intramuscular absorption of drugs is influenced by the ratio of the ionized to unionized drug, site of injection, blood flow to the site region, and the amount of drug metabolized before entry into the systemic circulation, all of which are variably affected by critical illness. Intramuscular injection typically requires musculoskeletal activity and adequate tissue perfusion to enhance absorption into the systemic circulation. Since patients in the ICU usually lie still, they tend to absorb drugs from the muscles erratically. ICU patients also frequently suffer from decreased tissue perfusion because of varying degrees of heart failure and multiorgan insufficiency, which also decrease the reliability of muscular absorption.

In the ICU, medications are generally administered intravenously. The intravenous administration of sedatives offers the advantage of close titration, a very big plus in the treatment of unstable patients. Insertion of central venous access is usually indicated to ensure that the drug continues to have access to the central circulation as peripheral IVs may infiltrate with very little warning, particularly in the middle of the night. Intraarterial catheters are indicated for constant blood pressure monitoring and easy access for blood sampling.

Most rapidly acting drugs (e.g., midazolam) are highly water soluble and can only be titrated by intravenous administration. However, the effective titratability of these drugs likely decreases with time as the volume of distribution throughout the body water compartments increases. Organ insufficiency, particularly liver failure, also decreases the short-term titratability of most sedatives by prolonging the serum half-life.

Continuous infusions of analgesics and sedatives are a very effective method of avoiding the “valleys” inherent in bolus medication therapies that initiate a “peak” of therapeutic action followed by a variable period of “valley” in which the patient has little or no drug effect. The current literature suggests that high-risk cardiac patients are jeopardized by relatively brief periods of analgesia ineffectiveness.

Intermittent periods of sympathetic stimulation due to ineffective analgesia and sedation can cause relatively profound deleterious effects on the compromised myocardium. Continuous intravenous infusions of short-acting agents such as midazolam, propofol, and fentanyl allow for a titration of the plasma level effects to a fluctuating baseline of pain, anxiety, and discomfort. This real-time titration of natural fluctuations may occur with minimum hemodynamic and respiratory suppression.

Pitfalls in the Treatment of Delirium in the ICU

1. Treatment of stress-induced delirium with inappropriate medication: Treating psychotic delirium with analgesic sedatives is ineffective and deceiving. These patients are usually not in pain and do not necessarily manifest excess circulating catecholamines. Therefore, the analgesic effect of morphine is lost, and the predominating effect remains that of hemodynamic and ventilatory suppression. Therefore, psychosis remains in the face of compro-

mised hemodynamics and ventilation, requiring the addition of additional monitoring technology with the potential for increased stress and agitation.

The treatment of psychotic delirium with CNS depressants (e.g., benzodiazepines) confuses the border between psychosis and organic brain dysfunction. In addition, benzodiazepines have no ability to reorganize aberrant brain chemistry; therefore, psychotic patients treated with sedatives simultaneously become more obtunded and confused, further obfuscating the treatment plan.

2. Treatment of pain with inappropriate medication: Attempts to avoid morphine's hemodynamic side effects by using benzodiazepines as analgesics are usually ineffective. The hemodynamic effects of benzodiazepines are minimal compared to morphine, but they do not significantly attenuate the humoral responses to pain. In fact, benzodiazepines superimpose a cloud of CNS depression over pain stimuli, producing the appearance of comfort but no actual analgesia. The patient may appear more comfortable but still has hypermetabolic humoral responses that continue unabated, ultimately causing end organ damage or dysfunction.

Neuroleptics (e.g., haloperidol) promote no analgesic effect and a sedative effect only in large doses in which side effects predominate. Attempts to treat agitation resulting from pain by antipsychotic neuroleptics superimpose bizarre neurologic side effects on top of pain responses. The issue may be further confused by bizarre CNS symptoms additive to the normal humoral response of catecholamines. The patient may then feel “weird” but still in pain, and agitation may increase as the patient's attempts to make sense of a distorted world.

3. Treatment of anxiety and discomfort by inappropriate medication: Attempts to ameliorate discomfort with analgesic sedatives (e.g., morphine) are frequently effective, but these drugs produce hemodynamic side effects. Patients who are uncomfortable often have a little pain and thus few attendant humoral catecholamine effects. Therefore, the side effects of narcotics (e.g., hypotension and respiratory depression) predominate. Patients with a compromised cardiorespiratory status tolerate these side effects poorly and may not benefit from the analgesic effects, even in low doses. The patient may appear more comfortable but will ultimately require additional monitoring devices applied to proctor the hemodynamic side effects, increasing discomfort and agitation.

Patients who are uncomfortable are not necessarily psychotic. The sedative actions of haloperidol are attenuated except in high doses, which may exaggerate the CNS side effects. The patient may struggle more in an attempt to escape the frightening CNS side effects. Since sedation is achieved only with high doses, the extrapyramidal side effects may also be expressed.

It is currently recommended that narcotics be first titrated to any pain, and then afterward sedative medications can be used as needed. Sedative medications should be avoided if possible.²⁰

PREVENTION OF DELIRIUM

There has been great interest in preventing patients from developing delirium. Not only would this likely reduce patient morbidity, but primary prevention also may be able to reduce the health care costs for the treatment of delirium and its complications. There are two main approaches to prevention of delirium: nonmedication- and medication-related therapies.

Nonpharmacologic strategies for delirium can manifest in several forms. ICU clinicians should encourage patients to maintain a normal sleep/wake cycle. This includes minimizing the lights and noise during the nighttime hours. Frequent reorientation to the day and time is often helpful. The presence of family members at the bedside can be reassuring to the patient and assist in the reorientation to place and time. Eyeglasses and hearing aids should also be provided to patients if normally used at home. Despite a lack of good-quality evidence supporting these interventions, they are relatively easy to perform at no cost to the health care system.

More aggressive interventions to prevent delirium have also shown some promise in clinical trials. A prospective trial of a multifaceted program in patients greater than 70 years old was successful in reducing delirium rates (9.9 vs. 15.0%, $P = 0.02$).²¹ This intervention targeted six risk factors: cognitive impairment, immobility, disordered sleeping, dehydration, and visual and hearing impairments. The cost of such a program is significant with regard to personnel and time requirements. This limits the ability to scale such a set of interventions.

Early mobility may be a potential method to reduce the incidence of delirium. Mobilizing ICU patients early has many benefits, including reduced ICU and hospital length of stay, more ventilator-free days, and fewer sedation requirements.^{22,23} It has even been shown to reduce the use of physical restraints, which has been associated with increased delirium.²⁴ In addition to these positive outcomes, the delirium length was reduced as well.

Prophylactic medication therapy for delirium has been studied to a limited degree. The majority of the evidence is conflicting and does not exhibit a clear benefit to prophylaxis.²⁵ The Society of Critical Care Medicine published guidelines that do not currently recommend any medication to prevent delirium. Antipsychotic medications may have some benefit for postoperative patients, but it is not clear if this is universally true for ICU patients.²⁶ Furthermore, there are definite risks to antipsychotic medications, particularly QT prolongation and subsequent torsades de pointes that preclude their widespread use.

Dexmedetomidine, a highly selective alpha2-adrenergic receptor agonist, has been suggested as a possible medication that may reduce the risk of developing delirium.²⁷ However, it is not clear if the use of dexmedetomidine prevents delirium or is simply less likely to cause it compared to more commonly used sedative medications. Propofol and dexmedetomidine likely reduce the duration of mechanical ventilation compared with benzodiazepines and ICU length of stay, but this does not necessarily translate into a lower risk of delirium.²⁸

There has also been great interest in cholinesterase inhibitors for the prevention of delirium. This is based on the proposed mechanism of abnormally low levels of acetylcholine in delirium. This has not been well studied at this point, but there has not been any clear evidence to support the prophylactic use of cholinesterase inhibitors.²⁹

Certain medications may be associated with higher delirium rates. Opioids and benzodiazepines may increase the risk of delirium, but the data are extremely conflicting. Withdrawal from alcohol and benzodiazepines can be associated with delirium. In addition, glucocorticoids, anticholinergic medications, and histamine-2 receptor antagonists can cause delirium.⁹ From a practical standpoint, it is unlikely that the clinician will be able to completely avoid medications

that can induce delirium. However, it is important to have an appreciation that some medications may cause delirium in susceptible patients. In these cases, it would be best to avoid triggering medications if possible.

LONG-TERM OUTCOMES

Delirium is a disorder that extends beyond the ICU course. Moreover, it is a risk factor for an extended length of stay in the ICU, as well as the hospital and has been associated with increased mortality. Patients who are delirious often require additional attention from ICU staff to prevent them from hurting themselves or others. In addition, patients who experience delirium are often restrained and given additional sedative medication that may lead to intubation. These extra interventions and therapies have the potential to cause harm and increase medication side effects. Family members find delirium in their loved ones to be deeply disturbing. The sudden changes in personality and affect can be difficult to understand when families are already facing serious and often new medical diagnoses.

It is important to diagnose properly, prevent, and treat delirium in ICU patients to avoid unnecessary morbidity and mortality. This is a remarkably common disorder among all types of ICU patients. Those who work in an ICU should be aware of the dangers of delirium and actively seek to reduce its occurrence.

KEY POINTS

1. Delirium is a disorder characterized by fluctuating or acute changes in mental status, coupled with inattention and disorganized thinking.
2. Many patients experience delirium in the ICU. It can increase hospital/ICU length of stay and mortality.
3. Some strategies for preventing delirium include frequent reorientation, avoiding delirium-inducing medications, and mobilizing patients.
4. Delirium is difficult to treat. The clinician should focus on adequate pain control and antipsychotic medications if needed while avoiding oversedating patients.
5. Severe ethanol withdrawal can result in delirium tremens. This can be treated with sedative infusions.

■ References for this chapter can be found at expertconsult.com.

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Stroke is currently recognized as the fifth most common cause of death and the leading cause of permanent disability in the United States, affecting nearly 795,000 people annually.¹ Acute ischemic stroke is a true medical emergency and must be treated with a swift yet pragmatic approach. The rationale for acute ischemic stroke treatment is based on the concept of the *ischemic penumbra*. When arterial occlusion occurs, an area of irreversibly infarcted brain (i.e., core infarct) is surrounded by a region that has reduced blood flow that impairs function (i.e., ischemic penumbra), although not of sufficient severity to result in irreversible infarction. If adequate blood flow can be restored within a critical time frame, this area of at-risk tissue may be salvageable and return to normal function. The relationship between blood flow levels and duration for human stroke is still being elucidated, but based on laboratory studies, the more quickly restoration of blood flow occurs, the greater the probability that the salvageable tissue will be spared from permanent damage.^{2,3}

In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group showed for the first time an improvement in ischemic stroke outcome with acute treatment.⁴ At present, intravenous tissue plasminogen activator (t-PA) is the only treatment that has been approved by the Federal Drug Administration (FDA) for acute ischemic stroke patients presenting within 3 hours of symptom onset. Intraarterial therapy with stent retriever thrombectomy should be considered in patients presenting with acute ischemic stroke within 6 hours of symptom onset.⁵ Other treatments for acute ischemic stroke, such as neuroprotective agents and cell replacement therapy, continue to be investigated.

EMERGENT STROKE EVALUATION

For patients in the field who develop symptoms concerning for acute ischemic stroke, once emergency medical services (EMS) are activated, a rapid neurologic assessment is performed using one of several pre-hospital stroke scales. These quick screening tools allow uniformity in assessing stroke deficits that clarify communication of the patient's status to the receiving emergency department. It is helpful if pre-hospital personnel are able to firmly establish with family or bystanders who witnessed the patient's symptom onset the precise time at which the patient last appeared normal. Upon arrival, or more ideally, before arrival at the emergency department, a "brain attack code" or "stroke code" is disseminated to members of the stroke team.

A stroke team typically consists of individuals from multiple disciplines with specialized knowledge and interest in acute stroke care and often includes a vascular neurologist, nursing coordinator, and where available, a neuro-interventionalist. A neurologist performs a National Institutes of Health Stroke Scale (NIHSS) (Table 52-1) assessment as an additional rapid neurologic assessment tool to better localize and ascertain the degree of clinical deficit, as the score may affect which therapies are available to the patient. For patients developing focal neurologic symptoms while already hospitalized in an intensive care unit (ICU) or other hospital floor, the algorithm should be identical.

Ischemic strokes generally are classified as large artery atherosclerosis, small vessel occlusion, cardioembolism, stroke of other determined etiology, or stroke of undetermined etiology.⁶ In the first few minutes to hours after ischemic stroke, identification of stroke mechanisms may be difficult or impossible. Emergent diagnosis is greatly

enhanced by imaging modalities, including computed tomography (CT) and magnetic resonance imaging (MRI).

IMAGING OF ACUTE STROKE

Differentiating ischemic from hemorrhagic stroke is necessary before deciding on thrombolytic administration, and imaging obviously plays a key role in this regard. However, imaging may provide much more information. At most stroke centers, time from symptom onset (i.e., time when patient was last confirmed to be seen at normal baseline) is a major determining factor in whether a patient is a candidate for intravenous thrombolysis (up to 3 hours) or intraarterial therapy (up to 6 hours). An emerging concept is that physiology rather than time should be used to decide on treatment eligibility.⁷ For example, some patients within the 3-hour time window may already have established infarction that would not reverse with thrombolysis and may result in hemorrhage owing to reperfusion of infarcted brain. Conversely, some patients may have salvageable brain tissue despite presentation well after the 3-hour time window. A physiologic estimate of tissue viability would be preferable to a fixed time interval if a study were found that reliably predicted viability of brain after stroke. CT and MRI have the potential to provide this measurement.⁸

Computed Tomography

A noncontrast head CT is the initial imaging modality of choice for patients with suspected stroke. The foremost reason is that CT scans can be readily and quickly obtained because of the widespread availability of CT scanners; the second reason is the ability of CT to exclude intracranial hemorrhage. In addition to differentiating ischemic stroke from hemorrhage, CT may demonstrate subtle parenchymal abnormalities indicative of early edema or infarction. Previously, it was believed that these changes did not occur on CT for at least 6 hours after ischemic stroke. More recent studies indicate, however, that early changes of ischemia frequently occur within a few hours of stroke onset and have been seen as soon as 1 hour after stroke.⁹ These changes include reduced attenuation in the basal ganglia,² loss of gray-white differentiation, particularly in the insular region,¹⁰ low density in the cortex and subcortical white matter, and loss of sulcal markings suggesting early mass effect and edema (Fig. 52-1, A and B).¹¹

A hyperdense middle cerebral artery occurs in 20% to 37% of cases,¹² indicating acute thrombus within the artery. This condition rarely occurs without at least one other early CT abnormality. Hyperdensity in the basilar artery associated with thrombosis also has been reported.¹³ In 100 patients studied within 14 hours (mean 6.4 hours) of stroke onset, multiple early CT abnormalities correlated with the size of the subsequent infarct and poor outcome.¹² In the ECASS I trial of t-PA for acute stroke, early CT changes correlated with larger subsequent infarct volume and a greater likelihood of hemorrhagic conversion after t-PA.¹⁴ Quantitative assessment of CT changes using the Alberta Stroke Program Early CT Score (ASPECTS) scale in patients treated with intravenous t-PA also showed a relationship between early CT hypodensity (ASPECTS <8) and hemorrhage.^{15,16} Thus, some experts recommend withholding thrombolytic therapy in patients with extensive early CT changes, particularly in those later in the thrombolytic time window,¹⁷ although this practice is controversial.

TABLE 52-1 National Institutes of Health Stroke Scale

| | | |
|---|---|--|
| 1A. LEVEL OF CONSCIOUSNESS (LOC) 0 = Alert 1 = Not alert, but arousable 2 = Not alert, obtunded 3 = Coma | 1B. LOC QUESTIONS Ask the month and his/her age. 0 = Answers both correctly 1 = Answers one correctly 2 = Answers neither correctly | 1C. LOC COMMANDS Open and close the eyes. Open and close the non-paretic hand. 0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly |
| 2. BEST GAZE (HORIZONTAL) 0 = Normal 1 = Partial gaze palsy 2 = Forced deviation or total gaze paresis | 3. VISUAL FIELDS 0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia | 4. FACIAL PALSY 0 = Normal 1 = Minor paralysis 2 = Partial paralysis (total or near total paralysis of lower face) 3 = Complete paralysis of upper and lower face |
| 5. MOTOR ARM Right Arm extended with palms down 90 degrees (if sitting) or 45 degrees (if supine) for 10 seconds 0 = No drift 1 = Drift; limb drifts down from position and does not hit bed or support in 10 seconds 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement Left | 6. MOTOR LEG Right Leg extended at 30 degrees, always tested supine for 5 seconds 0 = No drift 1 = Drift; limb drifts down from position and does not hit bed or support in 5 seconds 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement Left | 7. LIMB ATAXIA The finger-nose-finger and heel-shin tests 0 = Absent 1 = Present in one limb 2 = Present in two limbs |
| 8. SENSORY To Pinprick or Noxious Stimuli 0 = Normal 1 = Mild to moderate sensory loss 2 = Severe to total sensory loss | 9. BEST LANGUAGE 0 = No aphasia, normal 1 = Mild-to-moderate aphasia 2 = Severe aphasia 3 = Mute, global aphasia, coma | 10. DYSPARTHRIA 0 = Normal 1 = Mild-to-moderate 2 = Severe (including mute/anarthric due to aphasia) Do not score if intubated. |
| 11. EXTINCTION AND INATTENTION 0 = No abnormality 1 = Present 2 = Profound (two modalities) | | TOTAL SCORE: |

For example, subsequent analysis of the NINDS rt-PA trial data revealed that early ischemic changes did not predict symptomatic hemorrhage or response to treatment,¹⁸ and more recent evidence reports no association between early ischemic CT changes and outcome.¹⁹

Computed Tomography Angiography

CT angiography (CTA) can be performed using spiral CT, allowing for imaging of the intracranial and extracranial circulation. Optimally, CTA of the neck should also include visualization of the aortic arch. The typical single bolus of iodine contrast material is about 70 cc. This injection limits the use of CTA in patients with renal failure or contrast hypersensitivity. In acute stroke, CTA of the head and neck is highly reliable for diagnosis of intracranial occlusions and correlates with other imaging modalities.^{20,21} Three-dimensional reconstruction images can also be created, providing additional views and information about the carotid bifurcation and carotid lesions, revealing eccentric lesions and ulceration (Fig. 52-1, C and D).

Computed Tomography Perfusion

In addition to imaging the brain parenchyma with a noncontrast head CT and the cerebral vasculature with CTA, CT perfusion (CTP) adds assessment of cerebral blood volume (CBV) and cerebral blood flow (CBF) (Fig. 52-2). In patients with acute stroke, CTP has been correlated with final infarct size and outcome, particularly after recanalization.²² CTP maps combining CBV and CBF identify brain tissue that progresses to infarction if not reperfused, consistent with ischemic penumbra.²³ Recent evidence suggests that the inclusion of CTP in a stroke imaging protocol increases diagnostic performance.^{22,24,25}

Whereas CTP serves as a qualitative measure of CBF, there have been investigations into using xenon CT to measure CBF quantita-

tively.²⁶ Stable xenon is an inert gas inhaled as a mixture of 27% xenon and 73% oxygen. During inhalation over a few minutes, rapid scanning is performed, and pixel-by-pixel blood flow values are calculated at different brain levels (Fig. 52-3). In a series of patients with middle cerebral artery (MCA) occlusion studied with xenon CT, areas of penumbra were present in all patients, and the percentage of MCA territory in the penumbral range (CBF 8-20 mL/100 g/min) remained relatively constant across the group. In contrast, the percentage of MCA territory with CBF values representing infarcted tissue (CBF < 8 mL/100 g/min) varied greatly. Outcome correlated highly with the area of infarcted MCA territory, not the amount of ischemic penumbra. Thus, after the first few hours, the size of the core infarcted tissue, not the amount of penumbral tissue, may be the most important imaging parameter to determine suitability for acute stroke therapy.²⁷

Magnetic Resonance Imaging

Compared to CT modalities, MRI is advantageous because it is more sensitive to cerebral infarction, especially in the brainstem and deep white matter. Typical sequences included in an MRI stroke protocol include diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) to evaluate for potential acute ischemia, multiplanar gradient-recalled (MPGR) or gradient-recalled echo (GRE) to evaluate for hemorrhage, and fluid-attenuated inversion recovery (FLAIR) to evaluate for important signs in both hyperacute and acute stages of stroke (i.e., assessment for absence of flow void in major cerebral arteries, suggesting occlusion or slow flow in that artery). Perfusion-weighted imaging (PWI) is often used to determine abnormal tissue perfusion based on transit times for contrast material through brain parenchyma (Fig. 52-4).

DWI shows parenchymal abnormalities earlier than conventional T2-weighted images in patients with acute stroke.²⁸ DWI detects the

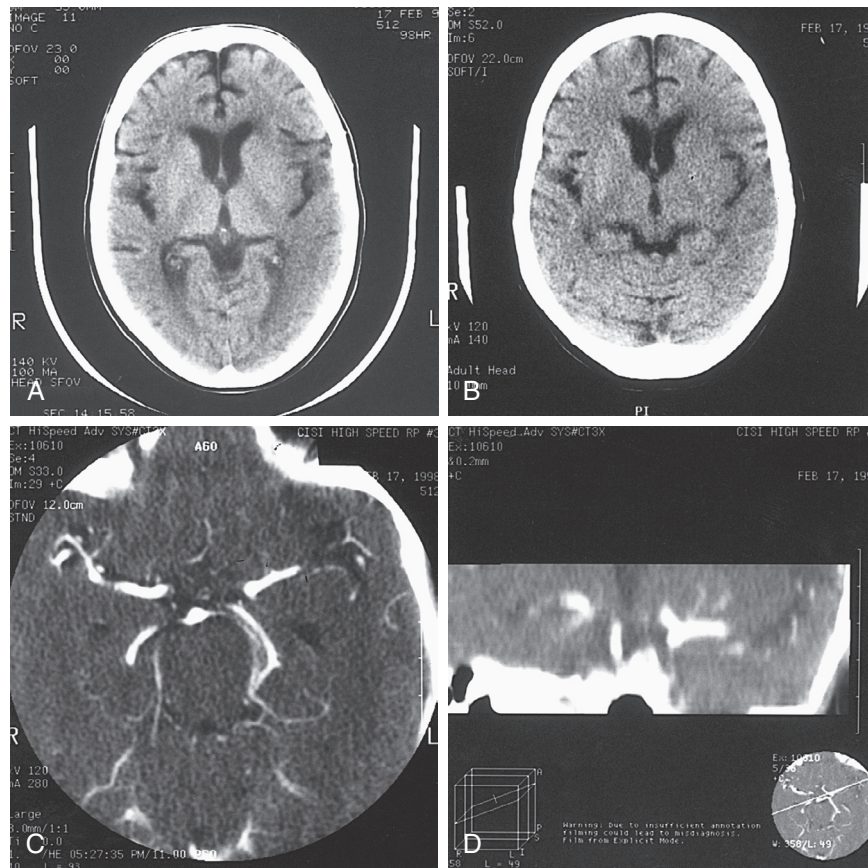


FIGURE 52-1 ■ **A**, Normal computed tomography (CT) scan of brain 2 hours after onset of aphasia and left hemiparesis. **B**, Repeat CT scan at 5 hours after stroke onset shows early CT changes, including basal ganglia hypodensity, loss of the insular ribbon, and slight effacement of the sulci on the left. **C**, CT angiogram at 5 hours after stroke onset shows complete occlusion of the left middle cerebral artery. **D**, Rapid reconstruction of the CT angiogram again shows occlusion of the left middle cerebral artery.

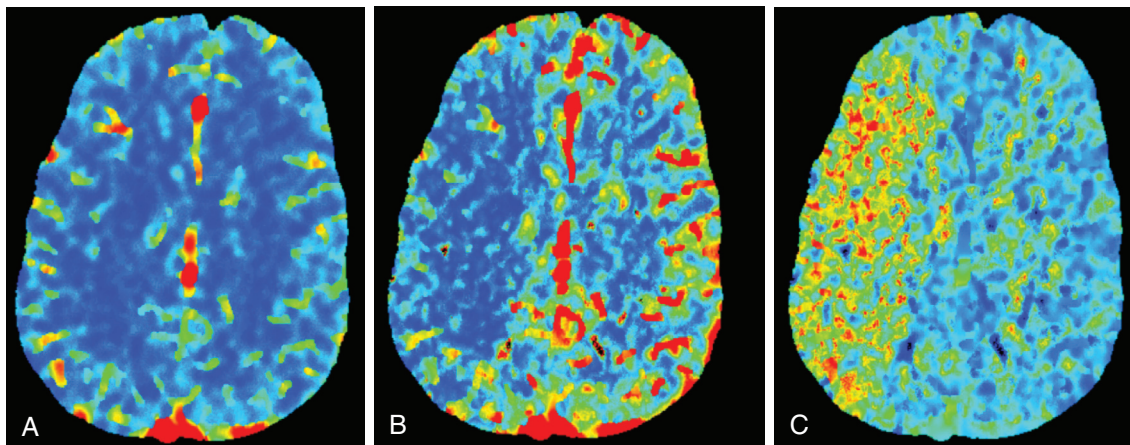


FIGURE 52-2 ■ Computed tomography brain perfusion scan with sequencing maps. **A**, Cerebral blood volume (CBV) showing no clear evidence of core infarct. **B**, Cerebral blood flow (CBF) showing a decrease in the right middle cerebral artery (MCA) territory. **C**, Mean transit time (MTT) showing delayed perfusion in the right MCA territory. These sequences together indicate a large ischemic penumbra in the right MCA territory.

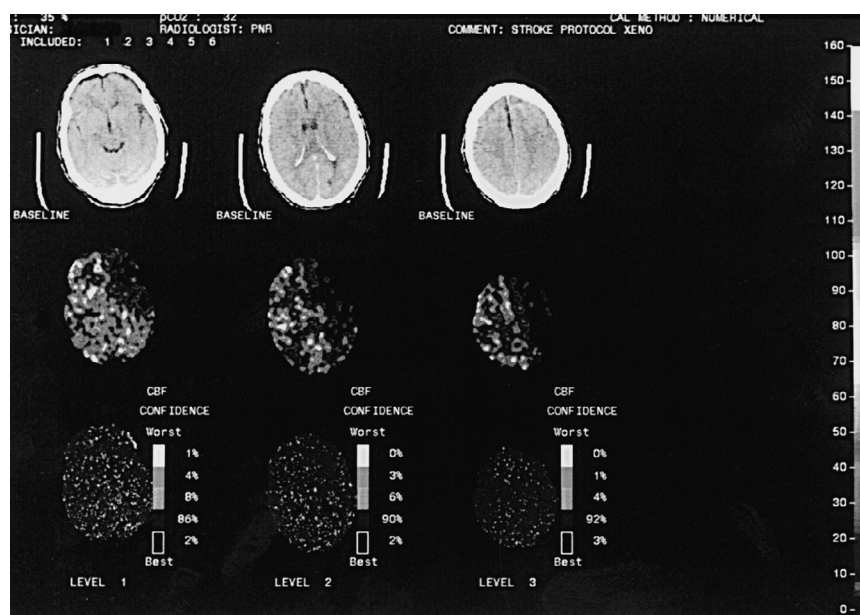


FIGURE 52-3 ■ Xenon computed tomography blood flow study from a patient with a large left hemisphere stroke 3 hours after onset of symptoms. Flow is nearly absent throughout the middle cerebral artery territory on the left.

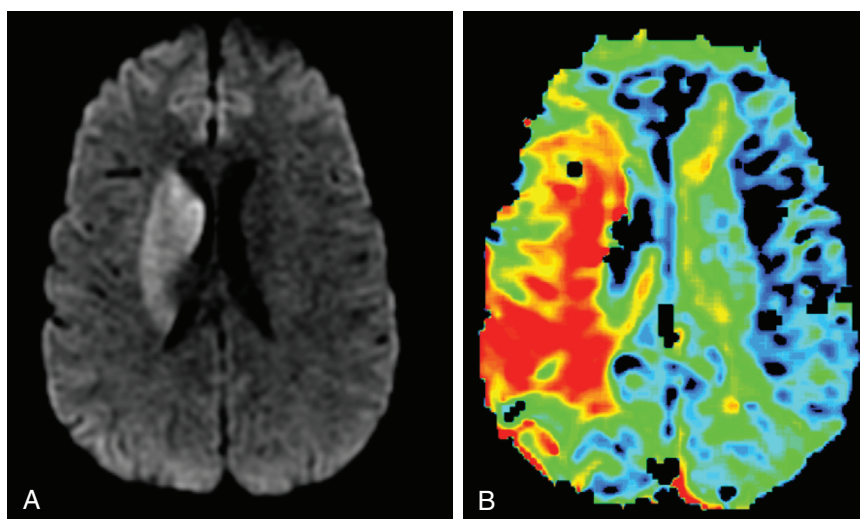


FIGURE 52-4 ■ Magnetic resonance imaging of the same patient in Fig. 52-2. **A**, Diffusion-weighted imaging (DWI) showing right basal ganglia stroke. **B**, Perfusion-weighted imaging (PWI) showing enhanced mean time to enhancement. These sequences together suggest a large ischemic penumbra in the right MCA territory.

diffusion of water in the brain and shows hyperintensity in areas of reduced diffusion (Fig. 52-4). As water moves from the extracellular to the intracellular space, there is less movement of water and loss of signal, resulting in hyperintensity.²⁹ Early detection of lesions by DWI helps differentiate cerebral ischemia from other conditions that mimic stroke, such as seizures or toxic-metabolic states. Additionally, combining DWI with PWI may identify reversibly ischemic tissue. If there is a large area of PWI abnormality indicating reduced CBF but limited established infarction as evidenced by DWI abnormality, penumbral tissue is likely present, indicating areas at risk of undergoing infarction.

In stroke patients, the size of the DWI lesion and the growth of these abnormal DWI regions are strong predictors of outcome. In acute stroke, a marker of tissue viability is needed, and some investigators

have suggested that the extent of mismatch between lesions on DWI and PWI could serve as this marker. The concept of DWI/PWI mismatch has been used as an inclusion criterion in several studies (DIAS, DIAS-2, among others) assessing thrombolytic agents and is being employed more frequently to select patients who may benefit from reperfusion therapy.³⁰⁻³⁷ Patients with mismatch might be more likely to respond to reperfusion therapy.³⁸ Patients with large areas of DWI abnormality or large severe PWI abnormalities may be at greater risk for hemorrhage if reperfusion therapy is pursued.³⁹

Magnetic Resonance Angiography

MRA of the head and neck offers a noninvasive method of imaging the intracranial and extracranial vasculature. MRA typically uses

gadolinium contrast in appropriate patients, but important information can be obtained based on time-of-flight techniques not utilizing contrast.^{40,41} Detection of dissection or occlusion in the circle of Willis and the extracranial vertebral and carotid arteries can be examined with MRA, but occlusions of small peripheral branch arteries may not be detected. Artifacts may also obscure proper identification of arterial pathology. Signal dropout may occur at the site of arterial stenosis owing to the effects of turbulent flow. If an artery is tortuous, it may extend out of the imaging section and appear occluded. MRI tends to overestimate the severity of stenosis, and evidence of severe stenosis should be confirmed with another modality. MRA is better for localizing the site of stenotic lesions than determining severity of stenosis. Similarly, differentiation between severe stenosis and occlusion is unreliable with MRI, and apparent occlusions by MRA should also be confirmed with angiography.

Digital Subtraction Angiography

Catheter-based digital subtraction angiography (DSA) remains the gold standard for determining the degree of vessel stenosis and understanding the collateral circulation. The high quality of anatomic delineation allows for precise determination of carotid stenosis as CTA, whereas MRA and carotid Dopplers can misclassify stenosis. Historically, the procedure has been associated with a high risk of complications, although more modern experience estimates a much lower risk of stroke (0.3%) at experienced centers.^{42,43} The technique requires specialized personnel and equipment and may not be readily available at centers.

TREATMENT OF ACUTE STROKE

Intravenous Thrombolysis

Acute stroke trials using intravenous thrombolytic agents date back to the early 1960s, with the use of streptokinase,⁴⁴ fibrinolytic,⁴⁵ and urokinase⁴⁶ showing either no benefit or a higher mortality in patients treated with thrombolysis. These studies preceded CT imaging and thus patients with hemorrhage were not excluded. The discouraging results hindered the development of more acute stroke trials until the 1980s, when several case reports showed favorable outcomes with intraarterial thrombolytic therapy within a few hours of stroke onset.^{47,48} These reports resulted in small randomized trials and feasibility studies of intravenous thrombolytics^{49,50} that ultimately gave rise to the pivotal NINDS rt-PA trial that showed a beneficial effect of thrombolytic therapy for acute stroke treatment when administered within 3 hours of symptom onset.⁴

Tissue Plasminogen Activator Within 3 Hours

The NINDS trial included more than 600 patients with acute ischemic stroke. All patients were treated within 3 hours, and half of the patients were treated within 90 minutes. Patients were randomly assigned to receive either intravenous t-PA at a dose of 0.9 mg/kg to a maximum of 90 mg or intravenous placebo. Primary outcome measures were favorable outcomes at 90 days measured by the NIHSS, Barthel Index, Glasgow Outcome Scale, and modified Rankin Scale (mRS). By all four measures, significantly more patients had a favorable outcome at 90 days in the t-PA group compared with placebo. Treatment with t-PA resulted in an 11% to 13% absolute increase in good outcomes and a minor, nonsignificant decrease in mortality at 3 months. The benefit was sustained at 12 months.⁵¹ Intracerebral hemorrhage with clinical deterioration occurred in 6.4% of patients treated with t-PA versus only 0.6% of placebo patients. Despite the increased hemorrhage rate, there was no significant increase in mortality or severe disability in the t-PA group versus placebo. All subtypes of strokes had more favorable outcomes with t-PA. There were no clear factors that predicted response to t-PA.⁵² Patients with large strokes as measured by NIHSS score >20 and evidence of early low density or edema on CT had a higher rate of hemorrhage after t-PA.⁵³

TABLE 52-2

Odds Ratios for Modified Rankin Score 0-1 in the Combined tPA Analysis

| TIME | N | ODDS RATIO | 95% CI |
|---------|------|------------|------------|
| 0-90 | 311 | 2.83 | 1.77, 4.53 |
| 91-180 | 618 | 1.53 | 1.11, 2.11 |
| 181-270 | 801 | 1.40 | 1.06, 1.85 |
| 271-360 | 1046 | 1.16 | 0.91, 1.49 |

CI, confidence interval; tPA, tissue plasminogen activator

Data from The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS and NINDS rt-PA stroke trials. *Lancet*. 2004;363(9411):768-774.

Based on these results, the FDA approved intravenous t-PA for treatment of stroke within 3 hours of onset in June 1996. This result was supported by the results of an analysis of patients treated within 3 hours of onset in the ATLANTIS trial.⁵⁴ A subsequent pooled analysis of NINDS rt-PA, ECASS, and ATLANTIS data showed that clinical benefit with t-PA is greatest when given early, especially if started within 90 minutes (Table 52-2).⁵⁵ Not all patients recanalize with intravenous t-PA. In a dose escalation trial of intravenous t-PA, angiography was performed before thrombolysis in all patients documenting the site of arterial occlusion and was repeated 2 hours later. Proximal occlusions in the MCA opened less frequently than distal branch occlusions, and only 8% of carotid occlusions recanalized.⁵⁶

Given the importance of early drug administration, much attention has been placed on improving systems of care to deliver the drug early and often. The use of telemedicine has played a great and expanding role in allowing patients presenting to stroke-ready hospitals without in-house vascular neurology expertise to receive remote clinical examination and imaging review via video streaming. Within our stroke network at the University of Pittsburgh, the implementation of telemedicine at 12 neighboring hospitals increased the use of IV thrombolysis from 2.8% to 6.8%, with a lower incidence of symptomatic hemorrhage. Similar experiences have been reported across the country. Emphasis has also been placed on minimizing additional tests (i.e., coagulation profile or platelet count) in selected patients and prioritizing imaging and early stroke team activation. Campaigns to improve times have driven door-to-needle times down to 22 minutes at some centers.

Tissue Plasminogen Activator Beyond 3 Hours

Several subsequent t-PA trials attempted to extend the window for treatment beyond 3 hours. The ECASS I and II trials and the ATLANTIS trial treated patients with intravenous t-PA up to 6 hours after stroke onset but failed to show benefit versus placebo.⁵⁷⁻⁵⁹ Pooled analysis of NINDS rt-PA, ECASS, and ATLANTIS data suggested a potential benefit beyond 3 hours. The ECASS III trial recently revealed that intravenous alteplase administered between 3 and 4.5 hours after symptom onset significantly improved clinical outcomes in patients with acute ischemic stroke, thereby potentially extending the therapeutic window in which patients may receive intravenous t-PA. In addition to standard intravenous t-PA exclusion criteria (Table 52-3), ECASS III exclusion criteria include the combination of previous stroke and diabetes, an NIHSS score >25, oral anticoagulant treatment, or age >80 years.⁶⁰ Whether patients in this time window with these exclusions also benefit from intravenous t-PA is unknown.

IST-3 is a clinical trial that randomized 3035 patients with ischemic stroke within 6 hours of symptom onset to intravenous alteplase (0.9 mg/kg; n = 1515) plus standard care or standard care alone (control; n = 1520). While the primary end point of good outcome was no different between groups, the study did show improved outcomes in patients presenting within early time windows and enrolled a high

TABLE 52-3

ASPECTS Measurement Tool for Early Changes on Computed Tomography

10 REGIONS OF INTEREST*

| AT THE LEVEL OF THE BASAL GANGLIA AND THALAMUS | AT THE LEVEL JUST ROSTRAL TO DEEP NUCLEI |
|--|--|
| Anterior middle cerebral artery (MCA) cortex | Superior to anterior MCA cortex |
| MCA cortex lateral to insula | Superior to MCA cortex lateral to insula |
| Posterior MCA cortex | Superior to posterior MCA cortex |
| Caudate | |
| Lentiform nucleus | |
| Internal capsule | |
| Insular ribbon | |

*One point is subtracted for each defined area of early ischemic change, such as focal swelling or parenchymal hypoattenuation. Score varies from 0 to 10.

Adapted from Pexman JH, Barber PA, Hill MD, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. *AJNR Am J Neuroradiol*. 2001;22(8):1534-1542.

percentage of elderly patients (age > 80), thus establishing the efficacy of intravenous tissue plasminogen activator (IV tpa) in this population. Several ongoing trials are investigating a role for IV tpa in patients presenting at late time windows with favorable imaging profiles (i.e., small core and large penumbra or DWI/FLAIR mismatch).

Mild and Rapidly Improving Symptoms

While the original NINDS study considered mild or rapidly improving symptoms as a relative contraindication for IV thrombolysis, subsequent retrospective analysis of this population has revealed poor outcomes, with up to 30% to 40% of patients requiring inpatient rehabilitation at discharge and a subset suffering further neurologic decline. While the natural history in this population may not be as benign as previously perceived, the benefit of IV thrombolysis remains to be proven. A review of patients within the SPOTRIAS database revealed practice variation across centers with a range of 2.7% to 18% of mild stroke patients receiving IV tpa. Furthermore, the proportion of patients with mild NIHSS increased from 4.8% in 2005 to 10.7% in 2009 ($P = 0.001$). This degree of practice variation highlights the uncertainty in this population and has prompted the initiation of a randomized clinical trial to investigate the role of IV alteplase in mild or rapidly improving symptoms (PRISMS trial).

Other Thrombolytic Options

Desmoteplase is a recombinant form of vampire bat saliva that is more potent than t-PA. Desmoteplase possesses high fibrin selectivity, allowing it to dissolve a clot locally with less effect on the blood coagulation system. This feature may potentially reduce the risk of intracranial and systemic bleeding versus less fibrin-specific plasminogen activators like t-PA. Desmoteplase was investigated in multiple trials to determine whether it could extend the treatment window for intravenous thrombolysis up to 9 hours.^{31,33} Unfortunately, no benefit was realized between 3 and 9 hours after stroke symptom onset.³² Tenecteplase is a modified form of human t-PA designed to achieve more effective thrombolysis. The half-life of tenecteplase is longer, allowing administration as a single bolus. Similar to desmoteplase, tenecteplase has greater fibrin specificity and less fibrinogen depletion than t-PA.⁶¹ A phase IIb study randomly assigned 75 patients to receive alteplase (0.9 mg per kilogram of body weight) or tenecteplase (0.1 mg per kilogram or 0.25 mg per kilogram) less than 6 hours after the onset of ischemic stroke. The two tenecteplase groups had greater reperfusion ($P = 0.004$) and clinical improvement ($P < 0.001$) at 24 hours than the alteplase group, with no differences in intracranial bleeding or serious adverse events. The

higher dose of tenecteplase (0.25 mg per kilogram) was superior to the lower dose and to alteplase for all efficacy outcomes, including absence of serious disability at 90 days. Reteplase is another recombinant form of human t-PA shown to be effective in the treatment of acute myocardial infarction.⁶² Reteplase also possesses a longer half-life than t-PA, and a small case series found that in patients treated 9 hours after stroke onset with intraarterial reteplase, 88% completely recanalized and 44% achieved clinical improvement at 24 hours.⁶³ Intraarterial reteplase has also been studied with intravenous abciximab, a glycoprotein IIb/IIIa inhibitor, in a phase I study administering the combination therapy to stroke patients presenting between 3 and 6 hours.⁶⁴ Abciximab may direct its effect through powerful antiplatelet effects or by direct thrombolysis.

Abciximab monotherapy as emergent stroke treatment has also been evaluated in a phase 2 trial, with improved outcome at 3 months in patients with mild to moderate strokes.⁶⁵ A phase 3 trial was then initiated but stopped prematurely due to an unfavorable benefit-risk profile.⁶⁶ The Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke-Enhanced Regimen (CLEAR-ER) trial showed safety of concomitant administration of r-tPA with another glycoprotein IIb/IIIa inhibitor, eptifibatide. A phase III trial is under way to compare this approach to rt-PA alone (CLEAR STROKE trial). The recently completed ARTIS trial compared alteplase to 300 mg intravenous aspirin within 90 min after start of alteplase treatment or to no additional treatment. This study was prematurely terminated at 642 patients because of an excess of symptomatic intracranial hemorrhage and no evidence of benefit in the aspirin group.

Intraarterial Therapy

Intraarterial Thrombolysis

An alternative approach to intravenous thrombolysis is direct delivery of thrombolytic agents by a microcatheter embedded in the clot (Fig. 52-5). The advantage of the intraarterial approach is direct visualization of the occluded artery and knowledge of the recanalization status as thrombolysis proceeds. Theoretically, delivery of the thrombolytic agent to the site of the clot should be more effective than intravenous infusion. The disadvantage is the additional time needed to bring the patient to the angiography suite, prepare the groin, catheterize the femoral artery, and guide the catheter from the femoral artery to the intracranial circulation before the thrombolytic agent can be administered.

Urokinase was used in early studies of intraarterial thrombolysis but is no longer available.⁶⁷ Recombinant prourokinase was evaluated formally in clinical trials,⁶⁸⁻⁷⁰ and the PROACT II study was the first acute stroke trial to show a significant improvement in outcome when administered within 6 hours of stroke symptom onset. The median time to treatment was 5.5 hours, and most patients were treated after 5 hours.⁶⁹ The clinical benefit was apparent despite this late time to treatment; a greater benefit may have been found had patients been treated earlier or mechanical manipulation also been allowed. Symptomatic hemorrhage occurred in 10% of patients treated with recombinant prourokinase and in 2% of controls. Although the hemorrhage rate was higher than previous intravenous thrombolytic studies, the median NIHSS score of 17 indicates that the patients in the PROACT II study had more severe strokes treated at a later time interval. A higher hemorrhage rate would be expected in these scenarios. There was also no differential effect of recombinant prourokinase across risk strata, indicating that all patients, regardless of risk, benefit equally from recombinant prourokinase.⁷⁰ Nevertheless, prourokinase has not been FDA approved to date, and t-PA tends to be more often used in cases of intraarterial thrombolysis. The exact dose, efficacy, and safety profile of intraarterial t-PA is limited, but recent studies have suggested doses up to 40 mg are reasonably safe for use.⁷¹

First-Generation Mechanical Devices

Although most thrombolytic studies concentrate on time to treatment, the most important factor for clinical outcome is probably time to

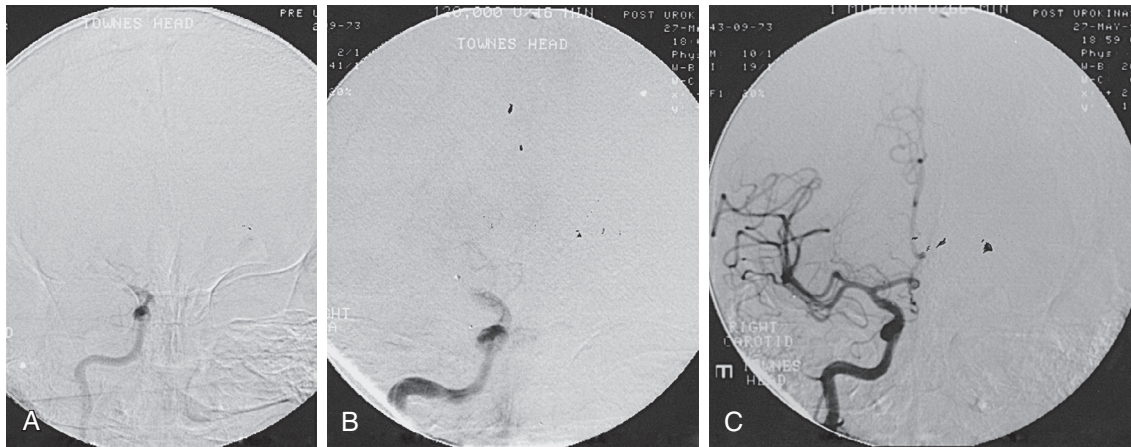


FIGURE 52-5 ■ **A**, Right carotid angiogram from a patient with embolic occlusion of the right middle cerebral artery (MCA) 4 hours after onset of symptoms. **B**, Angiogram from the same patient after placement of a microcatheter into the MCA clot and infusion of 120,000 U of urokinase. There is no recanalization. **C**, Angiogram after infusion of 1 million U of urokinase directly into the clot, showing complete recanalization of the MCA.

recanalization of an occluded vessel. When infusion of thrombolytic agents often requires 1 to 2 hours for complete thrombus dissolution, time to recanalization can be quite long. Mechanical devices offer the possibility of considerably shortening time to recanalization. Devices may be able to clear thrombi from large arteries within a few minutes. The use of thrombolytic agents may not be necessary, possibly reducing the rate of intracranial hemorrhage.

The revolutionary Merci Retriever clot retrieval device (Concentric Medical Inc., Mountain View, CA, USA) received FDA approval for the removal of blood clots from the brain in patients experiencing ischemic stroke after it was shown to be effective in restoring vascular patency in patients within 8 hours of symptom onset and could serve as an alternative therapy for patients who are otherwise ineligible for thrombolytic drug administration.⁷² The Merci device is a flexible nickel titanium (i.e., nitinol) wire that assumes a helical shape once it is passed through the tip of the guidance catheter. In practice, the catheter/wire is passed distal to the thrombus, the catheter is removed, and a helical configuration is assumed by the wire. The clot is then trapped in the helix and withdrawn from the vasculature. Second-generation Merci devices (e.g., L5 Retriever) have been developed and their use shown to be associated with higher rates of recanalization, although these differences did not achieve statistical significance. They also produced lower mortality and a higher proportion of good clinical outcomes.⁷³ Mechanical embolectomy using an aspiration platform was the basis for the creation of the Penumbra System (Penumbra Inc., Alameda, CA, USA), which uses a microcatheter and separator-based debulking approach that allows for continuous aspiration of thrombus. A recent trial found that the Penumbra System resulted in safe and effective revascularization in patients who present with large vessel occlusive disease within 8 hours of stroke onset, as 81.6% of patients achieved a Thrombolysis In Myocardial Infarction (TIMI) grade of 2 or 3.⁷⁴

First-Generation Randomized Trials of Intraarterial Therapy

Three clinical trials investigated the role of intraarterial therapy as an alternative or adjunctive treatment to standard medical therapy. The SYNTHESIS trial compared IV thrombolysis alone to intraarterial therapy alone and showed comparable outcomes in both cohorts despite an hour delay in initiating IA therapy.⁷⁵ While the trial did not observe improved outcomes in the IA therapy group, it did not require documentation of a large vessel occlusion before initiation of treatment; 92 patients were treated with IA therapy outside the context of

the trial, further diluting the study population of patients likely to benefit from IA therapy. The MR RESCUE trial implemented a penumbra imaging-based paradigm in which patients were randomized to medical versus intraarterial therapy.⁷⁶ There was no difference between groups. Finally, IMS 3 compared the additional benefit of mechanical thrombectomy in patients receiving IV tpa.⁷⁷ Once again, IA therapy proved to be safe but no more efficacious than medical therapy. However, it is likely that a high percentage of patients had little or no chance of benefit.⁷⁸ Time to treatment was prolonged, as the mean IV tpa start to groin puncture time was 81 ± 27 minutes and the mean groin to IA start time was 41 ± 21 minutes, with a greater than 2-hour delay between CT head and groin puncture.⁷⁹

Stent Retrievers and Recent Trials

These three first-generation trials highlighted an important concept in revascularization—namely, that treatment likely favors patients with a large clinical deficit in the setting of a small core on presentation who undergo early and effective recanalization. In 2012, the FDA approved two new devices for the indication of thrombus removal in acute stroke, SOLITAIRE and TREVO. Both devices are in the stent retriever class of mechanism and consist of intracranial stents that can be delivered across thrombus with the dual benefit of achieving a temporary endovascular bypass and trapping the clot within the struts of the stent. The stent retriever is subsequently recovered along with the thrombus. In comparison to the MERCI device, stent retrievers yield higher rates of high-quality recanalization (86%–89% vs. 60%–66%).^{80,81} Several randomized clinical trials have now tested the hypothesis that IA therapy may be superior to medical management if revascularization is achieved implementing this new technology.^{82–86} The first trial to be completed was MR CLEAN, which demonstrated an adjusted common odds ratio of 1.67 in favor of intervention and an absolute difference of 13.5% in the rate of functional independence. These results prompted several ongoing trials to review their outcomes, and a similar benefit was seen across studies (see Tables 52-4 to 52-6).

Most of these trials focused on patients presenting within early time windows and the role of IA therapy at later time windows remains uncertain. Many practitioners favor revascularization for late time windows in basilar artery occlusive disease, given the high rate of mortality in this stroke subtype.⁸⁷ The role of IA therapy versus medical therapy in anterior circulation strokes presenting between 6 and 24 hours is currently being investigated.⁸⁸

TABLE 52-4 Summary of Trial Design in Mechanical Thrombectomy Trials

| | AGE | TIME | IV tPA | NIHSS | LVO | IMAGING CRITERIA |
|------------------------------|-------|--------|--------|-------|--------------------|---|
| MR CLEAN (n = 500) | ≥18 | 6 hrs | ~90% | >2 | ICA M1, M2, ACA A2 | "Grey area principle" |
| EXTEND-IA (n = 70) | ≥18 | 6 hrs | 100% | None | ICA M1, M2 | RAPID Imaging: Core <70 cc Penumbra >10 cc Mismatch Ratio >1.2 |
| SWIFT PRIME (n = 196) | 18-80 | 6 hrs | 100% | >7 | ICA M1 | ASPECT >6 RAPID IMAGING encouraged (81%) |
| ESCAPE (n = 314) | ≥18 | 12 hrs | ~75% | >5 | ICA M1 | ASPECT >5 Moderate or good collateral circulation |
| REVASCAT (n = 206) | 18-85 | 8 hrs | ~70% | >5 | ICA M1 | ASPECT >6 DWI ASPECT .5 |

TABLE 52-5 Summary of Patient Population in Mechanical Thrombectomy Trials

| | AGE (YRS) | TIME (MIN) | NIHSS | LVO | BASELINE IMAGING |
|------------------------------|-----------------|-------------------|---------------|-----------------------------|--|
| MR CLEAN (n = 500) | 65.8 (55-76) | 260* (210-313) | 17 (14-21) | ICA 25% M1 66% M2 8% | ASPECTS: 9 (7-10) |
| EXTEND-IA (n = 70) | 68.6 ± 12 | 248 (204-277) | 17 (13-20) | ICA 31% M1 57% M2 11% | Core: 12.3cc (4-32) Penumbra: 106cc (76-137) |
| REVASCAT (n = 206) | 65.7 ± 11 | 355 (269-430) | 17 (14-20) | ICA 26% M1 64% M2 10% | ASPECTS: 7 (6-9) |
| ESCAPE (n = 314) | 71 (60-81) | 341 (176-359) | 16 (13-20) | ICA 28% M1 68% M2 4% | ASPECTS: 9 (8-10) Collaterals: 94% moderate to good |
| SWIFT PRIME (n = 196) | 66.3 ± 11 | 252 (190-300) | 17 (13=19) | ICA 16% M1 77% M2 6% | ASPECTS: 9 (8-10) |

TABLE 52-6 Summary of Outcomes in Mechanical Thrombectomy Trials

| TRIAL | PTS | % REPERFUSION IAT/MEDICAL | mRS 0-2 IAT/MEDICAL | sICH IAT/MEDICAL | MORTALITY IAT/MEDICAL |
|--------------------|-----|------------------------------------|----------------------------|------------------|-----------------------|
| ESCAPE | 238 | 72.4% tICI 2b/3 32.2% mAOL 2-3 | 53%/29.3% 53%/29.3% | 3.6% 2.7% | 10.4% 19% |
| EXTEND-IA | 70 | 89% mTICI 2b/3 34% mAOL 2-3 | 71%/40% 71%/40% | 0% 6% | 9% 20% |
| MR CLEAN | 500 | 58.7% mTICI 2b/3 57.5 mAOL 2-3 | 32.6%/19.1% 32.6%/19.1% | 7.7% 6.4% | 21% 22% |
| REVASCAT | 206 | 65.7% mTICI 2b/3 NA | 43.7%/28.2% 43.7%/28.2% | 1.9% 1.9% | 18.4% 115.5% |
| SWIFT-PRIME | 196 | 82.8% mTICI 2b/3 40.4% mAOL 2-3 | 60.2%/35.5% 60.2%/35.5% | 1.0% 3.1% | 9.2% 12.4% |

Surgical Options

Cerebral edema and herniation are frequent causes of death from stroke in the first few days after massive infarction. Edema gradually increases and peaks 2 to 3 days after stroke onset. Steroids do not effectively reduce edema due to stroke, and antiedema measures such as mannitol or hyperventilation are of limited benefit. Control of intracranial pressure (ICP) is associated with improved outcome, but whether ICP monitoring is helpful to guide therapy remains unclear. Surgical decompression of large hemispheric infarcts causing edema and increased ICP is logical because the edema is usually self-limited.

If herniation can be avoided, recovery may occur similar to stroke without severe edema. Several different approaches to decompression have been proposed.

Hemicraniectomy is the first and most commonly performed procedure. It involves removal of a generous bone flap ipsilateral to the side of the infarction. Often, a durotomy is performed to allow outward herniation of the brain to decrease ICP and prevent downward herniation. For large MCA infarctions, timing of surgery, side of lesion, presence of signs of herniation prior to surgery, and involvement of other vascular territories do not significantly affect outcome.⁸⁹ This

analysis was obtained from uncontrolled, retrospective data; thus, no meta-analysis could be completed.

The optimal timing of hemicraniectomy in patients with malignant MCA infarction is unclear. If herniation is in progress, irreversible brainstem damage may occur, thereby limiting the benefit of the operation. More recent evidence suggests that surgical intervention should occur early regardless of whether signs of herniation are present. Three concurrent European trials (i.e., DECIMAL, DESTINY, HAMLET) including patients undergoing hemicraniectomy for malignant MCA infarction were combined in a pooled analysis.⁹⁰⁻⁹² In this analysis, thresholds were established for 45 hours to randomization and 48 hours to surgery from stroke onset. The combined results showed that decompressive surgery undertaken within 48 hours of stroke onset decreased mortality and increased the number of patients with a favorable functional outcome.⁹³

Surgical decompression for hemispheric infarction should be considered for younger patients with a greater potential for recovery from massive stroke. The role of surgical decompression of extensive MCA stroke in patients greater than 60 years of age remains controversial. A comparison of medical management versus early decompression in patients greater than 60 years of age in the DESTINY 2 trial did show improved survival in the surgical group, although a majority of the survivors required assistance for most daily activities. Cerebellar infarction is a special case that requires urgent surgical intervention.⁹⁴ Compression of the brainstem and fourth ventricle leading to hydrocephalus or severe pontomedullary compromise can be reversed by rapid surgical decompression of the infarcted cerebellum.

Other Medical Therapies

Anticoagulation

The use of anticoagulants in acute stroke is controversial, although several randomized clinical trials provide information regarding its efficacy. Retrospective data previously suggested a significant incidence of early recurrences after ischemic stroke, with reported rates of 20%. These studies also suggested that anticoagulation with heparin reduced recurrences. Hemorrhagic complications were acceptably low, particularly when patients with large strokes and uncontrolled hypertension were excluded from treatment. The results of recent randomized clinical trials have challenged these findings and call into question the value of anticoagulation for treatment of acute stroke.⁹⁵ However, more recent studies indicate that for cardioembolic stroke, warfarin can be safely started shortly after stroke without bridging therapy with heparin or enoxaparin.⁹⁶

The studies do not support a reduced recurrence rate or improved outcome with anticoagulation when given within 24 to 48 hours of stroke onset. Hemorrhage rates ranged from 1% to 2.5%. The results suggest that there is little value in anticoagulation for all patients with acute stroke, but it remains possible that some subgroups benefit. The TOAST study suggested that patients with large vessel disease may achieve better functional outcome with anticoagulation.⁹⁷ The relatively high hemorrhage rate in some studies also may have obscured some benefit. In the International Stroke Trial (IST), a significant reduction in recurrent strokes from 3.8% in the control group to 2.9% in patients treated with subcutaneous heparin ($P < 0.01$) was offset by an increase in hemorrhagic stroke from 0.4% in controls to 1.2% in patients receiving heparin ($P < 0.00001$).⁹⁸ Even in patients with atrial fibrillation, the value of early anticoagulation is uncertain, with some studies showing benefit and others showing lack of benefit in reducing recurrent stroke.⁹⁵ If anticoagulation is started, it should only be given more than 24 hours after intravenous thrombolysis and after imaging confirmation that no hemorrhagic transformation has occurred. The roles of newer anticoagulant drugs such as rivaroxaban, apixaban, and dabigatran in the acute stroke setting remain unclear, although, similar to warfarin, acute administration of these medications is likely safe if the stroke burden is small. These medications have the added benefit of not requiring bridging therapy, as therapeutic dosage is reached early after administration.

Antiplatelet Therapy

There is less uncertainty about the benefit of aspirin in acute stroke. Two large, randomized controlled trials, CAST⁹⁹ and IST,⁹⁸ showed a small but significant improvement in outcome in patients treated with aspirin. In IST, patients received 300 mg of aspirin daily for 14 days. There was a significant reduction in stroke recurrence within 14 days in the aspirin group (2.8%) versus nonaspirin groups (3.9%) and a significant decrease in the risk of death or nonfatal recurrent stroke in the aspirin group (11.3%) versus nonaspirin group (12.4%). In CAST, 160 mg of aspirin was given per day for 4 weeks or until hospital discharge. In the aspirin group, there was a significant reduction in death within 4 weeks (3.3%) versus placebo (3.9%) and a significant reduction in death or nonfatal stroke during hospitalization. There also was a significant reduction in recurrent ischemic strokes in the aspirin group (1.6%) versus placebo (2.1%), which was offset only by a trend of excess hemorrhagic strokes (aspirin 1.1% versus placebo 0.9%).

CAST and IST were designed to be considered together and include more than 40,000 patients. Combining the results of both studies shows a significant reduction in recurrent stroke of 7 per 1000 ($P < 0.000001$) and reduction of death or dependency of 12 per 1000 ($P = 0.01$).¹⁰⁰ The risk of aspirin in the absence of thrombolytics is minimal, and the small but significant benefit argues in favor of routine treatment, but only after 24 hours if intravenous thrombolysis has been used and absence of hemorrhagic transformation is confirmed.

The initiation of dual antiplatelets (aspirin and clopidogrel) was shown to reduce recurrent ischemic events in patients with TIA or mild strokes in the CHANCE trial. The generalizability of this study across populations is unclear, as the trial was conducted in China where there is a higher incidence of intracranial atherosclerotic disease (compared to the U.S. population) and so the treatment effect may reflect a particular benefit of dual antiplatelets in this stroke subtype. Furthermore, the metabolism of the prodrug clopidogrel into the active form is dependent on several P450 enzymes, with highly variable degrees of active drug across individuals depending on particular genetic variants of the enzyme. A study design similar to CHANCE is being pursued in the ongoing POINT trial in the U.S. population.

Statin Therapy

Statins reduce the incidence of strokes among patients who are at increased risk for cardiovascular disease. However, whether statins reduce the risk of stroke after a recent stroke or TIA was established by the SPARCL trial. In SPARCL, patients who had a stroke or TIA within 1 to 6 months before randomization, had LDL of 100 to 190, and had no known coronary artery disease were randomized to receive 80 mg of atorvastatin or placebo. The primary end point was a first nonfatal or fatal stroke. In the cohort receiving high-dose atorvastatin, the overall incidence of strokes and cardiovascular events was reduced. High-dose atorvastatin should thus be administered in the setting of acute ischemic stroke.¹⁰¹

Special ICU Management Considerations

General Assessment

In patients with acute stroke, initial concerns include assessment of respiratory function, cardiovascular stability, and level of consciousness. An adequate airway must be established to ensure proper ventilation, particularly in obtunded or comatose patients. Aspiration is a serious concern that often results in pneumonia and serves as a major cause of morbidity and mortality during hospitalization. Supplemental oxygen is often administered, but the benefit is uncertain when oxygenation is already adequate. Hypoxemia should be corrected immediately, however, and its source aggressively investigated. Arrhythmias are common in acute stroke, as bradycardia may signal underlying increased ICP or cardiac ischemia. Atrial fibrillation associated with rapid ventricular response often impairs cardiac output requiring immediate treatment and may also be an embolic source of stroke. Ventricular tachycardia or fibrillation rarely occurs with stroke; when

present, it usually is the result of coexistent myocardial infarction. Hypotension should be corrected with intravenous fluids. Seizures should be controlled with anticonvulsants. Fever should be treated aggressively with antipyretics.

Blood Pressure

Hypertension often accompanies ischemic stroke, and in most cases abrupt lowering of blood pressure is not advised because of the risk of further impairing perfusion in the ischemic region.¹⁰² In the presence of a systemic or cardiac reason for reducing blood pressure, such as aortic dissection or acute myocardial infarction, the relative importance of the systemic and neurologic issues must be considered. Hypertensive encephalopathy is a syndrome of extreme hypertension, papilledema, altered mental status, microangiopathic hemolytic anemia, and renal insufficiency that responds to the lowering of blood pressure. In the absence of papilledema or systemic features, it is unlikely that acute neurologic deficits are caused by hypertensive encephalopathy, and acute lowering of blood pressure will more likely worsen than improve deficits.

When thrombolytic therapy is considered, reducing blood pressure within the prescribed limits is necessary. Before thrombolytic therapy is given, systolic blood pressure should be less than 185 mm Hg and diastolic less than 110 mm Hg.¹⁷ Labetalol typically is administered in increasing doses every 5 to 10 minutes to control blood pressure. Enalapril is a reasonable alternative. Sublingual nifedipine should be avoided because of its potential to lower blood pressure precipitously. If these agents do not provide adequate control, a nicardipine drip could be considered, although such patients may not be good candidates for thrombolysis. Following thrombolysis, blood pressure should be aggressively controlled, keeping systolic blood pressure below 185 mm Hg and diastolic pressures below 110 mm Hg for the first 24 hours.

Fluids

Most patients with acute stroke are volume-depleted, and intravenous fluids should be replete with either normal saline or lactated Ringer's solution. In patients with large strokes in danger of developing brain edema, fluid administration should be titrated carefully, and free water should be limited. Mild hyponatremia need not be treated acutely, but more severe hyponatremia should be corrected slowly and usually reverses with infusion of normal saline.

The role of hypertonic saline (3-23%) in the treatment of acute ischemic stroke and its ability to minimize cerebral edema remains controversial. Those who oppose its use cite that it can lead to rebound parenchymal swelling once it is weaned off. Proponents will usually use a goal serum sodium range of 145 to 150 mEq/L and a serum osmolality goal of 315 to 320 mOsm/L. Sodium and serum osmolality levels are usually checked every 6 hours.^{103,104}

Glucose

Evidence from animal models of stroke suggests that hyperglycemia increases the severity of ischemic injury.¹⁰⁵ Increased glucose concentration in the area of ischemia causes higher lactate concentrations and local acidosis, which increases free radical formation and thus damages neurons. Hyperglycemia also may increase ischemic edema, release excitatory amino acid neurotransmitters, and weaken blood vessels in the ischemic area. Studies of stroke in humans show an inconsistent association between outcome and initial blood glucose; however, admission glucose concentration correlates with initial stroke severity. Initial hyperglycemia also has been associated with higher mortality rates after stroke.¹⁰⁶ Some suggest that hyperglycemia in acute stroke is a stress reaction, but the relationship between initial blood glucose concentration and outcome is independent of initial stroke severity, arguing against a stress phenomenon.

The GIST-UK trial investigated whether treatment with a glucose-potassium-insulin (GKI) infusion to maintain euglycemia immediately after the acute stroke event had an impact on mortality at 90 days. This trial was stopped due to slow enrollment but concluded that whereas

GKI infusions reduced plasma glucose concentrations and blood pressure, treatment was not associated with clinical benefit. The study was underpowered, and alternative results should not be dismissed.¹⁰⁷ The GRASP pilot trial found that insulin infusion for patients with acute ischemic stroke is feasible and safe. Three treatment arms were used, employing controls that were tight (70-110 mg/dL), loose (70-200 mg/dL), and usual (70-300 mg/dL).¹⁰⁸ Additional comparative studies should help to clarify future treatment regimens.

SUMMARY

The availability of effective treatment to alter outcome within the first few hours after stroke onset is rapidly evolving. Patients with symp-

KEY POINTS

1. When an arterial occlusion occurs, an area of irreversibly infarcted brain (core infarct) is surrounded by a region of reduced blood flow impairing function (ischemic penumbra) that is not yet severe enough to result in irreversible infarction. If adequate blood flow can be restored within a critical time frame, this area of at-risk tissue may be salvageable and return to normal function.
2. Acute ischemic stroke imaging ideally involves some combination of a noncontrast head CT, CT angiography of the head and neck, CT brain perfusion, MRI brain, MRA of the head and neck, or MR brain perfusion.
3. The only FDA-approved therapy for acute ischemic stroke presenting within 3 hours of symptom onset is intravenous t-PA.
4. Evidence from the ECASS III trial indicates that the therapeutic window for intravenous t-PA may be extended to 4.5 hours in select patients.
5. Several studies (MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, and REVASCAT) have demonstrated improved outcomes in select patients undergoing intraarterial therapy with a stent-retriever device within 6 to 12 hours of symptom onset.
6. Intraarterial therapy for acute ischemic stroke presenting beyond 6 hours is currently under investigation in the DAWN study.
7. Surgical decompression for large infarctions is recommended to be completed within 48 hours from symptom onset in appropriately selected patients.
8. In patients receiving intravenous thrombolysis, no anticoagulation or antiplatelet agents should be administered in the first 24 hours until hemorrhagic transformation can be excluded. After that time, anticoagulation can be started in appropriate patients. If anticoagulation is not used, antiplatelet agents should always be started.
9. High-dose statin therapy can be administered acutely after ischemic stroke in patients with previous stroke or TIA and without history of coronary artery disease.
10. Patients presenting with TIA or mild stroke may be at high risk for recurrent events. A short course of dual antiplatelets may play a role in reducing the likelihood of recurrent ischemic events in patients.
11. Hyperglycemia needs to be treated aggressively, as it has been associated with higher mortality in acute ischemic stroke patients.

toms suggesting cerebral ischemia must be treated emergently, and imaging must be performed rapidly and in a high-quality manner. Therapy for acute stroke includes much more than thrombolysis, and understanding the benefits and hazards of thrombolysis continues to evolve with greater experience and additional clinical trials. Newer generations of mechanical devices are being developed, and neuroprotection and neurorestoration hold great promise as synergistic complements to stroke reperfusion therapies. Appropriate management of blood pressure, glucose, and intravenous fluids all

contribute to the overall outcome from acute stroke. At present, only a small fraction of patients with stroke (less than 5%) arrive at an emergency department in time for acute stroke therapy. Development of new acute stroke therapies and expected improvements in outcome with lower hemorrhage rates should encourage the medical system to further support the framework for a seamless and integrated stroke system of care. Such efforts should ensure that all stroke patients receive the optimal available therapy in the shortest time possible.

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■ References for this chapter can be found at expertconsult.com.

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INTRACEREBRAL HEMORRHAGE

Spontaneous (nontraumatic) intracerebral hemorrhage (ICH) accounts for approximately 10% of all strokes in North America and about 20% to 30% in East Asia. Outcomes are typically poor; up to half die within 30 days, and survivors often have significant disability.¹

Pathophysiology

The mechanisms that account for brain injury from ICH are complex. The primary damage is local tissue destruction as rupture of a vessel introduces a sudden stream of blood into the brain parenchyma. In many, further bleeding results in hematoma enlargement within the first few hours of onset.² The mass of the hematoma produces tissue distortion and shifts within the intracranial cavity.

Further damage is believed to occur after the bleeding stops. Proposed causes include ischemia, edema, and toxic effects of parenchymal blood. While each of these can be detected in animal models, their clinical importance remains unsettled.

Despite experimental models of ICH^{3,4} and studies in human patients⁵⁻⁷ consistently demonstrating reduced blood flow around the hematoma, this does not appear to represent ischemia.^{8,9} Positron emission tomography (PET) and magnetic resonance imaging (MRI) studies in humans indicate that the perihematomal cerebral metabolism is reduced to a greater degree than the cerebral blood flow (CBF) and that biopsies from ICH patients demonstrate impaired mitochondrial function.¹⁰ These findings suggest that hypoperfusion reflects reduced metabolic demand of the tissue surrounding the hematoma rather than ischemia.^{9,11}

Cerebral edema occurs within hours of experimental ICH and may result from the toxic effects of blood-derived enzymes, increased osmotic pressure exerted by clot-derived serum proteins, or ischemia.¹² The cause, time course, and importance of edema formation in humans are debated, and the best predictor of the edema volume is the size of the hematoma. Early edema does not appear to contribute to increases in mass effect,¹³ worsened functional outcome, or increased mortality.¹⁴

Causes and Risk Factors

The leading risk factor for ICH, present in over half of all cases, is chronic hypertension.¹⁵ There is a doubling of the rate of hemorrhage with each decade of life until 80 years of age.¹⁶ The impact of smoking,¹⁷ alcohol abuse,^{18,19} and diabetes mellitus^{20,21} on the risk of ICH is disputed.

Hypertensive Hemorrhage

Hypertensive ICH predominantly occurs deep in the cerebral hemispheres, most often in the putamen,²² thalamus, lobar white matter, cerebellum, and pons (Fig. 53-1). The link between these sites is that they are all supplied by small penetrating arteries²³—that is, perpendicular branches directly off major arteries that are subject to high shear stress and that have no collaterals.

Intracranial Aneurysms and Vascular Malformations

Although aneurysmal rupture is most commonly associated with hemorrhage in the subarachnoid space, the blood may also be directed into the substance of the brain. Aneurysms located at the middle cerebral artery bifurcation can produce hemorrhages into the basal ganglia similar to hypertensive hemorrhage, and anterior communicating artery aneurysms can produce flame-shaped hemorrhages at the base of the frontal lobes.

About half of adults with intracranial arteriovenous malformations (AVMs) present with hemorrhage.²⁴ In 60% of cases, the hemorrhage is parenchymal, involving virtually any location of the brain.²⁵ Hemorrhage due to AVM occurs more frequently in a younger population than that due to aneurysms or hypertension.

Other Causes

Cerebral amyloid angiopathy (CAA) is an important cause of predominantly lobar, often recurrent, ICH in the elderly. The prevalence of amyloid deposition in cerebral vessels increases dramatically with age^{26,27} and may contribute to the exponential rise in the risk of ICH with increasing age. Apolipoprotein E $\epsilon 2$ and $\epsilon 4$ genotypes are associated with an earlier age at onset of first hemorrhage and a higher risk of early recurrence.^{28,29} The presence of multiple or recurrent lobar ICH (including asymptomatic microhemorrhages detected on gradient-echo MRI) in individuals 55 years or older without other known causes of hemorrhage strongly suggests this etiology.³⁰

Hematologic causes of ICH include antithrombotic and thrombolytic agents, systemic disease (e.g., thrombocytopenia, leukemia, and hepatic and renal failure), and congenital or acquired clotting factor deficiencies. The incidence of oral anticoagulant-associated ICH has been increasing in parallel with the rising use of the anticoagulant warfarin. Although the risk of ICH is greater with a supratherapeutic international normalized ratio (INR), a significant number of hemorrhages occur when the INR is therapeutic.³¹ Hematoma expansion among warfarin users may be more common and occur over a longer time frame, contributing to a higher mortality rate versus spontaneous ICH.³² Recently, a new class of oral anticoagulants has been introduced, which act by inhibition of thrombin or factor Xa and may have a lower risk of ICH than warfarin.³³⁻³⁶

Most studies suggest that antiplatelet use at ICH onset is not associated with larger hematoma size, hematoma growth, or poor clinical outcome.³⁷ Platelet dysfunction is associated with hematoma expansion and worse outcome,³⁸ but, to date, platelet transfusion has not provided a mortality benefit or improved functional outcome.³⁹

Hemorrhage from an underlying neoplasm is rare but occasionally occurs with malignant primary CNS tumors such as glioblastoma multiforme and lymphoma as well as with metastatic tumors.⁴⁰

ICH may also occur in association with infection (e.g., infiltration of vessel wall by fungal organisms,⁴¹ necrotizing hemorrhagic encephalitis with herpes simplex⁴²), vasculitis,⁴³ venous sinus occlusion,⁴⁴ in a delayed fashion after head trauma,⁴⁵ following reperfusion (e.g., after carotid endarterectomy or acute thrombolysis),⁴⁶ and with the use of various drugs, particularly sympathomimetics (e.g.,



FIGURE 53-1 ■ Typical moderate-sized putaminal hemorrhage.

cocaine, amphetamines, pseudoephedrine, and phenylpropanolamine).⁴⁷ Finally, some degree of hemorrhagic transformation of acute cerebral infarcts is common,⁴⁸ although symptomatic ICH in this setting is rare in the absence of anticoagulation or thrombolytic therapy.

Clinical Features

The clinical presentation of ICH is often indistinguishable from that of ischemic stroke; however, ICH more commonly presents with an altered level of consciousness, headache, and vomiting.²² Blood pressure is elevated in the majority of patients (see below). Clinical as well as purely electrographic seizures may occur at onset or in the first few days, particularly in those with lobar hemorrhages or underlying vascular or neoplastic lesions.⁴⁹ Symptoms may be maximal at onset or evolve over minutes to hours. Neurologic deterioration within 48 hours after hospital admission has been reported to occur in 20% of patients.⁵⁰ A majority are related to hematoma expansion, but for some, the cause is not always evident.

Diagnostic Studies

Noncontrast computed tomography (CT) scanning is the gold standard for the diagnosis of acute ICH. The typical CT appearance of an acute hematoma consists of a well-defined area of increased density surrounded by a rim of decreased density. Over time, the borders of both the high- and low-attenuation regions become increasingly indistinct such that the hematoma is isodense with adjacent brain parenchyma by 2 to 6 weeks.⁵¹ Although MRI also has high sensitivity and specificity for the diagnosis of acute ICH,⁵²⁻⁵⁴ it is less accessible in the emergency department setting, and its use has safety concerns in patients with impaired consciousness, with hemodynamic compromise, or who are vomiting.⁵⁵ The benefits of MRI over CT are its greater accuracy in determining the approximate age of a hematoma⁵⁶ and its ability to detect evidence of previous asymptomatic hemorrhages.⁵⁷

Angiography is useful in evaluating the cause of ICH if an underlying aneurysm or vascular malformation is suspected, but the yield is extremely low when the patient has chronic hypertension and the hemorrhage is in one of the typical sites associated with hypertensive hemorrhage.⁵⁸ Multidetector CT angiography is an alternative imaging modality and has a sensitivity of 96% and a specificity of 99% to 100%.^{59,60} The yield is higher in younger patients (47%), those without hypertension or impaired coagulation, and those with lobar (20%) or infratentorial (16%) ICH locations.⁵⁹

Multidetector CT angiography can also be used to identify the presence of active contrast extravasation into the hematoma, an indicator of active hemorrhage. Termed the *spot sign*, these foci of intralesional enhancement are seen in up to one-third of patients with acute ICH⁶¹ and are associated with an increased risk of hematoma expansion, in-hospital mortality, and poor outcome in survivors.⁶²

Treatment

Initial Stabilization

Acute ICH is a medical emergency requiring careful attention to the airway, blood pressure, and correction of any underlying coagulopathy. As many as half of all patients with ICH require mechanical ventilation.⁶³ Blood pressure is often elevated at presentation, sometimes markedly so, and early control is an important component of initial stabilization. Finally, urgent identification and correction of coagulopathies are important.

Airway and Respiratory Management

With diminished consciousness, the pharyngeal and tongue musculature relax, and cough and gag reflexes are inhibited, leading to airway compromise. Additionally, if the hemorrhage is in the brainstem or cerebellum, there may be complete loss of pharyngeal tone and early airway obstruction.

Initial airway management includes proper positioning, frequent suctioning, and placement of an oral or nasal airway. If sonorous respiration, inability to manage oral secretions, or decreased oxygen saturation does not improve, intubation is necessary. Premedication should be administered to produce adequate sedation and jaw relaxation as well as to prevent elevation of intracranial pressure (ICP) due to hypoxia, hypercarbia, and direct tracheal stimulation. Short-acting intravenous (IV) anesthetic agents (thiopental 1 to 5 mg/kg, or etomidate 0.1 to 0.5 mg/kg) block this response⁶⁴ and additionally suppress brain metabolic rate,⁶⁵ theoretically improving tolerance of a transient fall in cerebral perfusion pressure (CPP) should it occur. Etomidate is generally preferred over thiopental since it is less likely to lower blood pressure. IV lidocaine (1 to 1.5 mg/kg) has been recommended to block this response,⁶⁶ although data supporting its use are lacking.⁶⁷ Paralytic agents are usually unnecessary, but, if needed, short-acting agents should be used.

Hemodynamics

Arterial blood pressure is elevated on admission in the majority of patients with ICH, even in the absence of a history of hypertension.^{22,68} Although this acute increase in blood pressure is often implicated as the cause of the hemorrhage, it more likely reflects chronic hypertension, the brain's attempt to maintain CPP in response to the sudden increase in ICP, pain, anxiety, and sympathetic activation. Even without treatment, blood pressure tends to decline to premonitory levels within a week of ICH.⁶⁹

There has been substantial controversy over if and when to lower elevated blood pressure after acute ICH.⁷⁰ Proponents of rapid treatment of acute hypertension argue that high blood pressure may predispose to hematoma enlargement and exacerbate vasogenic edema by increasing capillary hydrostatic pressure, especially in areas with a damaged blood-brain barrier. Another compelling reason to lower blood pressure in ICH patients with moderate to severe hypertension is the potential for end organ damage including myocardial ischemia, congestive heart failure, and acute renal failure.

The major argument against the treatment of elevated blood pressure has been that lowering blood pressure might reduce CBF and exacerbate ischemia surrounding the hematoma.⁷¹ Since chronic hypertension shifts the cerebral autoregulatory curve to the right, a higher CPP may be required to maintain adequate CBF.^{72,73} Lowering the blood pressure to "normal" levels might thus lead to ischemic damage. Similarly, lowering blood pressure may critically reduce CPP in patients in whom ICP is elevated due to a large space-occupying clot or hydrocephalus.

Several studies have addressed this issue in patients with mean arterial pressure (MAP) more than 130 to 140 mm Hg.⁷⁴⁻⁷⁶ These studies demonstrate that regional and global CBF are preserved when MAP is lowered to 110 mm Hg or about 80% of the admission MAP.

These observations set the stage for the INTERACT trial,⁷⁷ a prospective trial of blood pressure management beginning within 6 hours of symptom onset in 404 patients with spontaneous ICH and elevated systolic blood pressure (SBP, 150 to 220 mm Hg). Patients were randomized to an early, intensive blood pressure-lowering group (goal SBP <140 mm Hg within 1 hour), or a control group (goal SBP <180 mm Hg). After adjusting for initial hematoma volume and time from onset to CT, median hematoma growth at 24 hours differed by 1.7 mL (95% CI, 0.5-3.9, $P = 0.13$). Intensive blood pressure-lowering did not increase the risk of adverse events or improve 90-day clinical outcome. This was followed by the much larger INTERACT2, which used the identical protocol and enrolled almost 3000 patients.⁷⁸ Again there was a very small, if any, impact on hematoma expansion, although the hematoma sizes of those enrolled were fairly small (median, 11 mL). Although the study did not reach its primary endpoint, an ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive lowering of blood pressure. Based on this study, many clinicians are now more aggressive in treating early hypertension in these patients.

In the setting of ICH, the ideal antihypertensive agent would be easily titrated, have minimal cerebrovascular effects, and not be prone to sudden, large reductions in blood pressure. Vasodilators, especially venodilators, can raise ICP by increasing cerebral blood volume and should be avoided. Sodium nitroprusside and nitroglycerin increase ICP and lower CBF in patients with reduced intracranial compliance and should not be used. Calcium channel blockers, beta-blockers, and angiotensin-converting enzyme inhibitors have minimal effect on CBF within the autoregulatory range of MAP and do not alter ICP. Therefore, popular treatment options in the setting of acute ICH include intermittent boluses of labetalol, enalapril, and/or hydralazine, or continuous infusion of nicardipine or clonidine.

Prevention of Hemorrhage Extension

Because hemorrhage extension occurs within the first few hours after symptom onset in about one-third of patients (Fig. 53-2), it seems reasonable to correct any existing coagulopathy as rapidly as possible.

Patients taking warfarin should receive IV vitamin K and replacement clotting factors. Until recently, fresh frozen plasma (FFP) was used for this purpose, but it can precipitate congestive heart failure and transfusion-related acute lung injury. Prothrombin complex concentrate (PCC) is an effective alternative that can be administered much more quickly without these risks.⁷⁹

Management of hemorrhage in patients taking thrombin and factor Xa inhibitors is more difficult. Animal models suggest that PCC may be effective as a nonspecific reversal agent. Although there are currently no FDA-approved antidotes, andexanet alfa (a recombinant factor Xa derivative) and idarucizumab (a humanized antibody fragment) are in phase III trials.

Symptomatic ICH occurs after thrombolytic treatment of acute ischemic stroke in about 6% of patients.⁸⁰ It is substantially less common after thrombolytic treatment of extracerebral thrombosis.⁸¹ No reliable data are available to guide correction of the thrombolytic effect of recombinant tissue plasminogen activator (rt-PA). Current practice is highly variable and may include administration of FFP, PCC, cryoprecipitate, and platelets.

Even in those patients without coagulopathy, promoting early hemostasis might limit ongoing bleeding and decrease hematoma volume. Factor VIIa is a coagulation factor that interacts with tissue factor exposed in the wall of a damaged blood vessel to drive a burst of thrombin that initiates platelet aggregation and accelerates formation of a stable fibrin clot. A phase IIb study found that treatment with recombinant factor VIIa (rFVIIa) given as a single IV bolus within 4 hours of ICH onset decreased hematoma growth and improved clinical outcome despite a small increase in thromboembolic events. A much larger phase III trial comparing placebo to 20 and 80 µg/kg of rFVIIa followed, which confirmed the ability of rFVIIa to reduce hematoma growth; however, at 90 days there was no significant difference in clinical outcome.⁸² A post hoc exploratory analysis suggested that a subgroup of younger patients who present earlier and have no significant intraventricular hemorrhage might benefit from rFVIIa, but this has not been tested to date.⁸³

Intraventricular Hemorrhage and Hydrocephalus

In about 40% of patients with ICH, blood extends into the ventricular system (intraventricular hemorrhage, IVH).⁸⁴ Mortality in these patients is high.^{85,86} Hydrocephalus may develop after ICH either in

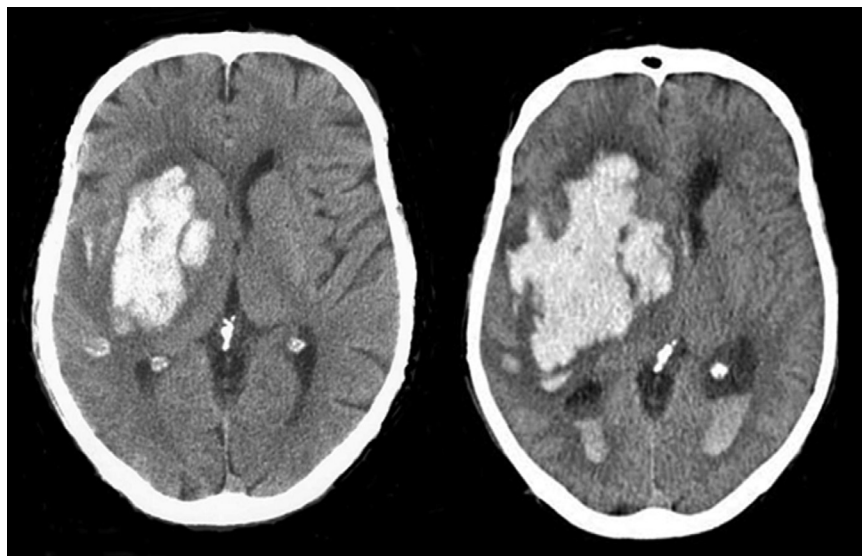


FIGURE 53-2 ■ Example of hematoma enlargement. Computed tomography (CT) on left was obtained 2 hours after onset of left hemiparesis and shows right putaminal hemorrhage. CT on right was obtained 1 hour later when patient acutely deteriorated and shows expansion of hematoma, with intraventricular extension, midline shift, and enlarging ventricles.

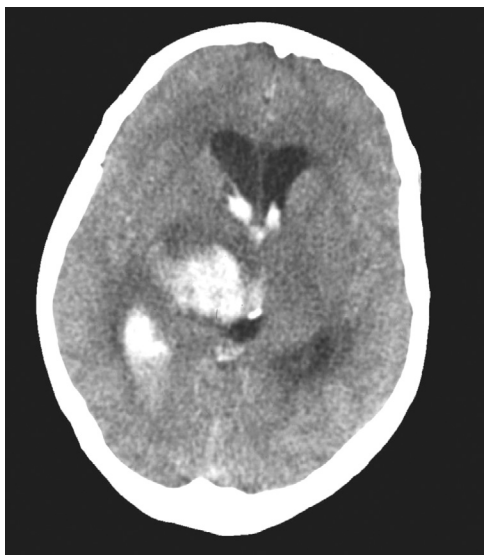


FIGURE 53-3 ■ Example of a small thalamic hemorrhage with blood obstructing the foramen of Monro, causing hydrocephalus.

association with IVH or because of direct mass effect on a ventricle (e.g., on the third ventricle with a thalamic hemorrhage; Fig. 53-3). External ventricular drainage (ventriculostomy) is often used to treat hydrocephalus and IVH, but its efficacy has never been established. Ventriculostomy in the setting of IVH is difficult to manage because the catheter frequently becomes obstructed with thrombus, interrupting drainage and raising ICP. Flushing the system helps remove thrombus from the catheter but increases the risk of ventriculitis. Recently, investigators have attempted to facilitate removal of blood from the ventricles via direct intraventricular administration of thrombolytic agents. Preliminary studies have been promising,⁸⁷ and a multicenter randomized trial is currently under way.

Intracranial Hypertension

The incidence, impact, and appropriate management of intracranial hypertension in ICH are not well understood. Factors likely to elevate ICP include large hematoma size, minimal degree of underlying cerebral atrophy, hydrocephalus, and edema, but the true incidence of intracranial hypertension is unclear, since routine ICP monitoring is not performed. Because the hematoma is localized and the increase in volume it produces can be compensated for to some degree by reduction in the size of the ventricles and subarachnoid space, a global increase in ICP may not be seen unless the hemorrhage is very large or is associated with marked hydrocephalus. However, mass effect from the hematoma and local tissue shifts can compress the brainstem or result in herniation in the absence of a global increase in ICP.^{88,89} Thus, the utility of ICP monitoring is not clear. In some cases, external ventricular drain (EVD) placement is considered to manage hydrocephalus. Patient selection and timing are controversial; however, patients with small parenchymal hematomas who have deterioration in the level of consciousness and enlarging ventricles are most likely to benefit. Those with very large parenchymal hematomas are least likely to benefit, and placement of an EVD in the contralateral ventricle typically worsens tissue shifts, often leading to clinical deterioration.

Elevated ICP, edema, and tissue shifts are often treated with osmotic agents (mannitol, hypertonic saline) and, if the ventricles are enlarged, CSF drainage. More details on ICP management can be found in Chapter 56 of this book on head injury. There are only a few small clinical trials of osmotic agents in ICH, which do not provide sufficient data to support their routine use.⁹⁰ Furthermore,

corticosteroids in ICH do not provide benefit and increase the rate of complications.⁹¹

Surgical Evacuation

The rationale for surgical evacuation of a hematoma is that reducing mass effect and removing neurotoxic clot constituents should minimize injury to adjacent brain tissue and hence improve outcome. Early randomized controlled trials of surgery for supratentorial ICH in the mid to late twentieth century, however, failed to show a benefit.⁹²⁻⁹⁵ A meta-analysis of three of these trials reported that patients undergoing surgical evacuation via open craniotomy had a higher rate of death or dependency at 6 months compared to those managed medically (83% vs. 70%).⁹⁶ Criticisms of these trials are that outdated surgical techniques were used, patient selection was inadequate, and surgery was delayed. Because open craniotomy is complicated by tissue damage sustained during the approach to the hematoma, a variety of new techniques for clot removal have been proposed, including an Archimedes screw, ultrasonic aspirator, modified endoscope, modified nucleotome, double track aspirator, intraoperative CT monitoring, and instillation of thrombolytics. However, the recurrence of bleeding due to the loss of tamponade effect on adjacent tissue that occurs in 10% of patients treated with open craniotomy remains a concern. In addition, because the newer techniques involve limited surgical exposure, concern exists that rebleeding will be more difficult to control than with open craniotomy.

A lack of benefit of surgery in ICH was also shown in the STICH trial, a multicenter study in which 1033 patients were randomized within 72 hours of ICH onset to surgical hematoma evacuation (open craniotomy or stereotactic aspiration, at the surgeon's discretion) or initial conservative management. Outcome did not differ between groups. Subgroup analysis, however, suggested a possible benefit of surgery in patients with superficial hematomas (less than 1 cm from cortical surface).⁹⁷ This led to the STICH II trial, which enrolled conscious patients with superficial lobar ICH of 10 to 100 mL and no intraventricular hemorrhage, admitted within 48 hours of ictus. There was a trend toward better survival in the surgical group.⁹⁸ In a new phase III trial, patients are randomized within 48 hours of ictus to stereotactic placement of a catheter in the hematoma and instillation of rt-PA for up to 72 hours or medical management.⁹⁹

Due to the high risk of brainstem compression and hydrocephalus, cerebellar hemorrhages were excluded from the randomized trials of surgery. Case series report good outcomes for surgically treated patients with cerebellar hemorrhages that are large or associated with brainstem compression or obstruction of the fourth ventricle. Recommended criteria for when to evacuate a cerebellar hematoma have thus included diminished level of consciousness, large size of the hematoma (>3 cm³), midline location, compression of basal cisterns and/or brainstem, and presence of hydrocephalus (Fig. 53-4).¹⁰⁰⁻¹⁰² Patient selection is important as many patients with smaller hemorrhages do well with medical management.¹⁰³

Management of Seizures

Although seizures may theoretically exacerbate ICH, they have not been shown to alter outcome. Prophylactic anticonvulsants may reduce the risk of early seizures in patients with lobar ICH but do not affect the risk of developing epilepsy.¹⁰⁴ Thus, reasonable approaches include either a brief period of prophylaxis or treating only if seizures occur. As for any hospitalized patient, the treatment of clinical seizures typically begins with an IV benzodiazepine such as lorazepam followed by an IV agent such as fosphenytoin. Monitoring for and management of subclinical seizures is covered herein in Chapter 54.

Supportive Care

Patients with ICH are prone to the same medical complications seen in patients with ischemic stroke, including fever, deep venous thrombosis (DVT), pulmonary embolism, and pneumonia.^{105,106} Given the association between fever and worsened outcome in experimental models of brain injury, it is reasonable for antipyretic medications to

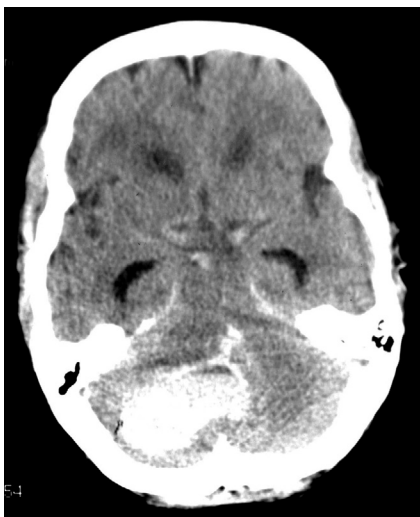


FIGURE 53-4 ■ Typical cerebellar hemorrhage with effacement of basal cisterns and early hydrocephalus manifest by enlargement of the temporal horns of the lateral ventricles.

be administered in febrile patients with ICH. The use of pneumatic sequential compression devices and elastic stockings significantly decreases the incidence of DVT in patients with acute ICH versus elastic stockings alone.¹⁰⁷ Subcutaneous heparin at a dose of 5000 units three times daily when initiated on day 2 after hemorrhage has been shown to significantly reduce the frequency of DVT relative to treatment begun on day 4 or 10, with no concomitant increase in hematoma expansion.¹⁰⁸ In another study, subcutaneous enoxaparin (40 mg daily) initiated at 48 hours after ICH was also safe. A benefit of enoxaparin over compression stockings could not be detected because of the low incidence of DVT in both treatment groups.¹⁰⁹

Similar to patients with ischemic stroke, ICH patients should not be fed orally until swallowing is evaluated. If aspiration is detected or the patient is not alert enough to eat safely, nasogastric tube feeding should commence promptly. Patients should be monitored for signs of aspiration pneumonia, whether taking food orally or via nasogastric tube.

Early mobilization and rehabilitation are generally recommended for clinically stable patients with ICH.

Prognostic Factors and Causes of Mortality

Mortality following ICH is high (25%-50%), with over half of the deaths occurring in the first 48 hours; the majority of ICH survivors have significant residual disability.^{1,110,111} The most consistent predictors of poor outcome are impaired level of consciousness and large hematoma size on admission. Other predictive features include age, hypertension, history of diabetes, antecedent warfarin use, male gender, in-hospital neurologic deterioration, hyperglycemia, elevated troponin level, elevated plasma S100B level, low serum cholesterol and triglyceride levels, and the presence of the apolipoprotein E ε2 or ε4 allele. Predictive radiographic features of poor prognosis include infratentorial hematoma location, intraventricular spread of blood, midline shift, hydrocephalus, hematoma growth, and the presence of the spot sign on CT angiography. A number of prognostic models have been developed to allow risk stratification upon presentation with ICH. One easy-to-use model is the ICH score,¹¹² which is based on point assignments for Glasgow Coma Scale score, ICH volume, presence of intraventricular hemorrhage, infratentorial location, and patient age and has been validated to accurately predict 30-day mortality.

Concern has been raised, however, that withdrawal of life-sustaining interventions in patients felt likely to have a poor outcome biases predictive models in ICH and negates the predictive value of other

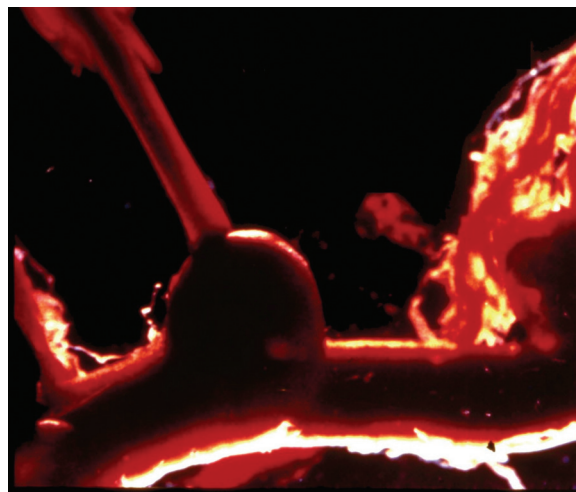


FIGURE 53-5 ■ Autopsy specimen of intracranial aneurysm filled with pressurized blood to simulate subarachnoid hemorrhage.

variables.¹¹³ Thus, the most frequent cause of death after ICH is withdrawal of care, followed by early (within 48 hours) transtentorial herniation with progression to brain death. Medical complications of immobility (pulmonary embolism, pneumonia, sepsis) account for most of the subsequent deaths.¹¹¹

SUBARACHNOID HEMORRHAGE

Subarachnoid hemorrhage (SAH) usually is a sudden, dramatic event that has multisystem consequences. One-quarter of patients die before reaching medical attention,¹¹⁴ and because of secondary insults—rebleeding, hydrocephalus, and delayed ischemia—more than half of those who reach medical attention either die or are left with significant neurologic deficits.

Pathophysiology

In SAH, the primary site of bleeding is the subarachnoid space, but it may also involve hemorrhage into the brain parenchyma, ventricular system, or subdural space. Rupture of an intracranial saccular aneurysm (Fig. 53-5) is by far the most common cause of spontaneous SAH. Saccular, or berry, aneurysms are small, rounded protrusions of the arterial wall occurring predominantly at bifurcations of the large arteries of the circle of Willis at the base of the brain. The most common sites of ruptured aneurysms are the distal internal carotid artery and its posterior communicating artery junction (41%), anterior communicating artery/anterior cerebral artery (34%), middle cerebral artery (20%), and vertebrobasilar arteries (4%).¹¹⁵ About 20% of patients have multiple aneurysms.

Most aneurysms rupture at the dome, where the wall may be as thin as 0.3 mm. Tension on the aneurysm wall is determined by the radius of the aneurysm and the pressure gradient across the wall (law of Laplace). The probability of rupture is related to size; aneurysms less than 5 millimeters in diameter have a very low rate of rupture. Aneurysm rupture causes local tissue damage due to the jet of blood under arterial pressure, as well as a transient increase in ICP to match arterial pressure.

Causes and Risk Factors

Genetic conditions that predispose to aneurysm formation include polycystic kidney disease, connective tissue disorders, and coarctation

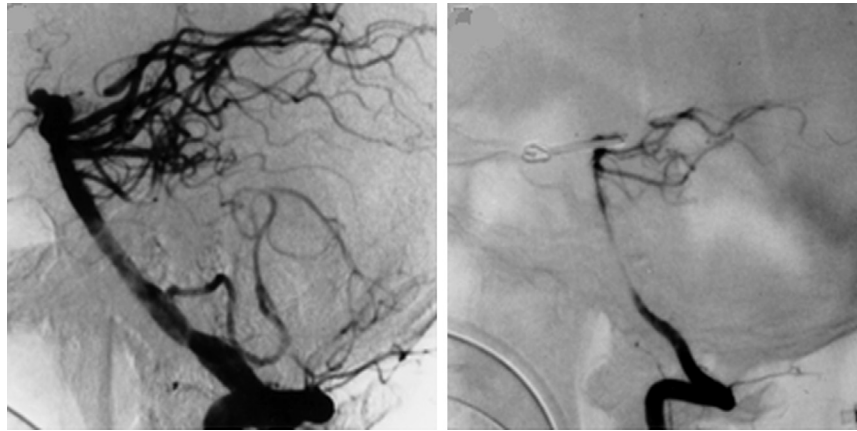


FIGURE 53-6 ■ Baseline angiogram obtained shortly after subarachnoid hemorrhage (*left*) and repeat angiogram obtained 7 days later (*right*) showing severe vasospasm of basilar artery, with reduced distal flow.

of the aorta. Recently, it has become clear that in some patient populations, genetic factors play a role in aneurysm formation without other associated conditions.¹¹⁶ There is a familial form as well.¹¹⁷ Other types of aneurysms that less commonly cause SAH include atherosclerotic, mycotic, and traumatic aneurysms. Trauma is the most common cause of nonaneurysmal SAH. Arteriovenous malformations, cocaine and stimulant abuse, neoplasia, and vasculitis account for the bulk of the remainder of cases. Bleeding into the subarachnoid space may accompany ICH, particularly in the setting of CAA. In 10% to 15% of cases of SAH, no source of bleeding is identified.

Clinical Features

Presentation

The most common initial symptom of SAH, occurring in over 90% of patients, is a sudden and severe (“thunderclap”) headache. Less severe warning (“sentinel”) headaches¹¹⁸ may precede the presenting event in as many as half of patients and are thought to represent minor aneurysmal leaks. In about half of patients, loss of consciousness accompanies the headache¹¹⁹ due to either the sudden surge in ICP at the moment of hemorrhage or cardiac arrhythmias. Vomiting can be a prominent symptom. Seizures may be reported,¹²⁰ but it is unclear whether this represents true epileptic seizures or reflex posturing related to the sudden rise in ICP. Focal deficits at the onset of hemorrhage occur in fewer than 10% of cases. After a few hours, a stiff neck can develop, reflecting the sterile meningeal inflammation induced by the presence of blood in the subarachnoid space.

Complications

A worsening of neurologic status often indicates one of the three major complications of SAH: rebleeding, hydrocephalus, or delayed cerebral ischemia (DCI). An understanding of the timing and nature of the deterioration facilitates rapid diagnosis and treatment. It must be emphasized that systemic perturbations such as infection, hyponatremia, fever, hypoxia, and hypotension may produce similar symptoms and should be sought and corrected as part of the evaluation process.

Early Complications. Rebleeding. Rebleeding is heralded by a sudden worsening of headache, vomiting, blood pressure elevation, development of a new neurologic deficit, or arrhythmia. It occurs in up to one-third of patients and is more often than not fatal. The risk of rebleeding is greatest during the first 24 hours (5%-10%), declining rapidly over the next 2 weeks.¹²¹ Rates of rebleeding are highest in women, those who are a poor clinical grade, those in poor medical condition, and those with elevated systolic blood pressure.

TABLE 53-1

Fisher Grade of Subarachnoid Hemorrhage on Initial Computed Tomography

1. No blood detected
2. Diffuse or vertical layers <1 mm thick
3. Localized subarachnoid clot and/or vertical layers ≥1 mm thick
4. Intraparenchymal or intraventricular clot with diffuse or no SAH

MODIFIED FISHER CT RATING SCALE

1. Minimal or diffuse thin SAH without IVH
2. Minimal or thin SAH with IVH
3. Thick cisternal clot without IVH
4. Thick cisternal clot with IVH

CT, computed tomography; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage.

Hydrocephalus. Hydrocephalus occurs after SAH because of disturbances of CSF flow or reabsorption: subarachnoid blood may impair CSF reabsorption at the arachnoid granulations, and ventricular blood may obstruct its flow. Acute hydrocephalus can develop within hours of SAH,¹²² often in the absence of intraventricular blood. It usually manifests as a gradual decline in the level of consciousness and can easily be treated by placement of an external ventricular drain. Delayed hydrocephalus may also develop gradually days to weeks later. If the acute hydrocephalus is untreated, about one-third of patients progress, one-third spontaneously improve, and one-third remain static.¹²³

Delayed Complications. Vasospasm. The term *vasospasm* refers to complex changes in intracerebral vessels, with segmental or diffuse narrowing of the lumen due to arterial wall thickening, vasoconstriction, and impaired relaxation that may reduce CBF. If the reduction in flow is severe enough, ischemia and infarction typically follow. The term *DCI* describes the clinical situation where these as well as other factors, including impaired autoregulation, hypovolemia, spreading cortical depression, and microthrombosis, combine to produce ischemia.¹²⁴ Arterial narrowing can be detected angiographically (Fig. 53-6) in up to 70% of patients,¹²⁵ of whom almost half will have symptoms. The onset of vasospasm is delayed, most commonly developing 5 to 10 days after initial hemorrhage, and may persist for up to 3 weeks. The strongest predictors of vasospasm are the clinical condition on presentation and the amount of subarachnoid blood on the initial CT scan. The highest risk is in those who have thick subarachnoid clots and intraventricular blood (graded using a modified Fisher Scale; Table 53-1).^{126,127} Focal neurologic deficits resulting from vasospasm may appear abruptly or gradually and may fluctuate,

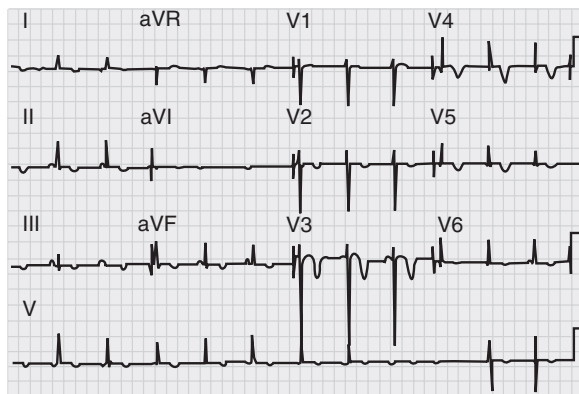


FIGURE 53-7 ■ Electrocardiogram in a patient with acute subarachnoid hemorrhage, demonstrating diffuse T-wave inversions.

exacerbated by hypovolemia, hypotension, or fever. If untreated, infarction may occur.

Medical Complications. Blood pressure is often elevated after SAH and is associated with a greater risk of rebleeding, vasospasm, and higher mortality. Multiple factors may underlie the rise in blood pressure, including increased sympathetic outflow, agitation, and pain. Early on, blood pressure management focuses on treating hypertension to help prevent rerupture of the aneurysm. Following repair of the aneurysm, the risk of rebleeding is virtually eliminated, and spontaneous elevations in blood pressure should be allowed to occur without intervention, since the risk of vasospasm becomes the primary concern at this point in management.

Disturbances in sodium and water balance occur in about one-third of patients, and hyponatremia and volume depletion after SAH is correlated with an increased risk of symptomatic vasospasm and poor outcome.¹²⁸ Although hyponatremia was previously attributed to inappropriate secretion of antidiuretic hormone (SIADH) and was, therefore, treated with fluid restriction, later evidence suggested that both sodium and water are lost. In fact, when administered normal, “maintenance,” volumes of fluid (2 to 3 L/day), as many as half of patients develop intravascular volume contraction.¹²⁹

Cardiac abnormalities are common in the first 48 hours after SAH. Electrocardiographic (ECG) changes (Fig. 53-7), including tall peaked T waves (“cerebral T waves”), diffuse T-wave inversion, ST-segment depression, and prolonged QT segments,¹³⁰ occur frequently and are linked to elevated levels of circulating catecholamines. These changes usually do not represent myocardial ischemia, as the myocardial lesions reported are pathologically distinct from ischemia. Cardiac enzymes may be mildly elevated.¹³¹ Cardiac rhythm disturbances occur in about 30% to 40% of patients, especially on the day of hemorrhage or in the postoperative period, and arrhythmias are typically benign but can be life threatening in about 5%.^{132,133} In rare cases, a stunned myocardium, often referred to as Takotsubo’s cardiomyopathy, may occur, with impairment of myocardial contractility leading to a fall in cardiac output, hypotension, and pulmonary edema.¹³⁴ Apical ballooning is a common echocardiographic finding. This can be dramatic but is transient, usually lasting 2 to 3 days, after which cardiac function recovers.¹³⁵ Management is the same as with other causes of cardiogenic shock.¹³⁶ During hemodynamic treatment for vasospasm, pulmonary edema may occur in up to one-quarter of patients,¹³⁷ though its incidence is now lower with careful monitoring.¹³⁸

Diagnostic Studies

CT is the imaging modality of choice in screening for SAH, having a sensitivity of over 90%.¹³⁹ Blood appears as high attenuation within the basal cisterns, Sylvian fissure, and sulci (Fig. 53-8). CT may fail to demonstrate SAH if the volume of blood is very small, if the

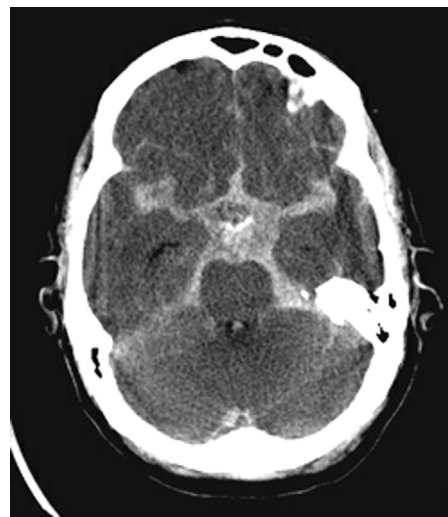


FIGURE 53-8 ■ Computed tomography scan of acute subarachnoid hemorrhage, with a thick layer of hyperdense blood filling the basal cisterns.

hemorrhage occurred several days before the CT scan, or if the hematocrit is extremely low.¹⁴⁰ Lumbar puncture for CSF analysis is indicated if CT is negative and clinical suspicion is high. Red blood cells in the CSF are indicative of SAH but can also be seen with traumatic puncture. The common technique of comparing cell counts in the first and last tubes collected is not reliable; however, the presence of yellow pigment (xanthochromia), resulting from red cell breakdown, can help distinguish between the two.¹⁴¹ Xanthochromia develops 2 to 6 hours after hemorrhage and persists for 1 to 4 weeks. It can also be seen in the setting of high protein levels due to diabetes, renal failure, or infection, in which case spectrophotometric analysis to identify hemoglobin breakdown products improves diagnostic accuracy.¹⁴²

Once SAH has been diagnosed, cerebral angiography should be performed as soon as possible. Angiography fails to identify a source of bleeding in 10% to 15% of patients with nontraumatic SAH. Repeat angiography in about 1 week is thus recommended.¹⁴³ There is a subset of patients in whom the blood on CT is localized to the perimesencephalic cisterns. In these cases, angiography is usually negative, and the bleeding is thought to be venous in origin; the prognosis is typically excellent, and repeat angiography is almost always negative.¹⁴⁴

With its wide availability, ease of use, and safety profile, CT angiography is increasingly being used as the initial diagnostic tool in the investigation of SAH. Overall sensitivity is more than 90% compared to conventional catheter angiography but is notably lower for aneurysms smaller than 5 mm¹⁴⁵; thus, a negative CT angiogram should be followed by conventional catheter angiography except in the case of perimesencephalic SAH.¹⁴⁴ Magnetic resonance angiography (MRA) has good sensitivity for detecting medium and large aneurysms, but sensitivity falls to less than 40% for small aneurysms. In addition, MRA is impractical for many acutely ill patients with SAH. MRA and CT angiography may also be of assistance in planning surgical or endovascular approaches to treatment.

Treatment

In 2011, an international consensus conference on the critical care management of patients with SAH was held and evidence-based recommendations were developed.¹⁴⁶

Initial Stabilization

The initial steps in the evaluation of a patient with suspected SAH should include assessment of airway, hemodynamic status, and the

level of neurologic function. The Hunt and Hess Scale¹⁴⁷ and the World Federation of Neurological Surgeons Scale¹⁴⁸ provide standardized measures of the patient's clinical condition (Tables 53-2 and 53-3). These scales should be scored after the patient is stabilized, including treatment of hydrocephalus if indicated. If the patient is lethargic or agitated, elective intubation should be considered before angiography because sedation is often necessary for angiography and may result in unrecognized hypoventilation or airway obstruction during the procedure.

Routine Care and Monitoring

The routine monitoring of all patients with acute SAH should include serial neurologic examinations, continuous ECG monitoring, and frequent determinations of blood pressure, electrolytes, body weight, and fluid balance. Initial use of anticonvulsants is no longer routinely recommended for patients who have not had a seizure. Anticonvulsants may be given in the perioperative period for patients who undergo aneurysm clipping; however, the duration of administration should be limited to several days.¹⁴⁹ Recent retrospective studies have suggested that routine use of anticonvulsants for a longer duration is associated with worse neurologic outcome.¹⁵⁰ In the past, dexamethasone was widely used to reduce meningeal irritation and intra- and postoperative edema, but given the lack of supporting evidence, its use has fallen out of favor.

Fluid Management. A stable intravascular volume should be maintained by hydration with isotonic saline and daily monitoring of fluid balance, body weight, and hematocrit. Monitoring of fluid balance alone may not be adequate to prevent hypovolemia, and combining multiple clinical indicators of volume status is needed.^{151,152} In some patients with severe cerebral salt wasting, large volumes of fluid are required to prevent intravascular volume contraction.¹⁵³ Hyponatremia can often be managed with restriction of free water, by administering only isotonic IV fluids, minimizing oral liquids, and using concentrated enteral feedings. It is important to adjust the *tonicity* of the fluid rather than the *volume* of fluids administered. Fludrocortisone is of marginal benefit in treating salt wasting^{154,155}; however, one study suggested that hydrocortisone may be helpful.¹⁵⁶ Persistent hyponatremia can be treated by using mildly hypertonic solutions (1.25% to 2% saline) as the sole IV fluid. There may be a role for antidiuretic hormone (ADH) antagonists such as conivaptan,

but since they increase urine volume, extreme caution must be exercised to avoid hypovolemia.¹⁵⁷

Hypertension. Initial attempts to treat hypertension should include analgesics and nimodipine; other antihypertensive agents should follow if needed. Useful medications include intermittent doses of beta-blockers and vasodilators. If a continuous infusion is needed, nicardipine or clevidipine are effective. When significant hydrocephalus is present, hypertension should not be treated until after the hydrocephalus is addressed. This is because the hypertension may be acting to maintain adequate cerebral perfusion in the face of elevated ICP.

Magnesium Sulfate. Magnesium antagonizes calcium and, thus, can potentially reduce vasospasm. Almost 40% of patients with SAH have low serum magnesium levels on presentation, leading to speculation that the administration of magnesium may improve outcome of SAH patients. Advantages of magnesium include ease of administration, low cost, and favorable safety profile.¹⁵⁸ Several studies have suggested benefit,^{159,160} but controlled trials have been inconclusive.^{161,162} A recent meta-analysis of ten randomized trials of magnesium sulfate found no support for its use.¹⁶³

Statins. Statins may be beneficial in SAH through their ability to induce nitric oxide synthetase, leading to dilation of cerebral vessels, or via antiinflammatory effects. Some preliminary studies have suggested that they may reduce vasospasm and improve outcome,^{164,165} while others have not.¹⁶⁶⁻¹⁶⁸ Over 800 patients were enrolled in a multicenter phase III trial of simvastatin 40 mg or placebo, which found no short- or longer term benefit of the drug.¹⁶⁹

Management of Secondary Complications

Rebleeding. Multiple clinical trials have demonstrated that antifibrinolytic agents such as epsilon aminocaproic acid and tranexamic acid reduce the risk of rebleeding, but this benefit is offset by an increased incidence of vasospasm and hydrocephalus.^{170,171} With the advent of early intervention, the use of these agents has declined dramatically. More recently, there has been interest in a shorter course of antifibrinolytic therapy while awaiting surgery or endovascular treatment. Tranexamic acid begun immediately upon SAH diagnosis and continued only until the aneurysm was secured (always within 72 hours) reduced the risk of rebleeding from 10.8% to 2.4% and did not increase risk of DCI.¹⁷²

Other measures directed at prevention of rebleeding include avoiding situations that produce sudden changes in the transmural pressure across the wall of the aneurysm (i.e., sudden increases in arterial or venous pressure or decreases in ICP). Patients are placed on bed rest and stimulation minimized. Agitated patients should be carefully sedated and long-acting agents avoided. Measures should be taken to minimize cough and Valsalva maneuvers. Stool softeners are administered to avoid straining. The definitive way to prevent rebleeding is to repair the aneurysm by surgical or endovascular means. Endovascular techniques involving electrolytically detachable platinum coils that thrombose the aneurysm are now routinely used to repair acutely ruptured aneurysms (Fig. 53-9).

The International Subarachnoid Aneurysm Trial compared surgical clipping with endovascular coiling of acutely ruptured intracranial aneurysms. Patients were eligible to be enrolled only if there was clinical equipoise regarding the best method to repair the aneurysm. Initial results favored endovascular coiling, with 23.7% dead or dependent at 1 year versus 30.6% in the surgery group.¹⁷³ Long-term follow-up indicated a small increased risk of recurrent bleeding from a coiled compared to a clipped aneurysm. Regardless, at 5 years the risk of death remained significantly lower in the coiled group, but the proportion of survivors who were independent did not significantly differ.¹⁷⁴ Longer term follow-up was reported on 1644 patients 10-18.5 years after treatment, and the odds of death or dependency were greater in the surgical group. Rebleeding was more common after coiling, but the risk was small, and the probability of disability-free survival was significantly greater in the endovascular group at 10 years.

TABLE 53-2 Hunt and Hess Clinical Classification of Subarachnoid Hemorrhage

- I. Asymptomatic or mild headache and neck stiffness
- II. Moderate to severe headache and neck stiffness ± cranial nerve palsy
- III. Mild focal deficit, lethargy, or confusion
- IV. Stupor, moderate to severe hemiparesis
- V. Deep coma, extensor posturing

TABLE 53-3 World Federation of Neurologic Surgeons Clinical Classification of Subarachnoid Hemorrhage

| GRADE | GLASGOW COMA SCALE | MOTOR DEFICITS |
|-------|--------------------|-------------------|
| I | 15 | Absent |
| II | 13 to 14 | Absent |
| III | 13 to 14 | Present |
| IV | 7 to 12 | Present or absent |
| V | 3 to 6 | Present or absent |

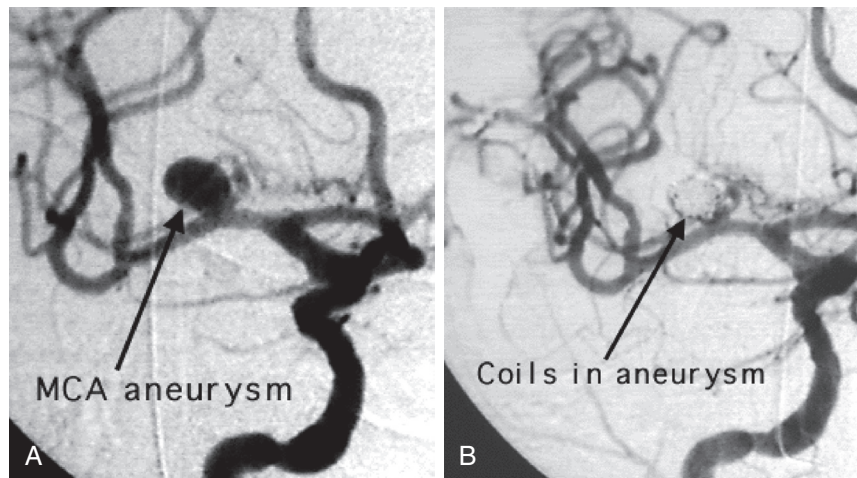


FIGURE 53-9 ■ Angiogram demonstrating middle cerebral artery aneurysm before (A) and after placement of detachable coils to thrombose the aneurysm (B).

Hydrocephalus. The decision to treat hydrocephalus is usually based on the CT appearance of enlarging ventricles in a patient whose level of consciousness is deteriorating. During placement of an EVD, the CSF pressure must be reduced slowly to lessen the risk of aneurysmal rerupture. CSF drainage may be needed for many days to clear intraventricular blood before it can be determined if a permanent shunt is required.

Delayed Cerebral Ischemia. Monitoring for DCI involves serial neurologic exams, serial transcranial Doppler (TCD) measurement of blood flow velocities,^{177,178} and catheter angiography. The use of CT angiography and CT perfusion for this purpose is growing. Neurologic signs may be vague, such as a global decline in responsiveness, or may be focal deficits. Symptoms may wax and wane, being exacerbated by hypovolemia or hypotension. Vasospasm can be identified on TCD by an increase in linear blood flow velocity (LBFV) and is defined as mild (>120 cm/sec), moderate (>160 cm/sec), or severe (>200 cm/sec).¹⁷⁹ Alternatively, the rate of rise in the LBFV is used to define the onset of vasospasm. The sensitivity of TCD in detecting vasospasm is about 80% when compared to angiography, at least partly because TCD samples only a small segment of the vasculature.¹⁸⁰ It has a negative predictive value, and the presence of normal velocities usually indicates the absence of vasospasm. Newer CT and MRI techniques including angiography and perfusion may have a future role in assessing for DCI.

When making a clinical diagnosis of DCI, alternative causes of neurologic changes such as sedatives, rebleeding, hydrocephalus, cerebral edema, metabolic derangements, and infections should be promptly excluded using radiographic, clinical, and laboratory assessments. Detection of clinical signs of DCI is particularly difficult in poor grade patients because of the limited exam that is possible. CT perfusion may aid in clinical decision making here.

Prevention. Routine measures taken to reduce risk of DCI include mechanical removal of subarachnoid blood at the time of aneurysm surgery or by CSF drainage, administration of the centrally acting calcium channel antagonist nimodipine, and avoidance of intravascular volume contraction or hypotension. Nimodipine (60 mg orally every 4 hours) for 3 weeks after SAH reduces the impact of symptomatic vasospasm and improves outcome.^{181,182} Its beneficial effect may be due to action on the cerebral vessels or by preventing calcium influx into ischemic neurons. Any hypotension developing with nimodipine use can usually be managed with fluids or by adjusting the dosage schedule to 30 mg every 2 hours. If the impact of nimodipine on blood pressure cannot be overcome in patients with DCI, it may have to be discontinued.

While there is general agreement that hypovolemia must be avoided, the use of prophylactic hypervolemia is more controversial.¹⁸³⁻¹⁸⁵

In a prospective controlled study, prophylactic volume expansion with albumin failed to reduce the incidence of clinical or TCD-defined vasospasm, did not improve CBF, and had no effect on outcome.¹⁸⁶ Costs and complications may be higher with the use of prophylactic hypervolemia.

Prophylactic use of transluminal balloon angioplasty was evaluated in a prospective, randomized controlled trial.¹⁸⁷ Although it reduced the need for therapeutic angioplasty and reduced ischemic deficits, these benefits were offset by procedure-related vessel complications.

Treatment of DCI. The trigger for instituting more aggressive interventions varies widely. Some centers actively intervene in the setting of rising TCD velocities¹⁸⁸ or angiographic vasospasm in asymptomatic patients,¹⁸⁹ whereas others institute aggressive measures in the setting of clinical deterioration. Aggressive measures include both hemodynamic and endovascular manipulations.¹⁹⁰⁻¹⁹² The goal is to improve CBF in ischemic regions. Since patients with SAH tend to become hypovolemic and lose pressure autoregulation,¹⁹³ it has been inferred that hypervolemia, induced hypertension, and augmentation of cardiac output would accomplish that goal.

Hemodynamic Augmentation. Hemodynamic interventions to improve CBF include hypervolemia, hypertension, and hemodilution, or “triple-H therapy.” Because of the risk of rebleeding, this therapy is reserved for patients who have had repair of the ruptured aneurysm. The presence of other small, untreated aneurysms does not exclude use of this therapy. Support for the benefit of hemodynamic augmentation is based on case series, and the relative contribution of each component is debated.

Data supporting the use of hypervolemia are scant. In one study of patients with symptomatic vasospasm, hypervolemia was reported to improve CBF, but a proper control group was not used.¹⁹⁴ Other studies question whether hypervolemia adds further benefit beyond correction of hypovolemia and report that the impact of volume expansion on CBF is modest compared to induced hypertension.¹⁹⁵

Hemodilution is perhaps the least understood component. The rationale is to augment CBF by reducing blood viscosity. The tradeoff is that oxygen-carrying capacity is reduced, reducing oxygen delivery. When studied in SAH patients, this was the case: while there was a rise in CBF, oxygen delivery fell following hemodilution.¹⁹⁶ For this reason, hemodilution has been abandoned.

More recently, use of blood transfusion in anemic patients has been suggested to improve cerebral oxygen delivery. Current recommendations are to maintain hemoglobin closer to 10 g/dL in patients at risk of ischemia (be it cardiac or cerebral) rather than use the standard transfusion threshold of hemoglobin of 7 g/dL.

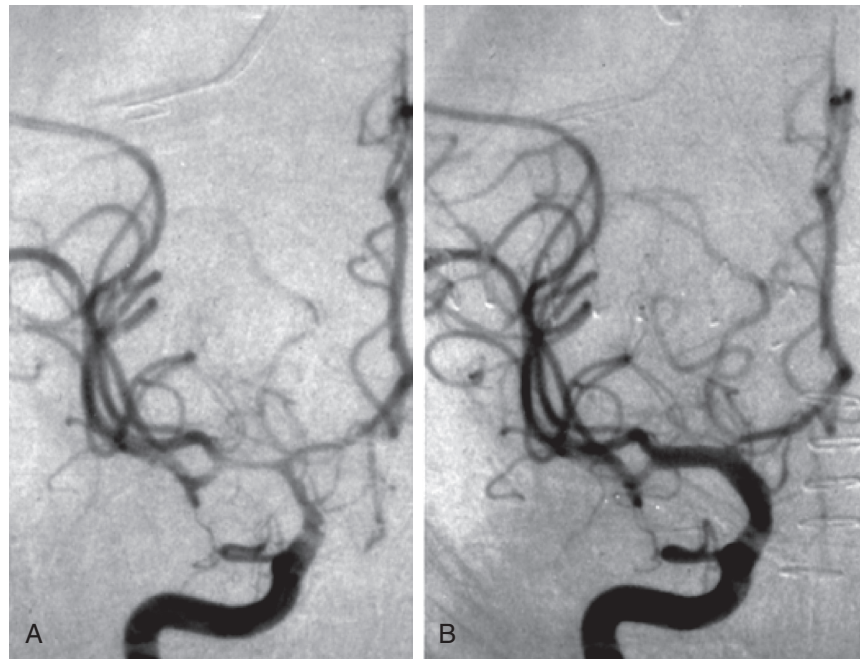


FIGURE 53-10 ■ Example of severe distal internal carotid and proximal middle cerebral artery vaso-spasm before (A) and after (B) angioplasty.

Blood pressure augmentation with dopamine and phenylephrine has been reported to modestly increase CBF, although the optimal target has not yet been identified.¹⁹⁵ Dobutamine and milrinone may be effective in improving cardiac output and CBF in some patients. In a retrospective comparison of the impact of hypervolemia, hypertension, and transfusion of 1 unit of red blood cells on cerebral oxygen delivery measured by PET in anemic patients, transfusion produced the biggest response.¹⁹⁷

The initial step is to rapidly correct any possible hypovolemia with isotonic crystalloid or colloid fluids. If there is no immediate response, vasoactive agents are instituted—vasopressors (phenylephrine, norepinephrine) or, alternatively, inotropes (dobutamine, milrinone).

Recently, there has been a decline in the use of Swan-Ganz catheters to manage hemodynamic augmentation. The arbitrary pulmonary capillary wedge pressure goals used in the past have been abandoned. Fluid administration should be adjusted to optimize cardiac output. Goals for blood pressure should be defined as a percent change from baseline (beginning with an approximately 15% change) rather than prespecified levels. The degree of hemodynamic augmentation should be titrated continuously to the patient's neurologic status; thus, if a goal is reached but there is no neurologic improvement, the goal should be modified. Once the optimal goals have been reached, they are usually maintained for 2 to 3 days and then gradually weaned, guided by neurologic status.

Anemia may contribute to DCI. While transfusion can have beneficial effects on brain physiology, it may be associated with medical complications, infection, vasospasm, and poor outcome after SAH. Still, given the high risk of ongoing cerebral ischemia, the results of the Transfusion Requirements in Critical Care Trial and subsequent observational studies on red blood cell transfusion in general critical care should not be applied to SAH patients, as with patients with cardiac ischemia.¹⁹⁸ Practice surveys indicate that transfusion thresholds of 8 to 10 g/dL are commonly used, with the higher range reserved for patients with DCI.

Endovascular Treatments. The endovascular approach to vasospasm involves treatment of constricted vessels with either balloon angioplasty or intraarterial infusion of vasodilating agents.^{151,199}

Angioplasty on the proximal segments of vasospastic cerebral vessels yields impressive sustained angiographic changes (Fig. 53-10).^{200,201} Vasoconstriction in more distal vessels usually cannot be reached by angioplasty catheters and can be treated with intraarterial infusion of vasodilators. Intraarterial papaverine rapidly dilates the entire cerebral vasculature, but reversal of clinical deficits is inconsistent.²⁰²⁻²⁰⁴ Its use has largely been abandoned because of its short-lived effect and complications, including increased ICP, apnea, worsening of vasospasm, neurologic deterioration, and seizures.²⁰⁵ It has been replaced by nicardipine, verapamil, nimodipine, and milrinone.²⁰⁶⁻²⁰⁸

The timing of when to initiate endovascular therapy is debated. It is generally used if, after a few hours, the response to hemodynamic augmentation is inadequate, but it may be the initial therapy in patients with poor cardiac function who are at high risk of complications of hemodynamic manipulation.²⁰⁹

Endothelin-1 Antagonists. Endothelin-1 (ET-1) is a 21-amino acid peptide that mediates vasoconstriction. In early studies, an endothelin antagonist clazosentan reduced angiographic vasospasm^{210,211} and tended to reduce vasospasm-related morbidity/mortality. Subsequently, two very large randomized controlled trials confirmed the reduction in angiographic vasospasm, but clazosentan did not change clinical outcome.²¹²

Fever. After SAH, fever develops in well over half of patients and is associated with increased length of stay, worse outcome, and higher mortality. Early in the disease course, most fevers are central in origin. Antipyretics are effective in a minority of patients, although intravenous forms may be more effective. Surface and intravascular cooling devices are much more effective, but benefits from cooling may be offset by negative consequences from shivering.²¹³

Prognostic Factors and Causes of Mortality

Untreated aneurysmal SAH carries a poor prognosis, with an estimated mortality rate of about 50%. Of those who make it to medical attention, mortality is 20% to 40%. Causes of death are about equally distributed among direct effects of the initial hemorrhage, rebleeding, vasospasm, and medical complications. Overall, less than one-third of patients achieve good neurologic recovery. Predictors of poor

prognosis include loss of consciousness or poor neurologic condition (i.e., high Hunt and Hess grade) on admission, older age, hypertension, preexisting medical illness, ≥ 1 mm thickness of subarachnoid blood on CT (Fisher grade 3), seizures, cerebral edema, aneurysm location in the basilar artery, and symptomatic vasospasm.²¹⁴⁻²¹⁸ Scales

quantifying degree of physiologic illness are also predictive of outcome in patients with SAH.²¹⁹ Long-term survivors of the initial hemorrhage continue to suffer a 3% annual risk of rehemorrhage unless the aneurysm is repaired.

KEY POINTS

Intracerebral Hemorrhage

1. Intracerebral hemorrhage (ICH) primarily injures the brain through direct mechanical compression and not ischemia.
2. Early hematoma expansion occurs in over one-third of patients who present within 3 hours and is the primary cause of early neurologic deterioration. Early treatment of hypertension and correction of coagulopathy may help limit expansion.
3. Open surgical hematoma evacuation and corticosteroid treatment have failed to show a benefit. The efficacy of osmotic agents has not been adequately evaluated.
4. Minimally invasive surgery combined with instillation of t-PA into the hematoma is promising, and a pivotal trial is under way.
5. The most common cause of death after ICH is withdrawal of life-sustaining interventions, followed by transtentorial herniation and medical complications of immobility.

Subarachnoid Hemorrhage

1. Subarachnoid hemorrhage (SAH) typically presents as the sudden onset of a severe headache, often with nausea, vomiting, and syncope. Focal neurologic deficits are uncommon.
2. Rebleeding, which is often fatal, occurs most commonly within the first 24 hours. It can be prevented by early surgical or endovascular repair of the aneurysm.

3. Hydrocephalus may develop acutely within hours of SAH or gradually up to weeks later and usually manifests as an insidious decline in mental status.
4. Delayed angiographic vasospasm occurs in more than two-thirds of patients, especially those with large amounts of subarachnoid blood. About one-third of patients develop delayed cerebral ischemia, which can cause focal neurologic deficits and infarction. Management options include nimodipine, hemodynamic augmentation, and endovascular maneuvers.
5. Management of SAH-associated "cerebral salt wasting" often requires the administration of large volumes of isotonic saline to prevent intravascular volume contraction and restriction of free water and mildly hypertonic saline solutions to treat hyponatremia.
6. Cardiac abnormalities, including electrocardiographic changes, mildly elevated cardiac enzymes, and arrhythmias, are common after SAH and are thought to be related to elevated catecholamine levels rather than myocardial ischemia. Rarely, a more extreme form of cardiac dysfunction occurs at the time of hemorrhage with cardiomyopathy, hypotension, and pulmonary edema.

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The routine use of continuous electroencephalographic (cEEG) recordings in intensive care demonstrates that clinical seizures in critically ill patients, both with neurologic and nonneurologic conditions, are the tip of the iceberg regarding seizure frequency in this vulnerable population. Nonconvulsive seizures are detected in 10% to 30% of critically ill patients with altered mental status and in up to 60% of critically ill patients who have been witnessed to have prolonged clinical seizures earlier during their hospital stay.¹ The presence of seizures in this population is associated with worse functional outcome at discharge,² multiple markers of disease severity,³ and long-term neurologic injury.⁴ The routine use of cEEG monitoring and quantitative EEG (qEEG) analysis leads to the diagnosis of electrographic seizures and timely modification of treatment,⁵ which may affect early- and long-term disability and mortality. The use of cEEG has become standard care in the intensive care unit (ICU). Its use is strongly recommended in cases of recent status epilepticus, unexplained coma, altered mental status, and behavioral changes and also in most patients with intracranial hemorrhage, as these cases are more likely to be associated with subclinical seizures.¹

Among patients without primarily neurologic conditions, the presence of a seizure may be the first indication of a central nervous system (CNS) complication; delay in recognition and treatment of seizures is associated with an increased risk of mortality.⁶ Thus, rapid diagnosis, treatment, and follow-up of epileptic activity and seizures is crucial. In addition, since epilepsy affects around 2% of the population, patients with a predisposition to seizures may enter the ICU for treatment of other systemic problems. These patients are at high risk for developing seizures and status epilepticus in the context of acute or severe illness.⁷ Patients developing status epilepticus often require critical care management as treatment escalates to include multiple antiseizure medications and sedatives that require airway protection, hemodynamic support, and close monitoring.

Status epilepticus refers to prolonged seizure activity beyond the usual duration of a self-limited, isolated seizure; it may be the primary indication for admission to the ICU, or it may occur in ICU patients. Seizures that persist longer than 5 minutes or recurrent seizures without recovery to the patient's neurologic baseline between seizures should be considered and treated as status epilepticus.⁸ Status epilepticus can also be subclinical, with little or no overt signs of seizures. Of patients monitored with EEG as part of a coma evaluation, 8% to 10% were reported to be in nonconvulsive status epilepticus (NCSE).⁹

Recognizing the risk factors, clinical presentation, diagnosis, and management of clinical and subclinical seizures in the ICU is a frequent task for the intensivist. Recent technologic advances enormously facilitate the diagnosis and follow-up of these patients in real time. Communication between the ICU team and the neurology/neurophysiology team is crucial to offer the patient timely therapy that significantly affects outcome.⁶

EPIDEMIOLOGY

Limited data are available on the epidemiology of seizures in the ICU. A 10-year retrospective study of all ICU patients with seizures revealed that 7 patients had seizures per 1000 ICU admissions.¹⁰ A 2-year prospective study of medical ICU patients identified 35 with seizures per 1000 admissions.¹¹ In a retrospective analysis of 570 patients undergoing continuous EEG monitoring, seizures were detected in 110 patients

(19%). Of those patients with seizures, the majority were in ICUs at the time of the EEG (n = 101; 89%). In this series, 92% of the recorded seizures were nonconvulsive, requiring EEG for the diagnosis.¹²

Up to 34% of hospital inpatients experiencing a seizure die during their hospitalization.¹¹ In a study of medical ICU patients, having even one seizure while in the ICU for a nonneurologic reason doubled in-hospital mortality.¹¹ Incidence estimates for status epilepticus in the United States and Europe vary from 10.3 to 41/100,000.^{3,13,14,15} The incidence has a bimodal distribution, peaking in young children and in the elderly.^{16,13} Mortality estimates vary widely, but data suggest that prolonged seizure duration is a negative prognostic factor. For patients whose generalized convulsive status epilepticus (GCSE) resolves within 30 to 59 minutes, the reported mortality is 2.7%, whereas patients seizing for more than 60 minutes have a mortality of 32%.¹⁷ If GCSE develops de novo in hospitalized patients, the mortality is 61%.¹⁸ For patients in NCSE, the mortality has been reported as high as 57%⁶ and correlates with the underlying cause, severe impairment of mental status, and the development of complications, especially respiratory failure and infection.¹⁹ Determining the contribution of status epilepticus to mortality is challenging due to the large impact of the underlying etiology on outcomes.

Table 54-1 summarizes the most common causes of status epilepticus in adults in the community. Almost 50% of the cases were attributed to cerebral vascular disease.²⁰ Antiseizure-drug noncompliance is the main cause of status epilepticus in patients with a previous history of epilepsy; CNS infection, stroke, and metabolic disturbances predominate in patients without previous seizures.⁷

Limited data are available concerning the functional abilities of GCSE survivors, and no data reliably permit distinction between the effects of status epilepticus and the effects of its causes. GCSE has the worst prognosis for neurologic recovery. Causes associated with increased mortality include anoxia, intracranial hemorrhages, tumors, infections, and trauma. In addition, intellectual ability declines as a consequence of status epilepticus.²¹ Survivors of status epilepticus often have memory and behavioral disorders out of proportion to the structural damage produced by the cause of their seizures. Case reports of severe memory deficits after prolonged complex partial status epilepticus have been published.²² Conversely, one prospective study of 180 children with febrile status epilepticus reported no deaths or new cognitive or motor handicap.²³ Experimental animal²⁴ and human epidemiologic²⁵ studies suggest that status epilepticus may be a risk factor in the development of future seizures. Whether treatment of prolonged seizures reduces the risk of subsequently developing epilepsy remains uncertain.

CLASSIFICATION

The most recent revision of the terminology and classification of seizures and epilepsy from the International League Against Epilepsy (ILAE) was published in 2010.²⁶ This new terminology abandons concepts such as dichotomous simple versus complex partial seizures, which implied the existence of only two possible states of awareness during seizures, in favor of more descriptive terms that may better represent the multiple possibilities of awareness, levels of interaction, responsiveness, and recollection seen in focal epileptic seizures (Table 54-2). The concept of focal and generalized seizures remains but is reinterpreted as the understanding of the pathophysiology of epilepsy

evolving away from a pure localization paradigm and more toward an understanding of cortical networks.

Focal seizures are defined by the presence of an epileptogenic network confined to one hemisphere or a single brain lobe; in generalized seizures, the epileptogenic network has bilateral hemispheric representation. These terms continue to be used in relation to the description of the clinical seizure initiation and presentation.

The new terminology emphasizes the etiology of epilepsy in three main groups: genetic, structural-metabolic, and unknown. These groups allow for epilepsy syndromes to move from one group to another as further research elucidates better understanding of specific clinical conditions over time. Electroclinical epilepsy syndromes remain at the core of the classification, in the hopes that their identification and study will advance our understanding of these conditions. The classification of nonsyndromic epilepsies in the structural-metabolic and unknown categories remains in place and acknowledges the value of semiology, EEG, and imaging in establishing the localization and classification of the epilepsy type and origin. Careful description of the phenomenology of seizures, etiology, and localization are emphasized as an important part of the patient's care.

Seizures are the clinical manifestation of the underlying predisposition for abnormal excessive and synchronous brain activity that defines epilepsy. Seizures can affect all measurable brain functions and follow a predictable clinical presentation largely related to the site of origin of the epileptic activity and the pattern of propagation. The identification of clean semiological descriptions and findings is challenging in the ICU, except for observation of motor manifestations. ICU patients often have altered awareness and a decreased level of interaction due

to medications, hypotension, sepsis, or intracranial lesions; thus, the presentation of focal seizures may be difficult to establish by observation alone. Modifiers to the description of focal or generalized seizures have been included in the classification (Table 54-3) and can be applied to focal and generalized seizures and to status epilepticus. Seizure classification is based on the combination of the seizure description and modifiers. An ICU patient who has continuous, regular repetitive contractions in a stable muscle group in the right arm while awake and responsive can be classified as having focal right arm clonic status epilepticus without impairment of consciousness or awareness.

Epilepsia partialis continua, a special form of focal status epilepticus in which repetitive movements of epileptic origin affect a small area of the body, can sometimes continue relentlessly for months or years.

The ILAE continues to work toward revising and updating the current classification system. For the most recent information regarding this ongoing project, refer to www.ilae.org.²⁷

PATHOGENESIS AND PATHOPHYSIOLOGY

The causes and effects of status epilepticus at the cellular, brain, and systemic levels are interrelated, but their individual analysis is useful for understanding them and their therapeutic implications. The ionic events of a seizure follow the opening of ion channels coupled to excitatory amino acid receptors. From the standpoint of the intensivist, three channels are important, as their activation may raise intracellular free calcium to toxic levels: alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA), *N*-methyl-D-aspartate receptor

TABLE 54-1

Causes of Status Epilepticus in Adults Presenting from the Community

| PREVIOUS SEIZURES | NO PREVIOUS SEIZURES |
|-------------------------------|----------------------|
| COMMON | |
| Subtherapeutic anticonvulsant | Ethanol-related |
| Ethanol-related | Drug toxicity |
| Intractable epilepsy | CNS infection |
| | Head trauma |
| | CNS tumor |
| LESS COMMON | |
| CNS infection | Metabolic aberration |
| Metabolic aberration | Stroke |
| Drug toxicity | |
| Stroke | |
| CNS tumor | |
| Head trauma | |

CNS, central nervous system.

TABLE 54-2

2010 Revised ILAE Seizure Descriptors*

1. Focal onset seizures
 - a. Without impairment of consciousness or awareness
 - b. With observable motor or autonomic components
 - c. Subjective sensory or psychic phenomena
 - d. With impairment of consciousness or awareness/dyscognitive
 - e. Evolving to bilateral convulsive seizure
2. Generalized onset seizures
 - a. Tonic-clonic (in any combination)
 - b. Myoclonic-tonic/atonic (in any combination)
 - c. Absence
 - Typical absence
 - Atypical absence
 - With special features
 - Eyelid myoclonia
 - Myoclonic absence
 - d. Clonic
 - e. Tonic
 - f. Atonic

*Adapted from Berg A, Millichap J. The 2010 revised classification of seizures and epilepsy. *Continuum (Minneapolis)* 2013;19(3 Epilepsy):571-97.

TABLE 54-3

American Clinical Neurophysiology Society Proposed ICU terminology*

| TERM #1 LOCALIZATION | TERM #2 TYPE OF ACTIVITY | PLUS MODIFIERS | ADDITIONAL MODIFIERS |
|-------------------------|-----------------------------|--------------------------|-------------------------------|
| Generalized | Periodic discharges | Plus fast +F | Persistence (% of the record) |
| Lateralized | Rhythmic delta activity | Plus rhythmic +R | Duration |
| Bilateral independent | Spike and wave | Plus sharp morphology +S | Frequency (Hz) |
| Multifocal | | No + modifiers | Sharpness |
| | | | Polarity |
| | | | Absolute amplitude (uV) |
| | | | Stimulus induced |

Each column functions independently (choose one term from columns 1-3, and add the additional modifiers in column 4 for each EEG pattern).

*Adapted from Hirsch LJ. Classification of EEG patterns in patients with impaired consciousness. *Epilepsia* 2011;52(Suppl. 8):21-24.

(NMDAR), and metabotropic channels. These excitatory amino acid systems are crucial for learning and memory. Counterregulatory ionic events are triggered by the epileptiform discharge as well, such as the activation of inhibitory interneurons suppressing excitatory neurons via ionotropic γ -aminobutyric acid (GABA_A) synapses.

The cellular effects of excessive excitatory amino acid channel activity include the following: (1) generation of toxic levels of intracellular free calcium; (2) activation of autolytic enzyme systems; (3) production of oxygen free radicals; (4) generation of nitric oxide, which both enhances subsequent excitation and serves as a toxin; (5) phosphorylation of enzyme and receptor systems, making seizures more likely; and (6) an increase in intracellular osmolality, producing neuronal swelling. If adenosine triphosphate production fails, membrane ion exchange ceases, and neurons swell further. These events produce the neuronal damage associated with status epilepticus. Longer status epilepticus duration produces profound alterations and an increasing likelihood of becoming refractory to treatment.²⁸

Many other biophysical and biochemical alterations occur during and after status epilepticus. The mechanisms by which status epilepticus damages the nervous system have been reviewed.^{29,30} Absence status epilepticus is an exception; it consists of rhythmically increased inhibition and does not appear to produce clinical or pathologic abnormalities.³¹

The electrical phenomena of status epilepticus seen in the scalp EEG reflect the seizure type (e.g., absence status epilepticus begins with a 3-Hz spike-and-wave pattern). The sustained depolarizations that characterize status epilepticus alter the extracellular milieu, raising extracellular potassium, which subsequently exceeds the buffering ability of astrocytes.

The increased cellular activity of status epilepticus increases oxygen and glucose demands, and cerebral blood flow initially increases. After about 20 minutes, however, energy supplies are exhausted, causing local catabolism to support ion pumps, which is thought to be a major cause of epileptic brain damage. GCSE also produces life-threatening systemic effects.³² Excess secretion of epinephrine and cortisol cause systemic and pulmonary arterial pressures to rise dramatically at seizure onset and produce hyperglycemia. Muscular work accelerates heat production, increases core body temperature, and raises blood lactate levels. Airway obstruction and abnormal diaphragmatic contractions impair respiration. Carbon dioxide production increases markedly while excretion falls. The combined respiratory and metabolic acidosis frequently reduces the arterial blood pH to 6.9 or lower. The associated hyperkalemia has deleterious effects on cardiac electrophysiology and may propagate seizure activity. Coupled with hypoxemia and the elevation of circulating catecholamine levels, these conditions can produce cardiac arrest. Neurogenic pulmonary edema is the likely cause of death in many cases. Rapid termination of seizure activity is the most appropriate treatment; the restitution of ventilation and the metabolism of lactate quickly restore a normal pH.

After about 30 minutes of continuous convulsions, motor activity may diminish while electrographic seizures persist. Hypotension and hyperthermia ensue, and gluconeogenesis can fail, resulting in hypoglycemia. GCSE patients often aspirate oral or gastric contents, producing chemical pneumonitis or bacterial pneumonia. Rhabdomyolysis is common and may lead to renal failure. Compression fractures, joint dislocations, and tendon avulsions are other serious sequelae.

The mechanisms that terminate seizure activity are poorly understood. Leading candidates are inhibitory mechanisms, primarily GABAergic interneurons and inhibitory thalamic neurons.

CLINICAL MANIFESTATIONS

The ICU environment poses a challenge to early seizure recognition because of multiple factors: (1) the occurrence of nonconvulsive seizures in patients with impaired awareness, (2) the occurrence of seizures in patients receiving neuromuscular blockade and/or sedation, and (3) misinterpretation of nonepileptic abnormal movements and behaviors as seizures. ICU patients often have depressed consciousness

in the absence of seizures owing to their disease, its complications (such as hepatic³³ or septic³⁴ encephalopathy), or drug administration. A further decline in alertness may reflect a seizure, but unless actions are taken to make this diagnosis, seizures and even status epilepticus may go unrecognized.

Patients receiving neuromuscular blocking agents do not manifest motor signs of seizures. Patients with increased intracranial pressure (ICP) from primary brain injury, hepatic encephalopathy, or other critical illnesses may be both paralyzed and sedated, making identification of seizures challenging in the absence of EEG monitoring. Tachycardia, tachypnea, and hypertension are signs of seizure that can be misinterpreted as evidence of inadequate sedation or primary cardiorespiratory conditions.

Seizures are the second most frequent neurologic complication after encephalopathy in critically ill patients with non–primarily neurologic conditions,¹¹ making it imperative for ICU providers to be able to identify and suspect the presence of seizures in all patients with altered awareness in the ICU setting.

Generalized motor seizures and convulsive status epilepticus are more common in patients with a prior history of epilepsy in relation to acute illness or medication nonadherence. However, even among patients without a history of epilepsy, subtle clinical seizures and NCSE are increasingly recognized in the context of systemic illness or acute brain injury. Nonconvulsive seizures and NCSE occur in 10% to 30% of patients with altered mental status in the ICU. Risk factors include the presence of CNS infection (meningitis or encephalitis) and focal lesions such as a brain tumor or an area of encephalomalacia. Seizures in the ICU are often subtle and may be related to the anatomic location of the brain lesion. Minor twitching of the face or extremities, fluctuating levels of awareness or level of interaction, nystagmus or eye deviation, abnormal orofacial movements, and repetitive blinking are more commonly seen than generalized convulsive events. Continuous EEG monitoring is warranted in this population if seizures are suspected, since a delay in the diagnosis and treatment of NCSE likely leads to worse functional prognosis at discharge and increased mortality.³⁵

Patients with metabolic disturbances, anoxia, and other types of CNS injuries may demonstrate abnormal movements that can be mistaken for a seizure. Asterixis is a brief asynchronous loss of tone at the wrist or hip joints that can appear in the setting of metabolic encephalopathy. Stimulus-sensitive massive myoclonus after anoxia can be dramatic but usually self-abates in a few days. Controversy exists as to the epileptic origin of this disorder, and post-anoxic myoclonus has been reported in the presence of almost total cortical suppression.³⁶ Brain-injured patients may manifest paroxysmal sympathetic hyperactivity and associated rigidity or extensor posturing.³⁷ Patients with tetanus are awake during their spasms and flex rather than extend their arms as seizure patients do. Psychiatric disturbances in the ICU occasionally manifest as psychogenic nonepileptic events. As these events tend to cluster and manifest as dramatic convulsive episodes, they are often treated in the emergency department as refractory status epilepticus, which may prompt ICU admission. The clinical manifestations of seizures and status epilepticus depend on the type and the cortical area of abnormality. Tables 54-2 and 54-4 present the classification of epileptic seizures recognized by the ILAE; all of these may be seen in the ICU.

Convulsive seizures or status epilepticus are described when the main characteristic of the seizures is a motor phenomenon. The primary motor manifestations can be described as tonic when there is a sustained muscle contraction of a group of muscle in a regional or generalized distribution. Tonic seizures are often associated with a vibration or tonic tremor, focal tonic seizures can be followed by versive seizures in which there is a forced, sustained, and unnatural rotation of the head or the eyes to one side and away from the midline. Clonic seizures are regular, predictable, rhythmic, and repetitive contractions of a muscle group. Myoclonic seizures are brief, involuntary muscle contractions; they are unpredictable and irregular. Motor seizures can manifest in any combination of the described motor

TABLE 54-4 **2010 Revised ILAE Classification of Seizures***

1. Elementary motor seizure
 - a. Myoclonic
 - b. Clonic
 - c. Tonic
 - d. Versive
 - e. Spasms
2. Negative motor events
 - a. Atonic
 - b. Negative myoclonic
 - c. Akinetic
 - d. Hypomotor/behavioral arrest
3. Complex motor seizures/automotor
 - a. Oroalimentary automatisms
 - b. Mimetic automatisms
 - c. Manual or pedal automatisms
 - d. Gestural automatisms
 - e. Dacrystic
 - f. Vocal
 - g. Hyperkinetic/hypermotor
4. Dyscognitive seizures
5. Autonomic seizures
6. Auras
 - a. Sensory
Epigastric, visual, olfactory, auditory, gustatory, somatosensory, cephalic or pain
 - b. Psychic-experiential
Affective, mnemonic, composite perceptual, hallucinations
 - c. Autonomic

*Adapted from Berg A, Millichap J. The 2010 revised classification of seizures and epilepsy. *Continuum (Minneapolis)* 2013;19(3 Epilepsy):571-597.

phenomena, in any order; they can involve the axial muscles and extremities from the beginning of the seizure without warning, or they can start regionally in one body part and progress into a generalized motor seizure.

When a patient with GCSE is treated with antiseizure drugs in inadequate doses, visible convulsive activity may stop, but the electrochemical seizure continues. A prospective evaluation of 164 patients showed that nearly half manifested persistent electrographic seizures in the 24 hours after clinical control of convulsive status epilepticus.³⁸ Thus, EEG monitoring after control of convulsive status epilepticus is essential in directing therapy.³⁹

Patients typically begin to awaken within 15 to 20 minutes after the successful termination of status epilepticus; many regain consciousness much faster. Patients who do not start to awaken after 20 minutes should be assumed to have entered NCSE. Careful observation may disclose slight motor activity as described above. However, patients may present in NCSE without an inciting episode of GCSE. Failure to recognize NCSE is common in patients presenting with nonspecific neurobehavioral abnormalities such as delirium, lethargy, bizarre behaviors, cataplexy, or mutism.⁴⁰ A high suspicion of this disorder should be maintained in ICU patients with unexplained alteration of consciousness or cognition.

■ DIAGNOSTIC APPROACH

Observation is very important when a patient has a single clinical seizure, as this is the time to collect evidence of a focal onset suggestive of structural brain disease. The postictal examination is similarly valuable; language, motor, sensory, or reflex abnormalities after an apparently generalized seizure may uncover evidence of focal pathology.

Seizures in ICU patients have several potential causes that must be investigated. Drugs are a major cause of ICU seizures, especially in the setting of diminished renal or hepatic function or when the blood-brain barrier is breached. Imipenem-cilastatin⁴¹ and fluoroquinolones⁴² can lower the seizure threshold, especially in patients with renal

dysfunction. They should be avoided in patients at risk for seizures. Other antibiotics, especially β -lactams, are also implicated.⁴³ Sevoflurane, a volatile anesthetic agent, is dose-dependently epileptogenic in patients with no predisposition to seizures.⁴⁴

Recreational drugs are overlooked offenders in patients presenting to the ICU. Acute cocaine or methamphetamine intoxication is characterized by a state of hypersympathetic activity followed by seizures.⁴⁵ Although ethanol withdrawal is a common cause of seizures, discontinuing any hypnotic agent may prompt convulsions 1 to 3 days later. Narcotic withdrawal may produce seizures in the critically ill.¹¹ In the absence of a structural etiology for the seizure, complete toxicologic, infectious, and metabolic screening should be performed.

Serum glucose, electrolyte concentrations, and serum osmolality should also be measured. Nonketotic hyperglycemia^{46,47} and hyponatremia can precipitate both focal and generalized seizures. Seizure activity may infrequently be the first presenting sign of diabetes mellitus. Hypocalcemia rarely causes seizures beyond the neonatal period; its identification on analysis must not signal the end of the diagnostic workup. Hypomagnesemia has an equally unwarranted reputation as the cause of seizures in malnourished alcoholic patients.

The physical examination should emphasize assessment for both global and focal abnormalities of the CNS. Evidence of cardiovascular disease or systemic infection should be sought and the skin and fundi examined closely. The need for imaging studies should be addressed as soon as the clinical seizure is controlled. The management of epileptic seizures and convulsive status epilepticus should not be delayed by the need to obtain images or neurophysiologic data. If possible, treatment and diagnostic strategies should be instituted simultaneously. A prospective study in medical ICU patients determined that 38 of 61 patients (62%) had a vascular, infectious, or neoplastic explanation for their seizures.¹¹ Magnetic resonance imaging (MRI) should be performed on all ICU patients with new-onset seizures. Many ICP monitors are compatible with MRI. Patients who need cerebrospinal fluid analysis always require imaging of the brain first. When CNS infection is suspected, empiric antibiotic treatment should be started while these studies are being performed.

EEG is a vital diagnostic tool for evaluating patients with diagnosed or suspected seizures. Focal seizures usually show EEG abnormalities that begin in the region of cortex that produces seizures. Primary generalized seizures show bilateral hemispheric involvement from the onset. Postictal slowing or an asymmetric EEG amplitude provides clues as to the focal cause of the seizures, and epileptiform activity helps classify the type and origin of epileptic activity and may guide treatment. An emergency EEG is necessary to exclude NCSE soon after clinical seizures have apparently been controlled (Fig. 54-1).

Continuous EEG can help establish the diagnosis, frequency, localization, and duration of seizures. It also aids in the evaluation of the response to treatment and degree of encephalopathy. It offers continuous and often long-term data and real-time feedback that can be lifesaving in the ICU, with few added risks or costs to the patient.⁴⁸ Given the high prevalence of NCSE in this patient population and the low relative risks associated with cEEG, a low level of suspicion should trigger such evaluation. The advent of modern techniques of EEG analysis and trend analysis as in qEEG are invaluable in the ICU, as they allow the reviewer to identify trends of electrographic activity over longer periods of time, identify subtle asymmetries, and aid in the identification and quantification of EEG seizures. The use of this technology has gained recent attention and interest from the EEG and the ICU community. Indications for cEEG include patients with altered mental status and history of epilepsy, fluctuating level of consciousness, acute brain injury, following convulsive status epilepticus, and abnormal stereotypical movements or behaviors. Other indications include assessing the level of sedation, vasospasm monitoring, and monitoring the response to antiepileptic medications or sedative weaning.⁴⁹ In the context of hypothermia after cardiac arrest, cEEG may provide prognostic information⁵⁰ and should be used throughout the cooling protocol and until rewarming has been completed. The value of cEEG in

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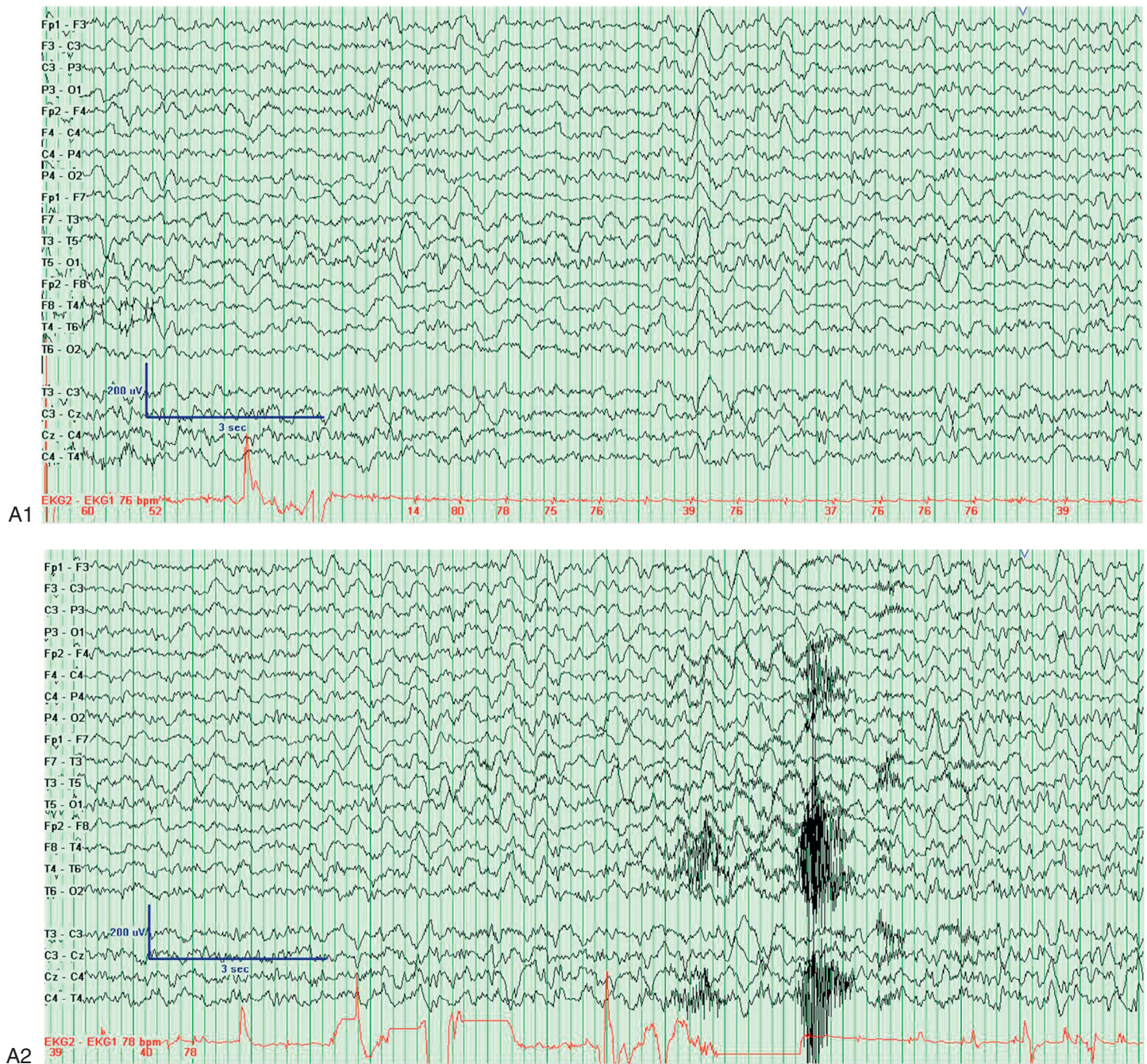


FIGURE 54-1 ■ **A**, Electroencephalographic (EEG) recordings during status epilepticus in an 18-year-old comatose patient with autoimmune encephalitis. Panels illustrate onset (A1), evolution (A2-A6), and subsequent offset (A7) of a seizure. **B**, Quantitative EEG display demonstrating recurrent nonconvulsive seizures in the same patient.

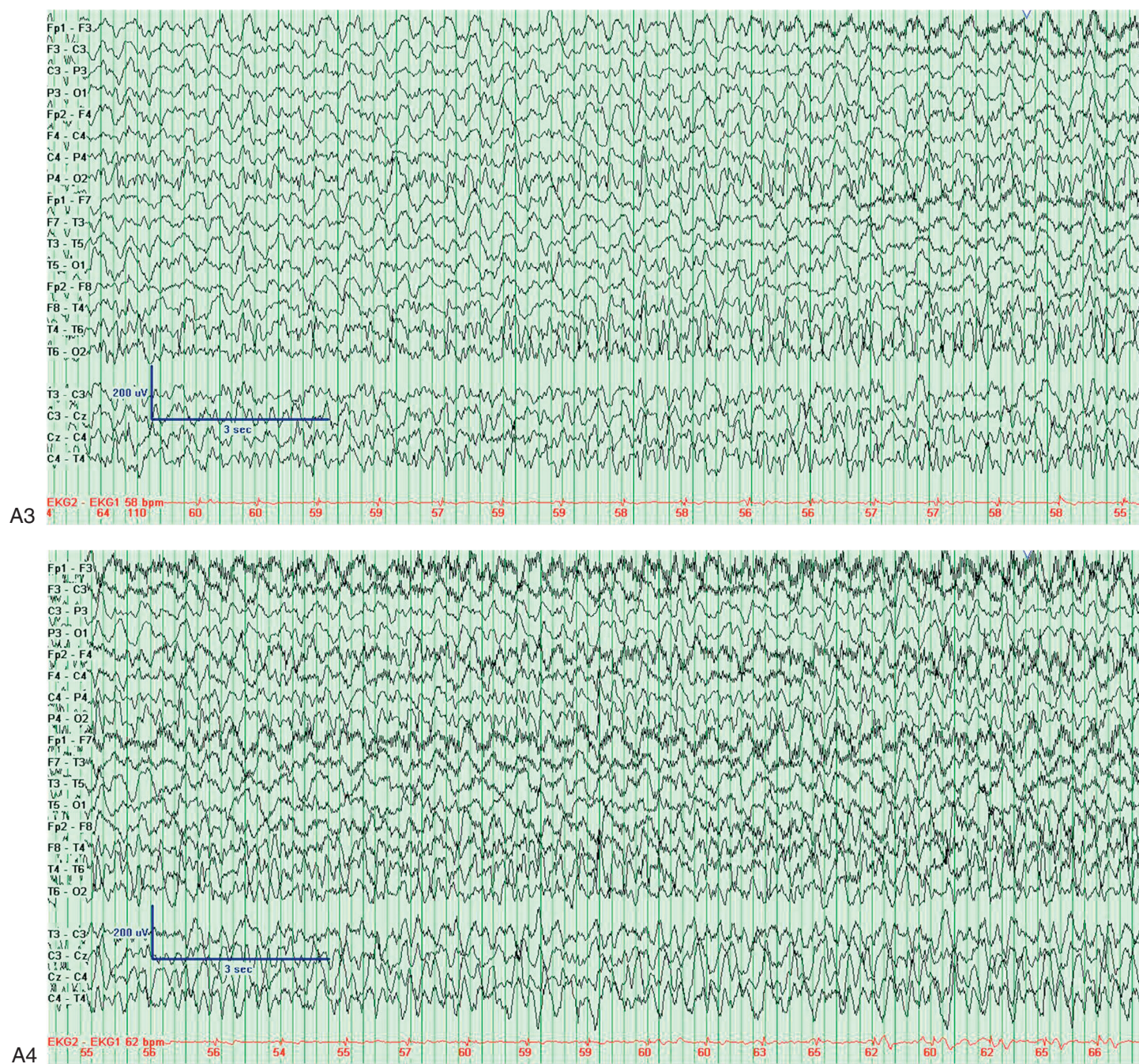


FIGURE 54-1, cont'd

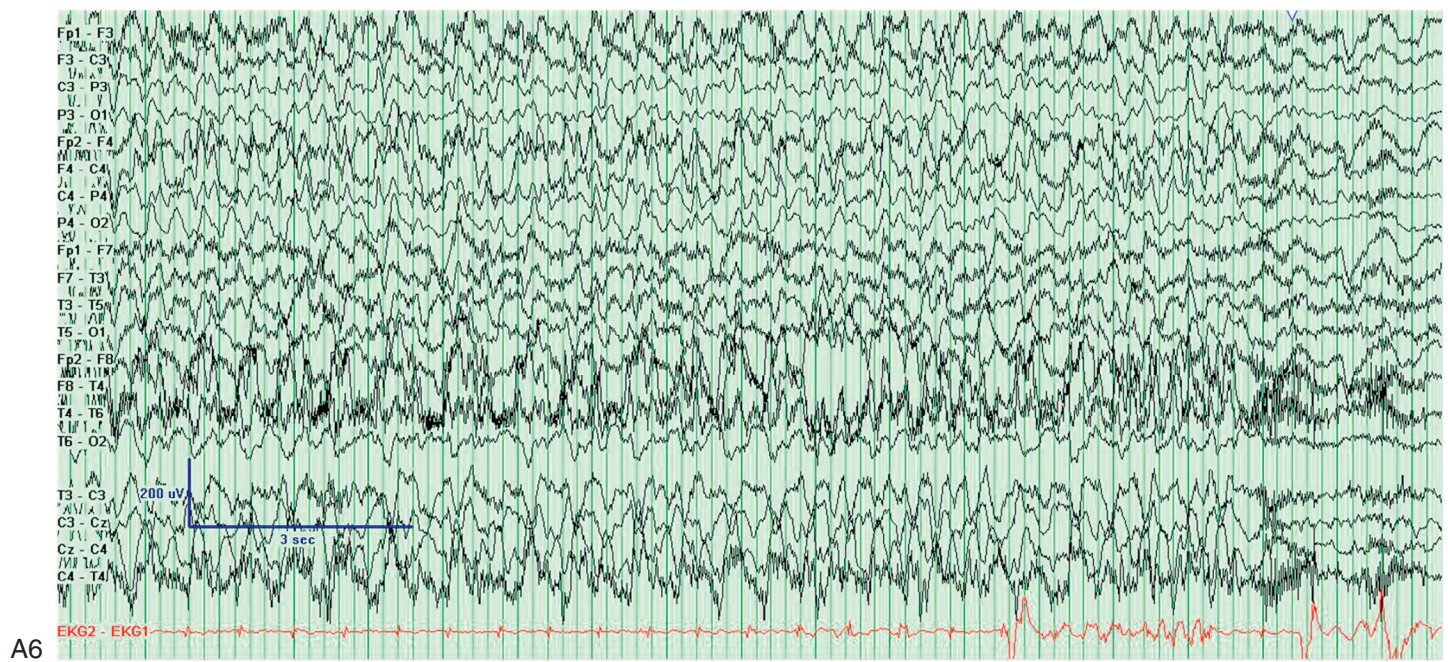
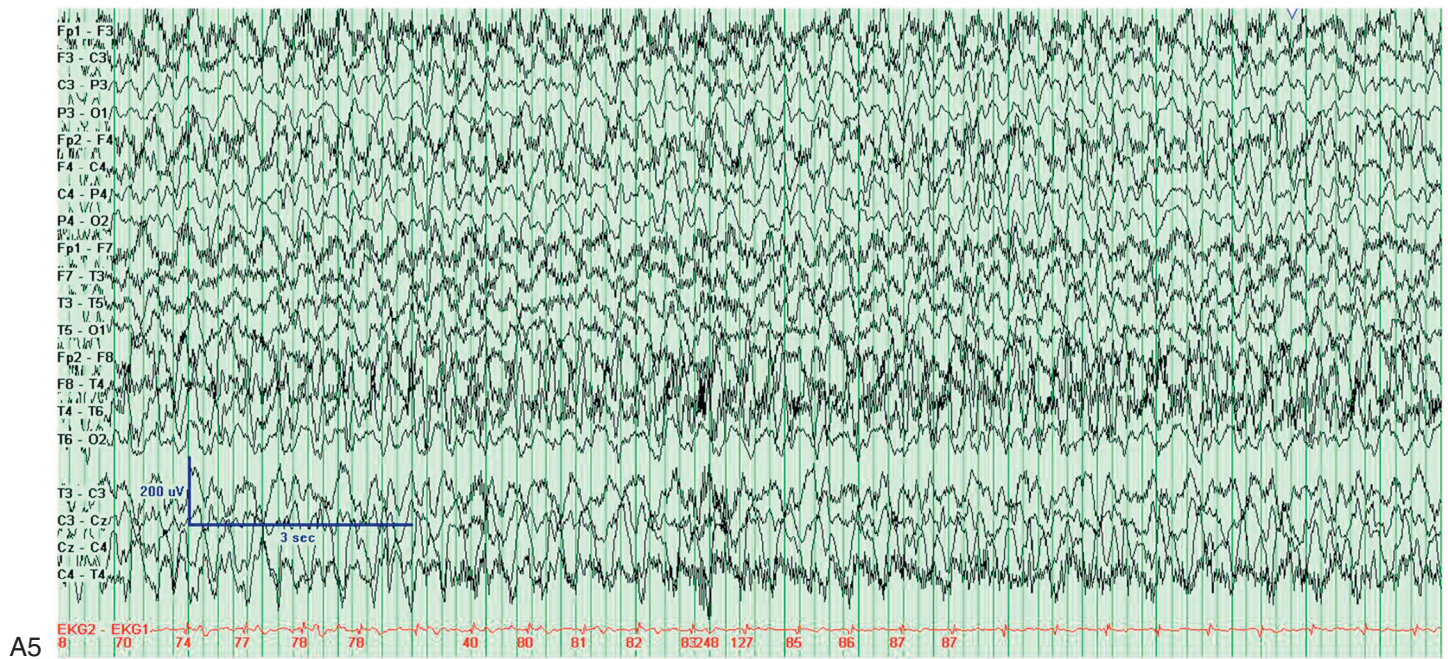
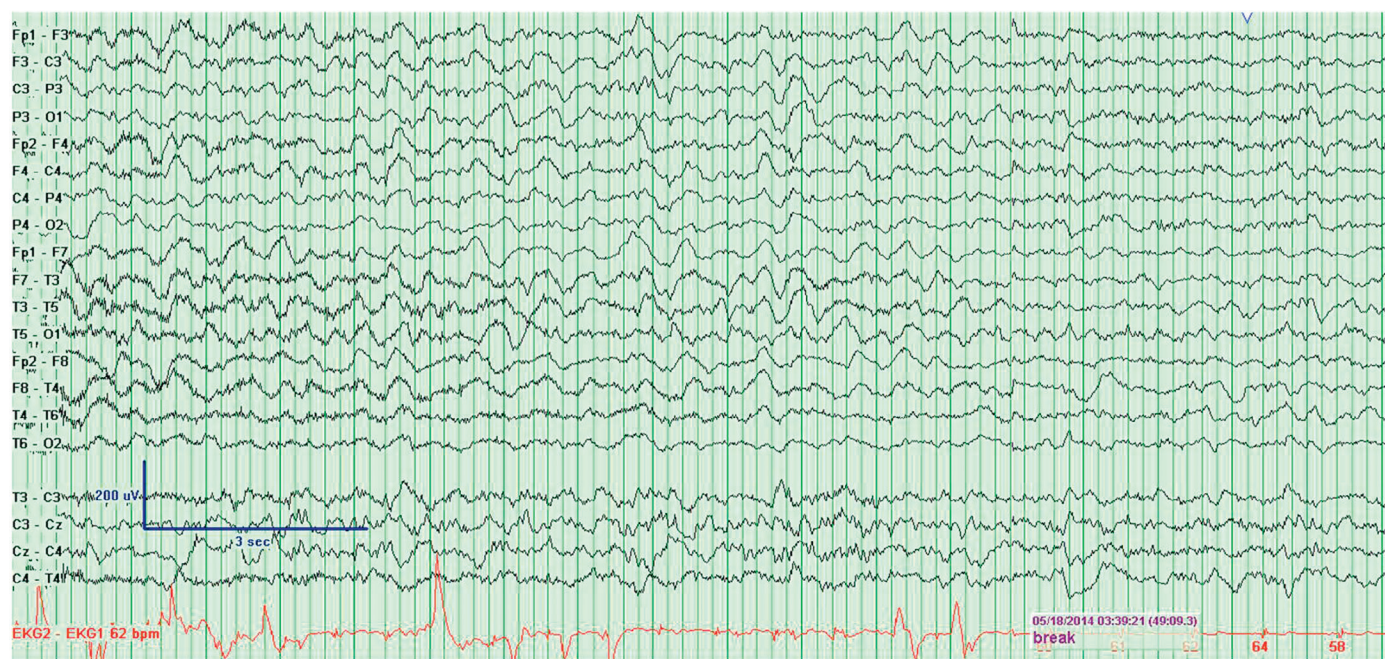


FIGURE 54-1, cont'd

A7



B

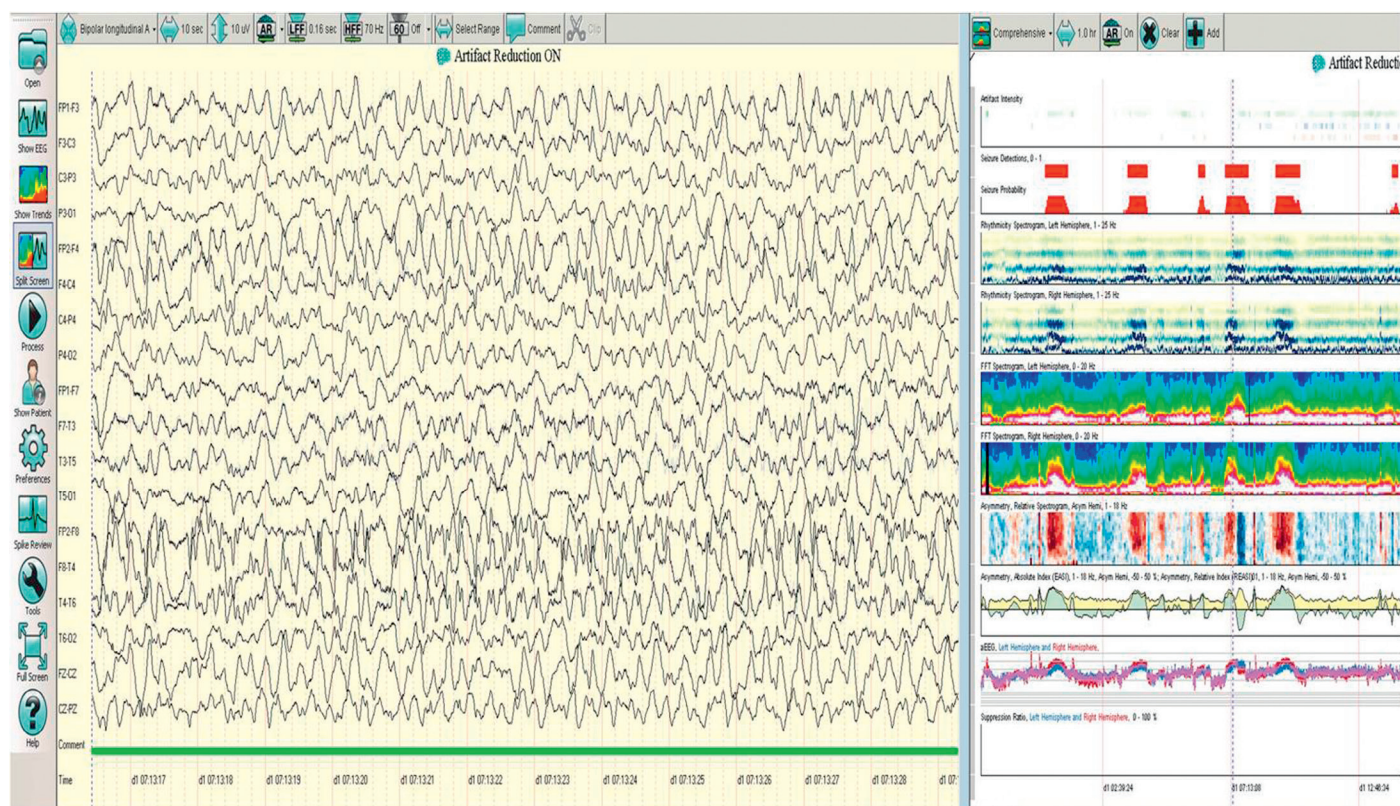


FIGURE 54-1, cont'd

the long-term evaluation of severe anoxic encephalopathy with or without myoclonus remains to be determined.

More than half of the seizures diagnosed in ICU patients with EEG monitoring are detected within the first 30 minutes of recording; a third of these patients are found to have interictal epileptiform discharges within the same period of time. The risk of seizures diminishes if no epileptiform abnormalities are seen within 2 hours.⁵¹ A routine EEG, however, may miss the chance to diagnose seizures in this population, and continuous EEG recording is recommended. The presence of NCSE, lateralized periodic discharges, generalized periodic discharges, and an abnormal EEG background is associated with worse outcomes.²

The interpretation of EEG findings seen in the ICU is challenging for neurophysiologists and clinicians alike. In an effort to unify criteria and establish the clinical significance of EEG patterns, the subcommittee of critical care monitoring of the American Clinical Neurophysiology Society has proposed a classification system for EEG patterns in patients with impaired consciousness.⁵² The classification system proposes descriptive grouping of EEG activity by location, periodicity, frequency, and morphology, followed by a series of modifiers (Table 54-3). The use of this system has been validated with acceptable interrater reliability. The use of standardized terminology will help advance research and establish clinical correlates that will affect ICU care.

■ MANAGEMENT APPROACH

Treating Isolated Seizures

Administering antiseizure drugs to an ICU patient experiencing one or a few seizures in the absence of structural CNS lesions requires consideration of a provisional cause, estimation of the likelihood of recurrence, and recognition of the utility and limitations of antiseizure drugs. For example, the occurrence of seizures during ethanol withdrawal does not necessarily indicate the need for chronic treatment. The patient may need prophylaxis against delirium tremens, but the few seizures themselves seldom require treatment. Patients with convulsions during barbiturate or benzodiazepine withdrawal, in contrast, should receive short-term treatment with a benzodiazepine to prevent status epilepticus. Prolonged or frequent seizures caused by metabolic disturbances can be treated temporarily with benzodiazepines while the abnormality is being corrected. For example, treatment of patients with focal seizures related to nonketotic hyperglycemia should be directed at correction of the hyperglycemia and hypovolemia rather than antiseizure drug therapy.⁴⁷ On the other hand, ICU patients with CNS disease who have even one seizure should be given chronic antiseizure-drug therapy. Initiating this treatment after the first *unprovoked* seizure may help prevent subsequent epilepsy,⁵³ although there is considerable difference of opinion regarding this concept.⁵⁴ If a critically ill patient's clinical condition would be seriously complicated by a convulsion, antiseizure drug therapy even after the first seizure may be vitally important.

In general, IV formulations are preferred for critically ill patients to avoid variability in drug absorption and metabolism. In the United States, IV formulations of levetiracetam, lacosamide, phenytoin/fosphenytoin, valproate, and phenobarbital are available.

Levetiracetam is a newer antiseizure drug that is being used increasingly in ICUs for seizure treatment and prophylaxis.⁵⁵ The recommended initial dose is 500 to 1000 mg per day every 12 hours. Monitoring of serum concentrations is not indicated. The efficacy of doses >3000 mg has not been established. Levetiracetam is efficacious against a wide variety of seizure types, is generally well tolerated, has minimal drug-drug interactions, and is not metabolized by the liver. Renal failure requires dose adjustments, and supplementary doses should be given after hemodialysis.

Lacosamide was approved as adjunctive therapy for focal onset seizures in adults in 2008 and is commonly used in ICUs given its efficacy and favorable side effect profile. It has a novel mechanism of action and has been studied for use in status epilepticus. The initial

dose is 100 mg twice a day, to be increased based on response and tolerability to a recommended dose of 150 to 200 mg twice a day. No target serum concentration has been established. It has no known drug-drug interaction, but dose adjustments for renal and hepatic impairment are recommended. It has not been studied in severe hepatic failure. The most common side effects include PR prolongation and hypotension.

Despite growing evidence of deleterious adverse effects on cognition, fever, and increased risk of poor outcome,^{56,57} phenytoin is still frequently selected for prophylaxis or treatment of seizures. It is indicated for all seizure types at a dose of 100 mg two to four times per day, with target serum levels of 10 to 20 µg/mL. Hypotension and arrhythmias may complicate IV administration. Because of the rare occurrence of third-degree atrioventricular block, an external cardiac pacemaker should be available when patients with known conduction abnormalities receive IV phenytoin. Phenytoin requires propylene glycol as a solvent, is highly protein bound, and free serum levels can vary widely depending on nutritional status. The phenytoin prodrug fosphenytoin is water soluble; local adverse effects are less common with fosphenytoin than with IV administration of phenytoin, although cardiovascular complications are just as frequent.^{58,59} Fosphenytoin is dosed by phenytoin-equivalent units, and no dosage adjustments are needed when converting patients from phenytoin to fosphenytoin. It is rapidly converted to phenytoin in vivo, and free phenytoin levels after fosphenytoin administration do not differ markedly from those of phenytoin. If seizures recur despite a serum phenytoin level of 10 to 20 µg/mL (corresponding to an unbound concentration of about 1 to 2 µg/mL if the albumin is normal), a second agent is typically required. Both renal and hepatic dysfunction interferes with metabolism and excretion of phenytoin; serum levels should be monitored closely. Adverse reactions to phenytoin and other antiseizure drugs have been reviewed elsewhere.⁶⁰

Due to its efficacy for generalized seizures, valproate may be the agent of choice for patients with a history of primary generalized epilepsy presenting with seizures. Caution is advised in patients with traumatic brain injury, as a trend toward higher mortality rates was seen in a trial of valproate versus phenytoin for prevention of post-traumatic seizures.⁶¹ The recommended starting dose is 10 to 15 mg/kg/day, targeting total serum concentrations of 50 to 100 µg/mL. Valproate is 80% to 90% protein bound and does not require dose adjustment in renal impairment. Lower doses should be used in hepatic impairment, and it is contraindicated in severe hepatic impairment. Side effects of chronic valproate therapy are numerous, including hyperammonemia, thrombocytopenia, hepatotoxicity, pancreatitis, as well as many drug-drug interactions.

Phenobarbital remains a useful antiseizure drug for patients who continue to have seizures or are intolerant of other antiseizure drugs. Initial dose recommendations are 1 to 3 mg/kg/day in one to two doses, with a target serum concentration of 20 to 40 µg/mL. Hepatic and renal dysfunction alter phenobarbital metabolism and require close monitoring of serum levels. Sedation is the major adverse effect; allergy to the drug occurs rarely.

Treating Status Epilepticus

The evaluation and management of status epilepticus has been reviewed recently.¹ The definition of status epilepticus has evolved to include continuous clinical and/or electrographic seizures lasting for 5 minutes or more, or recurrent seizures without recovery to the patient's neurologic baseline between seizures. Previous definitions included seizure activity lasting 30 minutes or more, but there is evidence that permanent neuronal injury may occur before this cut-off, and seizures lasting more than 5 minutes often do not stop spontaneously.¹

Figure 54-2 shows a management algorithm for status epilepticus, and Table 54-5 summarizes the management approach including details on drug administration.¹ Both GCSE and NCSE have been associated with increased morbidity and mortality and should be approached as neurologic emergencies. General ICU considerations include airway

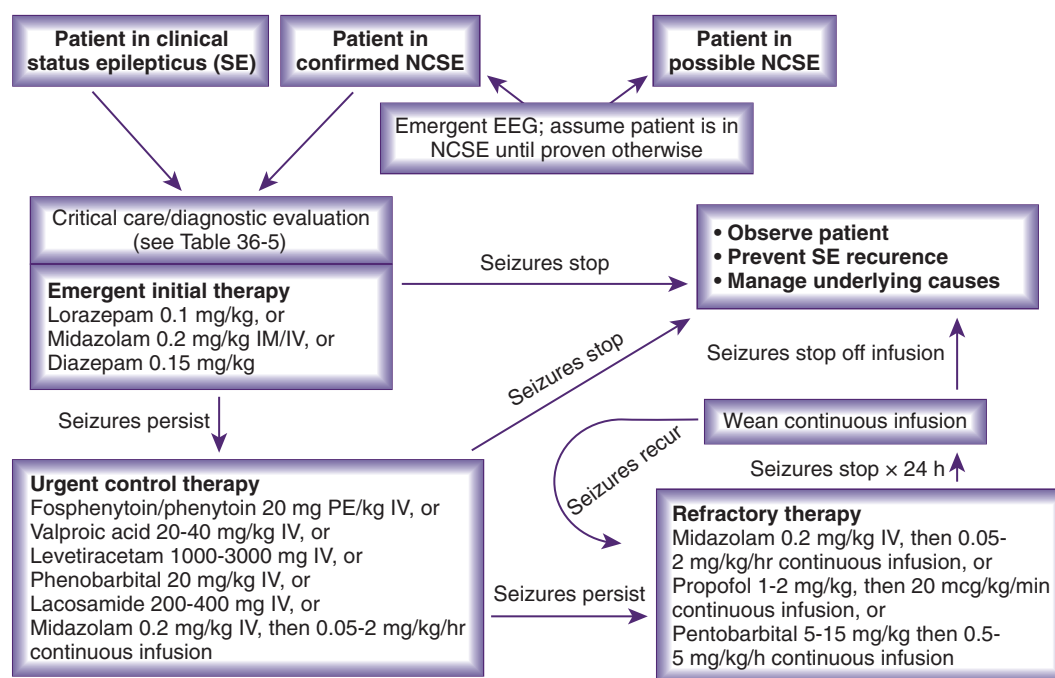


FIGURE 54-2 ■ Management algorithm for status epilepticus; NCSE, nonconvulsive status epilepticus; SE, status epilepticus.

protection, rapid exclusion of metabolic abnormalities (in particular, hypoglycemia), obtaining IV access, and ensuring hemodynamic stability. Antiseizure treatment should be initiated as soon as the diagnosis of status epilepticus has been established. The goal is the termination of clinical and electrographic seizure activity as soon as possible. The treatment approach has been subdivided into emergent initial therapy, urgent control therapy, and treatment of refractory status epilepticus.

Emergent initial therapy refers to the administration of first-line agents for termination of seizure activity. There is general consensus that benzodiazepines are the agents of choice as initial therapy. A large multicenter clinical trial compared multiple first-line regimens and found that the highest success rate was achieved with lorazepam.⁶² Preferred administration routes include IV (if IV access is available) and intramuscular (IM) injection, but buccal, nasal, or rectal routes are possible. Lorazepam is the agent of choice if IV access is available; midazolam is preferred for the IM route.⁶³ Diazepam is commonly used for rectal administration. Given the potential concern of respiratory depression with benzodiazepines, a randomized, controlled trial showed that patients treated with lorazepam had lower rates of respiratory or circulatory complications compared with placebo.⁶⁴ The initial dosing for lorazepam is 0.1 mg/kg IV, up to 4 mg per dose, which may be repeated after 5 to 10 minutes. Midazolam is given at a dose of 0.2 mg/kg IM or IV up to a maximum of 10 mg. Some advocate even higher doses for either of these benzodiazepines. In Europe, an IV formulation of clonazepam is available and has been used as emergent initial therapy. From a pharmacokinetic perspective, benzodiazepines are rapidly redistributed, resulting in a short duration of action. Hence, emergent initial therapy should be seamlessly followed by urgent control therapy that targets rapid attainment of therapeutic levels of conventional antiseizure drugs. If benzodiazepines fail to control seizures, urgent control therapy is initiated for seizure termination. If seizures are controlled by benzodiazepines, urgent control therapy targets prevention of seizure recurrence.

As with the treatment of isolated seizures in the ICU, IV formulation is preferred, especially since therapeutic drug levels can be achieved significantly faster. Phenytoin/fosphenytoin, valproate, levetiracetam, phenobarbital, and continuous infusion of midazolam have all been studied for urgent treatment. Additionally, lacosamide has emerged as an option to treat status epilepticus but has mostly been

investigated in refractory status epilepticus.^{65,66} Dosing of these drugs in status epilepticus is outlined in Table 54-5.

Refractory status epilepticus refers to status epilepticus that does not respond to a standard treatment regimen. There is controversy regarding this definition, but most experts agree that treatment has failed if seizures persist or recur after adequate doses of an initial benzodiazepine followed by one conventional antiseizure drug.¹ Continuous EEG monitoring is typically required to exclude ongoing electrographic seizure activity. It may be reasonable to attempt management of recurrent seizures with additional intermittent bolus therapy of alternate antiseizure drugs, provided the patient is clinically stable and has not required intubation for airway protection. Once it has been determined that intermittent bolus therapy has failed, treatment should be quickly escalated to a continuous infusion. The most commonly used drugs are midazolam, propofol, pentobarbital, and thiopental. Dosing recommendations are listed in Table 54-5. Patients who require any of these treatments will typically require mechanical ventilation and close cardiovascular monitoring. There is insufficient evidence to recommend any of these agents over another. Midazolam is the preferred agent at our institution because of its high efficacy in adults and children,^{67,68} its water solubility, and the lower incidence of cardiovascular adverse effects compared to pentobarbital or propofol. However, terminal half-lives of three to eight times normal have been reported with extended administration.⁶⁹ Propofol is reported to be effective in refractory status epilepticus, but comparisons with other agents have shown mixed results.^{70,71} Especially in younger patients, the risk of propofol-related infusion syndrome needs to be considered, particularly if high doses are required to control seizures. Severe hypotension is the most frequent side effect of pentobarbital therapy and is associated with increased mortality.⁷² Increases in nosocomial respiratory tract infection have been reported in patients treated with pentobarbital infusion.⁷³

Once clinical or nonconvulsive seizures have been controlled for about 24 to 48 hours, a gradual withdrawal of the continuous infusion should be initiated. If seizures recur upon withdrawal, the continuous infusion should be resumed until seizures are controlled. The addition of other antiseizure agents or other therapies such as hypothermia, immunomodulation, or neurosurgical resection of the seizure focus may be considered at that point.

TABLE 54-5 Treatment Approach to Status Epilepticus

Appropriate critical care treatment should be provided as soon as possible and simultaneously with emergent initial therapy for seizures. Treatment should be escalated quickly until seizures are controlled.

- 1a. Critical care treatment (dictated by clinical circumstances):
 - a. Intubation for airway protection and mechanical ventilation
 - b. Vital sign monitoring
 - c. Peripheral IV access
 - d. Treatment of hypotension with vasopressors
 - e. Finger stick blood glucose
 - f. Nutrient resuscitation (thiamine before dextrose)
 - g. Hypertension may be related to ongoing seizure activity and termination of status epilepticus often substantially corrects it. Additionally, many agents used to terminate status epilepticus can produce hypotension.
- 1b. Emergent initial therapy with benzodiazepines
 - a. Lorazepam 0.1 mg/kg up to 4 mg per dose, may repeat after 5-10 min
 - b. Midazolam 0.2 mg/kg IM/IV up to 10 mg
 - c. Diazepam 0.15 mg/kg up to 10 mg per dose, may repeat after 5 min
2. Urgent control therapy—antiseizure drugs available in IV formulations
 - a. Fosphenytoin/phenytoin 20 mg PE/kg IV, may repeat bolus of 5 mg/kg IV
 - b. Valproic acid 20-40 mg/kg IV, may repeat bolus of 20 mg/kg IV
 - c. Levetiracetam 1000-3000 mg IV
 - d. Phenobarbital 20 mg/kg IV, may repeat bolus of 5-10 mg/kg
 - e. Lacosamide 200-400 mg IV
 - f. Midazolam bolus 0.2 mg/kg IV, followed by 0.05-2 mg/kg/h continuous infusion
3. Refractory therapy—continuous infusion of antiseizure drugs, titrated to either seizure cessation, suppression-burst, or complete suppression on cEEG.
 - a. Midazolam bolus 0.2 mg/kg IV, followed by 0.05-2 mg/kg/h continuous infusion
 - b. Propofol bolus 1-2 mg/kg, followed by 20 mcg/kg/min continuous infusion, titrate up to 30-200 mcg/kg/min
 - c. Pentobarbital 5-15 mg/kg, may repeat bolus of 5-10 mg/kg, followed by 0.5-5 mg/kg/h continuous infusion
4. Treat complications

Complications of status epilepticus are numerous and can involve multiple organ systems. In particular, convulsive status epilepticus is associated with cardiac complications such as hypertension and tachycardia, as well as rhabdomyolysis and hyperthermia. Respiratory complications including respiratory failure, hypoxia, and neurogenic pulmonary edema may be seen. Status epilepticus is associated with neuronal damage and cerebral edema with increased intracranial pressure, which may require intracranial pressure monitoring and aggressive treatment with hypertonic agents.

KEY POINTS

1. Seizures and status epilepticus are common in ICU patients and are associated with high morbidity and mortality.
2. Observation is crucial when a patient has a single seizure. Post-ictal language, motor, sensory, or reflex abnormalities after a generalized seizure indicate focal pathology.
3. Seizures persisting longer than 5 minutes or two or more discrete seizures without neurologic recovery in between should be treated as status epilepticus. Patients who do not regain consciousness within 20 minutes after clinical seizure cessation should be considered to have entered NCSE, and cEEG monitoring is essential in directing the course of treatment.
4. The ICU patient with CNS disease who has even one seizure should be given chronic antiseizure drug therapy. This therapy should be reviewed before discharge.
5. Emergent initial therapy for treatment of status epilepticus is benzodiazepines (lorazepam, midazolam, diazepam) followed by urgent control therapy with IV formulations of levetiracetam, valproate, phenytoin/fosphenytoin, phenobarbital, or lacosamide. Status epilepticus refractory to an initial benzodiazepine and an appropriately chosen and dosed conventional antiseizure drug should be treated with continuous infusion of midazolam, barbiturates, or propofol.

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Abnormal neuromuscular function may precipitate a patient's admission to an intensive care unit (ICU) or may develop as a consequence of another critical illness and its treatment. This chapter focuses primarily on respiratory failure due to neuromuscular disease but also addresses autonomic dysfunction that occurs in this setting. To facilitate the understanding of the concepts involved, a brief review of the motor unit and its physiology is provided, and the specific muscles critical to ventilation are identified.

■ THE MOTOR UNIT AND ITS PHYSIOLOGY

Central nervous system (CNS) activity designated for motor output is ultimately conducted by the lower motor neurons, also known as *alpha motor neurons*. A motor unit is composed of a lower motor neuron and its distal ramifications, its neuromuscular junctions, and the muscle fibers it innervates. The cell bodies of the lower motor neurons are located in the brainstem for cranial musculature and the anterior horn of the spinal cord for somatic muscles. Motor axons project through the subarachnoid space and penetrate the dura mater as nerve roots. They may join with other motor axons and with sensory and autonomic fibers in a plexus and then travel via the peripheral nerves to the muscles they innervate. Alpha motor neurons are myelinated, a feature that accelerates nerve impulse propagation. The multiple terminal ramifications of the motor neuron synapse on individual muscle fibers.

The motor axon communicates with muscle via a specialized area termed the *neuromuscular junction*. On the presynaptic side of the neuromuscular junction, the neurotransmitter acetylcholine is synthesized, packaged in vesicles, and stored for release. Depolarization of the axon opens the presynaptic voltage-gated calcium channels, which activate the molecular machinery responsible for drawing the vesicles to the presynaptic membrane. The vesicles then fuse with the membrane and release acetylcholine into the synaptic cleft. Acetylcholine molecules bind to receptors on the postsynaptic membrane and cause an influx of sodium, which in turn increases the muscle end-plate potential. When the end-plate potential exceeds the threshold level, the muscle membrane becomes depolarized. This depolarization releases calcium ions from the sarcoplasmic reticulum, and muscle contraction occurs through a process known as *excitation-contraction coupling*. After activating the acetylcholine receptor complex, the acetylcholine molecule is degraded by cholinesterase, and the presynaptic neuron then recycles the choline released by this reaction.

■ MUSCLES OF RESPIRATION

Three muscle groups may be defined based on their importance for respiration (Fig. 55-1):¹

1. *Upper airway muscles*: palatal, pharyngeal, laryngeal, and lingual
2. *Inspiratory muscles*: sternomastoid, diaphragm, scalenes, and parasternal intercostals
3. *Expiratory muscles*: internal intercostal muscles (except for parasternals) and abdominal muscles

The upper airway muscles receive their innervation from the lower cranial nerves. Sternomastoid innervation arrives predominantly from the cranial nerve XI, with a small contribution from C2. The phrenic nerve originates from cell bodies located between C3 and C5, with a

maximum contribution from C4, and innervates the diaphragm. Innervation to the scalenes arises from C4 to C8, whereas that of the parasternal intercostals is from T1 to T7. The intercostal muscles receive innervation from T1 to T12, and the abdominal musculature receives it from T7 to L1.

Clinical Presentation of Neuromuscular Respiratory Failure

Patients experiencing respiratory dysfunction due to neuromuscular disease typically present with a combination of upper airway dysfunction and diminished tidal volume (V_T). Upper airway muscle weakness typically presents with difficulty swallowing liquids, including respiratory secretions, as well as a hoarse or nasal voice. In addition to the risk of aspiration, these patients have difficulty with negative-pressure ventilation since the weakened muscles cannot keep the airway open as the pressure falls.²

Loss of V_T occurs secondary to weakness of the inspiratory muscles. In addition to diaphragmatic weakness, which may present with paradoxical abdominal movement,³ parasternal intercostal muscle weakness also causes diminished V_T by preventing the chest wall from expanding against negative intrapleural pressure. Thereby, lower cervical spinal cord injuries may induce respiratory failure despite preserved phrenic nerve function. As parasternal intercostal muscles develop spasticity over weeks, respiratory function of this type typically improves.

Patients with progressive generalized weakness (e.g., Guillain-Barré syndrome) commonly begin to lose V_T before developing upper airway weakness. To maintain minute ventilation and carbon dioxide excretion, a patient's respiratory rate increases. The respiratory rate is thus one of the most important clinical parameters to monitor. As the vital capacity falls from the norm of about 65 to 30 mL/kg, a patient's cough weakens, and clearing secretions becomes difficult. A further decrease in the vital capacity to 20 to 25 mL/kg results in an impaired ability to sigh, resulting in progressive atelectasis. At this point, hypoxemia may be present because of ventilation-perfusion mismatching, and an increasing percentage of V_T is used to ventilate dead space. Respiratory failure is imminent, and ICU admission is recommended for all patients with a vital capacity <20 mL/kg. The precise point at which mechanical ventilation is necessary varies with the patient, the underlying condition, and especially with the likelihood of a rapid response to treatment.

Regardless of the vital capacity, indications for intubation and mechanical ventilation include evidence of fatigue, hypoxemia despite supplemental oxygen administration, difficulty with secretions, and a rising PaCO₂. In the absence of hypercapnia, occasional patients (e.g., those with myasthenia gravis) can be managed with very close observation in an ICU with less invasive techniques (e.g., bilevel positive airway pressure [BiPAP]).⁴

In addition to vital capacity, trended measurements of the maximum inspiratory pressure (P_Imax, more typically recorded as a negative inspiratory force [NIF]), are useful indicators of ventilatory capacity. The inability to maintain a P_Imax greater than 20 to 25 cm H₂O usually indicates a need for mechanical ventilation. Although the maximum expiratory pressure (P_Emax) is a more sensitive indicator of weakness,⁵ it has not proven to be as useful as an indicator of the need for mechanical ventilation.^{6,7}

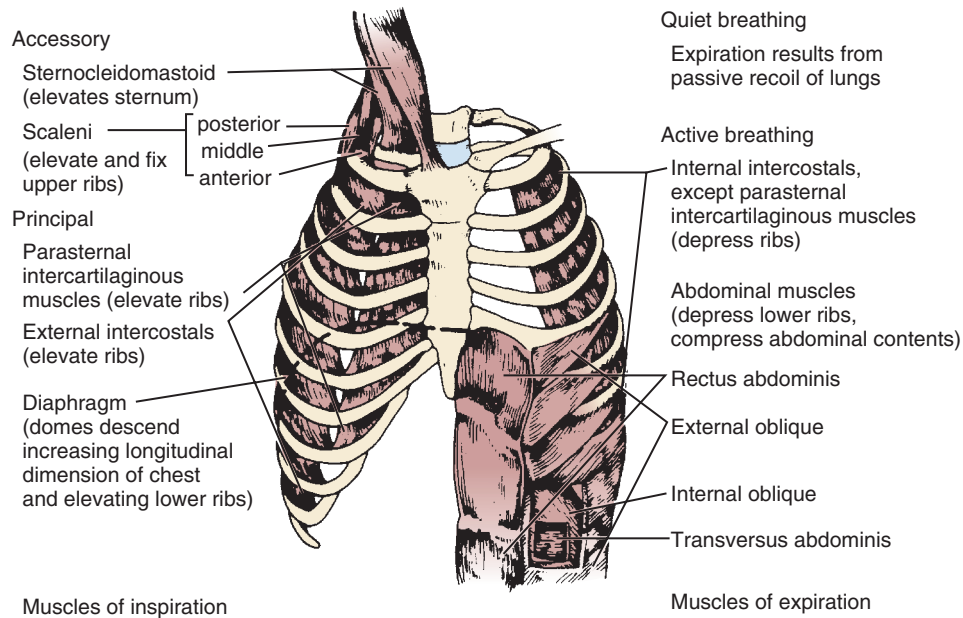


FIGURE 55-1 ■ Major respiratory muscles. Inspiratory muscles are indicated on the left, and expiratory muscles are indicated on the right. (From Garrity ER. Respiratory failure due to disorders of the chest wall and respiratory muscles. In: MacDonnell KF, Fahey PJ, Segal MS, editors. Respiratory intensive care. Boston: Little, Brown; 1987, p. 313.)

Since a patient with neuromuscular respiratory failure has an intact ventilatory drive,⁸ the fall in V_T is initially matched by an increase in respiratory rate, keeping the P_{aCO_2} normal or low until the vital capacity becomes dangerously reduced. Many patients initially maintain their P_{aCO_2} in the range of 35 mm Hg because of either (1) a subjective sense of dyspnea at low V_T or (2) hypoxia from atelectasis and increasing dead space. When the P_{aCO_2} begins to rise in these circumstances, abrupt respiratory failure may be imminent, as CO_2 displaces more oxygen from the alveolar gas. The modest degree of hypoxia in most of these patients worsens when the P_{aCO_2} begins to rise, displacing more oxygen from the alveolar gas. Moreover, aspiration pneumonia and pulmonary embolism are also frequent causes of hypoxemia in these patients. To determine the relative contributions of these conditions to a patient's hypoxemia, one can use a simplified version of the alveolar gas equation as follows (derived elsewhere)^{6,7}:

$$PAO_2 = PIO_2 - (P_{aCO_2}/R)$$

where PAO_2 is the alveolar partial pressure of oxygen, PIO_2 is the partial pressure of the inspired oxygen (in room air, 150 mm Hg), and R is the respiratory quotient (on most diets, about 0.8). This allows for the estimation of the alveolar-arterial oxygen difference ($PAO_2 - PaO_2$). Under ideal circumstances in young people breathing room air, this value is about 10 mm Hg, but it rises to about 100 mm Hg when the fraction of inspired oxygen (PIO_2) is 1.0. The alveolar air equation allows one to factor out the contribution of hypercarbia to the decrease in arterial partial pressure of oxygen (PaO_2); it should be used to determine whether there is a cause of significant hypoxemia in addition to the displacement of oxygen by carbon dioxide.

Physicians must observe patients for rapid, shallow breathing,⁹ recruitment of accessory muscles, and paradoxical movement of the abdomen during the respiratory cycle. Direct observation is particularly important as patients may have orbicularis oris weakness, causing an artificially low vital capacity and NIF measurements because they cannot form a tight seal around the spirometer mouthpiece. In addition to physical exam findings, fluoroscopy of the diaphragm is occasionally valuable for the diagnosis of diaphragmatic dysfunction.¹⁰

Autonomic dysfunction commonly accompanies some of the neuromuscular disorders requiring critical care, such as Guillain-Barré syndrome, botulism, and porphyria (Table 55-1). In Guillain-Barré

syndrome (discussed later) dysautonomia is common and may arise in parallel with weakness or may follow the onset of the motor disorder after 1 week or more.

■ NEUROMUSCULAR DISORDERS

Many chronic neuromuscular disorders and other CNS conditions affecting the suprasegmental innervation and control of respiratory muscles eventually compromise ventilation. In this chapter, we emphasize the more common acute and subacute neuromuscular disorders that precipitate or prolong critical illness due to ventilatory failure and autonomic dysfunction. A complete listing of neuromuscular diseases appears in Table 55-1; reviews of this subject^{11,12} and the references listed in Table 55-1 detail the more rare disorders. Some of the diseases listed (e.g., Lambert-Eaton myasthenic syndrome) rarely cause respiratory failure in isolation but may be contributing causes in the presence of other conditions,¹³ such as a neuromuscular junction blockade intended only for the duration of a surgical procedure.¹⁴

Neuromuscular Diseases Precipitating Critical Illness

Guillain-Barré Syndrome

Guillain-Barré syndrome, or acute inflammatory demyelinating polyradiculoneuropathy, is typically a motor greater than peripheral sensory neuropathy with subacute onset, monophasic course, and nadir within 4 weeks. Although the precise etiology is unknown, it is immune mediated and related to antibodies directed against peripheral nerve components. About 1.7 cases occur per 100,000 population annually.¹⁵ Most patients suffer from a demyelinating neuropathy, but in about 5% of cases, the condition is a primary axonopathy.¹⁶ Numerous antecedents have been implicated,¹⁷ the most common of which are listed in Box 55-1. The association with antecedent infections suggests that certain agents may provoke the production of antibodies that cross-react with peripheral nerve gangliosides. Ganglioside antibodies have been found in Guillain-Barré syndrome after *Campylobacter jejuni* infections, such as GM₁ antibodies in axonal forms¹⁸ and GQ_{1b} antibodies in the Miller-Fisher variant.¹⁹

TABLE 55-1 Neuromuscular Causes of Acute Respiratory Failure

| LOCATION | DISORDER | ASSOCIATED AUTONOMIC DYSFUNCTION? |
|------------------------|--|--|
| Spinal cord | Tetanus ¹¹⁹ | Frequent |
| Anterior horn cell | Amyotrophic lateral sclerosis ¹²⁰ | No |
| | Poliomyelitis | No |
| | Rabies | Frequent |
| | West Nile virus flaccid paralysis | No |
| Peripheral nerve | Guillain-Barré syndrome | Frequent |
| | Critical illness polyneuropathy | No |
| | Diphtheria | No, but cardiomyopathy and arrhythmias may occur |
| | Porphyria | Occasional |
| | Ciguatera (ciguatera poisoning) | Occasional |
| | Saxitoxin (paralytic shellfish poisoning) | No |
| | Tetrodotoxin (pufferfish poisoning) | No |
| | Thallium intoxication | No |
| | Arsenic intoxication ^{121,122} | No |
| | Lead intoxication | No |
| | Buckthorn neuropathy | No |
| Neuromuscular junction | Myasthenia gravis | No |
| | Botulism ¹²³ | Frequent |
| | Lambert-Eaton myasthenic syndrome ¹²⁴ | Yes, frequent dry mouth and postural hypotension |
| | Hypermagnesemia ¹²⁵ | No |
| | Organophosphate poisoning | No |
| | Tick paralysis | No |
| Muscle | Snake bite | No |
| | Polymyositis/dermatomyositis | No |
| | Acute quadriplegic myopathy | No |
| | Eosinophilia-myalgia syndrome ¹²⁶ | No |
| | Muscular dystrophies ¹²⁷ | No, but cardiac rhythm disturbances may occur |
| | Carnitine palmitoyl transferase deficiency | No |
| | Nemaline myopathy ¹²⁸ | No |
| | Acid maltase deficiency ¹²⁹ | No |
| | Mitochondrial myopathy ¹³⁰ | No |
| | Acute hypokalemic paralysis | No |
| | Stonefish myotoxin poisoning | No |
| | Rhabdomyolysis | No |
| | Hypophosphatemia ¹³¹ | No |

The initial findings of patients with Guillain-Barré syndrome are a subacute and progressive weakness, usually most marked in the legs, associated with sensory complaints but without objective signs of sensory dysfunction.²⁰ Deep tendon reflexes are often reduced or absent at presentation, though this finding may take several days to develop. The cerebrospinal fluid (CSF) typically reveals an albuminocytologic dissociation or elevated protein content without pleocytosis; however, this may not evolve until the second week of illness. The major reason to examine the CSF is to preclude other diagnoses. Although mild CSF lymphocytic pleocytosis (10-20 cells/mm³) may suggest the possibility of associated human immunodeficiency virus (HIV) infection, in most patients, the nucleated cell count is <10 cells/mm³.²¹ Although they may be normal initially, results of electrodiagnostic studies (motor and sensory nerve conduction studies and needle electromyography) often reflect segmental nerve demyelination with multifocal conduction blocks, temporally dispersed compound muscle action potentials, slowed conduction velocity, and prolonged or absent F waves.²² Diagnostic considerations for patients with suspected Guillain-Barré syndrome are primarily those listed in the Peripheral Nerve section of Table 55-1.

The components of treatment for patients with Guillain-Barré syndrome are as follows:

- Management of ventilatory failure
- Management of autonomic dysfunction
- Meticulous nursing care
- Psychological support
- Physical and occupational therapy
- Prevention of deep venous thrombosis
- Nutritional support

- Early planning for rehabilitation
- Immunotherapy for the underlying autoimmune condition

Patients with Guillain-Barré syndrome with evolving respiratory failure should be intubated when the vital capacity falls to about 15 mL/kg or when difficulty with secretions begins because the response to treatment is slow. If a patient has been immobile for several days before intubation and a neuromuscular junction blockade is needed, a nondepolarizing agent should be used to avoid transient hyperkalemia. Oral intubation is preferable to the nasal route because the tracheal tube is frequently required for a week or longer, raising the risk of sinusitis.

Many patients are too weak to trigger the ventilator, and in such cases, the assist/control or intermittent mandatory ventilation mode is initiated. Weaning patients with Guillain-Barré syndrome from mechanical ventilation must wait for an adequate improvement in strength reflected by a vital capacity of greater than 15 mL/kg and NIF greater than 25 cm H₂O. However, a formula using a combination of ventilatory and gas exchange variables may allow for a more accurate determination of a patient's ability to be weaned.²³ While pressure support ventilation is often used for weaning, evidence of its superiority over intermittent mandatory ventilation or synchronized intermittent mandatory ventilation modes is anecdotal. Most patients require mechanical ventilation for more than 4 weeks; however, as many as one-fifth need at least 2 months of support before they can breathe without assistance. Autonomic dysfunction typically presents as a hypersympathetic state and is often heralded by unexplained sinus tachycardia. The blood pressure may fluctuate wildly. Patients can also experience bradycardic episodes, which may require temporary pacing. Autonomic surges during tracheal suctioning or due to a

BOX 55-1

Major Antecedents of
Guillain-Barré Syndrome

FREQUENT

Upper respiratory tract infections
Campylobacter jejuni enteritis
 Cytomegalovirus (CMV) infection
 Epstein-Barr virus (EBV) infection
 Hepatitis A infection
 Hepatitis B infection
 Hepatitis C infection
 Human immunodeficiency virus (HIV) infection

INFREQUENT

Mycoplasma pneumoniae infection
Haemophilus influenzae infection
Leptospira icterohaemorrhagiae infection
 Salmonellosis
 Rabies vaccine
 Tetanus toxoid
 Bacille Calmette-Guérin immunization
 Sarcoidosis
 Systemic lupus erythematosus
 Lymphoma
 Trauma
 Surgery

QUESTIONABLE

Hepatitis B vaccine
 Influenza vaccine
 Hyperthermia
 Epidural anesthesia

distended viscus may be very dramatic and should be minimized. Autonomic failure and pulmonary embolism are now the major causes of mortality in Guillain-Barré syndrome.

Nursing care for patients with Guillain-Barré syndrome is similar to that for other paralyzed and mechanically ventilated patients, but special care must be taken to remember that patients are completely lucid. In addition to explaining any procedures carefully, arranging for distractions during the daytime (e.g., television, movies, conversation, or visitors) and adequate sleep at night is very important. For the most severely affected patients, sedation should be considered. In concert with physical and occupational therapists, passive exercise should frequently be performed throughout the day.

Deep venous thrombosis is a significant danger. An episodic arterial desaturation is a common event, presumably owing to transient mucous plugging; therefore, submassive pulmonary emboli may be overlooked. Adjusted-dose heparin (to slightly prolong the partial thromboplastin time) should be given, and sequential compression devices should be used on the legs. Moreover, therapeutic anticoagulation may be considered. The risk of fatal pulmonary embolism extends through the initial period of improvement until the patients are ambulatory.

Nutritional support should begin as soon as a patient is admitted, with appropriate concern for the risk of aspiration.²⁴ Most mechanically ventilated patients with Guillain-Barré syndrome can be fed via soft, small-caliber feeding tubes; autonomic dysfunction affecting the gut occasionally requires total parenteral nutrition.

Immunotherapy for Guillain-Barré syndrome includes the removal of autoantibodies with plasma exchange or immune modulation with a high dose of intravenous immunoglobulin (IVIg). The efficacy of the plasma exchange has been evaluated in a Cochrane systematic review of six class II trials comparing plasma exchange alone with supportive care.²⁵ Most of the trials employed up to five plasma exchanges of 50 mL/kg over 2 weeks. In a large North American trial,²⁵ the time needed to improve one clinical grade (i.e., being weaned from the ventilator or being able to walk) was reduced by 50% in the plasma exchange group compared to the control group. There was no significant benefit when the plasma exchange commenced later than 2

weeks after the onset of symptoms. A meta-analysis revealed more rapid recovery in ventilated patients treated with a plasma exchange within 4 weeks of onset.²⁶ The optimal number of plasma exchanges has been assessed in patients with mild (unable to run), moderate (unable to stand without assistance), and severe (requiring mechanical ventilation) Guillain-Barré syndrome by the French Cooperative Group.²⁷ On the basis of this trial, two exchanges are better than none in mild Guillain-Barré syndrome; four are better than two in moderate Guillain-Barré syndrome; and six are no better than four in severe Guillain-Barré syndrome. Albumin is the preferred replacement solution.²⁸ Treatment with IVIg for Guillain-Barré syndrome has also been examined in a Cochrane systematic review. Five randomized controlled trials in adults showed that IVIg (0.4–0.5 g/kg over 4–5 days) is as effective as plasma exchange in Guillain-Barré syndrome patients with impaired walking.²⁹ IVIg is also more likely to be completed than plasma exchange; although the adverse events were not different. A large international multicenter randomized trial compared plasma exchange (50 mL/kg \times 5 exchanges over 8–13 days), IVIg (0.4 g/kg \times 5 days), and plasma exchange followed by IVIg.³⁰ No significant outcome differences between these therapies were found with respect to functional improvement at 4 or 48 weeks.

Evidence-based guidelines for Guillain-Barré syndrome immunotherapy have been published by the Quality Standards Subcommittee of the American Academy of Neurology.³¹ Plasma exchange is recommended for adult patients who cannot walk within 4 weeks of symptom onset. IVIg is recommended in these patients within 2 or possibly 4 weeks of symptom onset. Both treatments are deemed equivalent in efficacy, and combining treatment with plasma exchange and IVIg confers no additional benefit. In light of their therapeutic equivalence, the decision whether to employ plasma exchange or IVIg in treating acute Guillain-Barré syndrome may be determined by resource availability and by avoiding potential side effects related to a patient's medical comorbidities. Patients with heart disease, renal insufficiency or failure, hyperviscosity, or IgA deficiency may be more susceptible to complications of treatment with IVIg, whereas plasma exchange may be complicated in patients with labile blood pressure, septicemia, and significant venous access problems.

Despite the autoimmune pathophysiology of Guillain-Barré syndrome and the efficacy of corticosteroids in more chronic forms of inflammatory neuropathy, corticosteroids have not shown effectiveness in Guillain-Barré syndrome and are therefore not recommended.³¹ A large multicenter trial failed to demonstrate efficacy of high-dose intravenous methylprednisolone,³² and another large multicenter trial reported no added clinical benefit with the combined treatment of IVIg and methylprednisolone.³³

West Nile Virus Acute Flaccid Paralysis Syndrome

The large outbreak of West Nile virus encephalitis in the summer of 1999 in New York City marked the emergence of a relatively new cause of neuromuscular weakness with the potential for neuromuscular respiratory compromise. West Nile virus is a flavivirus transmitted by birds and mosquitoes. Humans may acquire West Nile virus from the bite of an infected *Culex* species mosquito, and a corresponding peak in human disease occurs in the late summer and fall. West Nile virus may also be transmitted to humans by organ transplantation,³⁴ blood and blood product transfusion,³⁵ transplacental exposure,³⁶ breastfeeding,³⁷ and percutaneous laboratory injuries.³⁸ About 20% of humans experience a mild flulike illness lasting 3 to 6 days, and about 1 in 150 develops CNS disease, which usually presents as meningoencephalitis.³⁹

In the initial North American outbreak of West Nile virus, about 10% of infected patients experienced flaccid weakness with clinical features resembling Guillain-Barré syndrome.⁴⁰ Although patients with West Nile virus infection exhibit a spectrum of clinical weakness,^{41,42} the most prominent and distinctive syndrome documented in several subsequent reports of West Nile virus infection is an acute “poliomyelitis-like” or acute flaccid paralysis syndrome with pathology localized to the ventral horns of the spinal cord and/or ventral

roots.⁴³⁻⁴⁹ These relatively younger patients developed acute, asymmetric, flaccid weakness in the absence of sensory abnormalities, diffuse areflexia, or bowel/bladder dysfunction.⁵⁰ Some of the patients experienced concurrent meningoencephalitis, and a few required mechanical ventilation.^{44,45}

Electrodiagnostic studies in patients with West Nile virus acute flaccid paralysis syndrome exhibit normal sensory potentials, and the absence of findings suggests segmental demyelination (e.g., motor conduction block, reduced conduction velocities, prolonged distal, and F-wave latencies), low-amplitude compound muscle action potentials in the affected regions, and marked denervation changes in the affected limbs and in corresponding paraspinal muscles on the needle electromyography. Corresponding magnetic resonance imaging (MRI) findings are sometimes observed and include an abnormal signal in the spinal cord on T2-weighted images^{47,48} and abnormal enhancement of the nerve roots and cauda equina.^{46,47} CSF analysis usually reveals mild pleocytosis with lymphocytic predominance and a mild to moderate protein elevation and normal glucose.⁵¹ Prognosis for the recovery of strength in these patients appears to be poor.⁵²

West Nile virus infection may be diagnosed by demonstrating West Nile virus RNA in the serum, CSF, or other tissues by reverse-transcriptase polymerase chain reaction, although this test is not highly sensitive.⁵³ More commonly, a diagnosis is made by the demonstration of West Nile virus IgM in CSF or serum by antibody-capture enzyme-linked immunosorbent assay (ELISA). When serum West Nile virus IgM is present, diagnosis is confirmed by a fourfold increase in West Nile virus IgG titers between acute and convalescent sera obtained 4 weeks apart. Positive IgM and IgG antibody titers should be confirmed by a plaque-reduction viral neutralization assay to exclude false-positive results related to other flaviviral infections, such as St. Louis encephalitis. Serology may not become positive until 8 days after symptom onset.³⁹

Particularly in the absence of a more typical encephalitic presentation of West Nile virus infection, a high index of clinical suspicion is needed to make a diagnosis of West Nile virus acute flaccid paralysis syndrome and to distinguish such cases from Guillain-Barré syndrome in patients presenting with acute weakness in the late summer or fall. Electrodiagnostic studies may help localize the pathology to the ventral horns of the spinal cord or ventral roots in West Nile virus cases and to exclude findings of segmental demyelination suggesting Guillain-Barré syndrome. CSF evaluation can help discriminate between the albuminocytologic dissociation of Guillain-Barré syndrome and the lymphocytic pleocytosis in a West Nile virus infection.

There is no specific treatment for West Nile virus. A multicenter study to evaluate the efficacy of Israeli IVIg (containing high levels of West Nile virus antibodies) in patients with West Nile virus meningoencephalitis or weakness was terminated early due to the lower-than-expected enrollment, expiration of the study product, and insufficient quantities of control IVIg.⁵⁴ Two candidate vaccines against West Nile virus are currently being evaluated.^{55,56}

Myasthenia Gravis

Myasthenia gravis is a consequence of the autoimmune attack on the acetylcholine receptor complex at the postsynaptic membrane of the neuromuscular junction. This process results in clinical weakness with a fluctuating pattern that is most marked after prolonged muscle exertion. Myasthenia gravis occurs at a higher rate in early adulthood in women, but in later life, the incidence rates for men and women become nearly equal. The reported prevalence is 14.2 cases per 100,000 population.⁵⁵ Myasthenia gravis typically involves ocular muscle weakness producing ptosis and diplopia, as well as bulbar muscle weakness resulting in dysphagia and dysarthria. A clinical diagnosis of myasthenia gravis may be supported by edrophonium testing, by electrophysiologic studies including repetitive nerve stimulation studies and single-fiber electromyography, and by acetylcholine receptor and muscle-specific receptor tyrosine kinase (MuSK) antibody testing.

Approximately 20% of patients with myasthenia gravis develop myasthenic crisis with respiratory failure requiring mechanical ventilation.⁵⁶ The most common precipitating factors include bronchopulmo-

BOX 55-2 Drugs That May Increase Weakness in Myasthenia Gravis

Neuromuscular blocking agents
Selected antibiotics
 Aminoglycosides, particularly gentamycin
 Macrolides, particularly erythromycin and azithromycin
Selected cardiovascular agents
 Beta-blockers
 Calcium channel blockers
 Procainamide
Quinidine
Quinine
Corticosteroids
Magnesium salts
 Antacids, laxatives, intravenous tocolytics
Iodinated contrast agents
D-Penicillamine

nary infections (29%) and aspiration (10%).⁵⁷ Other precipitating factors include sepsis, surgical procedures, rapid tapering of immune modulation, beginning treatment with corticosteroids, pregnancy, and exposure to drugs that may increase myasthenic weakness (Box 55-2).⁵⁸ Patients with myasthenia gravis are exceptionally sensitive to nondepolarizing neuromuscular blocking agents but resistant to depolarizing agents.⁵⁹ Thymomas are associated with more fulminant disease and identified in about one-third of patients in a myasthenic crisis.⁵⁷

Upper airway muscle weakness is a common mechanism leading to the myasthenic crisis.⁶⁰ Oropharyngeal and laryngeal muscle weakness may result in upper airway collapse with obstruction. Dysphagia further contributes to the obstruction and aspiration of secretions. Since a direct assessment of oropharyngeal muscle strength is impractical, a focused history and examination to assess surrogate muscles in the head and neck region are important. Findings of bulbar myasthenia associated with upper airway compromise include flaccid dysarthria with hypernasal, staccato, or hoarse speech, dysphagia (sometimes associated with nasal regurgitation), and chewing fatigue. Patients may exhibit facial weakness with difficulty holding air within the cheeks. Jaw closure is often weak and cannot be maintained against resistance. Patients with myasthenic tongue weakness may be unable to protrude the tongue into either cheek. Although neck flexors are often weaker, a dropped head syndrome due to neck extensor weakness may occur. Vocal cord abductor paralysis may produce laryngeal obstruction with associated stridor.^{61,62}

Patients with features of impending myasthenic crisis, including severe bulbar weakness, marginal vital capacity (less than 20 to 25 mL/kg), weak cough with difficulty clearing secretions from the airway, or paradoxical breathing while supine should be admitted to an ICU and made NPO to prevent aspiration.⁶³ Serial vital capacity and NIF measurements may be used to monitor ventilatory function in an impending myasthenic crisis. However, with significant bulbar weakness, these measurements are often inaccurate if the patient has difficulty sealing the lips around the spirometer mouthpiece or is unable to seal the nasopharynx. Vital capacity measurements may not reliably predict respiratory failure in myasthenia gravis, owing to the fluctuating nature of the myasthenic weakness.⁶⁴ The criteria for intubation and mechanical ventilation are similar to those for Guillain-Barré syndrome. If the upper airway is competent and there is no difficulty handling secretions or gross hypercapnia ($Paco_2 > 50$ mm Hg), intermittent nasal BiPAP may be a useful temporizing measure.⁴ Most patients who develop hypercapnia in myasthenic crisis require intubation, as do those who are becoming fatigued.

Plasma exchange is an effective short-term immunomodulating treatment for myasthenic crisis and surgical preparation in symptomatic myasthenic patients. Significant strength improvement in myasthenic crisis is well documented in several series,⁶⁵⁻⁶⁹ although there have been no controlled trials. We perform a series of five to six exchanges of 2 to 3 L every other day. The onset of improved strength is variable but occurs after two to three exchanges.

IVIg may represent an alternative short-term treatment for myasthenic exacerbations or crises in patients who are poor candidates for plasma exchange because of difficult vascular access or septicemia. Comparable efficacy for plasma exchange and IVIg was demonstrated in myasthenic exacerbations and crises in a relatively small randomized controlled trial of IVIg at 1.2 and 2 g/kg over 2 to 5 days.⁷⁰ However, in a retrospective multicenter study of myasthenic crisis, plasma exchange proved more effective than IVIg in the ability to extubate at 2 weeks and in the 1-month functional outcome.⁶⁹ Treatment failures to IVIg subsequently responding to plasma exchange have also been reported.⁷¹ Recent experience with preoperative IVIg for thymectomy in myasthenia gravis suggests that the time course of the maximal response may be considerably delayed in some patients.⁷²

Corticosteroids (e.g., prednisone, 1 mg/kg/day) are occasionally used in prolonged myasthenic crises that fail to respond to plasma exchange or IVIg. If begun early in the course of the myasthenic crisis, the transient increase in myasthenic weakness associated with initiating corticosteroids may prolong mechanical ventilation. When preceded by an unequivocal improvement in strength after plasma exchange or IVIg treatment, long-term treatment with corticosteroids may begin, with a reduced risk for corticosteroid-related exacerbations.

In the context of myasthenic crisis, excessive dosing of cholinesterase inhibitors may superimpose a cholinergic crisis due to depolarization blockade and result in increased weakness. Other symptoms of the cholinergic crisis include muscle fasciculations and prominent muscarinic symptoms including miosis, excessive lacrimation and salivation, abdominal cramping, nausea, vomiting, diarrhea, thick bronchial secretions, diaphoresis, and bradycardia. Cholinergic crisis is rare in contemporary series of myasthenic crisis,⁵⁷ and it is now common practice to avoid repeated dose escalations of cholinesterase inhibitors in an impending myasthenic crisis and to discontinue the use of cholinesterase inhibitors after intubation to reduce muscarinic complications. When there is a question of cholinergic excess contributing to respiratory insufficiency, it is prudent to discontinue all cholinesterase inhibitors, protect the airway, and support respiration as necessary.

Thymectomy may result in the long-term improvement of patients with a suspected thymoma or with a life expectancy of more than 10 years. However, a patient in acute respiratory failure is considered a poor operative risk, and thymectomy is delayed until the patient's condition has improved.⁷³ Post thymectomy pain control and ventilatory function may be improved by the postoperative administration of epidural morphine.⁷⁴

Neuromuscular Diseases Secondary to Critical Illness and Its Treatment

Critical Illness Polyneuropathy

Critical illness polyneuropathy is a widespread axonal peripheral neuropathy that develops in the context of multiple organ failure and sepsis.⁷⁵⁻⁷⁹ In a prospective series of 43 patients with sepsis and multi-organ failure, 70% developed electrophysiologic evidence of a sensorimotor axonal neuropathy, and 15 patients developed difficulty weaning from mechanical ventilation as a consequence of the neuropathy.⁸⁰ Critical illness polyneuropathy is possibly the most common neuromuscular cause of prolonged ventilator dependency in patients without prior known neuromuscular disease.⁸¹ Given the limitations to the detailed clinical motor and sensory examinations in the setting of critical illness, the clinical features of critical illness polyneuropathy (extremity muscle weakness and wasting, distal sensory loss, and paresthesias) may not be recognized. Deep tendon reflexes are reduced or absent in the setting of superimposed CNS insult with pyramidal tract dysfunction; however, deep tendon reflexes may be normal or increased.⁸²

Electrodiagnostic studies are important in establishing a diagnosis of critical illness polyneuropathy because the clinical findings may be unobtainable or indeterminate in this setting.⁸² Nerve conduction findings include normal or near-normal conduction velocity and latency values and significantly reduced compound muscle action potential

and sensory nerve action potential amplitudes. Needle electrode examination reveals denervation changes that are the most marked in the distal muscles, including fibrillation potentials, positive sharp waves, and reduced recruitment of motor unit potentials.⁸³ With recovery over time, the denervation potentials abate, and the motor unit potentials become polyphasic and enlarged. Peripheral nerve histopathology has revealed widespread primary axonal degeneration in distal motor and sensory fibers, and that skeletal muscle has exhibited fiber-type grouping.⁷⁹

Although the clinical history is usually adequate to distinguish between critical illness polyneuropathy and Guillain-Barré syndrome, the latter can develop in the context of recent surgery complicated by infection.⁸⁴ However, Guillain-Barré syndrome is commonly associated with facial and oropharyngeal weakness,⁸⁴ which is rarely seen in critical illness polyneuropathy.⁸⁵ Furthermore, dysautonomia and occasionally external ophthalmoplegia is also observed in Guillain-Barré syndrome but has virtually never been attributed to critical illness polyneuropathy.⁸⁵

Electrophysiologic findings are also helpful in distinguishing between these two disorders. Features of segmental demyelination may be observed in Guillain-Barré syndrome on nerve conduction studies (e.g., reduced conduction velocity, prolonged distal and F-wave latencies, conduction block, and temporal dispersion of compound muscle action potentials); these findings are not observed in critical illness polyneuropathy. Needle electromyographic findings may differ in that relatively less spontaneous activity is observed in clinically weak muscles within the first few days in patients with Guillain-Barré syndrome.⁸³ Although electrophysiologic studies are quite helpful in demonstrating the classic demyelinating form of Guillain-Barré syndrome, an electrophysiologic distinction between the axonal forms of Guillain-Barré syndrome and critical illness polyneuropathy may not be reliable. The mean CSF protein level in Guillain-Barré syndrome is significantly higher than in critical illness polyneuropathy, although there is overlap between these populations.⁸³ Peripheral nerve histopathology may also distinguish between these two groups because segmental demyelination and inflammatory changes may be observed in Guillain-Barré syndrome and are not observed in critical illness polyneuropathy.⁷⁹

Although the overall prognosis in critical illness polyneuropathy is dependent on recovery from the underlying critical illness, most patients who survive experience a functional recovery from the neuropathy within several months.⁷⁹ Critical illness polyneuropathy may prolong ventilator dependence, but it does not worsen the long-term prognosis.⁸² Proper positioning and padding are important to prevent compression neuropathies because the prognosis from superimposed compression neuropathies in the context of critical illness polyneuropathy is less favorable.⁸²

The pathophysiology of critical illness polyneuropathy is unknown. No clear metabolic, drug, nutritional, or toxic factors have been identified,⁷⁹ although the severity of critical illness polyneuropathy has been correlated with the amount of time in the ICU, the number of invasive procedures, increased glucose levels, a reduced albumin level,⁸⁰ and the severity of multiple organ failure.⁸⁶ Given the common antecedents of multiple organ failure and sepsis in which release of cytokines occurs, increased microvascular permeability has been postulated to produce axonal hypoxia and degeneration as a consequence of endoneurial edema.⁸⁷

Prolonged Effects of Neuromuscular Blocking Agents

A prolonged neuromuscular blockade may occur with most depolarizing and nondepolarizing agents, particularly when the hepatic or renal function is impaired.⁸⁸ In one study, the administration of vecuronium for 2 or more consecutive days resulted in prolonged neuromuscular blockade and paralysis lasting from 6 hours to 7 days.⁸⁹ Although vecuronium is hepatically metabolized, patients with renal failure were susceptible to prolonged effects due to delayed excretion of the active 3-desacetyl metabolite. Acidosis and elevated serum magnesium levels were also associated with prolonged paralytic effects of

vecuronium. A peripheral nerve stimulator may be used to monitor muscle twitch responses to a train-of-four stimulus during the use of neuromuscular blocking agents. Drug dosage should be titrated to preserve one or two twitches to avoid overdosing. Two- to 3-Hz repetitive nerve stimulation studies may also be used to confirm neuromuscular blockade when it is suspected. Since atracurium and cisatracurium do not require organ metabolism for clearance, they are rarely associated with this problem.

Acute Quadriplegic Myopathy

The syndrome known as *acute quadriplegic myopathy*⁹⁰ or *acute myopathy of intensive care*⁹¹ was originally described in 1977 by a young woman who developed severe myopathy after treatment of status asthmaticus with high doses of corticosteroids and pancuronium.⁹² Subsequently, there have been many citations of an acute myopathy developing in critically ill patients without preexisting neuromuscular disease. Acute quadriplegic myopathy has developed most frequently in the setting of severe pulmonary disorders in which neuromuscular blockade is used to facilitate mechanical ventilation, and high doses of corticosteroids are concurrently administered. In most reported cases, myopathy developed when nondepolarizing neuromuscular blocking agents were used for more than 2 days.⁹⁰⁻¹⁰⁰ The development of acute necrotizing myopathy with myosin loss also occurs in patients receiving high doses of corticosteroids and hypnotic doses of propofol and benzodiazepines to induce paralysis.¹⁰¹ This observation highlights the significance of high-dose corticosteroid exposure in the development of this syndrome and suggests that the paralyzed muscles may be susceptible to the toxic effects of corticosteroids. The mechanism of this myosin abnormality appears to lie at the level of transcriptional regulation of protein synthesis.¹⁰² The occurrence of acute quadriplegic myopathy after organ transplantation may be caused by the use of high doses of corticosteroids to prevent graft rejection, along with perioperative exposure to neuromuscular blocking agents.¹⁰³ Although most cases of acute quadriplegic myopathy have been associated with critical illness and high doses of corticosteroids and paralytic agents, acute quadriplegic myopathy has developed after isolated corticosteroid exposure,^{90,104-107} isolated nondepolarizing neuromuscular blocking agent use,^{100,104,108} or neither.¹⁰⁹ Factors that may impair neuromuscular transmission (e.g., hypermagnesemia and aminoglycoside exposure), factors that may slow the elimination of nondepolarizing neuromuscular blocking agents (e.g., hepatic or renal failure), and factors associated with critical illness (e.g., sepsis and acidosis) are also associated with acute quadriplegic myopathy.⁹³

In typical cases, a diffuse flaccid quadriparesis with the involvement of respiratory muscles and muscle wasting evolves after several days of induced paralysis. External ophthalmoparesis has rarely been noted.^{110,112} Sensation remains intact, but deep tendon reflexes are reduced or absent. The creatine kinase level is commonly elevated, but this may not be observed if creatine kinase is measured well after the myopathy has developed. Although the paralysis may be quite severe and necessitate or prolong mechanical ventilation, the prognosis for the myopathy is good, with functional recovery over several weeks to months.⁹⁵ Electromyographic findings include reduced amplitude of compound motor action potentials with normal sensory nerve action potentials and normal nerve conduction velocities. M-wave amplitude improvement accompanies clinical recovery.¹⁰⁰ Repetitive nerve stimulation studies may yield decremental responses, while the residual effects of nondepolarizing neuromuscular blocking agents or their active metabolites persist.^{93,100} Needle electromyography often reveals small, low-amplitude, polyphasic motor unit potentials exhibiting early recruitment, along with positive sharp waves and fibrillation potentials. A spectrum of muscle histologic changes may be observed, ranging from type II fiber atrophy and the loss of adenosine triphosphatase (ATPase) reactivity in atrophic fibers to fiber necrosis in severe cases. However, the distinctive findings in most cases is an extensive loss of thick filaments corresponding to myosin loss.^{90,94,99,104,109} This finding may be demonstrated by immunohistochemical staining or electron microscopy. The increased expression of steroid receptors in

denervated and immobilized muscle¹¹¹ may render these muscles susceptible to toxic catabolic effects of steroids.^{90,113} Given the growing recognition of acute quadriplegic myopathy, the use of high doses of corticosteroids should be avoided if possible when neuromuscular blockade or induced paralysis is required.

However, in a recent Cochrane review of interventions for preventing critical illness polyneuropathy and critical illness myopathy,¹¹⁴ a randomized controlled trial of 180 patients with acute respiratory distress syndrome comparing corticosteroids to placebo that found no effect of treatment on critical illness polyneuropathy/myopathy¹¹⁵ was cited as moderate quality evidence. Additional results from the review found moderate evidence for intensive insulin therapy in reducing polyneuropathy/myopathy at the expense of increased hypoglycemia^{116,117} and for a potential benefit for early rehabilitation.¹¹⁸ Larger randomized controlled trials of early rehabilitation and electrical muscle stimulation is needed to explore the value of these therapies.

KEY POINTS

1. Respiratory dysfunction due to neuromuscular disease typically presents with a combination of upper airway dysfunction and diminished tidal volume (VT).
2. Along with vital capacity, trended measurement of the maximum inspiratory pressure (PImax or negative inspiratory force [NIF]) is a useful index of ventilatory capacity. Inability to maintain a PImax greater than 20 to 25 cm H₂O usually indicates a need for mechanical ventilatory assistance.
3. Autonomic failure and pulmonary embolism are now the major causes of mortality in Guillain-Barré syndrome.
4. Evidence-based guidelines for Guillain-Barré syndrome immunotherapy have been published by the Quality Standards Subcommittee of the American Academy of Neurology. Plasma exchange is recommended for adult patients who cannot walk within 4 weeks of symptom onset. Intravenous immune globulin (IVIg) is recommended in these patients within 2 or possibly 4 weeks of symptom onset. Plasma exchange and IVIg are considered equivalent in efficacy, and no additional benefit is conferred by combining these treatments. In light of the therapeutic equivalence, the decision whether to employ plasma exchange or IVIg in treating acute Guillain-Barré syndrome may be determined by resource availability and by avoiding potential side effects related to a patient's medical comorbidities.
5. In the initial North American outbreak of West Nile virus, about 10% of infected patients experienced flaccid weakness with clinical features resembling Guillain-Barré syndrome.
6. Approximately 20% of patients with myasthenia gravis develop myasthenic crisis with respiratory failure requiring mechanical ventilation.
7. Critical illness polyneuropathy is a widespread, axonal peripheral neuropathy that develops in the context of multiple organ failure and sepsis. Critical illness polyneuropathy is possibly the most common neuromuscular cause of prolonged ventilator dependency in patients without prior known the neuromuscular disease.
8. Acute quadriplegic myopathy has developed most frequently in the setting of severe pulmonary disorders in which neuromuscular blockade is used to facilitate mechanical ventilation, and high-dose corticosteroids are concurrently administered.

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An estimated 3.2 million people are living with long-term disability related to traumatic brain injury (TBI).¹ In addition to the personal toll, the direct and indirect costs of these disabilities are estimated to exceed \$60 billion annually.² Americans sustain an estimated 1.6 million TBIs each year. Approximately 290,000 require hospitalization, and 51,000 die of their injuries.³ TBI is the leading cause of morbidity and mortality for Americans between the ages of 1 and 45 years. Teenagers and the elderly are most at risk, although the primary causes vary demographically. Motor vehicle crashes are the main cause of head injuries in those 5 to 64 years old, whereas falls are most common in the pediatric population and people aged 65 years and older.⁴ The primary cause of penetrating head injury is gunshot wounds. Males have twice the risk of sustaining TBI as females across all age groups and are three times more likely to die as a result of their injury.

■ PATHOPHYSIOLOGY

Trauma to the head causes primary injury such as skull fracture, cerebral contusion, and hemorrhage that is a direct physical consequence of the impact. Hours or days after the traumatic incident, secondary injury occurs and may be a major determinant of the patient's ultimate neurologic outcome. Injury to the brain is caused by external forces to the head that strain the tissue beyond its structural tolerance.⁵ These forces can be classified as contact or inertial.⁶ Contact forces typically produce focal injuries such as skull fractures, contusions, and epidural or subdural hematomas. Inertial forces result from the brain undergoing acceleration or deceleration (translational, rotational, or both) and can occur without head impact.

Skull fracture results from a contact force to the head that is usually severe enough to cause at least a brief loss of consciousness. Linear fractures are the most common type of skull fracture and typically occur over the lateral convexities of the skull. A depressed skull fracture, in which skull fragments are pushed into the cranial vault, usually results from blunt force by an object with a relatively small surface area, such as a hammer (Fig. 56-1). Basilar skull fractures are most common in the anterior skull base and often involve the cribriform plate, disrupting the olfactory nerves (Fig. 56-2). Posterior basilar skull fractures may extend through the petrous bone and internal auditory canal, thereby damaging the acoustic and facial nerves.

Skull fractures per se are less detrimental than the associated damage to underlying tissues or vessels. For example, linear skull fractures that involve the squamous portion of the temporal bone are frequently accompanied by a tear of the middle meningeal artery, causing an epidural hematoma. They can also cause facial nerve injury, exhibited as facial asymmetry that can present immediately or in a delayed fashion. Depressed skull fractures are often associated with contusions of the underlying brain tissue, and a scalp laceration overlying a depressed skull fragment can contaminate the fragment with bacteria from the scalp and hair. With a basilar skull fracture, the dura underlying the fracture is often disrupted, resulting in a cerebrospinal fluid (CSF) fistula and leakage of CSF from the nose or ear. Such fistulas allow bacteria to enter the intracranial space from the normally colonized nose, paranasal sinuses, or external auditory canal.

Common posttraumatic intracranial lesions include hemorrhage (epidural, subdural, and intraparenchymal), contusion, and diffuse

brain injury. Subdural hematomas are seen in 20% to 25% of all comatose victims of TBI (Fig. 56-3). They develop between the surface of the brain and the inner surface of the dura and are believed to result from the tearing of bridging veins over the cortical surface or from disruption of major venous sinuses or their tributaries. The hematoma typically spreads over most of the cerebral convexity; the dural reflections of the falx cerebri prevent expansion to the contralateral hemisphere. Swelling of the cerebral hemisphere is common in those with subdural hematomas, given the associated damage to underlying brain tissue. Underlying cerebral contusions were found in 67% of patients with subdural hematomas in one series.⁷ Subdural hematomas are classified as acute, subacute, or chronic, each having a characteristic appearance on computed tomography (CT): acute hematomas are bright white, subacute lesions are isodense with brain tissue and are therefore often overlooked, and chronic hematomas are hypodense relative to the brain.

Epidural hematomas develop between the inner table of the skull and the dura, usually when the middle meningeal artery or one of its branches is torn by a skull fracture. They occur in 8% to 10% of those rendered comatose by TBI.⁸ The majority of epidural hematomas are located in the temporal or parietal regions, but they can also occur over the frontal or occipital lobes and (rarely) in the posterior fossa. They appear as hyperdense mass lesions on CT. Unlike subdural hematomas, their spread is limited by the suture lines of the skull, where the dura is very adherent (Fig. 56-4). Epidural hematomas are uncommon in infants and toddlers, presumably because their skulls are more deformable and less likely to fracture, and in TBI victims older than 60 years, because the dura is extremely adherent to the skull.

An intraparenchymal hematoma is a hemorrhage within the brain substance that occurs after TBI. It is usually associated with contusions of the surrounding tissue. Duret hemorrhage, or hemorrhage into the base of the pons or midbrain, is thought to result from disruption of the perforating arteries at the time of uncus herniation. Such brainstem hemorrhage almost always leads to death or minimally responsive survival.

Traumatic subarachnoid hemorrhage often results from tearing of the corticomeningeal vessels. Though common after severe TBI, subarachnoid hemorrhage does not produce a hematoma or mass effect.⁹ However, it may be associated with an increased risk for posttraumatic vasospasm, which may adversely affect clinical outcome.¹⁰

Contusions are heterogeneous lesions comprising punctate hemorrhage, edema, and necrosis and are often associated with other intracranial lesions. One or more contusions occur in 20% to 25% of patients with severe TBI. Because they evolve over time, contusions may not be evident on the initial CT scan or may appear as small areas of punctate hyperdensities (hemorrhages) with surrounding hypodensity (edema) (Fig. 56-5). Local neuronal damage and hemorrhage lead to edema that may expand over the next 24 to 48 hours. With time, contusions may coalesce and look more like intracerebral hematomas. Depending on their size and location, they may cause significant mass effect, resulting in midline shift, subfalcine herniation, or transtentorial herniation. Contusions are most common in the inferior frontal cortex and the anterior temporal lobes,¹⁰ where the surface of the inner table of the skull is very irregular. Direct blunt-force trauma to the head can produce a contusion in the tissue underlying the point of impact (coup contusion). If the head was in motion upon collision with a rigid



FIGURE 56-1 ■ Right frontal depressed skull fracture caused by an assault with a hammer (axial computed tomography scan, bone window).



FIGURE 56-3 ■ Acute subdural hematomas (SDH) typically spread over entire surface of the hemisphere. Occasionally, mixed-density SDH is seen, indicative of injuries occurring at different times.

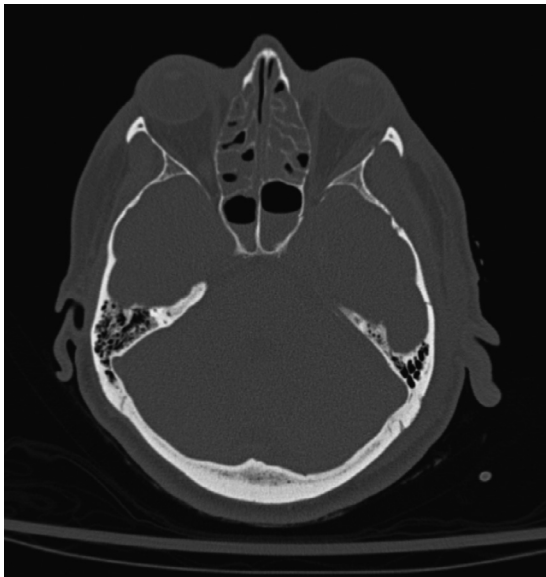


FIGURE 56-2 ■ Basilar skull fractures through the anterior skull base typically cause rhinorrhea and tears in adjacent dura. Computed tomography (CT) scans through the base of the skull may not show the fracture itself but often show fluid in the sphenoid sinus or other paranasal sinuses (axial CT scan, bone window).



FIGURE 56-4 ■ Epidural hematomas have a lens shape and smooth inner border because they strip the dura from the inner table of the skull as they enlarge (axial computed tomography scan).

surface, a contusion may occur in the brain contralateral to the point of impact (contrecoup contusion).

Diffuse axonal injury refers to lacerations or punctate contusions at the interface between the gray and white matter. Such punctate contusions are thought to result from the disparate densities of the gray and white matter and the consequent difference in centripetal force associated with a rotational vector of injury.¹¹ Diffuse axonal injury was once thought to result solely from mechanical disruption at the time of impact; however, more recent research has identified cases in which the histologic footprints of diffuse axonal injury, such as fragmentation of axons and axonal swelling, do not appear until 24 to 48 hours after the incident, suggesting that some cases are a secondary manifestation

of trauma.^{12,13} Diffuse axonal injury is present in almost half of all patients with severe TBI and in a third of those who die, and it is a common cause of persistent vegetative or minimally conscious state.¹⁴

Posttraumatic intracranial lesions cause neurologic dysfunction via direct and in some cases indirect mechanisms. By destroying brain tissue, contusions and intraparenchymal hemorrhage cause deficits directly related to the function of the damaged tissue. Uncal herniation is also an important mechanism of temporary or permanent neurologic deficits.^{15,16} Semirigid dural reflections divide the intracranial contents into compartments. The tentorium cerebelli separates the anterior and middle cranial fossae from the posterior cranial fossa. The brainstem, specifically the midbrain, traverses an opening, the tentorial foramen, in the anterior central portion of this partition. The medial portion of the temporal lobe, the uncus, lies on both sides of the



FIGURE 56-5 ■ Contusions are most common in the inferior temporal and frontal lobes. In the first few hours after injury, they appear only as areas of hemorrhage mixed with edematous brain. Within 24 to 48 hours after injury, further hemorrhage may occur, causing significant enlargement of the contusion and hematoma (axial computed tomography scan).

tentorial foramen. Hematomas and contusions located over the lateral surfaces of the brain can depress the brain medially and displace the medial portion of the temporal lobe (uncus) into the tentorial foramen (i.e., uncal herniation). Such displacement compresses the midbrain, which contains neurons that are part of the reticular activating system. Midbrain compression due to uncal herniation damages the reticular activating system, causing loss of consciousness; stretches the third cranial nerve and its associated parasympathetic fibers, causing pupil dilatation and loss of the light reflex; and injures the pyramidal fibers in the crus cerebri, causing abnormal posturing responses in the contralateral arm and leg.

Intracranial hypertension is a major cause of posttraumatic neurologic morbidity and mortality.¹⁷ The intracranial pressure (ICP) is defined by the volume of CSF, blood, and brain tissue in the cranial vault. The volume of these components is dynamic, and the brain can accommodate moderate changes in any of the three. Thus, the intracranial volume can gain 100 to 150 mL, equivalent to a moderate-sized subdural hematoma, without the ICP increasing significantly. When these buffering mechanisms have been exhausted, however, even a small increase in the size of a hematoma will cause a rapid rise in ICP. If appropriate treatment is delayed, the ICP may approach the mean arterial pressure (MAP), causing a hydrostatic block of blood flow to the brain and brain death.

■ PREHOSPITAL CARE

The acutely injured brain is vulnerable to further damage from systemic hypotension, cerebral hypoperfusion, hypercarbia, hypoxemia, and elevated ICP. Preventing these physiologic insults is crucial to limiting secondary brain injury. Care of the TBI victim always should begin with evaluating and securing a patent airway and restoring normal breathing and circulation, as such treatment has been shown to reduce mortality after severe TBI.^{18,19}

The airway is usually most easily and safely secured by orotracheal intubation. Patients with severe maxillofacial trauma may require nasotracheal intubation, but this is less desirable because it is a relatively blind procedure. A third alternative for securing the airway is the laryngeal mask airway, an easily learned and rapidly applied device

BOX 56-1

Recommended Rapid-Sequence Induction for Severely Head-Injured Patients

1. Preoxygenation
100% oxygen for 5 min or four vital capacity breaths
2. Pretreatment
Fentanyl (3 to 5 µg/kg IV)
3. Wait 2 to 3 min if possible
Continue preoxygenation
4. Neuromuscular blockade and sedation
Succinylcholine (1.5 mg/kg IV) or rocuronium (1.0 mg/kg IV)
5. Intubation with in-line cervical spine immobilization
Positive-pressure ventilation and possibly maintaining neuromuscular blockade with vecuronium and additional analgesia and sedation if prolonged transport time is anticipated

that has undergone successful field trials.²⁰ A surgical airway (cricothyroidotomy) should be performed only after other attempts to secure an airway have failed. Rapid-sequence intubation is recommended to prevent transient hypertension, tachycardia, increased ICP, and agitation that can interfere with the procedure. **Box 56-1** shows a recommended rapid-sequence intubation pathway.

Supplemental oxygen should be provided before and immediately after intubation. Ventilatory rates of 10 to 12 breaths per minute for adults, 20 breaths per minute for children, and 25 breaths per minute for infants should supply adequate oxygenation. Therapeutic hyperventilation is inadvisable unless neurologic deterioration is clearly evident during evaluation and transport. Aggressive hyperventilation can cause cerebral vasoconstriction, reducing already low cerebral blood flow (CBF) and potentially causing or exacerbating cerebral ischemia.²¹

Rapid fluid resuscitation and restoration of a normal BP are critical in the prehospital setting, because hypotension has been associated with doubling of the mortality rate after severe TBI.²² The most likely cause of hypotension is hemorrhage, usually in the abdomen or chest; therefore, hypovolemia should be assumed. Lactated Ringer's or normal saline solutions should be infused through a large-bore IV catheter as quickly as possible until normotension is achieved.

In all cases of severe TBI, defined as a Glasgow Coma Scale (GCS) score of 3 to 8 and an inability to follow commands, patients should be treated as if they have a spinal fracture until an adequate examination of the spine proves otherwise. Among those who survive long enough to reach the emergency department, the likelihood of a cervical spine fracture is 2% to 7%. More troubling, however, is that an estimated 10% to 25% of all posttraumatic spinal cord injuries are iatrogenic, occurring during transport to the hospital.²³ After respiratory and hemodynamic stabilization, the patient should be placed in a neutral position on a flat, hard surface. A rigid cervical spine collar should be placed, followed by immobilization on a long spine board.

■ EMERGENCY DEPARTMENT CARE

Upon arrival at the trauma center, the emergency medical personnel should concisely report their prehospital assessment and management, including mechanism of injury, stabilizing maneuvers, medications given, initial vital signs, GCS score, and hemodynamic stability during transport.¹⁸ A thorough physical and radiographic examination to identify all life-threatening injuries should then be performed. Most trauma centers follow the Advanced Trauma Life Support protocol, a comprehensive routine that has proved successful in quickly detecting all major injuries.²⁴ Any life-threatening injuries such as overt hemorrhage, tension pneumothorax, or cardiac tamponade should be treated immediately upon discovery. A brief neurologic examination is performed, including assessment of the GCS score (**Table 56-1**), pupillary size and reaction to light, and symmetry and extent of extremity movements. The head is palpated to detect fractures, lacerations, or

TABLE 56-1 Glasgow Coma Scale⁵⁹

| RESPONSE | POINTS |
|--|--------|
| SPEECH | |
| Alert, oriented, and conversant | 5 |
| Confused, disoriented, but conversant | 4 |
| Intelligible words, not conversant | 3 |
| Unintelligible sounds | 2 |
| No verbalization, even with painful stimulus | 1 |
| EYE OPENING | |
| Spontaneous | 4 |
| To verbal stimuli | 3 |
| To painful stimuli | 2 |
| None, even with painful stimuli | 1 |
| MOTOR | |
| Follows commands | 6 |
| Localizes painful stimulus | 5 |
| Withdraws from painful stimulus | 4 |
| Flexor posturing with central pain | 3 |
| Extensor posturing with central pain | 2 |
| No response to painful stimulus | 1 |

Data from Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet* 1974;2:81–84.

penetrating wounds, and lacerations are probed gently to ascertain the presence of a depressed skull fracture or foreign body. Large lacerations are compressed with pressure dressings or temporarily sutured to prevent further hemorrhage.

Coagulopathy resulting from TBI is thought to occur when hypoperfusion causes activation of the protein C pathway, thereby inducing alterations in the clotting cascade.²⁵ It is also commonly seen as a result of therapeutic anticoagulation with warfarin and novel anticoagulants, especially in the geriatric population. Fresh frozen plasma and cryoprecipitate can be used to correct the INR to 1.3 or less. Prothrombin complex concentrates (PCCs) and recombinant factor VIIa have been shown to decrease blood product requirements and costs associated with correction of coagulopathy.^{26–28}

After all life-threatening injuries have been identified and stabilized, the immediate concern is whether the patient requires a craniotomy to evacuate an intracranial mass lesion. A CT scan of the head should be performed at intervals of 5 mm or less from the C2 vertebra to the vertex. If no surgical intracranial mass lesion is evident on the scan of the head, CT scans of the cervical spine, chest, and abdomen can be performed to detect occult injuries in these areas. If a surgical mass lesion is seen on the head CT scan, it should be evacuated immediately, postponing any other imaging studies. Diagnostic peritoneal lavage may be performed during the craniotomy to detect abdominal bleeding if needed.

DEFINITIVE TREATMENT

Critical to determining the initial severity of the brain injury and appropriate treatment are CT findings combined with a reliable exam of neurologic function.²⁹ In the case of an acute subdural hematoma, for example, a patient with a moderate-sized lesion who has normal pupil size and reactivity and is able to follow commands might safely be treated nonoperatively.⁹ Conversely, surgery is unlikely to benefit an elderly patient with fixed and dilated pupils and a GCS score of 3 or 4, regardless of the CT findings.³⁰ Other determining factors include size and location of the hematoma, presence and extent of an underlying contusion or brain swelling, and results of the neurologic examination. Neurologic deterioration, particularly a decline in mental status, suggests enlargement of the hematoma, and a new CT scan should be obtained promptly. Hematomas less than 10-mm thick that cause a midline shift of less than 5 mm can usually be observed, especially if they do not involve the middle cranial fossa.³¹ If nonoperative management is chosen for an intracranial hematoma, the patient should be



FIGURE 56-6 ■ Temporal lobe contusions must be monitored closely because even a slight enlargement can cause uncal herniation, often without an increase in intracranial pressure (ICP) (axial computed tomography scan).

monitored with frequent neurologic assessments in the intensive care unit (ICU).

The classic presentation of a patient with an epidural hematoma is a period of unconsciousness immediately after impact to the head, followed by a so-called lucid interval in which consciousness returns for a few minutes to an hour or more before the patient lapses into a coma. This lucid interval actually occurs in less than a third of patients with epidural hematomas, however; most either remain conscious after the injury (smaller clots) or remain comatose.

A hematoma that compresses the temporal lobe is particularly ominous and can rapidly cause uncal herniation with minimal enlargement. Such lesions warrant a lower threshold for evacuation compared with hematomas in other locations. Small hemorrhages managed nonoperatively should be monitored with frequent CT scans during the first several days after injury. Enlarging middle fossa hematomas, even those large enough to cause herniation, do not always cause an increase in the ICP; therefore, ICP monitoring should not be relied on to follow their status.

The initial signs and symptoms of contusions vary greatly depending on their size and location and the presence of other associated lesions. A small contusion may cause only a headache or no symptoms at all. If located in an eloquent area of the brain, such as the speech or motor areas, it may cause focal neurologic symptoms. Larger contusions, especially those involving the frontal or temporal lobes, typically cause elevated ICP and coma. The contusion should be followed closely with serial CT scans because there is a 20% to 30% risk that the contusion will enlarge during the next 24 to 48 hours. The ICP should be monitored if the patient cannot follow commands. As with hematomas in the middle cranial fossa, contusions of the temporal lobes should be closely watched with CT scans. A temporal contusion can enlarge to the point of uncal herniation without a significant rise in ICP, so the threshold for evacuation of these lesions should be low (Fig. 56-6). Unilateral frontal or temporal lobectomies are usually well tolerated and do not cause measurable neurologic deficits, while allowing space for further brain swelling.³²

In the ICU, the primary goal is to prevent cerebral ischemia and thereby limit secondary brain injury. The most common preventable causes of cerebral ischemia are hypotension, hypoxemia, and intracranial hypertension. Comprehensive physiologic monitoring should be performed so that these physiologic insults can be detected and treated promptly.

■ PHYSIOLOGIC MONITORING

Continual monitoring of the end-tidal partial pressure of carbon dioxide (PCO_2) and frequent analyses of arterial blood gases enable the early detection of deteriorating ventilatory status, which should prompt appropriate ventilator adjustments. Oxygen saturation should also be monitored continually with pulse oximetry. BP monitoring is best accomplished with an indwelling arterial catheter coupled to a pressure transducer. Central venous pressure (CVP) monitoring should be considered for patients with severe TBI, particularly those with significant non-CNS injuries. In elderly patients or those with severe pulmonary contusions, intravascular volume may be more accurately assessed by pulmonary artery catheterization with a Swan-Ganz catheter or the less invasive, Flo-Trac Vigileo. Monitoring urine output with an indwelling Foley catheter is essential for determining the patient's fluid status.

Continuous ICP monitoring is essential for all patients who have severe TBI and abnormal CT findings, because intracranial hypertension develops in 53% to 63% of such patients.^{33,34} ICP monitoring is also recommended for comatose patients who are older than 40 years and have unilateral or bilateral motor posturing or a systolic blood pressure (SBP) less than 90 mm Hg, even if no abnormalities are seen on the initial CT scan. The gold standard for ICP monitors is the ventricular catheter coupled to an external strain-gauge transducer.^{35,36} It is accurate, reliable, and less expensive than newer self-contained pressure-sensing devices. In addition, ventricular pressure is considered more reflective of global ICP than is subdural, subarachnoid, or epidural pressure. Other advantages of the ventriculostomy method of ICP monitoring are that the system can be re-zeroed after insertion—not possible with most of the newer self-contained devices—and CSF can be withdrawn to treat intracranial hypertension. The overall complication rate for ventricular ICP monitoring is 7.7% (infection, 6.3%; hemorrhage, 1.4%).³⁷ Some studies indicate that the infection rate increases significantly when a catheter remains in place for more than 5 days,³⁸ although this is less likely with the use of antibiotic-impregnated ventricular catheters.

Alternatives to the ventriculostomy technique have been developed that provide relatively accurate measurements of global ICP, are easier to insert, and may cause fewer complications. They include devices that contain a pressure-sensing transducer (either strain-gauge or fiber-optic technology) within the tip of the catheter.³⁴ These pressure sensors provide reliable ICP measurements even if they are inserted into the white matter and are often used when a ventricular catheter is difficult to insert because of small or collapsed ventricles. The primary disadvantage is that CSF drainage is not possible. In addition, these devices can be calibrated only once, before insertion, and with some of them, measurement drift is as much as 1 to 2 mm Hg per day. Measurement of the ICP can then be used to calculate the cerebral perfusion pressure (CPP), defined as the difference between MAP and ICP, which describes actual cerebral perfusion. The current recommendation is to maintain a CPP above 50 mm Hg.³⁹

Devices that monitor the oxygen partial pressure of oxygen (Pbto_2) of brain tissue can be used to determine whether cerebral oxygenation is adequate. These monitors continually measure the tissue Pbto_2 in the small region of brain into which they are inserted. Studies suggest that mortality may be decreased in those undergoing oxygen directed therapy.⁴⁰⁻⁴² Although no methods are available for continuously monitoring global CBF, transcranial Doppler insonation of the middle cerebral arteries can provide indirect information. Positron emission tomography (PET) or CBF measurements with xenon, either as a radiolabeled agent or as a CT contrast medium, can provide periodic snapshots of the blood flow.

■ MEDICAL TREATMENT

Hypoxemia is best avoided with the use of tracheal intubation and mechanical ventilation. The fraction of inspired oxygen should be titrated to provide an arterial Po_2 of 100 mm Hg.⁴³ Maintaining an arterial PCO_2 of approximately 35 mm Hg is advised to avoid the

cerebral vasoconstriction associated with aggressive hyperventilation. A form of acute respiratory distress syndrome (ARDS) can develop in some patients. In such cases, adequate oxygenation requires the use of positive end-expiratory pressure (PEEP). Concern has been raised that the use of PEEP in patients with TBI may increase the ICP. However, clinical studies have shown that in the presence of ARDS, up to 14 to 15 cm H_2O of PEEP can be used without measurable changes in ICP.

Hypotension, defined as a SBP of less than 90 mm Hg, should be treated aggressively. Normovolemia should be restored by infusing isotonic saline as needed to achieve a central venous pressure of 7 to 12 cm H_2O .⁴³ Hypotonic intravenous solutions can exacerbate cerebral edema and should be avoided. If the patient is anemic, packed red blood cells should be transfused to restore the hematocrit to at least 30%. If hypotension is refractory to volume resuscitation, the patient should be started on vasopressors, with the dose titrated to raise the SBP above 90 mm Hg. Norepinephrine has been shown to be most efficacious at maintaining MAP and CPP without deleteriously affecting ICP.⁴⁴

Intracranial hypertension is defined as sustained ICP greater than 20 mm Hg. Several clinical studies have found that mortality and morbidity increase significantly when the ICP persistently remains above this threshold.⁴⁵ Based on this association and the widely accepted premise that elevated ICP can compromise cerebral perfusion and cause ischemia, the aggressive treatment of intracranial hypertension is almost uniformly endorsed. Seizures, hypercapnia, fever, jugular venous outflow obstruction (e.g., poorly fitting cervical collars), and agitation can cause or exacerbate intracranial hypertension. A stepwise approach for ICP treatment is usually followed, with the least toxic therapies used first and more toxic therapies added only if the initial treatment is unsuccessful. Sedation and neuromuscular blockade are often an effective first treatment, particularly if the patient is agitated or posturing.⁴⁶ Narcotics (e.g., morphine, fentanyl), short-acting benzodiazepines (e.g., midazolam), or hypnotic agents such as propofol can be used for sedation, and vecuronium bromide as the paralytic agent. Narcotic-induced hypotension can be averted by using relatively low doses and ensuring the patient is normovolemic before treatment. Because the ability to obtain an accurate GCS score is lost during this treatment, the pupil status, ICP, and CT scans must be closely monitored.

If intracranial hypertension is refractory to sedation and neuromuscular blockade, intermittent ventricular CSF drainage is used. Intermittent rather than continuous drainage enables reliable measurement of the ICP. If these measures fail to reduce the ICP, a bolus administration of mannitol (0.25 to 1 g/kg every 3 to 4 hours as needed) or hypertonic saline is recommended.⁴⁷⁻⁴⁹ Mannitol exerts its effect through osmotic diuresis, lowering the ICP and increasing the CPP by expanding the blood volume, reducing the blood viscosity, and increasing CBF and oxygen delivery to the tissues within a few minutes of infusion. Its duration of effect averages 3 to 5 hours. Continuous infusion is less desirable than bolus infusion, because the former is more likely to lead to extravasation of the drug into brain tissue, causing a reverse osmotic gradient and increased edema and ICP. The intravascular volume should also be closely monitored to prevent dehydration. Hypertonic saline appears to create osmotic mobilization of water across the blood-brain barrier. Concentrations ranging from 3% to 23.4% have been used to decrease ICP.⁴⁸ The serum osmolality and sodium level should be monitored frequently during the use of osmotherapy. The drugs should be discontinued if the serum sodium level exceeds 160 mg/dL or the osmolality exceeds 320 mOsm in order to minimize the risk of acute kidney injury.⁵⁰

If despite these measures the ICP remains above 20 mm Hg, the ventilatory rate can be adjusted to reduce the arterial PCO_2 to 30 mm Hg.²¹ Hyperventilation should be used cautiously during the first 24 to 48 hours after injury, because it will cause cerebral vasoconstriction at a time when CBF is already critically reduced. Evidence also suggests that even brief periods of hyperventilation can lead to secondary brain injury by causing an increase in extracellular lactate and glutamate levels.⁵¹ Prophylactic hyperventilation is always

contraindicated in the absence of elevated ICP.⁵² If hyperventilation is used, the brain tissue P_{bO_2} or jugular venous oxygen saturation should be monitored to detect any cerebral ischemia that the treatment might cause. The risk of tissue ischemia and poor outcome may increase if the brain tissue P_{bO_2} falls below 10 mm Hg.⁴²

If intracranial hypertension persists despite all these treatments, particularly if the ICP rises rapidly or if the patient's initial CT scan showed a small contusion or hematoma, another CT scan should be obtained immediately to determine whether there is a new mass lesion or a preexisting lesion has enlarged. Even if the lesion has enlarged only slightly, an emergent craniotomy and evacuation of the contusion or hematoma may be the best way to reduce the ICP quickly and effectively.

In the absence of new or expanding mass lesions, high-dose barbiturates can be considered in patients with salvageable neurologic exams. Pentobarbital is the most commonly used drug for this purpose and is administered as an IV loading dose of 10 to 15 mg/kg over 1 to 2 hours, followed by a maintenance infusion of 1 to 2 mg/kg per hour. Continuous electroencephalographic monitoring is recommended while increasing the dose until a burst suppression pattern is observed. Hypotension, the most common adverse effect of barbiturates, can usually be averted by ensuring a normal intravascular volume before administering the drug.

Therapeutic moderate hypothermia has been used in several clinical trials over the past decade. The body temperature is lowered to 32°C to 33°C as soon as possible after injury and kept at that temperature for 24 to 48 hours using surface cooling techniques. Although some clinical trials have not found that this treatment improves neurologic outcome compared with normothermia, they have consistently shown that hypothermia significantly reduces ICP.^{53,54}

The use of decompressive craniectomies, such as large lateral or bifrontal bone flaps, with or without a generous temporal or frontal lobectomy can be considered for a small subset of patients. Two studies report good outcomes in 56% to 58% of patients whose refractory intracranial hypertension was treated with decompressive craniectomy as a last resort,^{55,56} and another study suggested that decompressive temporal lobectomy, when performed soon after injury, improves the outcome for young patients.^{32,57} However, others found that decompressive craniectomy does not improve ICP, CPP, or mortality rates.⁵⁸ Because age has such a profound impact on the likelihood of a meaningful recovery, these second tier therapies are recommended only for patients who are younger than 40 years old.

Failure to control intracranial hypertension may result in brain death, the irreversible cessation of cerebral function. Clinically, this is manifested by loss of motor function and brainstem reflexes including pupillary response, corneal reflex, cough reflex, and oculovestibular reflexes.⁵⁹ Once these criteria are met, confirmatory testing such as apnea testing or cerebral perfusion studies can be performed.⁶⁰ Federal law requires notification of the local organ procurement office prior to formal brain death testing. Medical staff should avoid mentioning organ donation to family members to minimize the appearance of conflict of interest; this is best left to designated requestors after decoupling has occurred.

Patients who have TBI, particularly those who are comatose or have significant non-CNS injuries, are at high risk for pneumonia and other infections, fever, malnutrition, seizures, deep venous thrombosis (DVT), pulmonary embolism, and other maladies endemic to the ICU. Most of these complications cause secondary brain injury and should be diagnosed and treated without delay. Fever is very common in the ICU and has been shown to lengthen length of stay and worsen outcomes.⁶¹ Preclinical studies have found that there is a log increase in neuronal death in ischemic brain regions for every degree of brain temperature above 39°C, and this effect is observed for 24 hours or more after injury.⁶² Consequently, the body temperature should be kept below 37°C at all times, and infectious or other causes of fever should be aggressively sought and treated.

Patients who are comatose, those being maintained on neuromuscular blocking agents, and those with pelvic or long-bone fractures are

at high risk for deep venous thrombosis and pulmonary embolism. They should receive early prophylaxis, which typically includes the use of lower extremity sequential compression devices as well as subcutaneous heparin or enoxaparin. The early (2 to 3 days after injury) use of minidose heparin or low-molecular-weight heparin is safe and has not been found to cause or worsen intracranial hemorrhage after TBI.⁶³⁻⁶⁵

Malnutrition is also common after severe TBI. The resting metabolic expenditure typically increases by 140% in a nonparalyzed patient with severe TBI.⁶⁶ Nitrogen wasting is increased, with excretion of as much as 9 to 12 g/day. Thus, early enteral feeding is advisable, with the aim of providing at least 140% of the daily basal metabolic caloric requirements by the third or fourth day after injury.⁶⁷ For a patient expected to be in a prolonged coma, a percutaneous gastrostomy or surgical jejunostomy provides a convenient and well-tolerated route to administer tube feeding. Hyperglycemia is associated with TBI and is associated with prolonged hospital stays and increased mortality.⁶⁸ Aggressive management of hyperglycemia has been shown to decrease complications and improve long-term outcome,⁶⁹ but the optimal blood glucose range in patients with severe TBI remains controversial, and tight glucose control may be problematic.^{70,71}

Posttraumatic contusions and subdural hematomas are well-known causes of generalized seizures, which can precipitate secondary injury. Anticonvulsant prophylaxis is therefore recommended for patients with these lesions. The drug should be given for the first 7 days after injury; a prospective clinical trial found no advantage to longer prophylactic treatment.⁷² Subclinical seizures may occur in up to 33% of patients in the first week following TBI.⁷³ Therefore, EEG should be considered for those with unexplained depressed mental status, abruptly deteriorating cerebral oxygenation, or a sudden increase in ICP.

Several conditions may lengthen the ICU course of those recovering from severe TBI. Paroxysmal sympathetic hyperactivity, also known as *sympathetic storming*, may become evident when sedation weaning begins in up to 30% of patients. Hallmarks of storming include periodic episodes of seemingly unprovoked hypertension, tachycardia, tachypnea, diaphoresis, and hyperthermia.⁷⁴ Spontaneous posturing or dystonia may also be present during these episodes. Recognition of these symptom complexes as being neurologic in origin is key to avoid treatment delays and unnecessary diagnostic testing. Treatment protocols are individualized, with most patients requiring various combinations of gabapentin, opiates, propranolol, and bromocriptine to achieve adequate symptom control. Posttraumatic agitation (PTA) may follow coma emergence and is a favorable sign for TBI recovery. PTA may delay ventilator weaning, progress with therapy, and impact overall patient safety. Initial treatment should include a certain tolerance for agitation with benzodiazepines administered for emergent control. Ongoing PTA can be treated with agents such as propranolol, tricyclic antidepressants, and antiseizure medications (carbamazepine, valproic acid). Severe cases may require the use of atypical antipsychotics. Haloperidol should be avoided because of its impact on dopamine transmission and subsequent delay in TBI recovery.⁷⁵

PHYSICAL THERAPY AND REHABILITATION

Rehabilitation of TBI patients should begin in the ICU during the first few days after injury and include passive range-of-motion exercises and functional splinting of the extremities. Mobilization helps prevent DVT, and studies indicate that early sitting of comatose patients may hasten the return of consciousness. Recent studies suggest that administration of dopaminergic agents, specifically amantadine, after resolution of intracranial hypertension may hasten arousal and improve outcomes.^{76,77} Comprehensive TBI rehabilitation programs should involve a multidisciplinary team of physical, occupational, and speech therapists, neuropsychologists, and social workers, ideally coordinated by a physiatrist or a neurologist with special training in physical medicine and rehabilitation. Rehabilitation after TBI entails many other factors that are critical to optimizing outcome, but a thorough review is beyond the scope of this chapter.

PENETRATING INJURIES

Gunshot wounds to the head, the predominant cause of penetrating head injury, usually cause massive destruction of brain tissue, severe brain swelling, and if transcranial trajectory, death. The wounding potential of a bullet depends primarily on its velocity at impact and its mass, although the shape of the bullet and its lateral movements also play a role. The impact velocity is by far the most important determinant of a bullet's wounding potential. Consequently, high-velocity rifle wounds to the head are invariably fatal, whereas low-velocity open-chambered handgun wounds often are not. When a bullet enters the skull, it creates a variety of pressure waves within the brain, some of which can cause tissue pressures of nearly 100 atmospheres, resulting in further tissue injury. Bullets often fragment after they strike the skull, fracturing a portion of the skull into multiple fragments. Both the bullet and the bone fragments then become numerous secondary missiles that cause additional tissue damage.

Low-velocity missile wounds, such as those from knives, ice picks, or arrows, do not cause the massive brain injuries seen with bullets. Usually, only the tissue in the immediate path of the missile is damaged, and patients often have a complete neurologic recovery after the missile is surgically extracted. Nonetheless, vascular injuries are always possible with high- or low-velocity missile injuries to the head, especially those in or near the skull base or the sylvian fissures.

The initial assessment and resuscitation of patients with penetrating head injuries are the same as for those with closed head injuries. Knives or other missiles protruding from the head should never be removed in the field or emergency department; if they are tamponading a damaged intracranial vessel, removal could lead to massive intracranial hemorrhage. When a patient has a gunshot wound to the head, the neck, chest, and abdomen should be inspected carefully for other gunshot wounds, because wounds to the heart or great vessels in the chest or abdomen may be even more life threatening. A CT scan of the head defines the intracranial path of the missile and related skull and tissue damage. More importantly, it identifies any large intracranial hematomas or contusions that may significantly affect outcome. If the missile trajectory is in or near the skull base or sylvian fissures and the patient is deemed salvageable, cerebral angiography should be performed because this injury pattern is associated with development of pseudoaneurysm.¹⁰

Most patients who are expected to survive a penetrating head injury require limited operative treatment. Large intracranial hematomas should be evacuated promptly. A craniotomy is required for low-velocity missile wounds in which the object is still protruding from the head. After removing a segment of skull containing the missile and large enough to allow for intracerebral exploration, the surgeon can seek and immediately repair or occlude any vascular injuries caused by the missile. For gunshot wounds to the head, the surgeon should perform a limited débridement of the scalp and skull wound, removing scalp, bone, and bullet fragments penetrating the brain only if they lie near the surface. Easily accessible necrotic brain should be débrided and meticulous hemostasis achieved. Subsequent medical

management of penetrating injuries is as described previously for closed head injuries. Because a penetrating TBI by definition disrupts and contuses brain tissue, all patients with these injuries should also receive anticonvulsants for at least 7 days.⁷²

PROGNOSIS

Predicting outcome soon after a TBI can help guide acute and chronic care and help prepare family members for the typically protracted recovery process. Equally important is that further treatment may be deemed futile, and expensive critical care or surgery can be reserved for those who are likely to benefit. Of course, early prognostication must be reliable, especially when withdrawal of life support is a consideration.

Several clinical and radiographic characteristics have proven useful for outcome prediction, but they must be used in concert.⁷⁸ Moreover, these criteria are more reliable for predicting death or vegetative survival than for accurately predicting mild or no dysfunction and a complete return to normalcy. The most powerful outcome predictors are age, initial GCS score (particularly the motor component), pupil size and reaction to light, ICP, and the nature and extent of intracranial injuries.

Marshall and colleagues devised a CT-based classification scheme that proved prognostically useful when applied to the patients in the Traumatic Coma Data Bank study (Tables 56-2 and 56-3).⁷⁹ The classification emphasizes the mass effect of posttraumatic intracranial lesions. Not surprisingly, these investigators found the worst outcomes among patients with large intracranial mass lesions and uncal herniation.

The patient's salvageability and prognosis after a penetrating injury are far clearer than for those with closed head injuries. Most victims of high-velocity gunshot wounds to the head die before or shortly after

TABLE 56-2

Computed Tomographic Classification of Traumatic Brain Injury

| CATEGORY | DEFINITION |
|-------------------------------|--|
| Diffuse injury I | No visible intracranial pathology |
| Diffuse injury II | Cisterns present, with midline shift 0 to 5 mm; no high-density lesion >25 mL |
| Diffuse injury III (swelling) | Cisterns compressed or absent, with midline shift 0 to 5 mm; no high-density lesion >25 mL |
| Diffuse injury IV (shift) | Midline shift >5 mm; no high-density lesion >25 mL |
| Evacuated mass lesion | Any lesion surgically evacuated |
| Nonevacuated mass lesion | High-density lesion >25 mL; not surgically evacuated |

Data from Marshall LF, Marshall SB, Klauber MR, Clark M. A new classification of head injury based on computerized tomography. *J Neurosurg* 1991;75:S14–S20.

TABLE 56-3 Relationship of Computed Tomographic Classification to Outcome at Discharge

| CATEGORY | NO. OF PATIENTS | UNFAVORABLE OUTCOME* (%) | FAVORABLE OUTCOME† (%) |
|--------------------|-----------------|--------------------------|------------------------|
| Diffuse injury I | 52 | 38 | 62 |
| Diffuse injury II | 177 | 65 | 35 |
| Diffuse injury III | 153 | 84 | 16 |
| Diffuse injury IV | 32 | 94 | 6 |
| Evacuated mass | 276 | 77 | 23 |
| Nonevacuated mass | 36 | 89 | 11 |

Data from Marshall LF, Marshall SB, Klauber MR, Clark M. A new classification of head injury based on computerized tomography. *J Neurosurg*. 1991;75(Suppl.):S14–S20.

*Death, persistent vegetative state, or severe disability.

†Moderate disability or good recovery.

hospital admission. A meta-analysis of recent clinical studies examining civilian gunshot wounds to the head found that favorable outcomes (Glasgow Outcome Scale scores of 4 or 5) occurred in only 5 of 490 patients with initial GCS scores of 3 to 5.⁸⁰ Mortality rates ranged from 51% to 87% for patients with scores of 8 or less. In contrast, those whose initial GCS scores were 13 to 15 all survived and had favorable outcomes. Other clinical signs associated with death or a poor outcome are fixed and dilated pupils, intracranial hypertension, and hypotension.

The CT-defined extent of intracranial injury caused by the missile also has prognostic significance. Hyperdense lesions with a volume greater than 15 mL, midline shift of more than 3 mm, compressed or absent basal cisterns, subarachnoid hemorrhage, and intraventricular hemorrhage are all associated with mortality rates of 80% to 90%, as is a bullet trajectory that traverses both hemispheres, the basal ganglia, or the posterior fossa.^{81,82}

KEY POINTS

1. Severe traumatic brain injuries are the leading cause of morbidity and mortality for Americans between the ages of 1 and 45 years.
2. Outcome following traumatic brain injury is determined not only by the primary injury, such as skull fracture and subdural hematoma but also by secondary injuries initiated by posttraumatic ischemia.
3. Secondary brain injuries are primarily responsible for the development of delayed intracranial hypertension.
4. The goal of critical care management of patients with severe traumatic brain injury is to enhance cerebral perfusion and avoid therapy that may cause regional cerebral ischemia.
5. Early assessment and triage of patients with severe traumatic brain injury should use the advanced trauma life support protocol prescribed by the American College of Surgeons Committee on Trauma.
6. Patients with severe traumatic brain injury are best managed at a level I trauma center with immediate neurosurgical availability.
7. Patients with contusions or hematomas visible on head computed tomography scans and Glasgow Coma Scale scores of 8 or less benefit from intracranial pressure monitoring.
8. A ventricular catheter coupled to an external strain-gauge transducer is the optimal means of monitoring intracranial pressure, because it provides accurate measurements and allows for CSF drainage—the most benign way of treating elevated intracranial pressure.
9. Prophylactic hyperventilation therapy, particularly when the intracranial pressure is less than 20 mm Hg, should be avoided.
10. Patients with subdural hematomas, contusions, or penetrating injury benefit from anticonvulsive prophylaxis for 7 days after injury.
11. Early evaluation of brain-injured patients by a physical therapist and rehabilitation specialist is highly recommended to prevent immobility-related complications and facilitate rapid mobility.

ANNOTATED REFERENCES

Chestnut RM, Marshall SB, Piek J, et al. Early and late systemic hypotension as a frequent and fundamental source of cerebral ischemia following severe brain injury in the Traumatic Coma Data Bank. *Acta Neurochir Suppl (Wien)* 1993;59:121–125.

The authors reviewed blood pressure readings in a group of several hundred patients admitted to the Traumatic Coma Data Bank. They found that hypotension (systolic blood pressure <90 mm Hg) was associated with a twofold increase in the mortality rate compared with head-injury patients who did not have hypotension.

Haas B, Jurkovich GJ, Wang J, Rivara FP, Mackenzie EJ, Nathens AB. Survival advantage in trauma centers: expeditious intervention or experience? *J Am Coll Surg* 2009;208(1):28–36.

In a multicenter prospective cohort study of 1331 adult trauma patients cared for in trauma centers (TC) and nondesignated centers (NTC), times from admission to relevant interventions were assessed, as were relative risks of in-hospital death. The relative risk of death was 0.61 (95% CI,

0.43–0.86) among patients managed at TC compared with those admitted to NTC. This survival advantage was greatest among patients with penetrating trauma, though the relative risk of death at a TC among patients in the TBI group was 0.72 (95% CI, 0.50–1.0). These outcomes were not a result of more rapid assessment and intervention alone and emphasize the complex factors that contribute to the survival benefit of trauma center care.

Temkin NR, Dikmen SS, Wilensky AJ, et al. A randomized, double-blind study of phenytoin for the prevention of posttraumatic seizures. *N Engl J Med* 1990;323(8):497–502.

In this randomized, controlled, double-blind study of the benefit of prophylactic anticonvulsant therapy for patients with TBI, the authors found a significant reduction in the incidence of posttraumatic seizures during the first week of therapy, but no subsequent benefit was observed when therapy was continued longer than 7 days. This study has led most to discontinue the use of anticonvulsants 1 week after TBI, regardless of the nature of the injury.

■ References for this chapter can be found at expertconsult.com.

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Despite substantial improvements in emergency, diagnostic, and surgical care, spinal trauma continues to present a challenging spectrum of diseases for the neurosurgeon to manage. When spinal trauma results in a spinal cord injury (SCI), the emotional and financial toll inflicted on individuals and their families is enormous. Improvements in the quality of care delivered over the past few decades are partially reflected in the recognition that centers of excellence that focus on acute treatment and rehabilitation of the patient with SCI are best equipped to deal with the magnitude of services these patients require.

■ EPIDEMIOLOGY

Spinal cord injury typically occurs in males at the peak of their productive lives. The incidence of traumatic SCI is approximately 11,000 new cases each year in the United States,¹ with a prevalence of 191,000. The prevalence is increasing steadily owing to improved survival in both the acute and chronic stages of the disease. Depending on the age at injury, level, and severity of injury, life expectancy ranges from 4 to 50-plus years after injury. The cost of caring for the individual patient is directly related to the injury level of the spinal cord and to the patient's age, with the highest costs associated with older quadriplegic patients who are dependent on a ventilator.

The estimated lifetime cost for one person injured at the age of 25 with a high cervical injury is more than \$4.6 million.² Only 12%-24% of people with SCI return to work. Thus, the combination of increased survival, extensive medical expenses, and high unemployment has resulted in SCI becoming a significant public health burden. It is estimated to cost the United States at least \$9.7 billion annually.³

■ ETIOLOGY

Most spinal injuries result from high-speed motor vehicle accidents (Fig. 57-1). Falls and work-related injuries are other contributors. Spinal cord injury that is due to violence is on a dramatic rise secondary to an increased incidence of assaults. These injuries include both blunt and penetrating injuries, such as gun and knife wounds. Sports-related injuries, which include football, horseback riding, and hockey injuries, are relatively rare but receive media attention.^{4,5} Finally, recreational injuries from jet skis, snowmobiles, snow skiing, snowboarding, and parachuting, to name but a few, are on the rise as extreme sports become more prevalent.

■ INITIAL MANAGEMENT

Suspected SCI alters the basics of the ABCs of resuscitation in several important ways. With respect to airway management, suspected SCI dictates in-line immobilization of the spine at all times, so hyperextension of the neck is contraindicated. A jaw thrust must be used to open the airway, and required intubation must be done with the head and neck in a neutral position. This is an important point to remember because patients with a high SCI will have diminished or absent respiratory capacity and frequently require emergent intubation.

Aggressive resuscitation of patients with SCI proceeds as with all trauma patients. Upper SCI may be associated with neurogenic shock, requiring large-volume fluid replacement. Although pressors are likely

to be required in the setting of neurogenic shock, field management is commonly limited to fluid resuscitation. The high incidence of associated head injury often requires careful titration of fluids to resuscitate the patient adequately while minimizing exacerbation of cerebral edema.

IMMOBILIZATION AND DIAGNOSTIC EVALUATION

Rigid immobilization is indicated if there is any suspicion of the presence of SCI. The presence of altered mental status dictates the use of spinal cord precautions. These include use of in-line immobilization, maintenance of neutral position, cervical immobilization with a rigid collar, and use of backboards for transport.

After initial resuscitative efforts, diagnostic studies are undertaken. Fine-cut helical computed tomography (CT) with coronal and sagittal reconstructions have supplanted plain radiographs in most trauma centers as an initial evaluation for detecting spine fractures. Additional spine studies may be obtained after the patient has been stabilized and more emergent diagnostic studies have been undertaken. During this time, rigid cervical collar and backboard immobilization must be continued.

Further diagnostic studies will be dictated by the findings of the initial and secondary surveys as well as findings of initial diagnostic studies. Several points are important to keep in mind. First, important information can be obtained from studies performed for other reasons. For example, routine chest and abdominal radiographs may provide important information regarding the presence of significant thoracic or lumbar spine injury. Although these do not replace subsequent formal spine studies, they are often obtained as part of the routine trauma workup, may provide early clues to the presence of spine trauma, and may help prioritize subsequent imaging studies. Radiographs and particularly CT are the most sensitive tools in detecting a fracture of the spine, but occasionally it is difficult to clear the spine—that is, to rule out a spinal injury—even in the absence of a fracture because an unstable ligamentous injury may exist without a fracture.

Clearing the unconscious patient with high-resolution CT scans of the spine has greater than 99.9% sensitivity and specificity, indicating that CT alone is sufficient in detecting unstable C-spine injuries in patients with trauma.⁶ Magnetic resonance imaging (MRI) of the spine is used to quantitate ligamentous injuries and to rule out a hematoma or a disk herniation and to assess the degree of spinal cord compression. Malalignment and evidence of spine trauma on these imaging studies frequently determines subsequent management and diagnostic decision making. Cervical subluxations often require the use of traction or manual reduction of the fracture-dislocation. Diazepam or lorazepam, along with careful neurologic monitoring, often in the intensive care unit (ICU) setting, is required because application of traction can realign the spine but can also result in neurologic deterioration.

■ PEDIATRIC SPINAL CORD INJURY

Pediatric spine trauma is relatively uncommon, representing approximately 5% of all SCIs.⁷ For a specific discussion of pediatric SCI, please see Chapter 172. Guidelines have been published on this topic.⁸

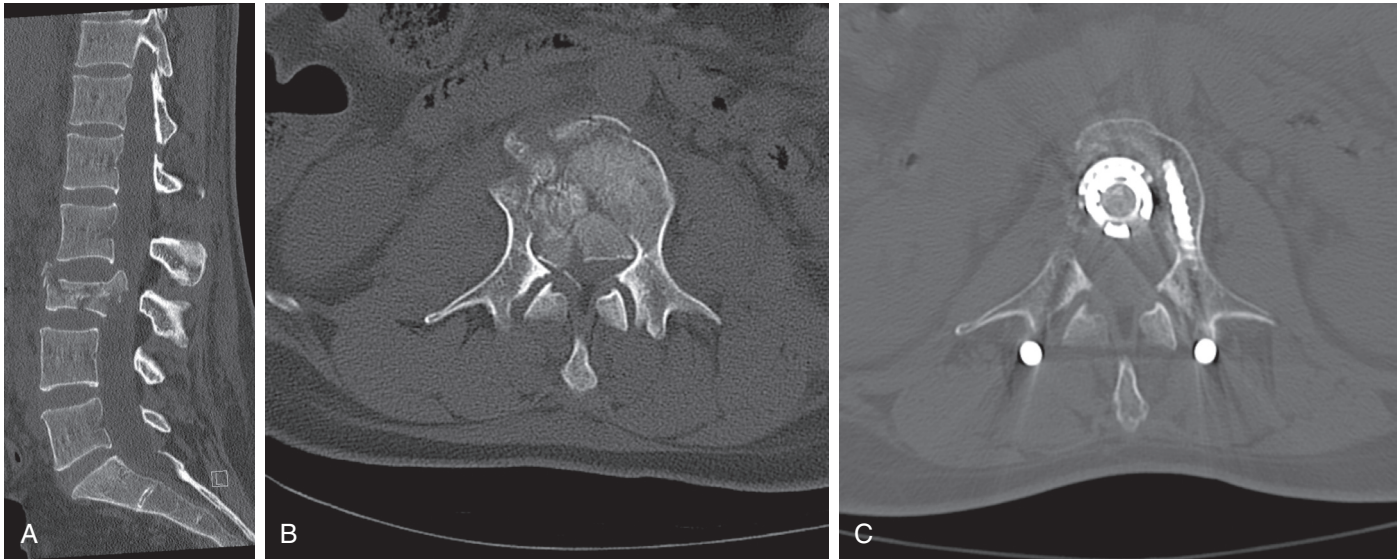


FIGURE 57-1 ■ **A**, Sagittal CT demonstrates an L3 burst fracture that presented with cauda equina syndrome. **B**, Axial CT demonstrates severe compression of the spinal canal. **C**, The canal was decompressed surgically with a minimally invasive approach resulting in significant root recovery.

■ PHARMACOTHERAPY

The concepts of primary and secondary SCI are important principles in understanding the pathophysiology and the role of pharmacotherapeutic agents in emergency treatment. The primary injury results from a mechanical insult that occurs at the time of impact and includes acute compression, impaction, distraction, laceration, and shear.⁹ Secondary injuries occur after the initial injury and account for some of the progressive pathologic changes associated with SCI that, if left untreated, can potentially result in limited recovery.⁹ A number of drugs have been tested in the laboratory, but only a few of these agents have progressed to clinical trials to evaluate their efficacy. Five randomized controlled trials of pharmacotherapy for acute SCI have been conducted, focusing on the therapeutic effect of either corticosteroids or gangliosides.

Corticosteroids and Gangliosides

A number of studies have shown improved neurologic recovery in animals with SCIs that have received either dexamethasone or methylprednisolone.¹⁰⁻¹³ Corticosteroid treatment initially held promise as a potential therapeutic agent for its putative role in reducing white matter edema and inflammation. Current evidence, however, suggests that the major mechanism of action is reduction of the effects of secondary injury, in particular, the destructive effects of lipid peroxidation on cell membranes.³ Other actions include improving spinal cord blood flow, enhancing the postinjury activity of Na^+/K^+ -ATPase, and facilitating the recovery of extracellular calcium ion.^{13,14}

The first NASCIS trial (NASCIS I) examined low- (100 mg) and high- (1000 mg) dose methylprednisolone given to patients with acute SCI for 10 days. Unfortunately, this trial had no control group, and no significant difference in outcome was found except for an increased number of wound infections among patients in the high-dose group.¹⁵ The second NASCIS trial (NASCIS II) was a prospective, randomized, double-blind, multicenter trial that showed improved neurologic outcomes after 6 weeks, 6 months, and 1 year in patients with nonpenetrating SCI who had received a methylprednisolone regimen, which included a bolus of 30 mg/kg.¹⁶ Improvement in motor and sensory scores associated with administration of methylprednisolone compared to naloxone or placebo was seen, but only if the drug was given within 8 hours of injury. Results of this study have been criticized.^{17,18}

Some of the questions relate to difficulties in randomization, reporting methods, analysis of benefit limited to small subgroups within the larger study, and lack of replication of results by an independent group of investigators, among others. The results of NASCIS III suggest that when patients are seen within 3 hours of their injury, they should receive a bolus dose of methylprednisolone (30 mg/kg intravenously [IV]) followed by 23 hours of treatment (5.4 mg/kg/h IV). Patients seen between 3 and 8 hours should receive the same bolus followed by a longer dosing regimen (48 hours). Complications from 48 hours of treatment included a significant increase in severe sepsis and pneumonia.¹⁹ The most recent neurosurgical guidelines for management of spine trauma do not recommend methylprednisolone as a treatment option, recognizing that the risks of use have been more clearly demonstrated than the benefit.²⁰ A prospective, randomized, double-blind, single-center study found a beneficial effect on functional neurologic outcomes when the ganglioside GM-1¹ was administered within 72 hours of human SCI.²¹ However, a multicenter trial showed no statistically significant benefit from this agent at 26 and 52 weeks after injury.²²

■ HYPOTHERMIA

Three recent studies were published on the safety and feasibility of mild to moderate intravascular cooling for SCI. Levi et al. reported on a series of 14 patients with American Spinal Injury Association (ASIA) classification A complete cervical cord injuries who underwent a protocol to achieve temperatures of 33.5°C using a closed-loop delivery system. The investigators found good correlation between intravascular and intrathecal cerebrospinal fluid temperature.²³ The average time between injury and induction of hypothermia was 9.17 ± 2.24 hours (mean \pm SEM), time to target temperature was 2.72 ± 0.42 hours, duration of cooling at target was 47.6 ± 3.1 hours, and total length of time of cooling was 93.6 ± 4 hours. A subsequent paper summarized the complications and neurologic outcomes in this initial group of patients treated with hypothermia and compared them to age- and injury-matched controls.²⁴ Approximately 42% of patients treated with hypothermia had improvement in their ASIA stage, with a frequency of cardiovascular complications similar to that of historic matched controls.²⁵ The most recent work includes a larger series ($n = 35$) of patients, of whom a similar proportion had an improved ASIA grade.²⁶ This has led the Joint Section of Spine and Peripheral Nerves to issue

a position statement that the current data provide level IV evidence for its use (www.spinection.org).

■ INTENSIVE CARE UNIT MANAGEMENT

Spinal cord injury is associated with profound effects on all vital system functions. With primarily class III medical evidence, numerous reports indicate lower morbidity and mortality rates in patients with SCI managed with ICU monitoring and aggressive medical management of physiologic changes.²⁷⁻³⁵ At the very least, these studies taken together indicate that a systematic approach must be taken to evaluate and treat each of the potential complications. Early and late complications will be seen, and the degree of involvement of each system is usually correlated with the level and severity of injury.

Respiratory System

Respiratory complications are a major source of morbidity and mortality after SCI, with an 18% to 30% mortality rate reported in patients with tetraplegia.^{30,36} In a study by Hachen and associates,^{28,34} most early deaths were related to pulmonary complications, with the likelihood of severe respiratory insufficiency related to SCI severity. Whereas most cervical spinal cord injuries occur below C4, so that the phrenic nerves continue to innervate the diaphragm, the respiratory system is frequently severely affected, particularly after cervical spinal cord injuries. Specifically, marked reductions in (forced) vital capacity, inspiratory capacity, and expiratory flow rates frequently result in hypoxemia.^{30,34,37,38-40} These changes may be attributed to variable paralysis of the intercostal muscles and accessory muscles of respiration. Loss of abdominal muscle tone and ileus also reduce the mechanical efficiency of breathing.

In general, there is a grace period in which patients with cervical SCI will maintain their respiratory status. However, respiratory failure can ensue 24 to 48 hours after admission. Additional injuries, such as rib fractures and hemothorax, can accelerate this respiratory deterioration. Preparation for such events should be undertaken early so that if intubation is required, it can be done with cervical stabilization using in-line traction, often supplemented by use of a fiberoptic intubation technique. Measurement of arterial blood gases, negative inspiratory force, and forced vital capacity may facilitate early detection of respiratory failure.

The most common respiratory complications include atelectasis, pneumonia, pulmonary embolus, pulmonary edema, and acute respiratory distress syndrome. In addition to difficulty taking deep breaths and coughing, patients are often unable to clear airway secretions. Accumulation of secretions and mucous plugs can result in respiratory failure. Prevention includes respiratory treatment with bronchodilators, frequent pulmonary toilet, chest physiotherapy, increasing airway humidity, intubation, and mechanical ventilation including the use of continuous positive airway pressure. The use of the RotoRest bed significantly decreases pulmonary complications associated with SCI^{30,41} because it improves pulmonary blood flow and reduces the incidence of pulmonary emboli.

Pulmonary infections often complicate SCI. Within days of admission, the normal flora of the oral cavity will contain increasing numbers of nosocomial organisms. Hospital-acquired pulmonary infections are heralded by fever, increased white blood cells in both sputum and peripheral blood, and changes on the chest radiograph. After obtaining appropriate cultures, treatment with broad-spectrum antibiotics should be instituted.

Most patients can be weaned from the ventilator after they have been medically stabilized, which usually means treatment of pulmonary infections, reestablishment of euolemia, enhancement of respiratory muscle function, and nutritional supplementation to offset the high caloric requirements of the trauma. Initially, weaning with intermittent mandatory ventilation is followed by weaning with positive airway pressure (either continuous or end expiratory). With prolonged periods of ventilation (>2 weeks) or multiple failed extubations, one

should consider a tracheostomy. The likelihood of requiring a tracheostomy increases with a high SCI, preexisting pulmonary disease, and the age of the patient. Tracheostomy effectively reduces the physiologic dead space.

Cardiovascular System

Significant confusion arises when the term *spinal shock* is used after SCI. The misunderstanding regarding its use stems from multiple causes. First, many physicians use the terms *spinal shock* and *neurogenic shock* interchangeably. Neurogenic shock, however, refers to a condition characterized by hypotension and bradycardia resulting from interruption of the sympathetic nervous system pathways within the spinal cord. The incidence of significant neurogenic shock increases with injuries above the T6 level, because unopposed vagal tone slows the heart and reduces systemic vascular resistance, resulting in venous pooling. The condition responds to administration of fluids or colloids and occasionally requires the use of pressors. Neurogenic shock is distinct from hypovolemic shock, which may occasionally occur concomitantly in the patient with SCI and multiple trauma who has evidence of either external or internal bleeding. Whereas isolated hypovolemic shock is characterized by hypotension with tachycardia, relative bradycardia (for a given degree of hypotension) is to be expected in the setting of multiple trauma with SCI.

Spinal shock encompasses a number of different neurologic manifestations of SCI with varying time courses. Traumatic injuries to the spinal cord interrupt or temporarily damage a number of descending and ascending pathways. The most common initial presentation of a complete SCI with respect to reflex and autonomic function is a period of areflexia and flaccidity that is gradually replaced by hypertonia, exaggerated reflexes, and (in many cases) spasticity. The transition period may last from days to weeks. The immediate onset of hyperreflexia and spasticity is uncommon; when it occurs, it is a bad prognostic sign. This period of transition in reflex and autonomic function is often referred to as *spinal shock*. Concomitant changes in motor and sensory function are also common.

Animal studies indicate that ischemia underlies many of the secondary mechanisms affecting patients post SCI, often dictating the resultant deficits.^{34,42-44} Human studies suggest a direct correlation between the severity of SCI and the incidence and severity of cardiovascular problems.^{34,45} Together, this suggests that reducing the magnitude of secondary injury should be at the forefront of medical management of SCI.

The typical patient with SCI without associated vascular or visceral injury presents to the emergency department with a mean arterial blood pressure of 80 mm Hg and a heart rate of 65 beats/min.³³ Persistent bradycardia is a frequent finding and is often profound enough to produce hemodynamic compromise.^{25,34} The patient's blood pressure may respond to volume resuscitation, but often these patients also require low-dose pressors. Aggressive medical management, including volume expansion and maintenance of mean arterial blood pressure greater than 85 mm Hg, is believed to potentially enhance neurologic outcome by maximizing spinal cord perfusion at the injury site, thus reducing the likelihood of secondary injury.⁹ Invasive hemodynamic monitoring will usually demonstrate a normal cardiac index with low systemic vascular resistance. In the elderly patients with SCI, careful attention to volume replacement is required so as not to precipitate heart failure.

Gastrointestinal System

Hypoactive bowel sounds and impaired peristalsis are common after SCI, owing to the lack of sympathetic modulation. To avoid gastric and small-bowel dilatation, it is wise to delay enteral feeding. When gastric distention impairs respiratory function, a nasogastric tube is indicated. Most cervical cord injuries require nasogastric suction because of impaired bowel motility, air swallowing producing gastric distention, and respiratory compromise due to intercostal muscle paralysis.

Patients with SCI are at high risk of developing gastric and duodenal stress ulcers. Use of steroids compounds the risk of significant gastrointestinal hemorrhage.⁴⁶ All patients with SCI should at minimum receive an H₂ blocker to prevent this dreaded complication. The reported risk of gastrointestinal hemorrhage in NASCIS II for the control group was 3% and for the methylprednisolone group, 4.5%.¹⁶

Urinary System

During the period of spinal shock after a cervical or thoracic SCI, the urinary bladder is atonic and flaccid. Over time it becomes an upper motor neuron bladder with small capacity. An indwelling Foley catheter is initially placed. After 3 to 4 days this is switched to intermittent bladder catheterization to maintain urinary volumes below 500 mL. Urinary tract infections are common, and if fever occurs, urine cultures must be obtained and antibiotics selected based on culture and sensitivities. Patients with spinal injuries above T6 may also develop autonomic dysreflexia if the bladder becomes overdistended or sometimes with catheterization. The result may be sympathetic overactivity, with headaches, hypertension, sweating, and reduced body temperature. Long-term complications include chronic infections, obstructive uropathy, and renal calculi; if left untreated, renal failure may develop.

Integument

The SCI patient is extremely susceptible to developing decubitus ulcers. Frequent log rolling is invaluable in preventing skin breakdown. Specialized beds to turn patients with SCI (e.g., RotoRest⁴¹ [KCI Therapeutic Support Systems, San Antonio]) can reduce the incidence of skin breakdown by preventing pressure on a single area. Early intervention for skin breakdown frequently involves application of the DuoDERM patch (ConvaTec, Princeton, NJ) to prevent progression.

Thromboembolic Complications

Patients with SCI are at high risk of venous thromboembolism, which may manifest as deep vein thrombosis (DVT) in the lower or upper extremities and lead to swelling and possibly to pulmonary embolism. Depending on injury severity, age, and diagnostic methods, the reported incidence of thromboembolic events ranges from 7% to 100%.⁴⁷ The majority of these events occurs within the first 3 months after injury, except in patients who are elderly, obese, or who have had prior thromboembolic events.⁴⁷ Numerous studies have addressed the issue of preventive measures for DVT. Prevention has traditionally included the administration of low doses of heparin (5000 units subcutaneously) twice daily or more. However, meta-analysis of the available literature suggests that better alternatives include the combination of pneumatic compression stockings with low-molecular-weight heparin or adjusted-dose heparin.⁴⁷

Current recommendations for evaluation of suspected thromboemboli include use of Doppler ultrasound for suspected DVT and venography if a strong clinical suspicion exists for DVT despite a negative ultrasound or if pulmonary embolism is suspected.^{47,48} Treatment of pulmonary emboli or above-the-knee DVT requires heparinization. Should there be a contraindication to heparin, an inferior vena cava filter should be placed. Prophylactic placement of inferior vena cava filters has been advocated,^{24,47,49,50} but these procedures are not without risk, and no study thus far compares success rates to the aforementioned conservative prevention modalities.^{1,44}

PROGNOSTIC FACTORS FOR RECOVERY

The clinician uses the neurologic examination, patient age, and appearance of the spinal cord on MRI as well as other clinical data to advise the patient and family on the expected outcome for a specific injury. In any traumatic SCI, it is important to ascertain whether the patient has a functionally complete or incomplete neurologic deficit. The distinction is important because the prognosis for neurologic recovery

differs for these two conditions. Patients with no evidence of motor or sensory function below the level of their injury are considered to have functionally complete injuries. No voluntary motor control and only slight sensory preservation in the lowest sacral dermatomes or some anal tone are considered to be an incomplete injury. Functionally, patients with complete cervical SCI whose deficits remain complete in the first 24 hours of admission are unlikely to regain significant ambulatory function (1% to 3%).^{52,53} However, most patients who enter the hospital with an incomplete neurologic injury attain some degree of recovery. The level and degree of an incomplete injury also provide important prognostic information. Cervical injuries have a higher potential for recovery when compared with thoracic or thoracolumbar injuries. The less severe the SCI, the more likely the patient will recover.⁵⁴

The majority of injuries occurs in males, with well over half occurring in the 16- to 30-year-old age group. Prognosis for recovery is inextricably linked to age, with younger patients faring much better than their older counterparts in regaining neurologic function after SCI.^{55,56} The two most important potential neurologic explanations are the capacity of the young spinal cord to function with major deficiencies in the neural circuitry and the possibility of some spontaneous regeneration of the CNS after injury.⁵⁷ The reverse also appears to be true. It is well recognized that patients with stable incomplete injuries may lose function as they age, and this may simply result from loss of the last few functioning neurons or axons in the damaged region of the spinal cord.⁵⁸ Neuronal loss is a normal part of aging in both brain and spinal cord, and the clinical deterioration seen after SCI may be likened to the postpolio syndrome.

MRI after SCI allows noninvasive visualization of the spinal cord (Fig. 57-2). The images provide immediate feedback to the surgeon about the degree of spinal cord compression, as well as information regarding the stability of the spinal column through an assessment of the integrity of the ligaments, disks, and surrounding soft tissues. In addition, intramedullary hemorrhage may be easily discerned, providing important prognostic information. Intramedullary hemorrhage is more commonly observed after neurologically complete injuries, and hemorrhage signifies a worse neurologic and functional outcome.^{59,60} MRI of SCI is discussed in greater detail in Chapter 38.

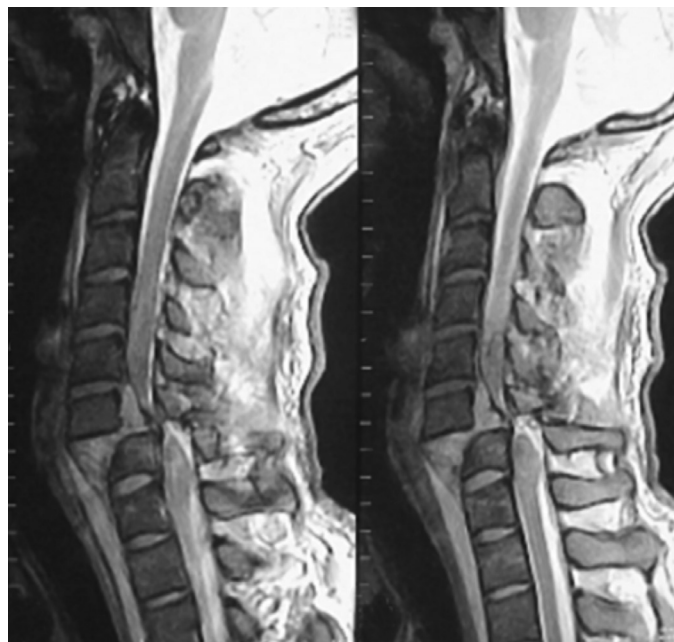


FIGURE 57-2 ■ Sagittal T2-weighted MRI demonstrates a C6-C7 fracture-dislocation with severe cord compression in a patient who presented with complete C6 quadriplegia-ASIA.

RESEARCH

Spinal cord injury research is an absolute priority of the National Institutes of Health. Models of SCI, mechanisms of secondary injury, treatment of the acute phase of SCI, and development of transplantation strategies to repair a damaged spinal cord are ongoing across North America and around the world. The treatment arms of research can be divided into two categories: (1) agents that can be given during the acute phase of injury to limit secondary injury mechanisms and (2) strategies to promote regeneration. What were thought to be two of the most promising drugs, methylprednisolone and ganglioside GM₁,¹ have yielded only modest results. Methylprednisolone, which is used in almost all major SCI centers, is coming under closer scrutiny as to its effectiveness.¹⁷ Drugs of the future include neurotrophins, which can promote survival and regeneration of injured nerve cells, drugs that prevent the inflammatory response to SCI,⁵⁹ and drugs that prevent apoptotic cell death.⁶¹ In the transplantation arena, cellular therapies to treat chronic injury are important. Cells of interest include Schwann cells, olfactory ensheathing glia, embryonic spinal cord, and neural progenitor cells. Antibodies that neutralize inhibitory proteins in myelin have also shown promise. Combination therapy is most likely to show benefit in the future.

CONCLUSION

It appears that despite enormous advances in the diagnosis and treatment of spinal fractures over the past 3 decades, there exist a number of unanswered questions regarding the most appropriate management of patients with traumatic spinal fractures. Although only a few aspects of the surgical management of spine trauma are raised in this chapter, it is clear a number of issues remain unresolved.

Technologic advance in spinal instrumentation and pharmacotherapeutics will continue in the 21st century. It is vital that neurosurgeons

and orthopedic surgeons work together to test both the efficacy and cost-effectiveness of some of the newer treatment modalities, because both the best possible treatment and cost containment will be part of the management equation in the future. Outcome assessment should be at the forefront of all new ideas. Only through a critical and open-minded analysis of our treatment strategies will we be able to provide the best care for these patients who will often be disabled for the remainder of their lives by their injuries. Applying the best strategies is a particular challenge because of the rapid sequence of events that revolve around these patients' acute hospitalization.

KEY POINTS

1. Most spinal injuries result from high-speed motor vehicle accidents.
2. The primary mechanisms of injury are mechanical insults that occur at the time of impact and may include acute compression, impaction, distraction, laceration, and shear. Secondary injuries occur after the initial injury and account for some of the progressive pathologic changes associated with spinal cord injury (SCI).
3. Respiratory complications are a major source of morbidity and mortality after SCI.
4. In the elderly patient with SCI, careful attention to volume replacement is required so as not to precipitate heart failure.
5. The prognosis for recovery and survival from SCI is inextricably linked to age, with younger patients faring much better than their older counterparts.

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This chapter reviews available neuroimaging methods and their application to children with suspected neurologic disorders

METHODS

Plain Radiographs

Plain radiography quickly identifies surgical or unstable traumatic injuries. However, computed tomography (CT) or magnetic resonance imaging (MRI) is necessary when intracranial or intraspinal injury is suspected.¹

Computed Tomography

CT is widely available, rapid, and accurate, with virtually no contraindications in the acute setting. The radiation risk should be considered in young patients and patients likely to require numerous studies.² Rapid acquisition usually makes sedation unnecessary. Axial images can be reconstructed along other planes. Iodinated IV contrast can be given to identify areas of blood-brain barrier breakdown and, with angiography (CTA), to visualize blood vessels. CT perfusion can estimate cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time.³

Magnetic Resonance Imaging

MRI uses an intense magnetic field without ionizing radiation. MRI “sequences” vary the imaging parameters to highlight different anatomic and physiologic properties.⁴ Gadolinium-based, noniodinated IV contrast agents are used although there are no concerns about their extravasation into brain tissues. MR angiography (MRA) and qualitative MR perfusion-weighted imaging (PWI) can be done without IV contrast.

Functional MRI (fMRI) analyzes CBF during task performance or in the resting state. Diffusion-weighted imaging (DWI) evaluates the freedom of water molecule movement. Increased diffusion is seen in areas with fewer cells or increased extracellular water, and restricted diffusion is seen in areas with tightly packed or swollen cells. Water also diffuses more freely parallel to well-organized white matter tracts. DWI can be used to identify acute ischemia, differentiate necrotic tumor from abscess, and grade tumors.^{5–7} PWI studies can show areas of reduced perfusion that may respond to reperfusion.^{8,9}

Magnetic resonance spectroscopy (MRS) measures metabolites that can help characterize a lesion or grade its severity.^{10,11} Diffusion tensor imaging (DTI) can map white matter fiber tracts and their relation to lesions and to planned surgeries.¹²

Patients with ferromagnetic metal devices, prostheses, or fragments cannot be exposed to the powerful MRI magnet.¹³ Some patients may be too unstable to leave the intensive care unit long enough for an MRI.

Nuclear Medicine Studies

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are used to measure cerebral metabolism and/or perfusion.¹⁴ PET studies are easier to coregister with MRI

but require the use of isotopes with shorter half-lives that are not widely available. PET is useful in diagnosis, staging, and monitoring of tumors and in the surgical evaluation of intractable epilepsy.^{15,16} SPECT is often used to assess CBF in suspected brain death.¹⁷

Angiography

Conventional angiography using percutaneous transfemoral catheterization, injected iodinated contrast, and fluoroscopy is the gold standard for evaluating cerebral and spinal vessels. While invasive, serious complications are rare.^{18,19}

BRAIN

Patterns of Disease

Edema

Cerebral edema can be divided into three types, defined as follows:

1. Vasogenic: water from leaky capillaries
2. Cytotoxic: water within swollen cells injured by energy failure
3. Interstitial (transependymal): water crossing from the ventricles into the parenchyma

Increased water content appears dark on CT because of hypodensity. It also appears dark on T1-weighted imaging (T1WI) but bright on T2-weighted imaging (T2WI), including fluid-attenuated inversion recovery (FLAIR) studies in which the CSF appears dark. Vasogenic edema extends along white matter tracts, creating “fingers” extending toward the cortex (Fig. 58-1). This edema does not follow a vascular distribution and often has a mass effect. Cytotoxic edema often follows a vascular distribution and produces less mass effect (Fig. 58-2). DWI shows increased diffusion with vasogenic edema and restricted diffusion with cytotoxic edema. Interstitial edema is best seen on FLAIR.²⁰ Increased CBV can mimic edema but is differentiated by perfusion studies.²¹

Hemorrhage

The appearance of hemorrhage depends most on timing. On CT, hemorrhage may be isodense in the hyperacute stage, then hyperdense within hours (Fig. 58-3A) before becoming isodense again over days and then hypodense over weeks (Table 58-1). Acute hematomas may remain isodense longer in anemia or coagulopathy.^{22,23} Remote hemorrhage can be inapparent on CT or appear hypodense due to tissue injury or hyperdense due to calcification.

The evolving MRI appearance of hemorrhage results from hemoglobin (Hb) metabolism. Acutely, oxy-Hb appears hypo- to isointense on T1WI and iso- to hyperintense on T2WI. As Hb becomes deoxygenated, it appears hypointense on T2WI. In the subacute stage, Hb is broken down to intracellular methemoglobin, which appears hyperintense on T1WI and hypointense on T2WI. As red blood cells lyse and release methemoglobin, its signal becomes hyperintense on T1WI and T2WI. In the chronic stage, methemoglobin is degraded to hemosiderin, appearing hypointense on T1WI and T2WI (Figs. 58-3B and C).⁷ Susceptibility-weighted imaging (SWI) has made MRI more sensitive for hemorrhages.²⁴

Intraparenchymal bleeds are associated with surrounding vasogenic edema and can expand significantly in the first 3 hours,²⁵

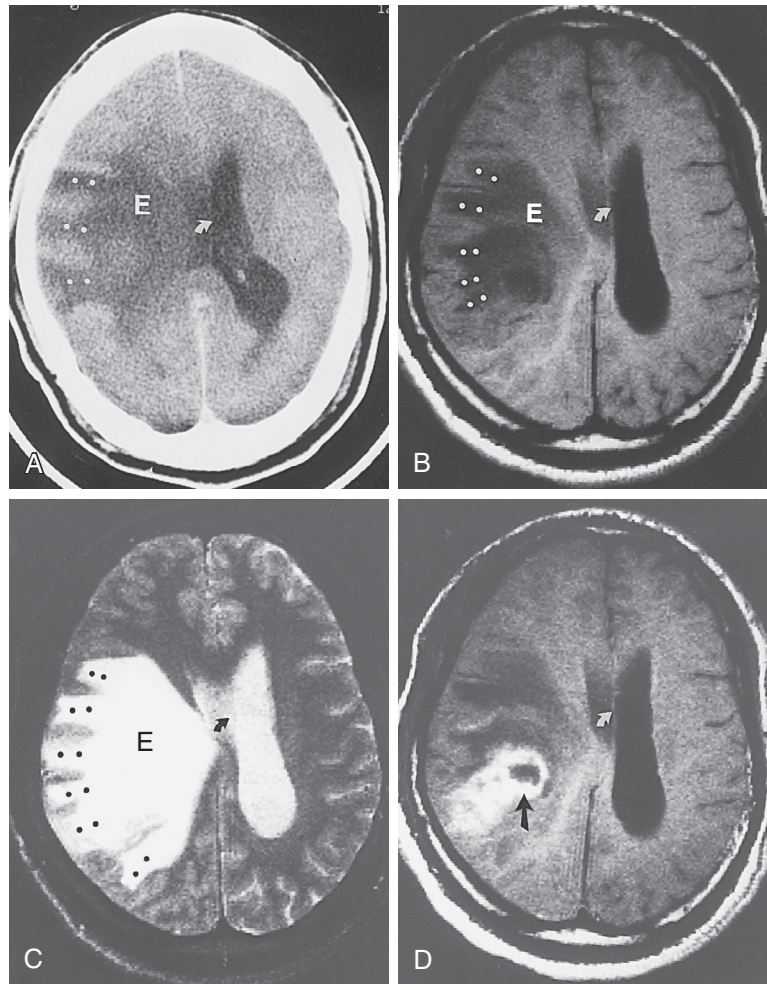


FIGURE 58-1 ■ Vasogenic edema in glioblastoma. Non-contrast-enhanced axial computed tomography scan (**A**), axial T1-weighted magnetic resonance imaging (MRI) scan (**B**), and axial T2-weighted MRI scan (**C**) all demonstrate an area of edema (E). Edema extends along white matter fibers (dots), with normal gray matter interposed. Axial T1-weighted MRI scan following contrast enhancement (**D**) demonstrates the enhancing tumor nidus (arrow), distinct from surrounding edema. Subfalcine herniation is also demonstrated on these images by displacement of the falx (curved arrows).

especially when the hematoma shows initial contrast enhancement.²⁶ Vasogenic edema can expand significantly over several days.

Mass Effect, Shift, and Herniation

Intracranial lesions can lead to brain herniation as a result of lesion growth, vasogenic edema, or obstructive hydrocephalus.²⁷ The dural partitions within the skull, the falx cerebri and the tentorium cerebelli, create compartments across which the brain may herniate.

Subfalcine herniation occurs when the medial surface of a hemisphere is pushed under the falx. Early imaging signs may show lateral ventricular distortion (see Fig. 58-1). Later stages show deviation of the falx, structures crossing the midline, and ischemia from compression of the anterior cerebral artery.

Transalar herniation occurs when brain tissue is pushed above (ascending) or below (descending) the ridge of the greater sphenoid wing, which may lead to ischemia from compression of the middle cerebral artery.

Transtentorial herniation can also be ascending or descending. Downward herniating brain can push against and rotate the brainstem, producing widening of the ipsilateral brainstem cistern and effacement of the contralateral cistern (Fig. 58-4). The contralateral temporal horn may dilate secondary to trapping. Ascending transtentorial herniation

often causes symmetric effacement of the brainstem cisterns, compression of the cerebral aqueduct, and acute hydrocephalus.

Tonsillar herniation through the foramen magnum can result in brainstem compression.

Specific Disease Processes

Traumatic Brain Injury

Noncontrast head CT continues to be the primary modality for initial evaluation.²⁸ Its advantages include short examination time, wide availability, fracture detection, paucity of contraindications, and high accuracy. Although MRI is more sensitive in detecting intracranial injuries, its use is limited by longer examination times, the need for sedation in uncooperative patients, and difficulties in monitoring potentially hemodynamically unstable patients. Once patients have been stabilized, MRI becomes the modality of choice for fully elucidating the nature and extent of injury.²⁹

Traumatic brain injury (TBI) may result in contusion, axonal (shear) injury, or hematoma. Larger contusions may contain petechial microhemorrhages and appear as ill-defined heterogeneous lesions with little or no mass effect. As edema and mass effect increase in the first 48 hours, lesions become more evident.

Shear injuries are most common within the white matter. Except for location, the imaging characteristics of nonhemorrhagic contusions and shear injuries are similar. Initial studies may be normal or demonstrate small foci of edema. Shear injuries may be apparent on MRI, particularly with the use of (1) SWI, which is exquisitely sensitive to the microhemorrhages; (2) DWI, which may show cytotoxic edema; and (3) MRS, which may show choline (Cho) and myoinositol (mI) elevations and decreases in *N*-acetylaspartate (NAA) proportional to injury severity.

TBI may also lead to hemorrhage into the epidural, subdural, and subarachnoid spaces. On CT, intraventricular and subarachnoid hem-

orrhage is identified by replacement of the normal low-density CSF by high-density blood. When subtle, a subarachnoid hemorrhage can be mistaken for generalized edema, with loss of the basal cisterns and cortical sulci. Subdural hematomas appear as crescentic mixed or hyperdense collections that cross suture lines but not dural attachments (Fig. 58-5A). Epidural hematomas appear as biconvex hyperdense collections that cross dural attachments but not suture lines (Fig. 58-5B). With rapid accumulation of blood, an unretracted, semiliquid clot may be present. In this situation, CT demonstrates hypodense areas within the hyperdense hematoma (swirl sign).³⁰ Distinction between epidural and subdural hematomas is important, because



FIGURE 58-2 ■ Cytotoxic edema and acute infarct. Axial non-contrast-enhanced computed tomography scan demonstrates an area of decreased density (asterisk) involving the left middle cerebral artery territory. Gray and white matter structures are involved, and there is little mass effect.



FIGURE 58-4 ■ Right descending transtentorial herniation in patient with large right parietal subdural hematoma. Axial non-contrast-enhanced computed tomography scan of head at level of mid-brain shows that ipsilateral subarachnoid cistern is widened (arrow), and contralateral subarachnoid cistern is obliterated because of brainstem rotation. Left temporal horn is also dilated (asterisk), indicating trapping of left lateral ventricle.

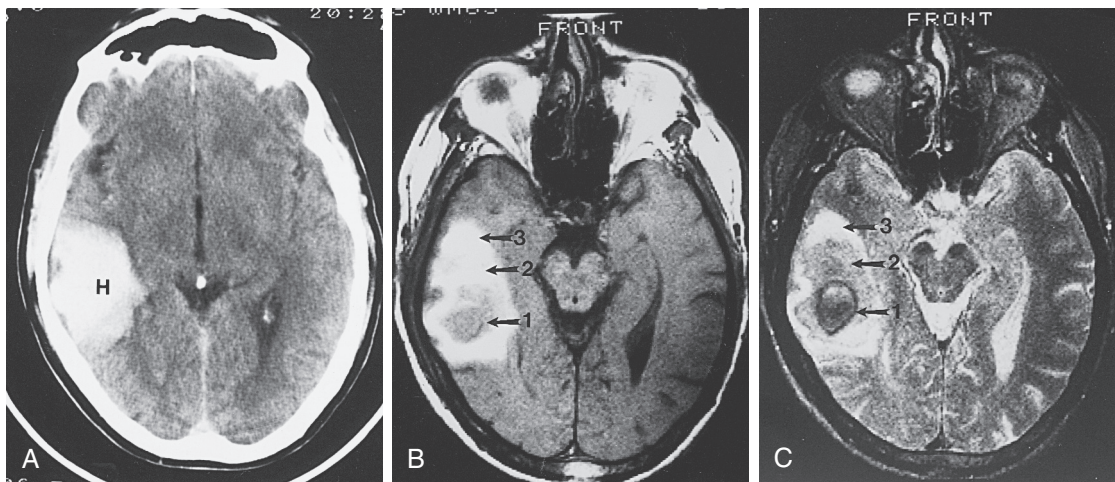


FIGURE 58-3 ■ Hemorrhage. Axial computed tomography image (A) demonstrates a large area of acute hemorrhage (H) in right temporal lobe. T1-weighted (B) and T2-weighted (C) magnetic resonance imaging scans demonstrate the hemorrhage in various stages of breakdown. Center of lesion is dark on T1- and T2-weighted images, indicating oxyhemoglobin (1). Intermediate zone is bright on T1-weighted image and gray on T2-weighted image, indicating intracellular methemoglobin (2). Outer rim is bright on both T1- and T2-weighted images, indicating extracellular methemoglobin (3).

TABLE 58-1

Evolution of Computed Tomography and Magnetic Resonance Imaging Appearance of Hemorrhage

| STAGE | TIME PERIOD | BLOOD PRODUCT | CT* | T1WI† | T2WI† |
|----------------|-------------|-----------------------------|--------|--------|-------|
| Hyperacute | <12 hours | Oxyhemoglobin | ↔ or ↑ | ↓ or ↔ | ↑ |
| Acute | 1-3 days | Deoxyhemoglobin | ↑ | ↓ or ↔ | ↓↓ |
| Early subacute | 3-14 days | Intracellular methemoglobin | ↔ | ↑ | ↓↓ |
| Late subacute | 2-4 weeks | Extracellular methemoglobin | ↔ | ↑↑ | ↑ |
| Chronic | >2 weeks | Hemosiderin | ↓ | ↔ | ↓↓ |
| | | Nonparamagnetic hemichromes | ↓ | ↓ | ↑ |
| | | Calcification | ↑↑ | ↓ | ↓ |

*Density relative to brain parenchyma

†Intensity relative to brain parenchyma

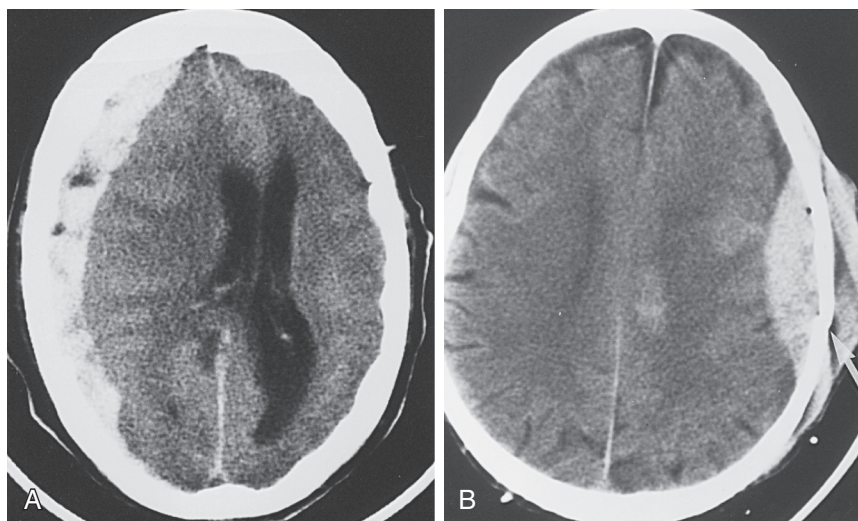


FIGURE 58-5 ■ Subdural and epidural hematoma. **A**, Axial computed tomography (CT) scan of head demonstrates a mixed-density subdural hematoma along the right frontoparietal lobes. Mixed-density appearance is most likely due to presence of unretracted semiliquid clot. **B**, Axial CT scan of head demonstrates a left biconvex hyperdense collection that is classic for epidural hematoma. A fracture (arrow) can also be identified.

epidural hematomas often have an arterial source, expand rapidly, and require emergent drainage.³¹

Abusive head trauma (AHT) is a significant cause of neurodevelopmental morbidity and mortality in children less than 2 years old.³² Injuries commonly encountered include skull fractures, subdural hematomas, subarachnoid hemorrhages, and shear injuries. Subdural hematomas in young children are more often associated with AHT than with accidental trauma.³² MRI can estimate the age of a hemorrhage; coexistence of blood products of different ages (Fig. 58-6) suggests recurrent bleeding from repeated abuse, although this finding must be interpreted with caution.⁷

Vascular Lesions

Ischemia, Hypoxia, and Infarction. CT reveals only about half of ischemic infarcts within the first 48 hours but is frequently used to exclude a hemorrhagic etiology. Features on CT can identify patients who are at a higher risk of hemorrhagic transformation.³³ CT can suggest a thromboembolic etiology for ischemia by showing cerebral edema in a vascular distribution or by showing a hyperdense clot within a thrombosed artery. CT can also show mass lesions (e.g., malignant cerebral edema) that require emergency surgical treatment.⁵ Small lacunar infarcts and infratentorial strokes are difficult to visualize by CT.³⁴

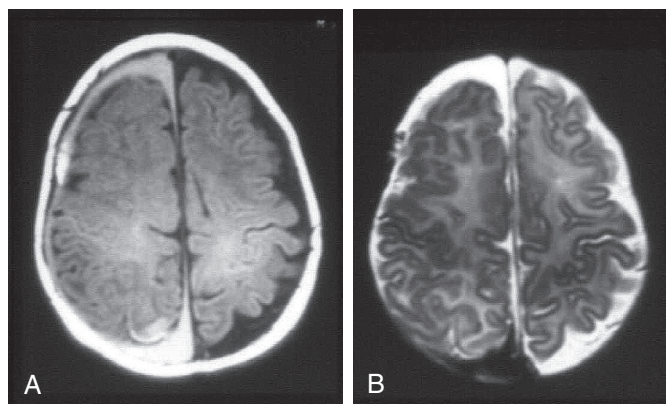


FIGURE 58-6 ■ Abusive head trauma. Axial T1- (**A**) and T2-weighted (**B**) magnetic resonance imaging scans of an infant reveal bilateral subdural blood collections of different ages. Right collection shows blood in the late subacute phase (2-4 weeks old), and left shows blood in the chronic phase (>1 month). This finding is highly suggestive of repeated abuse.

In the hyperacute stage (first 24 hours), an infarcted area may appear normal on CT or show a subtle loss of density and gray-white differentiation (Fig. 58-7). During the acute stage (first week), the infarct shows mass effect and decreased density from cytotoxic edema (see Fig. 58-2). In the subacute stage (second to third weeks), the edema and mass effect gradually resolve. Chronic infarcts demonstrate parenchymal replacement and contraction, with sharply margined zones of cystic encephalomalacia and gliosis.

The MRI appearance of an ischemic infarct also evolves (Fig. 58-8). Nonhemorrhagic infarcts begin with subtly increased signal intensity

on T2WI and minimal changes on T1WI. Subtle findings include stagnation of blood flow (arterial enhancement) and swelling of the involved gyri. DWI (Fig. 58-9) can show cytotoxic edema minutes after an infarct occurs, but the intensity is typically maximal at 3 to 5 days and fades over 1 to 2 weeks. Because cytotoxic edema and T2 hyperintense lesions both appear bright on DWI (T2 shine-through), cytotoxic edema is best evaluated using the apparent diffusion coefficient (ADC) map, on which cytotoxic edema appears hypointense.

CT and MRI perfusion techniques can demonstrate diminished perfusion within minutes of an insult. When MRI perfusion studies

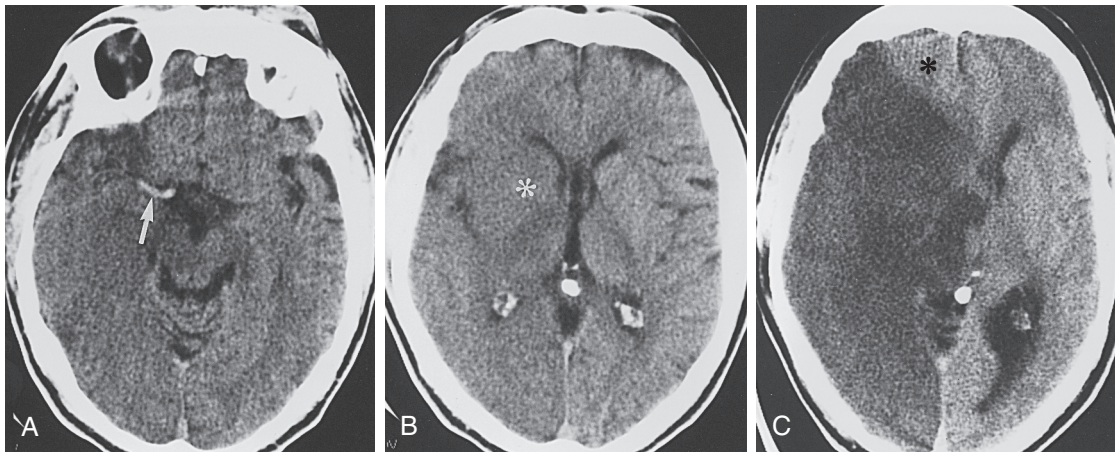


FIGURE 58-7 ■ Acute infarct. Axial non-contrast-enhanced computed tomography (CT) images obtained at level of temporal lobe (A) and through level of basal ganglia (B) demonstrate area of low density involving gray and white matter of right hemisphere. There is loss of gray-white matter differentiation, especially noticeable in region of basal ganglia (asterisk, B). Compare right and left sides. High density is identified within right middle cerebral artery (arrow, A), representing clot. Axial non-contrast-enhanced CT scan obtained 48 hours later (C) demonstrates marked edema involving territories of right, middle, and posterior cerebral arteries. Note sparing of right anterior cerebral artery territory (asterisk, C).

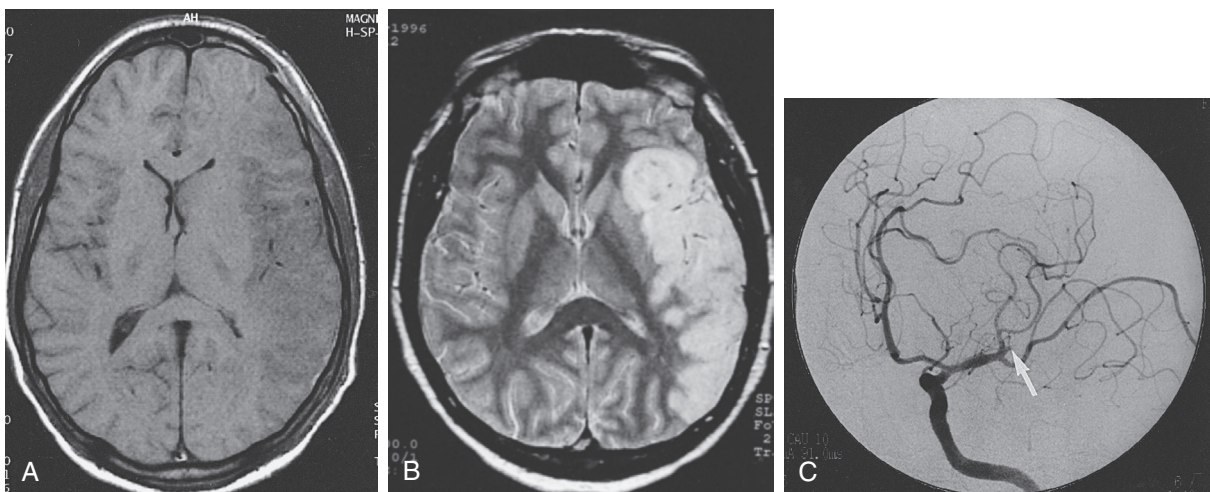


FIGURE 58-8 ■ Infarct. Axial T1-weighted (A) and T2-weighted (B) magnetic resonance imaging (MRI) scans of patient being evaluated for stroke. Initial computed tomography scan (not shown) was normal. Magnetic resonance imaging demonstrates an area of cytotoxic edema involving distal left middle cerebral artery territory. Edema is hypointense to brain on T1-weighted image and hyperintense to brain on T2-weighted image. Left internal carotid artery angiogram (C) demonstrates occluded branch of left middle cerebral artery (arrow). Within the proper time frame, intraarterial thrombolysis would be a method of management for this patient.

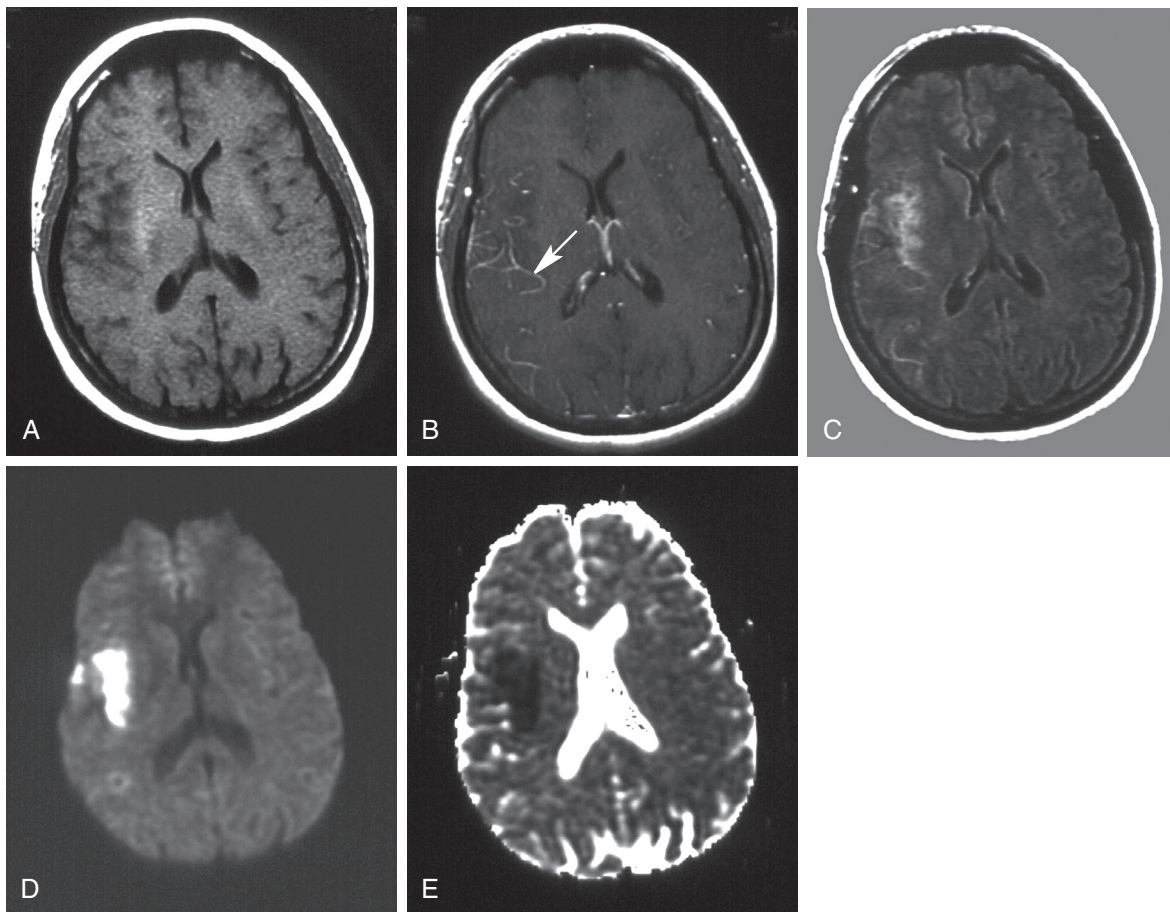


FIGURE 58-9 ■ Hyperacute infarct. Axial T1-weighted image before (A) and after (B) contrast administration reveal subtle low-intensity and arterial enhancement (arrow) in right insular cortex. Fluid-attenuated inversion recovery (FLAIR) sequence (C) helps define area of involvement. Diffusion-weighted sequence (D) shows infarct most clearly. Acute phase is confirmed by low signal on apparent diffusion coefficient map (E).

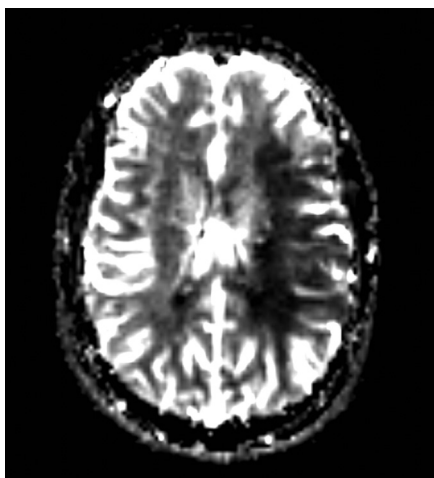


FIGURE 58-10 ■ Perfusion deficit. Magnetic resonance imaging perfusion study shows hypoperfusion in the territory of the left middle cerebral artery after thromboembolic obstruction at the M1 segment.

are coupled with diffusion images, a penumbra can be identified as a zone of viable but hypoperfused tissue (Fig. 58-10).⁹

Imaging protocols using several MRI sequences for acute evaluation of a suspected stroke can provide information about anatomy, presence of blood, extent of infarction, vascular anatomy, blood flow, and metabolic alterations (see Fig. 58-10).³⁵

MRI findings in hypertensive encephalopathy include symmetric vasogenic edema in the subcortical white matter, primarily in the occipital and parietal lobes. Radiologically similar lesions, referred to as *posterior reversible encephalopathy syndrome* (PRES), have been seen in association with hypertension but also with a number of other conditions. Most perfusion studies have been consistent with decreased blood flow.³⁶ In up to 25% of cases, cytotoxic edema and hemorrhage are also seen.^{37,38}

In contrast to arterial infarctions, venous infarctions are typically hemorrhagic and primarily affect the white matter. CT and MRI are able to detect the hemorrhage and edema as well as venous sinus thrombosis. Venography can be helpful in fully characterizing and following an occlusion.

The brain of a term infant has its greatest myelination and metabolic activity in the brainstem, basal ganglia, cerebellum, and periorbital cortex. Global hypoxic-ischemic injuries in term neonates are

most commonly seen in these regions.³⁹ The full extent of an ischemic injury may not be apparent on MRI in the first 72 hours because of ongoing neuronal apoptosis. Within a year, the patterns of injury seen from vascular insults become similar to those seen in older children and adults, with selective vulnerability in the striatum, lateral geniculate bodies, hippocampi, and frontal and parieto-occipital cortex, with sparing in moderate injuries of the thalami and perirolandic cortex (Fig. 58-11).³⁸ The relative sparing of the cerebellum, even with severe global hypoxic-ischemic injury of the cerebral hemispheres, can result in a “cerebellar reversal” sign on CT.⁴⁰

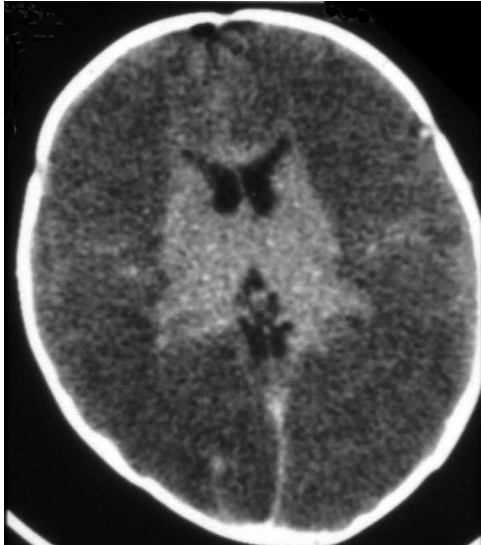


FIGURE 58-11 ■ Global anoxic injury. Axial computed tomography scan of a child following cardiac arrest. There is diffuse low density in cerebral hemispheres and compression of ventricles and sulci, reflecting increased water accumulation (edema) and resultant mass effect. Basal ganglia and thalami appear bright.

Congenital Aneurysm and Subarachnoid Hemorrhage. Evaluation of suspected subarachnoid hemorrhage usually begins with a non-contrast head CT (Fig. 58-12). If subarachnoid blood is seen on CT or lumbar puncture, a conventional angiographic study can be done to look for cerebral aneurysms (see Fig. 58-12). MRA and CTA are insufficiently sensitive to exclude an aneurysmal source of bleeding.⁴¹ Conventional angiography provides the superior anatomic detail needed for planning treatment.

From 10% to 30% of patients with aneurysmal subarachnoid hemorrhage will develop a delayed ischemic neurologic deficit from vasospasm.⁴² Angiographic studies show vasospasm but do not clearly differentiate between symptomatic and asymptomatic narrowing. Treatments for patients with symptomatic vasospasm show promise.^{43–45}

Vascular Malformations. AVMs are the most common vascular malformation. An unruptured AVM may be apparent on CT as tubular structures that enhance with contrast. On MRI, the abnormal vessels may appear hypointense because of blood flow. Conventional angiography is preferred for the evaluation of suspected AVMs, as it is best able to differentiate them from arteriovenous fistulas, identify associated aneurysms, and assess the feeding arteries and draining veins (Fig. 58-13).⁴⁶ An interventional radiologist may be able to embolize some or all of the arterial feeders, making surgery either less complex or unnecessary.⁴⁷ Capillary telangiectasias and cavernous angiomas are best evaluated by MRI because angiography is typically normal and CT is insensitive. The MRI signal characteristics vary based on the presence or absence of associated hemorrhage.

Developmental venous anomalies (DVA) are composed of a large draining vein surrounded by small feeding veins. The veins are typically inapparent on non-contrast-enhanced CT but enhance with contrast and can be seen on conventional MRI as flow voids. DVAs are rarely symptomatic other than when associated with a cavernous angioma or AVM, and conventional angiography is recommended only when an apparently simple DVA is associated with unexplained hemorrhage or edema.⁴⁸

Neoplasia

On CT, low-grade gliomas may appear as subtle nonenhancing masses, but higher-grade gliomas with large areas of necrosis and vasogenic edema often demonstrate heterogeneous enhancement (Fig. 58-1).

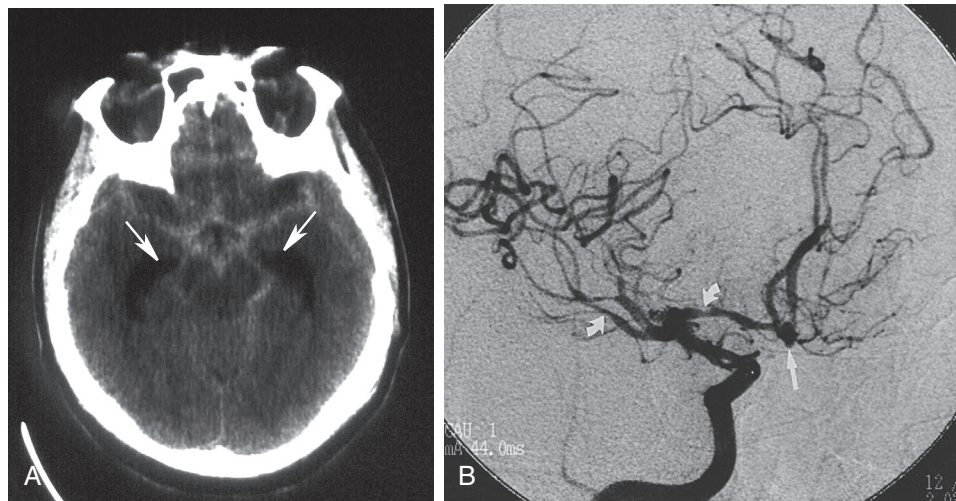


FIGURE 58-12 ■ Subarachnoid hemorrhage and aneurysm. **A**, Axial non-contrast-enhanced computed tomography scan of head reveals high density (blood) replacing normal low density of cerebrospinal fluid within suprasellar cistern and subarachnoid spaces, indicating subarachnoid hemorrhage. Also note dilated temporal horns (arrows), indicating acute hydrocephalus. **B**, Right internal carotid artery angiogram demonstrates presence of congenital anterior communicating artery aneurysm (arrow), as well as vasospasm (curved arrows).

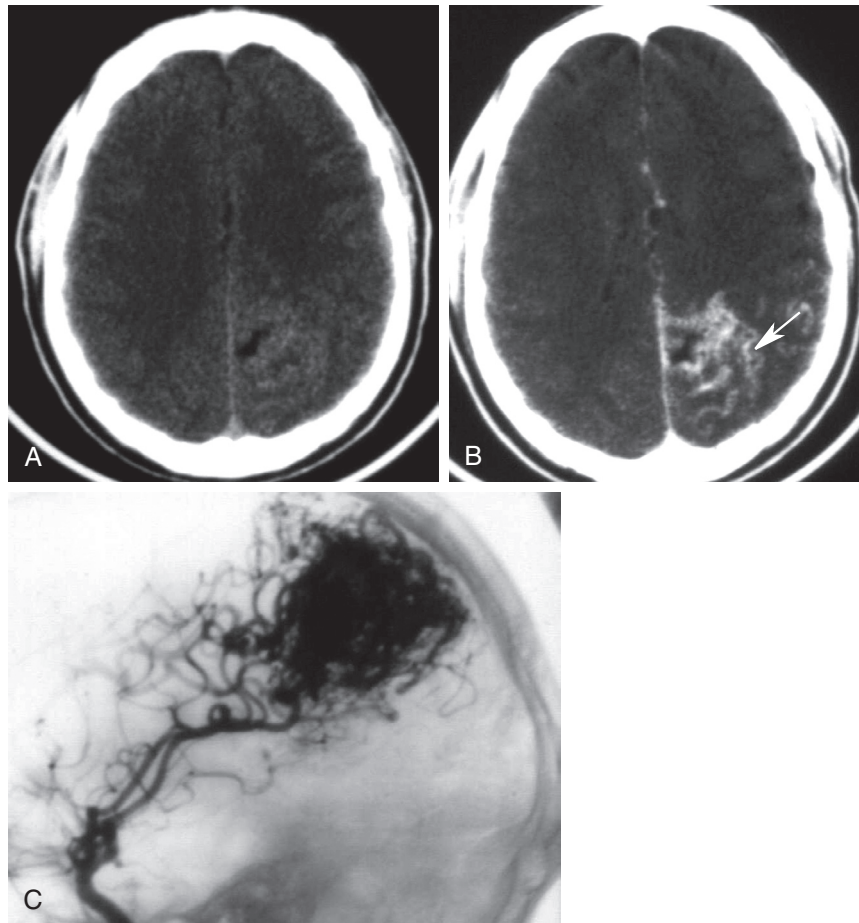


FIGURE 58-13 ■ Arteriovenous malformation. **A**, Axial non-contrast-enhanced computed tomography (CT) scan of head reveals a vague area of hyperdensity in posterior left parietal region. **B**, Contrast-enhanced CT scan demonstrates serpiginous enhancement of this lesion (arrow). **C**, Internal carotid artery angiogram demonstrates arteriovenous malformation being fed by middle cerebral artery.



FIGURE 58-14 ■ Intracranial metastatic disease. Axial contrast-enhanced computed tomography scan of head reveals multiple enhancing nodules throughout gray and white matter structures, consistent with metastatic disease.

Metastatic lesions may be low-density-enhancing masses, or they may have high density secondary to hemorrhagic components (Fig. 58-14). Cystic tumors may have the density of CSF (Fig. 58-15). Epidermoid and dermoid tumors frequently contain areas of fat density that appear hypodense to CSF.

MRI has high sensitivity but low specificity in the evaluation of neoplasms. Tumors are typically of low intensity on T1WI and high intensity on T2WI (see Fig. 58-1). DWI and MRS are helpful in pre-surgical staging and grading, selection of biopsy sites, and monitoring response to therapy.^{15,49} DTI and fMRI can show the relationship between a tumor and eloquent cortex and critical white matter tracts, defining and minimizing the risks of resection.⁵⁰ MRS, DWI, and PET can distinguish postradiation necrosis from tumor recurrence.^{10,51}

Infection and Inflammation

CT and MRI may initially appear normal in encephalitis but later show areas of cortical edema or hemorrhage. DWI can show areas of diffusion restriction early in the disease.⁶ The herpes simplex virus (HSV) shows a strong predilection for the temporal, insular, and cingulate regions in older children and adults but less specificity in neonates.⁵² Acute disseminated encephalomyelitis (ADEM) is an immune-mediated, often postinfectious encephalitis that usually

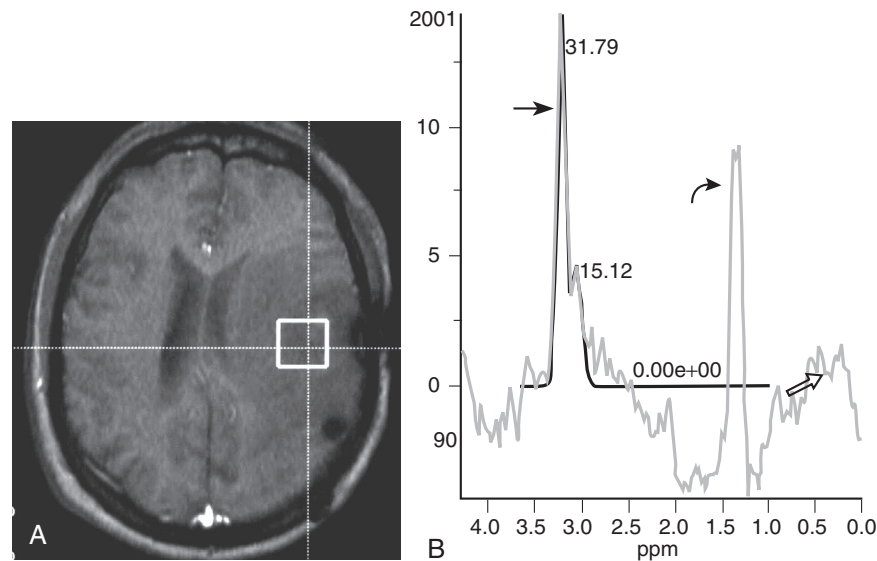


FIGURE 58-15 ■ Recurrent high-grade astrocytoma. Study performed after radiation therapy (not shown) showed increased edema and mass effect; differential diagnosis included recurrent tumor and radiation necrosis. **A**, Axial magnetic resonance imaging scan shows volume of tissue (box) selected for spectroscopy. **B**, Proton spectroscopy reveals increase in choline peak (arrow), decrease in *N*-acetyl aspartate peak (curved arrow), and appearance of a lactate peak (open arrow). This appearance is consistent with recurrent tumor, which was verified by repeat surgery and biopsy.

appears as symmetric demyelination and edema in the subcortical white matter.⁵³

On CT, an abscess cavity demonstrates central hypodensity, a thin, isodense wall that enhances with IV contrast, and surrounding low-density edema. On MRI, the central cavity varies in intensity but the capsule is typically iso- to hyperintense on T1WI, hypointense on T2WI, and enhances with contrast. DWI and MRS can be useful in distinguishing an abscess from other cystic lesions.⁶

In meningitis, CT and MRI may be normal or demonstrate diffuse meningeal contrast enhancement. Ventriculitis shows contrast enhancement of the involved ventricular walls. On CT, subdural and epidural empyemas most often have a density intermediate between CSF and acute blood. On MRI, these pyogenic collections are hypointense to brain on T1WI and hyperintense on T2WI.

White Matter and Metabolic Diseases

MRI is preferable to CT for determining the presence and extent of white matter disease (Fig. 58-16). Lesions appear hypointense on T1WI and hyperintense on standard T2WI; subependymal lesions are more conspicuous on FLAIR.

Most white matter diseases are slowly progressive, but acute presentations occur with toxic and vascular insults.⁵⁴ Carbon monoxide poisoning causes selective injury to the putamina, thalami, caudate heads, cerebellum, and cerebral white matter.⁵⁵ With Wernicke encephalopathy, MRI can show selective injury to the thalami, hypothalamus, periaqueductal dorsal midbrain, mammillary bodies, and medullary tectum.⁵⁶ Methanol ingestion can cause hemorrhagic necrosis of the caudate heads, putamina, pons, optic nerves, and subcortical white matter.⁵⁷

Immunosuppressive medications have been associated with PRES, and several chemotherapeutics, particularly intrathecal methotrexate, can cause toxic demyelination.¹⁰ Osmotic myelinolysis due to rapid correction of hyposmolality may affect the central pons but sometimes involves the thalami, basal ganglia, and deep white matter.⁵⁸

Encephalopathy due to liver disease can appear as T1WI hyperintensity in the globus pallidi, subthalamic nuclei, and midbrain; T2WI hyperintensity in the cortex; and MRS evidence of decreased Cho and mI and increased glutamine and glutamate.⁵⁹

SPINAL CORD

Patterns of Disease

Spinal cord pathology can be classified according to location (Fig. 58-17), usually requiring MRI.⁶⁰ With acute trauma, however, initial bony alignment and stability are better assessed by plain radiography and CT.

Intraductal lesions expand the spinal cord, compressing the subarachnoid space (Fig. 58-17, A), and are usually neoplastic, presenting with slowly progressive symptoms.

Extraductal-intradural lesions displace the arachnoid layer of the meninges but leave the dura in place such that the subarachnoid CSF flares out to form a “cap” at its interface with the lesion (Fig. 58-17, B). Meningiomas, nerve sheath tumors, and other benign tumors account for most lesions in this space.⁶¹

Extradural lesions usually displace the subarachnoid space and spinal cord (Fig. 58-17, C). Excluding disk disease, the most common extradural pathology is metastatic disease.

Specific Disease Processes

Spinal Cord Injury

Plain x-rays are able to identify most unstable injuries. However, some vertebral fractures and misalignments will be missed (Fig. 58-18, A). CT with axial, coronal, and sagittal reconstructions should be considered whenever fractures are seen or suspected (Fig. 58-18, B and C).⁶²

MRI is recommended when the patient has neurologic deficits, an unstable injury by previous imaging, or symptoms of an unstable injury despite a normal CT⁶³ but may be unnecessary in most obtunded

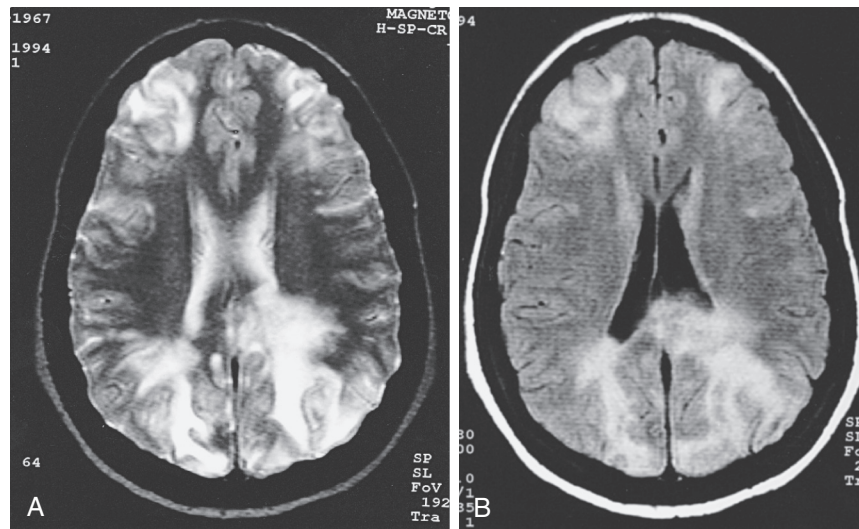


FIGURE 58-16 ■ Progressive multifocal leukoencephalopathy. Axial T2-weighted (A) and fluid-attenuated inversion recovery (FLAIR) (B) images in patient with human immunodeficiency virus (HIV). Multiple areas of white matter disease are identified; FLAIR image clarifies the involvement of periventricular white matter. These findings in an HIV-positive patient strongly suggest progressive multifocal leukoencephalopathy.

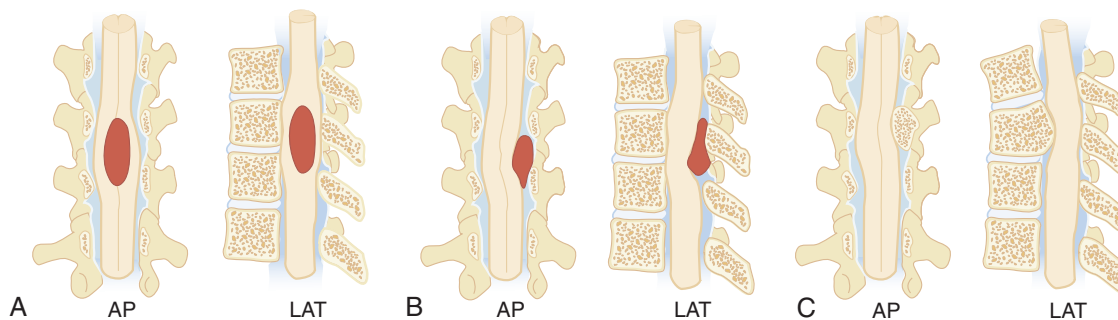


FIGURE 58-17 ■ Spinal compartments. Anteroposterior (AP) and lateral (LAT) views of spinal cord and canal demonstrate appearance of an intramedullary lesion (A), extramedullary intradural lesion (B), and extradural lesion (C).

and comatose trauma patients.⁶⁴ MRI can directly visualize intrinsic spinal cord and soft tissue injuries and can distinguish between hemorrhagic (poorer prognosis) and edematous cord injuries. A disk herniation with cord compression can change management from nonsurgical to surgical or change the surgical approach. MRI is also useful in detecting ligamentous injuries and the extent to which hematomas or bony displacements compress the spinal cord or nerve roots (Fig. 58-18, D).

Spinal Infection

MRI has a higher sensitivity than plain films and CT for spinal infections.⁶⁵ In spondylitis, MRI findings include narrowing of the disk space, contrast enhancement, hypointensity on T1WI in the vertebral bodies, and hyperintensity on T2WI in the vertebral bodies and disk (Fig. 58-19). Skip lesions and associated large paraspinal abscesses suggest mycobacterial infection. Nuclear medicine studies may help identify chronic spondylitis or surgical hardware infection.⁶⁶ In myelitis, typical MRI findings are focal or diffuse areas of T2WI hyperintensity with variable contrast enhancement.⁶⁷

Neoplasia

MRI is the primary modality for the evaluation of suspected spinal and paraspinal tumors.⁶⁸

The spinal column is the third most common site for tumor metastasis. Plain radiographs can show the “moth-eaten” outline of diffuse vertebral body cortical destruction. Vertebral collapse is more likely caused by neoplasia than degenerative disease when there is unilateral bone destruction, irregular or angular distortion of the vertebral endplates, involvement of the upper thoracic spine, a soft tissue mass, or pedicle destruction.⁶⁹ The bone marrow of vertebral bodies with neoplastic infiltration appears hypointense on T1WI and hyperintense on T2WI (Fig. 58-20). The bone marrow of vertebrae with benign fractures shows normal imaging characteristics (Fig. 58-21).

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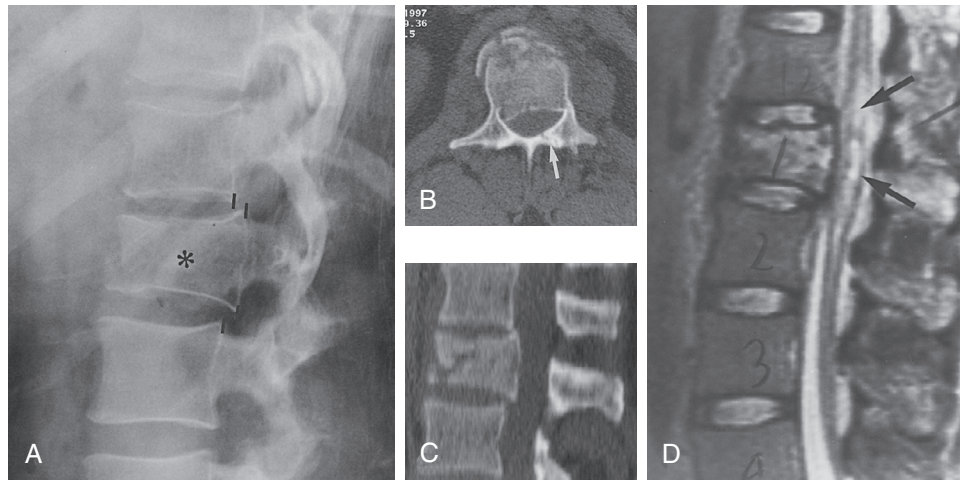


FIGURE 58-18 ■ Posttraumatic vertebral body compression fracture. Lateral plain film (**A**) of thoracolumbar junction reveals a compression fracture involving L1 vertebral body (*asterisk*). Decreased height of vertebral body and inferior anterior corner fracture are well seen. Retropulsed body can also be seen when outline of adjacent vertebral bodies (*lines*) are compared. Axial (**B**) and sagittal reconstructed (**C**) computed tomography scans of same patient add substantial detail to degree of canal narrowing secondary to retropulsed fragment. Left lamina fracture (*arrow*, **B**) is also seen—not apparent on the plain film. **D**, Sagittal T2-weighted magnetic resonance imaging demonstrates compression fracture of L1 and retropulsed posterior body, as well as contusion and swelling of conus (*arrows*) as a direct result of compression fracture.

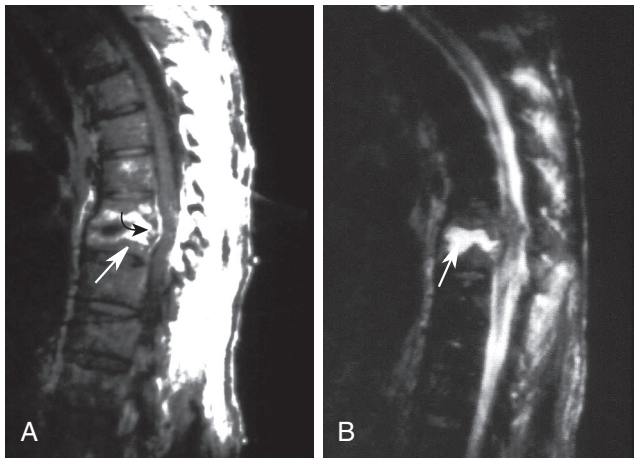


FIGURE 58-19 ■ Discitis with epidural abscess. Sagittal postcontrast T1-weighted (**A**) and T2-weighted (**B**) magnetic resonance imaging scans demonstrate features of discitis and adjacent osteomyelitis. Vertebral bodies and disc space are of low signal intensity on T1-weighted image and of bright signal intensity on T2-weighted image (*straight arrows*). Epidural abscess surrounding and compressing cord is also identified (*curved arrow*).

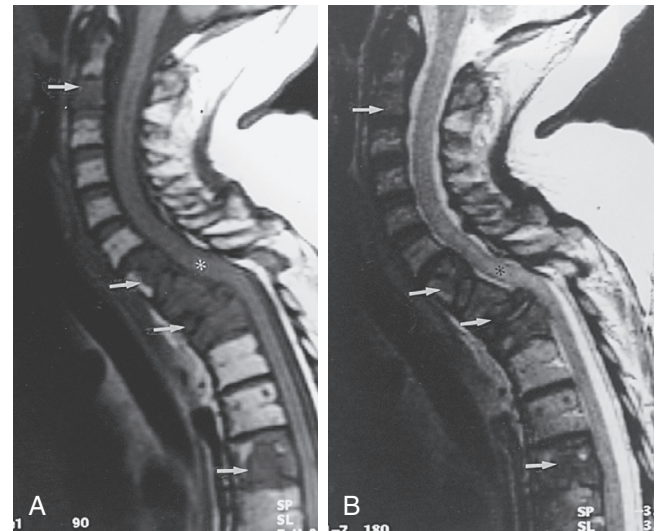


FIGURE 58-20 ■ Metastatic disease. Sagittal T1-weighted (**A**) and T2-weighted (**B**) magnetic resonance imaging scans of spine show metastatic lesions (*arrows*) as low intensity on T1-weighted image, replacing normal bright marrow. High signal within uninvolved vertebral bodies represents postradiation changes. Hypointense lesions on T2-weighted image (in contrast to more typical hyperintensity) reflect posttreatment appearance. Multiple compression fractures are identified within upper thoracic spine, with collapse, retropulsed fragments, and cord compression. Edematous changes within cord secondary to compression (*asterisk*) are also identified.

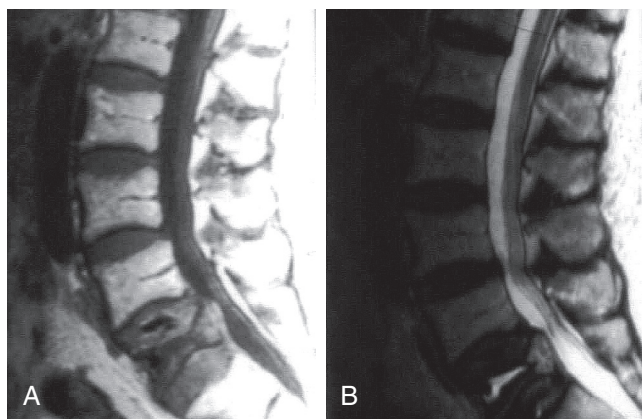


FIGURE 58-21 ■ Benign compression fracture. Sagittal T1-weighted (A) and T2-weighted (B) magnetic resonance imaging scans demonstrate compression fracture of L5. Compare signal characteristics of remaining bony elements and pedicles with signal of normal bony structures.

KEY POINTS

Methods

1. CT can be acquired quickly with few contraindications. MRI provides greater detail and uses no ionizing radiation but requires more time to acquire.

Brain

1. CT and MRI help differentiate lesions of different etiologies.
2. Infarctions and hemorrhages change in appearance over time.
3. CT is useful for acutely evaluating SAH, obstructive hydrocephalus, and mass lesions.
4. CT can exclude hemorrhage in patients with suspected infarction.
5. Multiple imaging modalities are useful for evaluating CNS tumors.

Spine

1. CT can identify unstable spinal trauma requiring surgical intervention. MRI is more sensitive for soft tissue and spinal cord injuries.
2. MRI is preferable for evaluating diseases affecting the spinal cord.

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The evolving appearance of blood on CT and MRI is described in detail.

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Appropriate neurocritical care is fundamental to the success of neurosurgical interventions involving the brain and spinal cord. Great technical advances in operative procedures have made lesions previously considered inoperable now treatable, and advances in anesthesia have led to an increased number of operative procedures in both elderly and critically ill patients. Consequently, the number of patients requiring postoperative intensive care has increased.

Successful care of the neurosurgical patient requires close collaboration between various specialists: neurosurgeons, anesthesiologists, intensivists, and neuroradiologists. The results of a technically perfect operation can be ruined by inadequate postoperative care, while a complex operative procedure requires expert intensive care to correct abnormalities in homeostatic mechanisms, ensure adequate cerebral perfusion and oxygenation, and promote recovery of brain function. The complex interaction between the central nervous system (CNS) and systemic functioning requires detailed knowledge of both general intensive care and cerebral and spinal pathophysiology. Anticipation and early response prior to the full-blown development of complications are hallmarks of good neurocritical care. For example, when serum sodium levels are decreasing, correction should be implemented before hyponatremia develops, as hyponatremia may lead to increased brain edema. The best care for neurosurgical patients can be provided by dedicated specialists with knowledge of both fields and a large amount of experience in treating such patients.

The benefit of concentration of care in hospitals and units with sufficient case volume has been well established in different fields of intensive care medicine, including trauma,¹ neonatology, and specifically neurointensive care.²⁻⁸

Treatment of patients with spontaneous intracerebral hemorrhage in a dedicated neurointensive care unit (neuro-ICU) is associated with reduced mortality, when compared with patients admitted to a general intensive care unit (ICU),^{9,10} and mortality following aneurysmal subarachnoid hemorrhage (SAH) is lower in centers with a higher case volume.^{5,11} Patel and colleagues¹² unequivocally showed a 2.15 times increase in the odds of death (adjusted for case mix) for patients with severe traumatic brain injury (TBI) treated in nonneurosurgical centers versus neurosurgical centers. Their report makes a strong case for transferring all patients with severe TBI to a setting with 24-hour neurosurgical and neurocritical care facilities. A subsequent study demonstrated that transfer of nonsurgical patients with TBI to neuroscience centers resulted in substantial improvements in the risk-adjusted odds ratio for mortality (0.52; confidence interval [ci], 0.34-0.80).¹³ Protocol-driven approaches in adult and pediatric intensive care, as well as treatment in centers with higher patient volumes, are associated with better outcome.¹³⁻¹⁷

The admission policy for postoperative neurosurgical care in ICUs varies widely among countries and centers and even within centers. In some centers, all patients who have undergone intracranial procedures are admitted for a 24-hour observation period following surgery; this is motivated by the observation that some patients, although fully alert and neurologically intact initially, may subsequently develop complications necessitating prompt intervention.

In other centers, patients are only admitted to the ICU after intracranial complications have been detected. Some hospitals have dedicated neuro-ICUs, and in others, patients are admitted to a general ICU, sometimes even to different ICUs within one hospital. In general, the

scarcity of ICU beds has also led to a more restrictive admission policy for postoperative neurosurgical care. The institution of high-care units, sometimes termed “step-down units”, may permit more efficient use of scarce intensive care resources, while at the same time affording sufficient guarantees for adequate postoperative monitoring. Here again, however, care should be provided by personnel well experienced in the care of such patients, thus permitting early detection of possible deterioration and prevention of secondary complications.

PRIORITIES AND GOALS OF POSTOPERATIVE NEUROSURGICAL CARE

The principal goal of postoperative neurosurgical intensive care is early detection and treatment of postsurgical complications. The second goal is to prevent second insults that may initiate or exacerbate secondary damage in a vulnerable CNS.

Consequently, priorities are to ensure adequate monitoring facilities, which may in the sedated and ventilated patient require further invasive monitoring of the intracranial system, and to ensure adequate oxygenation and perfusion of the brain. Postoperative complications may be systemic or neurosurgical (Table 59-1).

PREVENTION AND MANAGEMENT OF SYSTEMIC COMPLICATIONS AFTER NEUROSURGERY

General Principles and Second Insults

The prevention and management of systemic complications after neurosurgical procedures follow general principles of “intensive care” medicine. Systemic complications and second insults may initiate or aggravate cerebral damage. Aggressive treatment aimed at preventing and limiting second insults is of paramount importance. The main second insults, along with their causes and adverse effects on brain homeostasis and function, are summarized in Table 59-2. This table illustrates the complex interactions between systemic events and CNS function.

Conversely, CNS events may induce systemic derangements. For example, in response to raised intracranial pressure (ICP), mean arterial blood pressure (MABP) may increase as a compensatory mechanism to ensure adequate cerebral perfusion (Cushing response). In such situations, treatment of hypertension is contraindicated, as this may exacerbate cerebral ischemia. In other situations, however, arterial hypertension may aggravate the occurrence of cerebral edema and/or increase the risk of intracranial bleeding. Surgeons may request preventing any episode of high blood pressure (BP) in situations where adequate hemostasis was difficult, or conversely, they may wish to maintain BP at relatively high levels when cerebral vasospasm may be a problem, such as after cerebral aneurysm surgery. The clinical dilemma is to balance the desire of limiting edema formation and the risk of postoperative hemorrhage with the goal of maintaining adequate perfusion. Knowledge of the operative findings and close interaction with the surgeon are of paramount importance.

TABLE 59-1 Postoperative Complications

| SYSTEMIC COMPLICATIONS | NEUROSURGICAL COMPLICATIONS |
|--|--|
| <ul style="list-style-type: none"> Coagulation disorders: blood loss, disseminated intravascular coagulation, drug induced Thromboembolic: DVT, pulmonary embolism, myocardial infarction Pulmonary: atelectasis, pneumothorax, ventilator-associated pneumonia Hypovolemia: insufficient pre- and perioperative hydration, blood loss Infection: pneumonia, urinary tract infection, catheter sepsis Metabolic: hyperglycemia (steroid-induced), diabetes insipidus, hyponatremia Air embolism: sitting position, opening of large cerebral veins during surgery Pressure sores and decubitus ulcers: intraoperative positioning, cervical traction, paraplegia | <ul style="list-style-type: none"> Postoperative hematoma: subgaleal, epidural, subdural, intraparenchymal Cerebral ischemia: subarachnoid hemorrhage, vasospasm, vessel occlusion Brain swelling: edema, vasodilation Infection: meningitis, subdural empyema, cerebral abscess Seizures: infection, depressed compound skull fracture, cortical lesions Hydrocephalus: obstruction/resorption Tension pneumocephalus CSF fistula Inverse cerebellar herniation Cranial nerve lesions |

CSF, cerebrospinal fluid; DVT, deep venous thrombosis.

Many drugs routinely used in neurosurgical patients (e.g., steroids, antiepileptic agents) may cause complications or side effects. Awareness of these potential side effects is essential. CNS damage, particularly to the hypothalamus region, brainstem, and cervical spinal cord, may lead to disturbances in temperature control, causing hypo- or hyperthermia. In patients with spinal cord injury, loss of autonomic sympathetic function may further lead to peripheral vasodilation and low BP. In the absence of beta-blocking agents, hypotension in combination with bradycardia is strongly suggestive of damage to the spinal cord.

Cardiac Dysfunction

Electrocardiographic abnormalities, usually ST-segment changes mimicking cardiac ischemia and cardiac arrhythmias, may be caused by SAH, TBI, or raised ICP. Cardiac complications in the acute phase of SAH are well known.¹⁸ The left ventricle suffers a typical bulging (indicating ischemic changes and functional impairment), which has been awarded the term *takotsubo syndrome*, with reference to the shape of a pot used by ancient Japanese fishermen for catching octopus. The extent of left ventricular dysfunction is variable, but it may lead to cardiac failure and pulmonary edema.^{19,20} A 2014 study reported echocardiographic abnormalities in 22.3% and a reduced left ventricular ejection fraction in 12% of patients with isolated TBI.²¹

Neurogenic Pulmonary Edema

The development of neurogenic pulmonary edema has been described early in the postoperative period after a variety of neurosurgical procedures, including brain tumors (particularly those resected in the posterior fossa), cysts, hydrocephalus, intracranial hemorrhages, and brainstem lesions.²²⁻²⁵ Although an infrequent event, neurogenic pulmonary edema is potentially life-threatening and requires rapid evaluation and emergent therapy in the ICU.²⁵ A 9% mortality rate directly attributable to neurogenic pulmonary edema has been reported in a review of this condition. Generally, this complication appears in the initial 4 hours after the neurologic event and is more common in women than in men, possibly related to the preponderance of cases in

TABLE 59-2 Systemic Second Insults

| EVENT | MAIN CAUSES | ADVERSE EFFECT |
|---------------|--|--|
| Hypoxemia | Hypoventilation Aspiration atelectasis Pneumothorax Pneumonia Anemia | Decreased oxygen delivery and increased risk of ischemic damage |
| Hypotension | Hypovolemia Cardiac failure Sepsis, spinal cord injury | Decreased CPP, decreased CBF, increased risk of ischemia |
| Anemia | Blood loss | Decrease in oxygen transport and delivery, increased risk of ischemic damage |
| Hypercapnia | Respiratory depression | Increased cerebral blood volume, raised ICP |
| Hypocapnia | Hyperventilation (spontaneous or induced) | Cerebral vasoconstriction with increased risk of ischemic damage |
| Hyperthermia | Hypermetabolism, stress response, infection Central dysregulation | Metabolic requirements may exceed substrate delivery, resulting in energy depletion |
| Hypothermia | Exposure, central dysregulation | May be neuroprotective but can cause significant coagulopathy and electrolyte disturbances |
| Hyperglycemia | IV infusion of dextrose, steroids, stress response | Acidosis, electrolyte disturbances |
| Hypoglycemia | Inadequate nutrition, insulin overdose, pituitary insufficiency | Energy depletion in the brain, seizures |
| Hyponatremia | Inadequate salt intake (hypotonic fluids) Excessive sodium loss (cerebral salt wasting/CSF drainage) Syndrome of inappropriate ADH | Increased edema, seizures |
| Hypernatremia | Diabetes insipidus Osmotic agents (mannitol, hypertonic saline) | Lethargy, coma |

ADH, antidiuretic hormone; CBF, cerebral blood flow; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; ICP, intracranial pressure; IV, intravenous.

patients with SAH.²⁵ The mechanisms underlying this condition are unclear; a sudden central sympathetic discharge may trigger pulmonary vasoconstriction, systemic arterial hypertension, increased left ventricle afterload, and increased capillary permeability in the pulmonary vascular bed and simultaneously cause cardiac ischemia and ventricular failure.^{20,26} Because of these multiple mechanisms, neurogenic pulmonary edema can be interpreted as noncardiogenic or, at least in part, as cardiogenic.²⁷ Both low- and high-protein content has been reported in the edema fluid.^{25,28} It is commonly associated with raised ICP, and, in addition to therapies directed at intracranial hypertension, therapeutic measures are mostly supportive. To attenuate the massive sympathetic discharge, opioids and sedatives are used. Supplemental oxygen is uniformly required, and tracheal intubation with mechanical ventilation and the application of positive end-expiratory pressure have been reported in about 75% of patients.²⁵ Diuretics have been used, provided that volume status is adequate, but they are less effective than in cardiac edema. Most patients require vasoactive drugs.²⁸

Hypercoagulopathy and Thrombosis Prophylaxis

Release of factors from damaged brain tissue may induce local and systemic hypercoagulopathy.²⁹⁻³¹ Various studies have confirmed a transient hypercoagulopathy syndrome both in the immediate postoperative phase after brain surgery and in patients with TBI.^{29,32,33,34} In patients with a subdural hematoma, consumption of clotting factors may lead to coagulopathy in up to 22% of patients.³⁵ The current hypothesis for the development of coagulopathy in brain injury implicates a combination of both hypo- and hypercoagulable states, triggered by damaged brain tissue, and resulting in secondary injury via subsequent ischemic or hemorrhagic lesions. The proposed underlying mechanisms include the release of tissue factor, hyperfibrinolysis, and, more specifically in trauma patients, hypoperfusion (with triggering of the protein C pathway) and the development of disseminated intravascular coagulation.^{36,37}

Deep venous thrombosis (DVT) has been reported to occur in 18% to 50% of neurosurgical cases³⁸ and pulmonary embolism (PE) in 0% to 25%. The incidences of DVT and PE are particularly high in brain tumor patients. Nevertheless, neurosurgeons tend to underestimate the risk of DVT and PE³⁹ and are sometimes reluctant to routinely prescribe anticoagulant prophylaxis for fear of increasing the risk of postoperative bleeding.⁴⁰ Options for prevention of thrombosis prophylaxis in neurosurgical patients include both mechanical (e.g., graduated compression stockings, intermittent pneumatic compression stockings), and pharmacologic (e.g., low dose of classic heparin, low-molecular-weight heparin) therapies. Intuitively, mechanical therapies carry less associated risk, but pharmacologic approaches are more effective in preventing thrombotic complications. Various studies have indeed shown a higher incidence of postoperative hemorrhagic complications,⁴¹ but not all are clinically relevant.

Overall, existing evidence, however, shows that the beneficial effects in reducing DVT, and in particular PE^{42,43} outweigh a slightly increased risk of clinically significant hemorrhagic complications with anticoagulant prophylaxis. These data support the administration of antithrombotic prophylaxis to patients undergoing neurosurgical procedures,⁴⁴ including those with intracranial hemorrhagic lesions⁴⁵ or closed TBI,^{46,47} as well as high-risk trauma patients.^{48,49} Practice recommendations from the Trauma Quality Improvement program of the American College of Surgeons advise initiation of venous thromboembolism prophylaxis within the first 72 hours after TBI in most patients (<https://www.facs.org/quality-programs/trauma/tqip>). However, opinions differ, and careful estimation of the balance of benefits versus risk should be sought, informed by objective assessments of coagulation status.⁵⁰⁻⁵³ It has been recommended that removal of catheters or drainage tubes in the postoperative phase be performed when anticoagulant effects are low (e.g., just prior to administration of the next dose of antithrombotic agent).⁵⁴

Some uncertainty, however, exists regarding the preferred choice of medication, optimal dosing regimen, and time of initiation of thrombosis prophylaxis, particularly in patients with a higher risk for bleeding. Any decision regarding the use of thrombosis prophylaxis must weigh efficacy against harm from the proposed intervention. In addition, early mobilization in the postoperative phase, whenever possible, is recommended. More consensus exists concerning routine administration of anticoagulant therapy in patients with spinal cord injuries.

PREVENTION AND MANAGEMENT OF NEUROSURGICAL POSTOPERATIVE COMPLICATIONS

Supratentorial Procedures

Postoperative Subgaleal Hematoma

Postoperative subgaleal hematoma may occur in up to 11% of procedures. These hematomas generally result from inadvertent damage of

the superficial temporal artery with inadequate hemostasis or hemorrhage from the temporal muscle. If the superficial temporal artery is damaged during the operation, ligation is preferred over coagulation. The occurrence of subgaleal hematomas can be minimized by routine use of postoperative wound drainage for 24 hours. Reoperation for subgaleal hematomas is seldom necessary unless there is a communication with the intracranial compartment with secondary compression of the brain.⁵⁵

Intracranial Hemorrhage

Intracranial postoperative hemorrhage occurs in about 1% of procedures and mainly includes intraparenchymal hematomas (43%-60%), epidural hematomas (28%-33%), and subdural hematomas (5%-7%). After every supratentorial procedure, some blood may accumulate in the epidural space. Appropriate surgical techniques aim to minimize this epidural space by circumferentially suturing the dura to the bone, periosteum, or galea. Nevertheless, inadequate hemostasis of meningeal arteries, blood loss from the temporal muscle, or blood loss from bone or the sites of skull penetration by the pins of a Mayfield clamp may induce a larger postoperative epidural hematoma. In cases of neurologic deterioration considered to be due to a postoperative epidural hematoma, surgical evacuation is indicated. Postoperative subdural hematomas occur less frequently and may develop after a delay, due to later rupture of bridging veins following large intracerebral decompression. On occasion, such subdural hematomas may occur distant from the primary site of operation.

Parenchymal hemorrhages are the most frequent cause of postoperative hematomas after supratentorial procedures and generally occur at the site of operation, particularly following partial tumor resection. An increase in systemic BP at the end of surgery may increase the risk of parenchymal hemorrhage. In rare cases, the hematoma may be located distant from the primary site of operation, and cerebellar hematomas have even been described after supratentorial surgery.^{56,57} The possibility of a postoperative hematoma should be considered in all patients who are not fully alert after anesthesia, as well as in those who exhibit secondary deterioration.

Postoperative Brain Swelling

Modern neuroanesthesiology techniques have diminished the incidence of peri- and postoperative brain swelling. Nevertheless, significant swelling may sometimes occur, causing surgical difficulties and possibly critical problems in the ICU. Predisposing factors are hypercapnia, arterial hypertension, hyponatremia, obstruction of venous drainage, and silent or overt seizures during surgery or in the immediate postoperative phase. Further, significant brain swelling after uneventful surgery has been attributed to intracranial hypotension caused by subgaleal suction.⁵⁸ In any patient with brain swelling during the surgical procedure, the possibility of a deep hematoma should be considered and urgent computed tomography (CT) should be performed. Brain swelling due to vasodilation can be corrected by hyperventilation and barbiturate administration; brain swelling due to cerebral edema should preferentially be treated by osmotic agents.

Tension Pneumocephalus

Some air collection is generally observed on postoperative CT scans.⁵⁹ In rare circumstances, rewarming of air in the intracranial compartment postoperatively or continuous air leakage due to a cerebrospinal fluid (CSF) fistula of the skull base may lead to a tension pneumocephalus, with clinical symptomatology including decreasing level of consciousness, signs of raised ICP, and occasionally seizures. Generally, postoperative air accumulations are self-limiting and do not require specific treatment.

Seizures

An epileptic seizure in the early postoperative phase should be considered a serious complication that may cause significant deterioration because of vasodilation, increased cerebral oxygen consumption, and

increased brain edema. Subclinical seizure activity can occur in 15% to 18% of patients with moderate and severe TBI.⁶⁰ The benefits of prophylactic antiseizure medication should be balanced against risks. In some centers, routine prophylaxis is prescribed in all patients undergoing supratentorial brain surgery. In others, the indications are restricted to patients with a higher risk:

- Cerebrovascular surgery (e.g., arteriovenous malformation, aneurysm)
- Cerebral abscess and subdural empyema
- Convexity and parafalcine meningiomas
- Penetrating brain injury
- Compound depressed skull fracture

Opinions vary regarding the duration of prophylactic antiseizure therapy, with some centers recommending a treatment duration of 1 week and others continuing treatment for at least 3 months. In any case of unexplained neurologic deterioration or delayed awakening from anesthesia, the possibility of seizures should be considered.

Infratentorial Procedures

The care of patients in the early postoperative phase following infratentorial procedures poses specific problems. Postoperative complications in the posterior fossa can lead to rapid deterioration because of the relatively small infratentorial volume reserve and immediate compression of the brainstem, resulting in respiratory insufficiency and acute herniation. Irritation of the brainstem may induce large swings in arterial BP, enhancing the risk of postoperative hemorrhage during hypertensive episodes. Cranial nerves are more susceptible than peripheral nerves to damage caused by surgical manipulation.⁶¹ Lesions of the lower cranial nerves may lead to a diminished gag reflex, increasing the risk of aspiration and pneumonia. After surgery in the cerebellopontine angle, specific attention should be paid to the function of the trigeminal and facial nerves, and prophylactic measures should be taken to prevent damage of the cornea.

After any infratentorial procedure, the risk of acute hydrocephalus due to obstruction at the level of the fourth ventricle is present. In rare instances in which supratentorial CSF drainage is performed, increased pressure in the infratentorial compartment may cause upward (inverse) herniation. These specific aspects warrant routine admission to the ICU of all patients who have undergone posterior fossa surgery to allow careful observation and monitoring. Particular attention should be paid to the presence of the gag reflex before extubation and in the early stages after extubation, and frequent monitoring of the respiratory status and adequacy of respiration is imperative.

After posterior fossa surgery, some patients may develop a syndrome of aseptic meningitis.⁶² This is characterized by meningeal symptoms, headaches, and an inflammatory response of the CSF in the absence of evidence for infection. The origin of this syndrome has not been fully clarified, but symptoms may resolve sooner with intermittent CSF drainage.

An infrequent transitory complication observed after resection of large midline posterior fossa tumors is cerebellar mutism.⁶² The exact cause is poorly understood, but a vascular phenomenon has been hypothesized.⁶³

Cerebrovascular Procedures

The postoperative care for patients undergoing cerebrovascular surgery poses specific challenges in neurointensive care. After surgery for arteriovenous malformations, the risk of seizures is particularly high, and focal deficits may occur secondary to changes in cerebral hemodynamics. Following treatment for a cerebral aneurysm, medical and cerebral complications can occur that are related to the disease or the treatment (surgical clipping or endovascular coiling). Medical complications specifically linked to SAH are neurogenic pulmonary edema, cardiac arrhythmias, and ventricular failure.¹⁹ Electrolyte disturbances, in particular hyponatremia, are also frequently observed.⁶⁴

The main cerebral complications are:

1. Rebleeding
2. Delayed cerebral ischemia (DCI)
3. Hydrocephalus

Rebleeding occurs mainly in the first weeks after aneurysmal rupture, and current approaches to prevent rebleeding involve early surgical clipping or endovascular obliteration (coiling) of the aneurysmal sac. DCI (often the result of vasospasm) is a common cause of death and disability due to SAH, second only to rebleeding. The reported incidence of this complication varies widely, but angiographic vasospasm is seen in over 67% of untreated patients with angiography at the time of maximum spasm, around the end of the first week.⁶⁵

Although DCI may be caused by vasospasm, not all patients with DCI have vasospasm. Conversely, not all patients with vasospasm develop clinical symptoms and signs of DCI. Recent studies show that DCI may not always be attributed to vasospasm but more to the occurrence of microthrombosis.^{66,67} DCI is associated with activation of the coagulation cascade within a few days after SAH, preceding the time window during which vasospasm occurs. Furthermore, both impaired fibrinolytic activity and inflammatory and endothelium-related processes may lead to the formation of microthrombi, further promoting the development of DCI.

Clinically evident delayed ischemic deficits (DID) affect approximately one-third of patients. Various studies have shown a beneficial effect of the administration of oral calcium antagonists in preventing DID.^{68,69} Beneficial effects of intravenous administration of nimodipine remain unproven, however.

Following evidence that patients with SAH had reduced blood volume, plasma volume, and erythrocyte mass, triple H (HHH) therapy (hypervolemia, hypertension, and hemodilution) was proposed for both prophylaxis and treatment of DID after SAH. Various studies have shown a reduction in DID with HHH prophylaxis,⁷⁰ but some debate remains.^{71,72}

The usefulness of HHH treatment is generally accepted, but it has never been unequivocally shown by a randomized controlled trial to be superior to simple moderate fluid loading. The relative importance of the three components of HHH therapy is uncertain.^{73,74} Adequate fluid loading should be considered the most important aspect of early treatment and prophylaxis of DID, but it may be considered reasonable to reserve more vigorous loading and induced hypertension for situations in which there is clinical evidence of delayed ischemia.⁷⁴⁻⁷⁶

Progressive signs of DID may require more aggressive approaches, including angioplasty.⁷⁷ Transluminal balloon angioplasty is generally recommended, but this requires special equipment and a highly skilled and experienced interventional neuroradiology team. Alternatively, so-called chemical angioplasty, in which the angiography catheter is used to install papaverine or nimodipine, may be considered.⁷⁸

Chemical angioplasty often has to be repeated within hours or days, and it carries the risk of complications, including pupillary changes, seizures, or respiratory arrest, with vertebral artery injection. The possibility of cisternal therapy should also be considered, injecting recombinant tissue plasminogen activator or urokinase into the basal cisterns to break down accumulated blood⁷⁹ or nitric oxide donors to improve vascular tone. Various studies have shown clinical benefit of this approach, with the added benefit of reducing the incidence of hydrocephalus.

Acute hydrocephalus after SAH is not uncommon. The reported frequency depends on the criteria used for diagnosis and ranges from 9%⁸⁰ to 67%.⁸¹ Spontaneous improvement of the hydrocephalus has been reported in about half of patients with acute hydrocephalus and impaired consciousness on admission, but it may be difficult to predict spontaneous improvement because treatment is generally instituted. In the absence of a hematoma with mass effect or an obstructive element, serial lumbar punctures may be the initial optimal method of treatment, reserving continuous CSF drainage procedures for patients in whom the hydrocephalus does not resolve over time.

ADMISSION EXAMINATION AND MONITORING IN THE INTENSIVE CARE UNIT

Specific care and monitoring of the postoperative neurosurgical patient require accurate knowledge of the preoperative situation and the intraoperative course, including the surgery, anesthesiology, and any surgical complications or difficulties. Pertinent aspects are summarized in Table 59-3.

On admission to the ICU, a full examination of the patient is required, including, whenever possible, an assessment of the level of consciousness and neurologic functioning. Medical care for the patient should be provided in joint collaboration between an intensivist and neurosurgeon. Intensive care monitoring includes clinical surveillance, technical monitoring, and follow-up CT or magnetic resonance imaging (MRI). The various approaches to monitoring are summarized in Table 59-4. These are discussed in detail in Chapter 47.

Clinical Surveillance

Even in this era with advanced monitoring procedures, routine clinical examinations are essential. The clinical assessment has the purpose of disclosing major, life-threatening complications early after surgery and of assessing and tracking neurologic deficits in the hours to days that follow.

Early Evaluation

A simple check of consciousness, pupils, and the development of focal (mostly motor) deficits remains the most important method for assessing patients in the neuro-ICU. Neurologic assessment should be repeated at regular intervals throughout the ICU course, as a change

in examination findings is the most sensitive method for detecting neurologic deterioration.

The level of consciousness should be assessed by the Glasgow Coma Scale (GCS).^{82,83} In this scale, standardized assessment of three aspects of responsiveness is performed: the eye, motor, and verbal reaction (Table 59-5). When administration of stimuli is necessary to assess the level of responsiveness, standardized administration is required. Pressure on the nail bed is recommended as a peripheral stimulus, and supraorbital pressure or trapezius pinch is recommended as a central stimulus when testing for a localizing response on the motor scale (Fig. 59-1). Accurate determination of the full GCS is not always possible because of sedation and paralysis, but at least the best motor score should be recorded, when possible. Daily interruption of sedation allowing intermittent wake-up in ventilated patients not only facilitates monitoring of the neurologic status, but it has also been shown to result in better outcomes.⁸⁴

Some authors advocate imputing the eye and verbal scores from the motor score in sedated and/or ventilated patients.⁸⁵ We prefer an approach in which only the motor score is assessed at times when the level of sedation permits, as this is an important parameter of neurologic function and the main predictor of outcome in unconscious patients. Reasons for not being able to assess one of the components of the GCS should be recorded. When used for describing the level of

TABLE 59-3

Postoperative Intake After Neurosurgical Operations

| | |
|---|--|
| Preoperative situation | <ul style="list-style-type: none"> Neurologic deficit (level of consciousness, focal paresis, cranial nerve lesions, hormonal deficits) Preexisting disease (especially pulmonary and cardiac) Preoperative medication History of seizures Allergy |
| Intraoperative anesthesia details | <ul style="list-style-type: none"> Opioid medications and antagonists Blood loss and substitution Intraoperative laboratory values Intraoperative second insults, diabetes insipidus, etc. |
| Intraoperative surgical course | <ul style="list-style-type: none"> Indication, approach, and duration of surgery Surgical position Surgical difficulties and complications (brain swelling, difficult hemostasis, temporary or definite vascular occlusion, opening of air sinus) Immobilization/positioning of patient. |
| Postoperative instructions (surgeon and anesthesiologist) | <ul style="list-style-type: none"> Postoperative medication (e.g., anticonvulsants, antibiotics, steroids, mannitol, antithrombosis prophylaxis) Instructions for postoperative care and monitoring Instructions for removal of drainage, tubes, and stitches Preferred duration of postoperative artificial ventilation Instructions for follow-up computed tomography or MRI examination (if indicated) |

MRI, magnetic resonance imaging.

TABLE 59-4

Postoperative Monitoring After Intracranial Procedures

| | |
|---------------------------|---|
| Clinical surveillance | Level of consciousness (Glasgow Coma Scale), pupillary reactivity, focal deficits, cranial nerve lesions |
| Systemic monitoring | Electrocardiogram and heart rate, respiration, pulse oximetry, end-tidal carbon dioxide partial pressure, blood pressure (invasive or noninvasive), temperature, central venous pressure, cardiac output monitoring |
| Brain-specific monitoring | Intracranial pressure and cerebral perfusion pressure, jugular oximetry, brain oxygen tension monitoring, microdialysis, transcranial Doppler, electroencephalogram, evoked potentials |
| Access devices | Central or peripheral venous catheter, arterial catheter, urinary catheter, gastric tube |
| Laboratory examinations | Blood gases, hematology, electrolytes, glucose, coagulation status (if indicated) |
| Imaging examinations | Chest radiograph (ventilated patients and after lung procedures), computed tomography or magnetic resonance imaging follow-up (as required) |

TABLE 59-5

Glasgow Coma Scale

| EYE OPENING | MOTOR | VERBAL |
|------------------|-------------------------|--------------------------------|
| 1: none | 1: none | 1: none |
| 2: to pain | 2: abnormal extension | 2: incomprehensible (groaning) |
| 3: to speech | 3: abnormal flexion | 3: inappropriate words |
| 4: spontaneously | 4: flexion (withdrawal) | 4: disoriented, confused |
| | 5: localizing | 5: oriented |
| | 6: obeying commands | |

Notes: the best score for each response should be documented and communicated in the format described above. Assessment of the best motor score is based on the best response of the arms. For use in individual patients, separate descriptions of the three components of the Glasgow Coma Scale (GCS) are strongly recommended. For purposes of classification, the total GCS can be calculated by adding the best score obtained in each category. The GCS should be annotated to indicate confounding factors: T = intubated patient, S = sedation, and P = neuromuscular blockade.

consciousness in an individual patient, the three components of the GCS should be described separately. For purposes of classification and research, the GCS sum score can be calculated.⁸³

The development of pupillary abnormalities is a sensitive indicator of pressure on the midbrain (tentorial herniation). The pupillary reaction to light is mediated through parasympathetic fibers of the third cranial nerve (oculomotor nerve). Afferent light perception, conducted through the second cranial nerve (optic nerve), connects at the level of the internal eye muscle nuclei to the oculomotor nerve supplying parasympathetic fibers to the sphincter pupillae muscle via the ciliary ganglia.

Pressure on the oculomotor nerve leads to loss of function of the parasympathetic fibers, causing a diminished pupillary response or absent pupillary reactivity, generally located initially on the side of the lesion (Fig. 59-2). With a progressive increase in pressure, both pupils become dilated and unresponsive to light. In patients with a lesion of the optic nerve, the consensual light reflex—contraction of the pupil when a light is shone into the opposite eye—remains intact.

Pupillary examination (of diameter and light reactivity) may be difficult in the ICU, where lightening is usually intense. It is especially difficult in patients under the effects of opioids, as these drugs cause miosis. In these circumstances, a computerized system known as *pupillometry* is available for precise assessment of pupil diameter and constriction to light.⁸⁶⁻⁸⁹

Further Evaluation

When major complications have been ruled out, it remains necessary to evaluate the persistence of previous deficits, their improvement after surgery, or the appearance of new signs attributable to surgery. It is expected, for example, that following surgical removal of a vestibular schwannoma, some degree of damage to cranial nerve VII can occur. After surgical intervention on structures located in, or close to, the brainstem, deficits of the lower cranial nerves can occur as well. A careful, complete neurologic examination is required at this stage, since the simple assessment proposed in the previous section is not meant to fully evaluate cranial nerve function. This evaluation is important since the presence of cranial nerve deficits may require action: for

example, protection of the ocular bulb to prevent keratitis or avoidance of oral feeding if swallowing is impaired.

SYSTEMIC MONITORING: CARDIOPULMONARY STATUS, RESPIRATORY STATUS, AND TEMPERATURE

The goal of cardiopulmonary and respiratory monitoring is to ensure adequate control of systemic hemodynamic and respiratory function, which is essential for optimization of cerebral oxygenation. Invasive arterial BP monitoring is recommended, with the reference point set at the same level as the ICP measurement to allow accurate calculation of the cerebral perfusion pressure (CPP).

The combination of a careful prescription of maintenance fluids, additional replacement solutions tailored to the patient's needs, and a rational but not aggressive goal-directed approach to resuscitation fluids seems to be the best approach to avoiding fluid-related morbidity in the perioperative period, including after neurosurgery.⁹⁰

Hypovolemic shock is most common in the setting of multisystem injury or intraoperative blood loss with inadequate replacement. Tachycardia and signs of peripheral vasoconstriction, such as skin pallor and poor capillary refill, may precede a drop in BP. To achieve rapid fluid resuscitation, therapeutic options include isotonic crystalloid fluids, volume expanders, small volume resuscitation (hypertonic saline), and blood transfusions. Isotonic balanced crystalloids seem to be the best pragmatic choice for resuscitation purposes.⁹⁰ Colloids, and particularly albumin, should be used with caution or even avoided in patients with several central neurologic disorders. Post hoc analysis of critically ill patients with TBI included in the Saline versus Albumin Fluid Evaluation study revealed that fluid resuscitation with albumin was associated with higher mortality rates than resuscitation with saline.⁹¹

Central venous pressure monitoring or cardiac output monitoring can guide the use of intravenous fluids and vasopressor therapy, aiming to optimize organ perfusion. Several hemodynamic monitors and parameters may be useful for guiding volume therapy, including cardiac output, stroke volume variation monitoring, and global end-diastolic volume index.⁹² Early goal-directed hemodynamic therapy after SAH has been shown to improve clinical outcomes in patients with a poor clinical grade or coexisting cardiopulmonary complications.⁹²

After initial volume resuscitation, we suggest a hematocrit of approximately 30% to 33% as optimal in the acute postoperative period in patients in the neuro-ICU. Although debate still exists, available evidence suggests that restrictive blood transfusion strategies may be less appropriate in neurointensive care.⁹³⁻⁹⁷ However, a 2014 randomized clinical trial in TBI, which compared two hemoglobin transfusion thresholds (7 versus 10 g/dL), found no difference between groups in neurologic outcomes but a higher incidence of adverse events in the group managed at the higher hemoglobin level.⁹⁸ Most likely, treatment should be individualized, aiming at optimal oxygen delivery to the brain for those patients who need it most. After intracranial or spinal cord procedures, we would advocate a more liberal use of blood transfusions than generally recommended in intensive care medicine, aiming for a hemoglobin of at least 5.5 to 6.0 mmol/L (approximately 9.0-9.5 g/dL) in order to promote adequate oxygenation of the CNS.

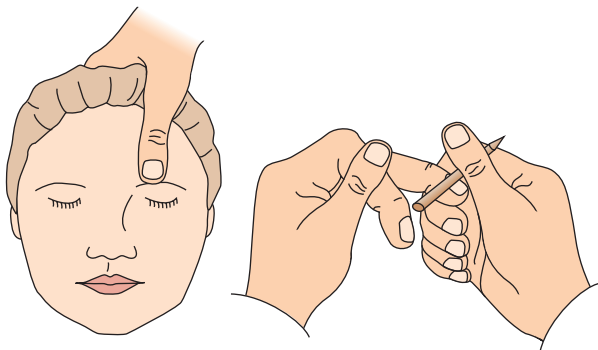


FIGURE 59-1 ■ Supraorbital and nail bed pressure for assessment according to the Glasgow Coma Scale.

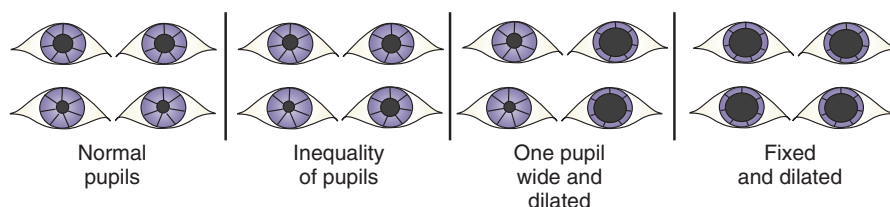


FIGURE 59-2 ■ Pupillary reactivity and size.

This corresponds to the recommendations proposed by Goodnough et al.⁹⁹ in cases of ischemia.

Cardiogenic shock due to primary loss of cardiac function is uncommon in neurosurgical patients, but it may occur, especially in elderly patients with secondary cardiac ischemia or arrhythmias or patients with takotsubo syndrome. These patients may require sequential echocardiographic follow-up and/or cardiac output monitoring to optimize volume status and cardiac output.

Large pulmonary emboli, sepsis, or spinal paraplegia should be considered in patients with systemic hypotension. In patients with spinal distributive shock, typically the hypotension is associated with bradycardia, with a heart rate in the range of 35 to 50 bpm. These patients should not be managed with excessive volume resuscitation but rather with vasopressors to restore alpha-adrenergic peripheral vasomotor tone. The combination of hypertension and bradycardia (Cushing response) should alert the physician to the potential of an expanding intracranial lesion and risk of brainstem herniation. In this situation, the use of antihypertensive agents is contraindicated, and therapy should be aimed at the raised ICP.

Temperature monitoring is important in the neuro-ICU, since hyperthermia can depress neurologic function to the point of obtundation or coma. Conversely, fever, by increasing metabolic requirements, may exacerbate secondary injury. Mean energy expenditure may be increased up to 200% in patients following brain injury,¹⁰⁰ and it would, therefore, appear appropriate to not risk increasing metabolic requirements even further. Thus, we recommend that core temperature should be kept below 38.0°C, using medications (e.g., acetaminophen, diclofenac) and external or intravascular cooling.

Hypothermia may be due to adrenal or pituitary insufficiency, hypothalamic disorders, hypoglycemia, or intraoperative exposure. Deliberate hypothermia is sometimes used in complicated cerebrovascular procedures and as third-tier therapy in patients with TBI to reduce ICP. For TBI, hypothermia has been shown to effectively reduce ICP, but conflicting results have been reported regarding its clinical benefits.^{101,102} The recent Eurotherm trial, in which patients with raised ICP were randomized to hypothermia or other second-tier therapies, was halted prematurely after enrollment of 387 patients because of safety concerns. In the final analysis, outcomes were statistically significantly poorer in patients treated with hypothermia.¹⁰² One difference between Eurotherm and other randomized controlled trials examining hypothermia for TBI is that Eurotherm was conducted in a large number of countries and centers (47 centers across the world). Even if hypothermia may produce some benefit in high-level research centers, the results of Eurotherm have unequivocally demonstrated that it is harmful in broader settings.¹⁰²

Various approaches to cooling have been adopted, but the most frequently used employ surface cooling or gastric lavage with cold fluids. Marion¹⁰³ reported favorable results with the use of devices for intravascular cooling, and this technique can be expected to become standard for induction of hypothermia in the near future.

Hypothermia has been associated with several complications, including cardiovascular instability (mainly arrhythmias), coagulopathy, electrolyte shifts, fluid overload, and increased risk of infection and shivering.^{104,105} The management of a patient treated with hypothermia over longer periods of time for control of raised ICP can be much more complex than the use of short-term hypothermia after cardiac arrest. Ideally, normothermia could represent the best trade-off between the dangers of hyperthermia and the complexities and side effects of hypothermia. In practice, a trial in neurointensive care comparing conventional treatments to hyperthermia with prophylactic normothermia, induced and maintained with intravascular cooling systems, has failed to show benefit.¹⁰⁶ (See annotated references for further details.)

Biochemical Parameters: Electrolytes, Osmolarity, and Blood Glucose

The major focuses in neurointensive care are to prevent and limit brain damage and to provide the best conditions for natural brain recovery

from surgery or injury by ensuring optimal oxygenation, perfusion, ionic homeostasis, glycemic control, and temperature management. Keeping biochemical parameters within their physiologic range is desirable but challenging. Repeated determinations are necessary for early detection of derangements and to prevent overcorrection. Patients with comorbidities (e.g., diabetes, cardiac failure) and concomitant medications are especially at risk.

Electrolytes and Osmolarity

A direct link exists between plasma osmolarity and water flux into and out of brain cells.^{107,108} If the blood-brain barrier is intact, any decrease in plasma osmolarity will cause an increase of intracellular water within the brain, potentially leading to an increased ICP, altered transmembrane potentials, and other changes.¹⁰⁹ It is, hence, important to prevent the development of hyponatremia, as this may exacerbate the development of brain edema in the postoperative setting. Particularly in pediatric patients undergoing external CSF drainage, replacement of drained CSF by physiologic saline is recommended.

Various factors may contribute to the high risk of electrolyte disorders in neurointensive care:

- Use of osmotically active drugs (e.g., mannitol, hypertonic saline [HTS], or other diuretics) for the treatment of raised ICP. These may induce electrolyte derangements or increase serum osmolarity to levels that compromise kidney function. Careful and frequent monitoring is, therefore, required. The general recommendation is that serum osmolarity should be kept below 320 mOsm/L. When using hypertonic saline, serum sodium should be kept below 160 mmol/L.
- Common use of steroids in brain surgery to prevent cerebral edema. These may increase blood glucose to levels that exceed the maximum renal capability for glucose transport. If glycosuria follows, it causes osmotic diuresis.
- Reduced release of antidiuretic hormone (ADH) secondary to surgery or injury impacting neurohypophyseal function, which leads to sudden episodes of diabetes insipidus.¹¹⁰ In addition to administering exogenous ADH, large urinary volumes have to be replaced with appropriate solutions to preserve euvolemia and normal serum osmolarity.
- Cerebral salt wasting. This disorder is still poorly understood¹¹¹ and is often difficult to differentiate from inappropriate ADH syndrome. Fluid restriction for correction should generally be avoided; it is often better to administer hypertonic saline.

Glucose

Glucose is an essential substrate for brain metabolism, and every effort should be made to ensure adequate glucose delivery to the nervous tissue. In general intensive care, tight glycemic control has been advocated based on the knowledge that outcomes are poorer in the presence of hyperglycemia and following the results of the study by van den Bergh et al.¹¹² showing reduced mortality of surgical intensive care patients by keeping glycemia within narrow limits (80–110 mg/dL). These findings have, however, been challenged in subsequent studies.¹¹³

Although various studies in neurointensive care patients have demonstrated an association between elevated glucose levels and poorer outcome,^{114–117} the question remains whether this association is causal or not. In neurointensive care, the particular concern is that the injured brain cannot tolerate hypoglycemia, which might occur as an adverse event from overly enthusiastic glycemic control. There is a strict relationship between increased use of insulin (for tight glycemic control) and the occurrence of hypoglycemia.^{118,119} Moreover, lowering blood glucose to “normal” levels may result in unacceptably low levels of glucose in the brain, depriving the most complex organ in the human body of its most essential metabolic substrate. Evidence for this concern has been shown using microdialysis.^{120–122}

These observations illustrate the complex interactions between systemic and cerebral parameters and highlight that correction of

biochemical parameters in the blood may not always be good for the brain, particularly when recovering from surgery or injury. The currently available evidence does not support the use of tight glucose control in the neuro-ICU.

BRAIN MONITORING AND SPECIFIC THERAPEUTIC APPROACHES

In comparison to the setting of cardiac intensive care, the possibilities for brain monitoring are limited.¹²³ In cardiac care, routinely measured parameters include a multitude of pressure indices and a number of different serum markers (e.g., creatine kinase fractions, troponin) to determine whether the heart is at risk for further injury. Physiologically, the heart is monitored by electrocardiography and intermittent echocardiography. In contrast, routine brain monitoring is restricted in most centers to ICP and CPP monitoring. The field is, however, rapidly evolving. Monitoring of cerebral oxygenation is now being increasingly implemented into practice,¹²⁴⁻¹²⁶ and continuous electroencephalography (EEG) is performed in some centers.¹²⁷⁻¹²⁹ MRI spectroscopy offers opportunities to noninvasively assess brain metabolism.^{130,131} Advances in the field of biomarkers offer hope that detection and tracking of pathophysiologic processes in the brain may be within reach.¹³²⁻¹³⁵ Different markers are relevant to different stages after injury. In the acute and subacute phases, cellular degradation products and markers of inflammatory responses have potential usefulness, while in the chronic phase, markers of neurodegeneration are being explored for in vivo detection of degenerative disorders linked to brain injury, such as chronic traumatic encephalopathy and Alzheimer's disease. In patients with severe TBI, increased levels of S-100B and neuron-specific enolase have been shown to be correlated with increased ICP, decreased CPP, and more structural damage visualized on CT scanning.¹³⁶ A clear association between increased levels of glial fibrillar acidic protein and ubiquitin C-terminal hydroxylase L1 (glial and neuronal markers) and poorer outcome has been confirmed.¹³⁷

Current approaches to brain-specific monitoring include measurements of ICP, cerebral oxygenation, and cerebral blood flow (CBF), as well as electrical monitoring and metabolic monitoring. These specific modalities are discussed in detail in Chapter 47. Here, we focus on essential aspects of the interpretation of the monitoring results and their therapeutic implications.

Intracranial Pressure and Cerebral Perfusion Pressure

ICP monitoring is most commonly performed in trauma patients. It is indicated in patients with a severe brain injury (GCS < 8) with abnormalities on the initial CT scan and in patients with a normal admission CT scan if two or more of the following features are present: age more than 40 years, unilateral or bilateral motor posturing, or systolic BP below 90 mm Hg.

Routine ICP monitoring is generally not indicated in patients with mild or moderate TBI, but it may be considered when other severe extracranial injuries are present, necessitating anesthesia for surgery, or when the initial CT shows traumatic lesions with space-occupying effects.¹³⁸ ICP monitoring is further indicated in poor-grade patients with SAH.¹³⁹⁻¹⁴¹ Further, it may be considered in patients with other intracranial disorders who are sedated and ventilated and who are considered to be at risk of developing raised ICP (e.g., postoperative swelling, stroke, Reye's syndrome). The value of ICP monitoring has been questioned by some since publication of the BEST-TRIP trial that showed no difference in outcome between patients with TBI treated according to ICP monitoring versus those in whom "ICP-targeted" therapy was based on clinical observation and CT scanning.¹⁴² ICP monitoring, however, contributes to a better characterization of the pathophysiology and, thus, facilitates precise treatment approaches. Recommendations regarding the indications for and techniques of ICP monitoring in various disease states were recently summarized.¹⁴³

ICP monitoring carries a 0.5% risk of hemorrhage and a 2% risk of infection.¹⁴⁴ Intracranial hemorrhages are a rare complication of ICP monitoring and are usually caused by multiple punctures in the presence of a coagulopathy. The risk of infection is higher for ventricular monitoring, and the rate of infection is proportional to the duration of monitoring.¹⁴⁵ Intraventricular catheters are preferable because they are accurate, can be recalibrated, and allow drainage of CSF. Intracranial probes are user-friendly and accurate. Less accurate data are provided by subdural catheters,¹⁴⁶ and epidural probes are unreliable.^{147,148} The accuracy of ICP monitoring can be enhanced by use of computer-supported systems.¹⁴⁹ Attempts to monitor ICP noninvasively have been unsatisfactory.^{150,151}

Relatively few data exist regarding routine ICP monitoring in the postoperative period. In a series of 30 patients after severe TBI and elective craniectomy, 156 instances of ICP increases and/or CPP decreases were recorded.¹⁵² These were accompanied by clinical deterioration in only 15 cases. Telemetric ICP control has been proposed for use after posterior fossa surgery.¹⁵³ In a series of 514 patients after supra- and infratentorial surgery, Constantini et al.¹⁵⁴ described raised ICP in 13% and 18% of cases, respectively. Neurologic deterioration occurred in about half of the patients with an ICP rise, and deterioration was always preceded by the ICP increase. In a series of 780 patients submitted to routine ICP monitoring after intracranial surgery, 47% required ICP-directed therapy.¹⁵⁵ In a report involving 850 cases, Bullock et al.¹⁵⁶ concluded that ICP monitoring allows earlier identification of recurrent hematomas. These data would support more routine use of ICP monitoring after intracranial surgery, particularly in more complex cases. In some institutions, ICP is routinely measured as part of postoperative surveillance after major neurosurgical procedures, especially when there is the risk of postoperative bleeding. Figure 59-3 illustrates a case in which a substantial ICP rise was detected in the first postoperative hours. It was caused by an enlarging hemorrhage that required reintervention.

Normal values for ICP are up to 15 mm Hg in adults. Consensus exists that ICP should preferably be maintained below 20 mm Hg. The absolute value of ICP measured should, however, never be considered in isolation. More important is the trend over time and the relationship to the arterial BP. CPP is calculated as:

$$CPP = MABP - ICP$$

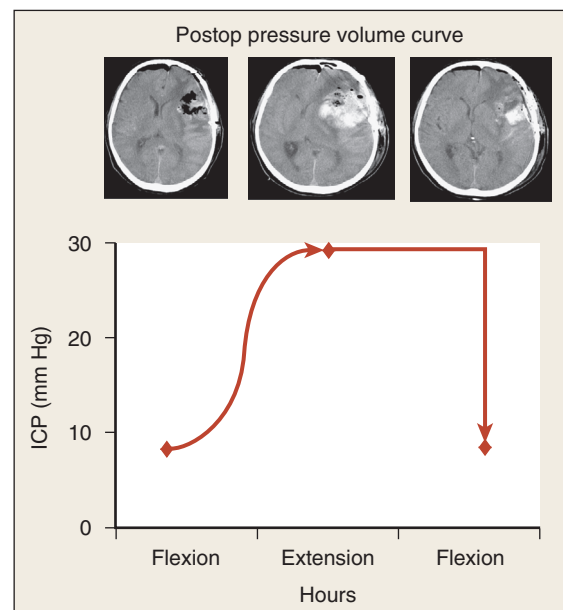


FIGURE 59-3 ■ Raised intracranial pressure (ICP) as the first indication of a developing postoperative hematoma.

BOX 59-1**Remediable Extracranial Causes of Intracranial Hypertension**

Calibration errors
 Airway obstruction (kinked endotracheal tube, tongue, sputum retention, pneumothorax)
 Hypoxia (low inspired oxygen concentration, lung disease or collapse)
 Hypercapnia (hypoventilation)
 Hypertension (pain, sedation, coughing or straining)
 Hypotension (hypovolemia, sedation, cardiac)
 Posture (Trendelenburg position, neck rotation)
 Hyperpyrexia
 Seizures
 Hypoosmolality (low sodium, protein)

Physiologic and nonphysiologic ICP waveforms may occur. Technical artifacts and systemic causes should be excluded before specific diagnostic procedures are instituted or ICP-directed therapy initiated or intensified (Box 59-1).

In some patients, the normal pressure autoregulatory mechanisms are disturbed, and the risk exists that increasing the CPP may worsen cerebral edema. Careful observation of the change in ICP with respect to arterial BP changes is required to determine whether autoregulation is disturbed or intact. For continuous evaluation of the autoregulatory status, it has been proposed that the pressure reactivity index (PRx) be calculated, as a moving correlation coefficient between MABP and ICP.¹⁵⁷⁻¹⁵⁹ PRx is easy to monitor because it is available as long as an ICP probe and arterial line are in place. Continuous monitoring with PRx can be used to provide individual thresholds in CPP-oriented management of trauma patients in the ICU, by revealing the optimal CPP for pressure reactivity.¹⁶⁰ Use of autoregulation monitoring offers a promising perspective for better characterization of pathomechanisms, but confirmation of the anticipated benefits of optimal CPP-directed management is required.

Treatment of Cerebral Herniation and Elevated Intracranial Pressure

The development of cerebral herniation (tentorial herniation or cerebellar tonsillar herniation) constitutes a neurosurgical emergency. Rapid intervention is required prior to further investigations to determine the cause. According to the concept of the pressure-volume curve (Fig. 59-4), a small reduction in intracranial volume will significantly decrease a raised ICP and may reverse herniation. The emergency measures to be taken include:

- Ventricular CSF drainage (if access is available)*
 - Bolus administration of high-dose hyperosmolar agents (mannitol 1-1.5 g/kg body weight; HTS: 7.5% saline 1-2 mL/kg body weight, infused over 5 min)
 - Rapid-sequence intubation and moderate hyperventilation
- Following these emergency procedures, an emergency head CT scan should be performed to detect the cause of the raised ICP and permit targeted treatment, such as evacuation of a postoperative clot or further treatment of acute obstructive hydrocephalus.
- The main intracranial causes of raised ICP are:
- Mass lesions (e.g., hematoma)
 - Edema (vasogenic, cytotoxic, osmotic, or hydrostatic)
 - Increased cerebral blood volume (e.g., vasodilation)
 - Disturbance of CSF flow (e.g., hydrocephalus, benign intracranial hypertension)

In the absence of acute cerebral herniation, elevated ICP is addressed first by ruling out treatable intracranial mass lesions and remediable extracranial causes or to monitor malfunction (see Box 59-1).

*Lumbar CSF drainage should never be attempted in this situation, as it may exacerbate the herniation.

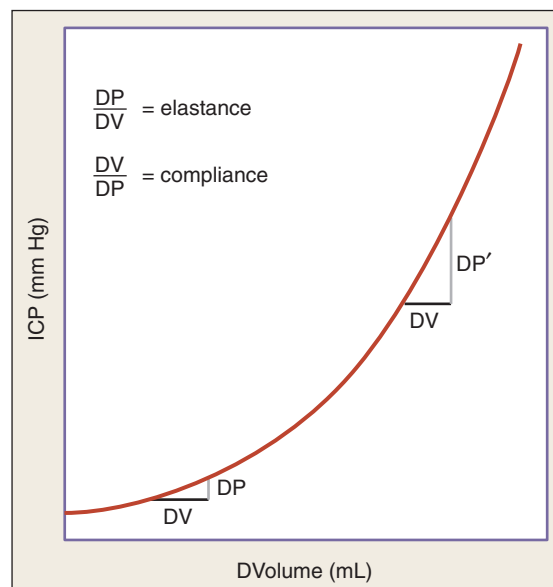


FIGURE 59-4 ■ Intracranial pressure (ICP)-volume curve.

When appropriate, surgical intervention is indicated. Conservative therapy of elevated ICP includes these first- and second-tier approaches:

- Sedation, analgesia, and mild to moderate hyperventilation (arterial carbon dioxide partial pressure [PaCO_2]: 4-4.5 kPa [30-35 mm Hg])
- Osmotic therapy: preferably mannitol given as a bolus infusion (dose: 0.25-0.5 g/kg body weight or as indicated by monitoring). Alternatively, HTS may be considered. Effective bolus doses range between 1 and 2 mL/kg of 7.5% saline. Effective continuous infusion doses range between 75 and 150 mL/hour of 3% saline. Although comparing the effectiveness of mannitol versus HTS is often confounded by the wide variability in concentrations and doses used for HTS, a recent study reported that HTS given as bolus therapy was more effective than mannitol in lowering the cumulative and daily burden of ICP in patients with TBI.¹⁶¹ Table 59-6 presents an overview of the osmolality and electrolyte concentrations of different commercially available hypertonic solutions used for treating raised ICP. Serum osmolality should be maintained below 320 mOsm/L and serum sodium below 160 mmol/L if possible. Particular vigilance is warranted when mannitol and HTS are given concomitantly. If osmotherapy has insufficient effect, furosemide can be given additionally.
- CSF drainage
- Volume expansion and inotropes or vasopressors when arterial BP is insufficient to maintain CPP and CBF in a normovolemic patient
- If these methods fail, third-tier therapies for raised ICP include:
 1. Mild or moderate hypothermia
 2. Decompressive surgery
 3. Administration of barbiturates
 4. More intensive hyperventilation (which should be accompanied by monitoring cerebral oxygenation to detect cerebral ischemia)

Cerebral Blood Flow

The past decade had witnessed great advances in approaches to monitor CBF and CBF-related variables, particularly from the field of neuroimaging. Both CT and MRI techniques have been developed for perfusion imaging and angiography. Thus, possibilities for determination of areas of the brain at risk for ischemia are now routinely available to the clinician. These approaches have replaced measurements of CBF with stable xenon CT scanning. Positron emission tomographic studies for CBF and metabolic studies of the brain have largely remained in the domain

TABLE 59-6

Composition of Different Commercially Available Hypertonic Solutions Used for Treatment of Raised Intracranial Pressure Compared to Isotonic Solutions (*)

| DRUG | OSMOLARITY (mOsm/L) | SODIUM (mmol/L) | CHLORIDE (mmol/L) | COLLOID |
|-------------------------|---------------------|-----------------|-------------------|---------|
| Ringer's lactate (*) | 277 | 130 | 112 | — |
| 0.9% NaCl (*) | 309 | 154 | 154 | — |
| 1.7% NaCl | 598 | 268 | 268 | — |
| 3% NaCl | 1030 | 515 | 515 | — |
| 5.85% NaCl | 2000 | 1000 | 1000 | — |
| 20% NaCl | 6800 | 3400 | 3400 | — |
| 23.8% NaCl | 8200 | 4100 | 4100 | — |
| 7.5% NaCl/6% dextran 70 | 2567 | 1283 | 1283 | Dextran |
| 7.2% NaCl/6% HES 200 | 2264 | 1132 | 1132 | HES |
| 20% Mannitol | 1098 | — | — | — |
| 40% Sorbitol | 2200 | — | — | — |
| 10% Glycerol | 1379 | 77 | 77 | — |

HES, hetastarch; NaCl, sodium chloride.

of research. Thermal diffusion flowmetry has been introduced as a bedside technique to continuously monitor CBF, but experience with this method is limited.^{146,162,163} A major drawback of this sensor is that it is not MRI compatible. Transcranial Doppler (TCD) provides a noninvasive assessment of blood flow velocity through the basal cerebral arteries. TCD is widely used to detect and track cerebral vasospasm,¹⁶⁴ but various studies have shown a disappointing correlation when measured flow velocities are compared with measurements of CBF.^{165,166} In patients with stroke, detection of emboli is possible with most current TCD devices.¹⁶⁷

Vasopressors may be needed in the postoperative care of patients in the neuro-ICU. They are often required to treat SAH and severe TBI (see Chapters 50 and 53). It is important, however, to realize that the pathophysiologic mechanisms in the two diseases differ, and that commonly employed approaches for treatment of DID following aneurysmal SAH cannot be directly translated to TBI.

In analogy to the laws of electricity, in which current (I) is dependent on voltage (V) and resistance (R) according to the formula $I = V/R$, CBF is dependent on the driving pressure (CPP) and cerebrovascular resistance (CVR):

$$CBF = CPP/CVR$$

With reference to the Hagen-Poiseuille equation, CVR is determined by the radius and length of the blood vessel and the viscosity of the blood according to the formula:

$$\frac{8 \eta l}{k \pi r^4}$$

where k = a constant, r = radius of the blood vessel, l = length of the blood vessel (which is essentially constant), and η = dynamic blood viscosity. The most powerful factor in this equation is the vessel radius.

The concept behind HHH and CPP therapy is that if CVR is increased, a high driving pressure is required to overcome the increased resistance. After SAH, multiple mechanisms, including cortical spreading ischemia, may contribute to delayed ischemia. Even if vasospasm is not the only cause of reduced brain perfusion, however, it may cause substantial CBF reduction. To maintain cerebral perfusion, a considerable elevation of CPP is required. By contrast, in patients with TBI, the major basal cerebral arteries are not clearly constricted in the acute phase, and it is still uncertain whether the observed reductions of CBF in the acute phase after injury are caused by vasoconstriction within the microcirculation or are secondary to decreased metabolic requirements, possibly due to mitochondrial dysfunction. Furthermore, after TBI, the normal pressure autoregulatory mechanisms may be disturbed, and the risk exists that increased CPP may worsen cerebral edema.

TABLE 59-7

Vasopressors Commonly Used in the Neurocritical Care Unit

| AGENT | ADRENERGIC EFFECT | DOSES ($\mu\text{g/kg/min}$) IN ADULTS |
|----------------|--|--|
| Norepinephrine | Mixed α and β ($\alpha \gg \beta$) | 0.02-1.5 |
| Phenylephrine | Pure α | 0.1-9.0 |
| Adrenaline | Mixed α and β ($\alpha > \beta$) | 0.1-1.0 |

The use of dopamine, a precursor of norepinephrine, has been mainly abandoned because of interference with hormone secretion.

The vasopressors most frequently used in the care of the postoperative neurosurgical patient are listed in Table 59-7. Dose ranges are provided, but it is generally recommended that the required dose be titrated to achieve the desired BP or CPP.

Cerebral Oxygenation and Metabolism

Three approaches to the monitoring of cerebral oxygenation are available to the clinician. These include jugular bulb oximetry (measuring jugular venous oxygen saturation [SjVO_2]), noninvasive cerebral oximetry (i.e., near-infrared spectroscopy [NIRS] determination of regional venous oxygen saturation [Somanetics] or tissue index of oxygenation [Hamamatsu]), and cerebral parenchymal oxygen monitors (measuring brain tissue oxygen tension [PbO_2] [LICOX; Raumedic]).

Global cerebral oxygenation may be assessed using jugular venous oximetry, which is discussed in Chapter 47. When hemoglobin concentration and arterial hemoglobin oxygen saturation remain constant, the arteriojugular difference in oxygen content may be estimated by simply recording the SjVO_2 . A decrease in SjVO_2 indicates that the brain is extracting more oxygen, suggesting that the oxygen supply is not adequate for metabolic demands. Values below 55% indicate increased oxygen extraction relative to perfusion and suggest the presence of ischemia.^{165,168,169}

Interpretation of the results of jugular venous oximetry requires that both systemic information (hemoglobin concentration and arterial oxygen saturation), as well as intracranial data (CPP), be combined. The technique has several limitations. First, continuous monitoring of SjVO_2 with fiberoptic devices is prone to artifact, and second, under conditions of anemia or arteriovenous shunting, hypoxia may be present at the tissue level despite normal values of SjVO_2 .¹⁷⁰ Moreover,

SjVO₂ is a measure of global cerebral oxygenation and does not reflect disturbances due to focal lesions, thus potentially failing to detect ischemia in relevant portions of brain tissue.¹⁷¹

NIRS is a noninvasive technique that permits estimation of oxyhemoglobin, deoxyhemoglobin, and oxidized cytochrome oxidase over the combined arterial, capillary, and venous compartments.¹⁷² Various assumptions are made in the algorithm for calculating cerebral oxygen saturation with NIRS, which may not always be valid, and uncertainty exists whether NIRS, as claimed, mainly measures the intracranial compartment or whether the recorded values are “contaminated” by the extracranial compartment.¹⁷³ The main clinical applications are in neonatology and coronary or carotid artery surgery.^{174,175} Recent intracranial surgery and subcutaneous swelling or wounds to the scalp, which are common in patients with TBI, preclude use of this technique. We, therefore, do not consider NIRS suitable for routine use in monitoring oxygenation in patients undergoing neurosurgical operations, but a noninvasive technique to assess cerebral oxygenation is attractive, and further clinical research is encouraged.

Monitoring Pbo₂ is possible by inserting an oxygen-sensitive electrode into the cerebral cortex or white matter. By definition, this represents a regional technique, and there is still considerable debate whether it should be employed in relatively undamaged parts of the brain (and thus represent more global oxygenation and metabolism) or whether it should be preferably used in the penumbra zone of lesions, with the aim being to limit secondary damage in potentially viable regions. Pbo₂ indicates the balance between oxygen delivered to the tissue and oxygen consumption in a specific area, and Pbo₂ can indicate regional hypoxia if it falls below 15 to 20 mm Hg.^{176,177} The diameter of microvascular vessels and diffusion barriers might also influence recorded values.^{178,179} In TBI, low values of Pbo₂ occur in over 50% of patients during the first 24 hours, and the depth and duration are related to outcome. Increased hyperventilation has been shown to further reduce Pbo₂.^{171,178} Experimental and clinical evidence suggests that CPP therapy may be targeted toward appropriate levels, based on the results of Pbo₂ monitoring.¹⁸⁰ Nonrandomized studies have indicated benefit of a Pbo₂-targeted protocol.¹⁸¹⁻¹⁸³

Microdialysis

The technique of microdialysis involves catheter insertion into the cerebral parenchyma to enable continuous sampling of extracellular cerebral fluid. It allows for the measurement of metabolites (glucose, lactate, and pyruvate) and amino acids (glutamate), as well as indicators of cerebral damage (glycerol or proteins, such as tau or beta-amyloid), in the extracellular fluid of the brain.¹⁸⁴⁻¹⁸⁷ Dialysate fluid obtained after infusing saline through a semipermeable membrane reflects the composition of the extracellular fluid around the probe. Microdialysis is employed in various specialized neuro-ICUs, mainly for research purposes. Technical and logistic considerations, as well as delays in obtaining real-time values, have hindered routine application of the results toward individualized targeted treatment. The availability of microdialysis catheters with a high cut-off membrane now permits detection of larger molecules and may offer opportunities for tracking the inflammatory response.¹⁸⁸⁻¹⁹³

Electrical Monitoring

Continuous EEG (cEEG) monitoring has the potential for detecting nonconvulsive status epilepticus in ICU patients. As a primary monitor of brain function, cEEG can be used to titrate continuous infusions of sedatives, and the technique can further alert physicians to the development of focal or global ischemia.^{194,195} The sensitivity for detecting ischemia and hypoxia is high, but the specificity is low because of the effects of sedatives. cEEG may permit detection and treatment of these adverse events at an early stage, with a potentially positive effect on outcome.¹⁹⁶ Electroencephalographic bispectral analysis may also be useful in assessing the level of sedation in neurocritical care patients.¹⁹⁷

In the research setting, interest exists in monitoring cortical spreading depression. Traumatically damaged neurons decrease their firing

BOX 59-2 Main Approaches in Neuroprotection

- Strategies aimed at improving metabolism and microenvironment
- Examples: hypothermia, mannitol
- Agents acting on specific mechanisms
- Examples: anti-inflammatory agents, apoptosis inhibitors, calcium channel antagonists, neurotransmitter-targeted agents, free radical scavengers, inhibitors of lipid peroxidation
- Pluripotent agents affecting various mechanisms (so-called dirty drugs)
- Combination therapies (including sequential administration)
- Strategies promoting cell survival and regeneration (cellular replacement, gene therapy, and neurotrophic factors)

rates substantially in the early post injury period. Waves of depolarization result in ionic flux and loss of resting membrane potential, which worsens neurochemical dysregulation and places extra metabolic demands on damaged tissues.¹⁹⁷⁻²⁰¹ Measurement of evoked potentials,²⁰² assessing the integrity of sensory and motor pathways, may provide diagnostic and prognostic information, but because of the complexity of this technique, it is not recommended for general use.

NEUROPROTECTION

The original concept of neuroprotection depended upon the initiation of treatment before the onset of an event leading to brain damage, and the methods employed aimed to minimize the intensity of an insult or its immediate effects upon the brain.

Over the past decades, the concept of neuroprotection has been extended to include treatment started after the onset of an insult, reflecting our increased understanding of progressive pathophysiologic mechanisms causing and/or enhancing secondary brain damage. In neuroprotection, four main approaches can be discerned (Box 59-2).

Strategies Aimed at Improving Metabolism and Microenvironment

Methods for improving metabolism and the microenvironment include hypothermia to minimize the effects of energy failure and hyperosmolar therapy to reduce ICP and improve CBF. Hypothermia decreases CBF by about 5.2% per degree reduction in body temperature. The cerebral metabolic rate for oxygen (CMRO₂) and arterial-venous oxygen difference (AVDO₂) fall after the institution of moderate hypothermia. This reflects a reduction in energy requirements and, hence, less energy loss in the injured brain. Many other effects of hypothermia, such as stabilization of cell membranes²⁰³ and reduction of neurotransmitter turnover, may also contribute to the benefits seen in models of ischemia.²⁰⁴ Consequently, hypothermia is currently seen more as a neuroprotective approach than as a metabolic depressant. The use of hypothermia is, however, not without risks and requires high-level neurointensive care.

Hyperosmolar therapy is widely used in neurosurgery to treat raised ICP, decrease brain bulk during intracranial operations, and treat cerebral ischemia. Hypertonic fluids are considered to exert beneficial effects by two mechanisms:

1. Immediate plasma-expanding effect, reducing the hematocrit and blood viscosity and consequently increasing CBF and cerebral oxygen delivery
2. Osmotic effect, which is delayed for 15 to 30 min, while gradients are established between the plasma and cells. Hypertonic solutions may be given in acute emergency situations, such as cerebral herniation, or as part of a conservative approach to treat raised ICP.

Agents Acting on Specific Mechanisms

An increased understanding of the existence of progressive pathophysiologic mechanisms causing or enhancing secondary brain damage has led to the development of a large range of specifically targeted, neuroprotective agents aimed at ameliorating these mechanisms.²⁰⁵

Although marked beneficial effects have often been shown in experimental studies, these promising results have unfortunately not translated into clinical efficacy. In addition to the heterogeneity of patient populations, the lack of clinical parameters to identify mechanistic targets has contributed to these failures. The emerging field of biomarkers and advanced neuroimaging offer hope for the future.

Pluripotent Agents and Combination Therapies

The realization that various pathophysiologic mechanisms are frequently concurrently or sequentially active has increased interest in the use of agents with multiple mechanisms; for such agents, the term *dirty drugs* has been coined.²⁰⁶ Corticosteroids, barbiturates, and magnesium are examples of pluripotent neuroprotective agents. Despite their efficacy in treating vasogenic edema encountered in brain tumors, corticosteroids are not efficacious in improving cytotoxic edema seen after TBI or SAH. Various studies support a neuroprotective effect of magnesium in patients with SAH.^{207,208} A 2010 randomized, controlled trial, however, could not confirm benefit.²⁰⁹ In TBI, greater mortality and poorer outcomes were found in a randomized clinical trial investigating the efficacy of magnesium.²¹⁰ Erythropoietin, cyclosporine, and progesterone are agents with neuroprotective potential that have

recently undergone clinical investigations or are still under study. In 2014, two large phase III trials of progesterone use in TBI failed to show benefit.^{211,212} Rather than seeking the “silver bullet” of one agent targeting multiple mechanisms, it may be better to consider combining agents with complementary targets and effects.²¹³ Fundamental to any neuroprotective strategy would be the correct detection and tracking of pathophysiologic processes occurring in individual patients, which would provide better evidence for combining or sequential administration of neuroprotective agents.²⁰⁵

Strategies Promoting Cell Survival and Regeneration

Strategies to promote cell survival and regeneration include cellular replacement, gene therapy, and administration of trophic factors. These are aimed at promoting regeneration and neuroplasticity and may ultimately improve functional recovery.^{214,215} The potential of these novel approaches is strengthened by promising experimental and clinical results obtained in neurodegenerative diseases, including Parkinson disease, Huntington disease, and strokes.²¹⁵⁻²¹⁸ This approach is the focus of large research efforts, which will provide possibilities to further improve long-term outcome.

KEY POINTS

1. Successful care for the neurosurgical patient requires excellent collaboration among the anesthetist, neurosurgeon, and intensivist. The results of a technically perfect operation can be ruined by inadequate postoperative care, and a complex operative procedure requires expert intensive care to correct abnormalities in homeostatic mechanisms, ensure adequate cerebral perfusion and oxygenation, and promote recovery of brain function.
2. Specific care and monitoring of the postoperative neurosurgical patient require accurate knowledge of the preoperative situation and the intraoperative procedure, including the surgery, anesthesia, and any surgical complications or difficulties.
3. The principal goal of postoperative neurosurgical intensive care is early detection and treatment of postoperative complications. The second goal is to prevent second insults, which may initiate

or exacerbate secondary damage in a vulnerable central nervous system.

4. The goal of cardiovascular and respiratory monitoring is to ensure adequate hemodynamic and respiratory function, which is essential for optimization of cerebral oxygenation. The driving force here should be formed by cerebral parameters, rather than simply keeping systemic parameters within normal ranges. Invasive arterial BP monitoring is recommended with the reference point set at the same level as the intracranial pressure measurement to allow accurate calculation of the cerebral perfusion pressure.
5. The development of cerebral herniation (tentorial herniation or cerebellar tonsillar herniation) constitutes a neurosurgical emergency. Rapid intervention is required prior to further investigations to determine the cause.

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available evidence in the field of SAH, acute ischemic stroke, and TBI is reviewed. Both severe anemia and red blood cell transfusion are associated with poor clinical outcomes in neurocritical care patients. Transfusion may improve cerebral oxygenation and brain microcirculation but has not been shown to improve clinical outcomes. However, higher hemoglobin levels result in improved clinical outcomes. Parameters for cerebral oxygenation have potential as transfusion triggers in the near future.

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In this chapter we outline the epidemiology, presentation, course, and management of key disorders in pediatric neurointensive care. Critically ill infants and children with a compromised central nervous system (CNS) are complex patients and are often highly vulnerable to secondary brain injury. Minimizing physiologic derangements and optimizing therapy are essential from the scene of trauma through the pediatric intensive care unit (ICU). In most cases, transport to a specialized pediatric facility is desirable. Trained specialists in pediatric critical care medicine, pediatric neurologic surgery, and child neurology should deliver the ICU care to these infants and children, with appropriate pediatric ancillary support. The information provided in this chapter is germane to practitioners involved in stabilization, emergency treatment, and transport and to pediatric subspecialists at the tertiary care centers. Recommendations in the areas of trauma (head and spinal cord injury) are addressed in Chapter 56. Neurointensive care issues relevant to the field of neonatology are outside the scope of this chapter; specialized textbooks and reviews in this area should be sought for information in that field.

■ ISSUES UNIQUE TO PEDIATRICS

Two key factors contribute to the unique nature of the practice of pediatric neurointensive care: differences in the specific insults to the CNS in infants and children versus adults and age-related differences in the response to these insults.

Central Nervous System Insults in Infants and Children

Unlike in adults, atherosclerotic vascular disease resulting in stroke, intracerebral hemorrhage, and cardiopulmonary arrest plays little role in pediatric neurointensive care. For example, cardiopulmonary arrest in infants and children results primarily from asphyxia rather than myocardial infarction. Similarly, traumatic brain injury (TBI) in infants younger than 2 years of age is largely the result of abusive head trauma (shaken baby syndrome, child abuse). Unique issues in victims of child abuse, such as chronic injury or delay in presentation, contribute to important differences in diagnosis, treatment, and outcome. The specific CNS insults relevant to pediatric neurointensive care include TBI and spinal cord injury, cardiopulmonary arrest, status epilepticus, stroke, critical CNS infections, postoperative neurosurgical conditions, and several other less common disorders. (Traumatic brain and spinal cord injury are addressed in Chapters 56 and 57.)

Age-Related Differences in the Response to Central Nervous System Insults

Brain Water and Blood-Brain Barrier

Many biochemical, physiologic, and physical factors exhibit large fluctuations during brain development. Although the magnitude of these changes are most dramatic during prenatal development, they may contribute to age-related differences in response to critical CNS disorders.^{1,2} Large decreases in brain water content occur throughout postnatal development into adult life.³⁻⁵ These changes are global and correlate with the degree of myelination. The impact of these changes on edema formation after brain injury is unclear; however, the rapid

and diffuse cerebral swelling phenomenon described in many CNS insults in infants and children may be related to this high water content in the immature brain. This is suggested by studies showing that parenchymal injection of glutamate into the immature (but not adult) rat brain rapidly produces a large area of edema.⁶ The rapidity of development and the great magnitude of edema may result in part from rapid diffusion of glutamate and other mediators through the immature brain. In contrast to the changes in brain water during development, there is little contemporary evidence to support similar changes in blood-brain barrier permeability^{7,8} or enhanced vulnerability of the barrier to insults such as ischemia or trauma.⁹ Blood-brain barrier permeability after CNS insults has received little study in pediatric patients.

Cerebral Blood Flow and Energy Metabolism

Postnatal changes in cerebral blood flow (CBF) and energy metabolism have been reported in numerous mammalian species including humans.¹⁰⁻¹⁷ In all cases, CBF is quite low both before birth and during infancy, rapidly increases to a peak during childhood, and then decreases to a plateau with a gradual decline with increasing age during adulthood. In a study of 42 normal infants and children, cortical CBF in newborns was between 30 and 45 mL/100 g/min—lower than that reported in adults. In contrast, cortical flow in children between the ages of 5 and 6 years was between 50% and 85% higher than in adults. CBF decreased to adult values by about age 15 years (Fig. 60-1).^{18,19} Increased CBF in children (versus either adults or infants) corresponds to the period of maximal postnatal brain growth, specifically, maximal increases in the number of synapses.²⁰⁻²² Similarly, the cerebral metabolic rate for glucose is maximal in children between the ages of 3 and 9 years.¹⁵ The impact of these factors in CNS injury is poorly understood. Hyperemia has been implicated as an important facet of the pathophysiology of pediatric CNS injury. Because the level of CBF in the normal child is greater than in adults, the frequency of hyperemia in children is probably lower than has been suggested. Hyperemia in most gray matter structures in children between the ages of 3 and 10 years should probably be based on a flow value greater than about 70 mL/100 g/min^{17-19,22} rather than the value of about 45 mL/100 g/min suggested for adults.²³ Alterations in metabolic demands after injury must also be considered. Recent studies in both developmental brain injury models and children after cardiac arrest have demonstrated regional hyperemia.^{24,25} In children, the combination of hyperemia with a reduced apparent diffusion coefficient on MRI after cardiac arrest was associated with an unfavorable outcome.²⁵

Cerebral Perfusion Pressure

Cerebral perfusion pressure (CPP = mean arterial blood pressure – intracranial pressure [ICP]) is a critical determinant of CBF outside the limits of autoregulation or when autoregulation of blood pressure (BP) is disturbed. In adults, the normal limits of autoregulation are generally accepted to be between 60 and 150 mm Hg.^{26,27} Based on studies in normal immature animals, the lower limit for BP autoregulation of CBF is directly related to age.²⁸⁻³⁰ This is anticipated, since CPP is a function of arterial blood pressure, which is dependent on age. Few data are available on normal values for CPP in infants and children. A mean value of 37.5 ± 4.9 mm Hg (\pm SD) was reported in normal preterm infants.³¹ The lower limit of BP autoregulation was not

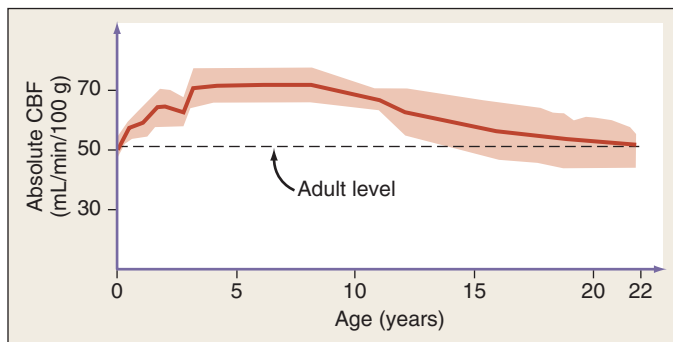


FIGURE 60-1 ■ Mean (curve) and ± 1 SD (pink area) for normal cerebral blood flow in 42 children from 2 days to 19 years of age, compared with adult values (dashed line). Compared with adult values, cerebral blood flow is lower in infancy, but thereafter values throughout childhood exceed those of adults. (From Chiron C, Raynaud C, Maziere B, et al. Changes in regional cerebral blood flow during brain maturation in children and adolescents. *J Nucl Med*. 1992;33:696-703. Reprinted by permission of the Society of Nuclear Medicine.)

determined. There are also limited data available on the lower limit of BP autoregulation of CBF in brain-injured infants and children. Vavilala et al.³² studied CBF autoregulation in 53 healthy infants and children. Surprisingly, the lower limit of autoregulation was between 50 and 60 mm Hg across the age groups of younger than 2 years, 2 to 5 years, 6 to 9 years, and 10 to 14 years. This suggests that there is less autoregulatory reserve (the difference between baseline MAP and the lower limit of autoregulation) in infants and young children than in older children or adults. It suggests that modest BP reductions in infants with severe TBI could compromise CBF. This may help explain the important deleterious effects of hypotension as a side effect in pediatric TBI.³³ It suggests that a lower limit for CPP in brain-injured infants and young children of ~50 mm Hg might be wise. Recent studies by Chambers et al.³⁴ and Allen et al.³⁵ in pediatric TBI suggest age-related targets. Chambers et al.³⁴ suggest values of 53, 63, and 66 mm Hg for children 2 to 6, 7 to 10, and 11 to 16 years of age, respectively. Allen et al.³⁵ suggest values of 40, 50, and 50-60 for children 0 to 5, 6 to 17, and >17 years of age, respectively. However, the impact on outcome of inducing mild hypertension in this setting remains to be studied.

Myelination

In humans, considerable myelination occurs during postnatal life.²¹ The impact of this process on the age-related response to pediatric CNS injury is not known but has been suggested by many to contribute to enhanced plasticity in the pediatric brain. White matter injury is common after CNS insults in children such as TBI.³⁶

Excitotoxicity

Increases in brain interstitial concentrations of excitatory amino acids such as glutamate are part of a fundamental response to CNS insults across all ages.³⁷⁻⁴² Excitotoxicity-mediated damage after brain injury is also suggested in clinical reports in children.^{37,40-42} There are important age-dependent facets of excitotoxicity. At several periods in development, large numbers of excitatory amino acid receptors are produced, and these periods correlate temporally with increased synaptic plasticity.^{38,39} Experimental data suggest that the immature brain is at great risk for excitotoxicity.^{38,39} Excitotoxicity may trigger neuronal death via multiple pathways (necrosis, apoptosis, necroptosis, and autophagy among others).⁴³ Extrasynaptic *N*-methyl *D*-aspartate receptors may be important.⁴³ Hypothermia may target this pathway in part, but an optimal pharmacologic agent remains elusive here.

Apoptosis

Experimental models and human data have made it increasingly clear that cells dying after CNS insults can be categorized on a morphologic continuum from necrosis to apoptosis.⁴⁴⁻⁴⁶ The importance of balanced apoptosis (or programmed cell death) in embryogenesis, as well as reports examining apoptosis in experimental TBI, suggest that there may be important age-related differences in the cell death cascades in response to traumatic or ischemic brain injury.⁴⁷ For example, neurons in developing animals appear to be more vulnerable to apoptosis than those in mature animals.^{44,47} Also, physiologic levels of excitatory amino acids are necessary for neuronal survival in the developing brain.⁴⁸ These data, including studies in primates,⁴⁹ raise concern about the ability of therapies such as barbiturates, ketamine, propofol, or inhibitors of excitatory amino acid receptors to actually induce neuronal death during development. What remains unclear, however, is if this enhanced apoptotic response is limited to prenatal development or if it is important during treatment of infants and children in the pediatric ICU. Nevertheless, an important role for apoptosis in pediatric brain injury is suggested by the fact that analysis of cerebrospinal fluid (CSF) in infants and children with severe TBI has provided some of the most compelling molecular data for the participation of these pathways in humans.² These data include participation of death effectors such as cytochrome-c and Fas receptor/ligand interactions and failure of antiapoptotic pathways in infants and children with poor outcome after severe brain injury.^{2,50-53} How these findings will influence our therapies remains to be determined, but they suggest that apoptotic neuronal death may represent a particularly important therapeutic target in pediatric neurointensive care.

Mitochondria Failure and Oxidative Stress

It is well known that the developing brain exhibits enhanced vulnerability to oxidative stress, in part related to deficiency of glutathione peroxidase.⁵⁴ Recent studies in developmental models of TBI and cerebral ischemia have demonstrated an important role of mitochondria in initiating the oxidative stress that is seen in these two insults.^{55,56} Mitochondrial targeting therapies may thus be important to develop for clinical trials,^{55,56} since clinical studies in TBI have confirmed a marked depletion of antioxidant defenses in infants and children.⁵⁷

Extracerebral Factors

Many extracerebral factors play a role in the age-related differences in the response to critical CNS disorders. Age-related differences in the response to hypoxemia-ischemia and hypotension are the prototype examples.

Hypotension and hypoxemia are the two most important secondary insults in patients with critical CNS disorders. Hypotension is the most important extracerebral factor associated with poor outcome after severe TBI.⁵⁸ This may contribute to the reported high mortality rate (62%) in this condition in children younger than age 4 years.⁵⁹ Nearly 50% of these children present with shock, versus only 30% of adults.⁵⁹ The limited blood volume of infants and young children make relatively small amounts of blood loss from scalp lacerations or other foci important. In contrast, the immature brain and cardiovascular systems are resistant to hypoxic-ischemic insults compared with mature individuals.⁶⁰ The duration of asphyxia resulting in cardiac arrest is inversely related to age.⁶¹⁻⁶⁴ Resistance to asphyxia-induced cardiac arrest in the immature individual, however, could have complex effects. For example, children may survive protracted episodes of hypoxemia and hypotension that would be lethal in adults. Resistance of the immature myocardium to asphyxia does not preclude the development of cerebral damage from hypoxemia, because between 25% and 56% of children who suffer asphyxia without cardiac arrest have poor neurologic outcomes.⁶⁵ This might also explain some of the severe pathology seen in infants after abusive head trauma, in which apnea, seizures, and agonal states occur.⁶⁶ Ichord et al.⁶⁷ showed that a hypoxic-ischemic injury pattern was commonly seen on diffusion-weighted magnetic resonance imaging (MRI) in victims of abusive head trauma. Similarly,

Berger et al.⁶⁸ showed that the serum biomarker profile of neuron-specific enolase in infants with abusive head trauma was more similar to that seen in children with asphyxia than TBI.

SPECIFIC DISEASES OR CONDITIONS

Cardiopulmonary Arrest

Cardiopulmonary arrest in adults is addressed in detail in Chapter 50. Although some of that chapter is germane to pediatric patients, the importance of asphyxia as the etiology in children mandates a separate discussion.

Epidemiology

The causes of cardiopulmonary arrest in childhood are heterogeneous. Causes of arrest in the prehospital setting include trauma, sudden infant death syndrome, poisoning, and respiratory distress secondary to drowning, choking, severe asthma, or pneumonia.⁶⁹ Traumatic arrest secondary to exsanguination, massive head injury, or airway compromise is the leading cause of death in childhood and young adulthood. Nontraumatic arrest typically occurs as a consequence of hypoxemia and hypercarbia, leading to respiratory arrest, bradycardia, and ultimately asystole or pulseless electrical activity.⁶⁹⁻⁷¹ Ventricular tachycardia or fibrillation occurs less commonly in children than adults, but it is not rare; 5% to 15% of children with prehospital arrest have these rhythms.⁷²⁻⁷⁴ About 50% of arrests in the prehospital setting occur in previously healthy patients, whereas most in-hospital arrests occur in children with preexisting medical conditions.⁷⁵ Children with special healthcare needs are especially vulnerable to acute deterioration.

Outcome

The rate of survival of pediatric cardiopulmonary arrest is about 13%, with survival of in-hospital arrest greater than that of prehospital arrest (24% versus 9%).⁷¹ Patients with asystole have the lowest rate of survival (~5%), whereas survival is higher in patients with ventricular fibrillation or ventricular tachycardia (~30%). Patients presenting with isolated respiratory arrest have the highest rate of survival (~75%).^{76,77} Witnessed arrest and bystander cardiopulmonary resuscitation (CPR) are associated with survival, whereas CPR of greater than 30 minutes and administration of more than two doses of epinephrine are associated with a poor outcome.^{69,72,78,79} About 60% of survivors will have good neurologic outcome, with the remainder showing severe disabilities. Intermediate outcomes are uncommon. Accurate prediction of poor outcome can enable withdrawal of support and decrease the possibility that children are rescued to survival but in a neurologically devastated state.^{80,81} Predictors of poor outcome in children include remaining comatose at 24 hours, a Glasgow Coma Scale (GCS) score of less than 5, absence of spontaneous respirations, absence of pupillary reflex, and specific abnormalities found on electroencephalography (EEG) or after testing of somatosensory evoked potentials. Predictors of poor outcome should be applied with caution to children suffering cardiopulmonary arrest caused by drug overdose or hypothermic exposure (ice-cold water drowning), in which good outcomes have been reported in some cases after even prolonged durations of arrest.

Treatment

The optimal treatment of pediatric cardiopulmonary arrest is prevention. If cardiopulmonary arrest occurs, the most important first step is to provide immediate CPR. Many infants and children, especially in the prehospital setting, will be rescued solely by the administration of CPR.⁶⁹ Important differences are emerging in resuscitation of adults versus children with cardiac arrest. Although there has been a general movement toward bystander compression-only CPR in adults, Kitamura et al.⁸² compared conventional versus compression-only CPR in over 5000 children in Japan. In arrests of noncardiac origin, both survival and favorable neurologic outcomes were better in children given conventional CPR. In addition, outcomes were similar in

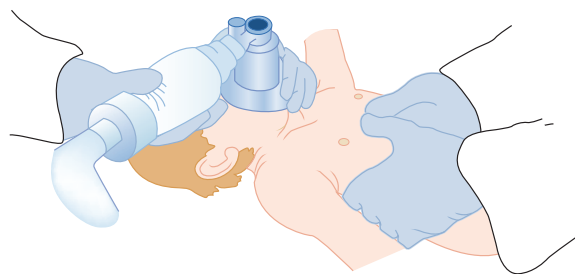


FIGURE 60-2 ■ Two-person technique for cardiopulmonary resuscitation in infants and young children. (Reprinted from Pediatric Basic Life Support. Guidelines 2000 for Cardiopulmonary and Emergency Cardiovascular Care: International Consensus on Science. Circulation. 2000;102(Suppl):I253-290.)

the setting of arrests of cardiac origin. This study strongly suggests that the lay public should be taught conventional CPR for all children who suffer cardiac arrest. A recent large study in adults also showed that continuous compressions did not lead to higher survival or better outcomes than did the use of chest compressions with interruption for ventilation.⁸³ In addition, the technique for compressions in children is different than in adults. Only one hand is used to deliver chest compressions to children younger than age 8 years. Two methods are approved for delivering chest compressions to infants. When two or more rescuers are available, one rescuer provides chest compressions by encircling the chest with two hands and depressing the sternum with both thumbs while the other rescuer provides ventilation (Fig. 60-2). When only one rescuer is present, two fingers from one hand are used to provide chest compressions, and the other hand is used to maintain the head-tilt. Providing adequate ventilation is especially important for children, because most pediatric arrests are secondary to airway compromise. In contrast, adults frequently suffer from cardiac causes of arrest and require intensified efforts at providing chest compressions and early defibrillation. Thus, the recommended ratio of chest compressions to ventilations for young children is 5:1, compared with a ratio of 15:2 for older children and adults. Once the patient is intubated, ventilations should be asynchronous. Although ventricular fibrillation and ventricular tachycardia are uncommon in children, survival with this rhythm is high (about 30%), so cardiac rhythm should be ascertained as early as possible.⁷¹ Automated external defibrillators that can deliver a 50-J dose are now available and are appropriate for use in children aged 1 to 8 years.⁸⁴

Intubation of pediatric patients is a difficult task for inexperienced providers. Furthermore, the short length of the trachea combined with patient movement during transport and patient care can easily result in displacement of the tracheal tube.⁸⁵ Secondary confirmation of tracheal tube placement is critical. End-tidal CO₂ detection is the method most commonly utilized for secondary confirmation of tracheal tube placement in children. However, a false-negative reading can occur when circulatory collapse is so severe that CO₂ is not delivered to the alveolar space. If CO₂ is not detected during CPR, tube placement can be confirmed by visualizing the airway with a laryngoscope. Although no single confirmation technique is 100% reliable in all circumstances, some effort of secondary confirmation of tube placement can be helpful.

Patients are initially resuscitated using 100% oxygen. The rationale is that hypoxia often causes or contributes to the development of cardiac arrest, and an oxygen debt accumulates during cardiac arrest. However, there is increasing awareness that oxygen might contribute to reperfusion injury, and thus *prolonged* delivery of *unnecessarily* high concentrations of oxygen should be avoided.^{86,87}

Adults resuscitated from cardiac arrest demonstrate intact cerebrovascular CO₂ reactivity with evidence of hyperventilation-associated ischemia.⁸⁸ Although there is evidence that the injured brain has diminished metabolism, which may offset the decrease in blood flow,

it seems prudent to avoid decreasing CBF to the injured brain. Therefore, hyperventilation should be reserved for patients with signs of cerebral herniation syndrome or suspected pulmonary hypertension. It is also prudent to guard against inadvertent hyperventilation during patient transport.⁸⁹ Increased use of quantitative continuous CO₂ monitors throughout the health care system would decrease the occurrence of inadvertent hyperventilation.

Establishing vascular access in children can be challenging. Fortunately, intraosseous access can be achieved within 30 to 60 seconds and provides a route for drug and fluid administration when intravascular access cannot be readily achieved. Drugs including lidocaine, epinephrine, atropine, and naloxone (mnemonic LEAN) can be administered through the tracheal tube. Optimal doses for drugs given via the tracheal tube are not established, but the recommended dose of epinephrine is 0.1 mg/kg (10 times the intravenous [IV] dose). A bedside glucose measurement should be obtained, and if hypoglycemia is present, it should be treated with 0.5 to 1 g/kg of IV glucose. There is experimental evidence that hyperglycemia and hypoglycemia exacerbate ischemic injury. Thus, euglycemia is desirable. Initial resuscitation fluids should be limited to isotonic crystalloid solutions such as normal saline or lactated Ringer's solution.

The most commonly used drugs in pediatric resuscitation are epinephrine, atropine, and sodium bicarbonate (Table 60-1). Magnesium and calcium are reserved for specific indications such as torsades de pointes, hypocalcemia, and calcium channel blockade. Amiodarone has recently been added to the American Heart Association (AHA) pediatric algorithms, based on extrapolation from experience with adults.⁹⁰ Adults with ventricular fibrillation or ventricular tachycardia in the prehospital setting are more likely to be successfully defibrillated after IV administration of amiodarone compared with lidocaine.⁹¹ Accordingly, amiodarone (5-mg/kg bolus) is a therapeutic option for children with pulseless arrest. Amiodarone (5 mg/kg infused over 20 to 60 min) is also an option for ventricular tachycardia with a pulse but should be used with extreme caution because of the risk for profound hypotension. Vasopressin has been added to the AHA adult algorithms as an alternative to epinephrine on the basis of its improved myocardial and CBF effects. However, subsequent clinical data in adults have not consistently yielded positive results, and pediatric data are limited to small case series.^{92,93} The optimal vasopressor for hemodynamic support after return of circulation in children is not known.

Extracorporeal membrane oxygenation (ECMO) has been used to successfully resuscitate children from selected causes of in-hospital cardiac arrest.⁹⁴⁻⁹⁸ ECMO-CPR provides greater cerebral and myocardial blood flow than either closed- or open-chest CPR and facilitates titration of temperature, blood flow, and oxygen-carrying capacity.

Good outcomes have been documented with the use of ECMO even when initiated after durations of conventional CPR typically associated with poor outcomes. It is best reserved for patients with reversible conditions or as a bridge to cardiac transplantation.

Post-resuscitative Care

Temperature control is a priority for patients who remain comatose after cardiac arrest. In investigations carried out a decade ago, adults cooled to 32°C to 34°C for 12 to 24 hours after resuscitation from ventricular fibrillation demonstrated improved survival and neurologic outcome.⁹⁹ However, recent investigations suggest that targeted temperature management at 36°C may be as beneficial as 32°C to 34°C.¹⁰⁰ In contrast, fever worsens outcome in experimental models of brain injury and has been associated with worse clinical outcome in adults with ischemic brain injury. Children resuscitated from cardiac arrest often develop mild hypothermia followed by delayed fever.¹⁰¹ There is a consensus that initial hypothermia, if tolerated, should be permitted to continue and fever should be vigilantly avoided. The practice of inducing hypothermia in normothermic children is more controversial. Clinical trials of induced hypothermia for neonatal asphyxia have been remarkably positive,¹⁰²⁻¹⁰⁴ and important data in newborns with asphyxia indicate that even one degree of hyperthermia after the insult is associated with neurologic morbidity.¹⁰⁵ The recent therapeutic hypothermia after cardiac arrest (THAPCA) trial for out-of-hospital arrests in children did not reveal a significant benefit for cooling for 48 hours after cardiac arrest in children.⁷⁵ However, the study was underpowered and suggested trends toward improved outcomes and reduced mortality by hypothermia, and some have advocated for its use based on the results of this trial.¹⁰⁶

During recovery from global ischemia, there may be a period of prolonged, multifocal, decreased CBF. Hypotension and hypoxia should be avoided during this period to prevent development of a secondary brain injury. As previously mentioned, the optimal regimen of oxygen and pressor therapy is not known and requires further study.

Sustained elevation of ICP may be more common after asphyxial arrests versus arrests of cardiac origin¹⁰⁷ and is a poor prognostic sign in children with drowning. ICP monitoring fell out of favor in the 1980s when it was found not to influence outcome in small case series.¹⁰⁸ However, studies using contemporary ICP-directed therapy (perhaps including induced hypothermia) deserve reevaluation.

Miscellaneous

Most pediatric victims of cardiopulmonary arrest will not be successfully resuscitated. The difficulty of accepting this reality often results in prolonged attempts at resuscitation. The AHA guidelines state, "In

TABLE 60-1 Drugs Commonly Used in Arrest or Peri-arrest Conditions

| DRUG | DOSE | MAXIMUM SINGLE DOSE | ROUTE |
|------------------------------|-------------------------------------|---------------------------------------|---|
| Adenosine* | 0.1 mg/kg Repeat dose: 0.2 mg/kg | 12 mg | IV (rapid push) |
| Atropine | 0.2 mg/kg (0.1 mg/min) | Children: 0.5 mg Adolescents: 1 mg | IV, IO, ET |
| Amiodarone | 5 mg/kg | 300 mg | IV, IO (bolus in pulseless arrest, otherwise give slowly) |
| Calcium chloride (10%)** | 20 mg/kg | 500 mg | IV, IO (slowly) |
| Dextrose | 0.5-1 mg/kg | N/A | IV, IO |
| Epinephrine | 0.01 mg/kg (0.1 mg/kg if given ET) | 5 mg | IV, IO, ET |
| Lidocaine | 1 mg/kg | 100 mg | IV, IO, ET |
| Narcan | 0.1 mg/kg | 2 mg | IV, IO, ET |
| Magnesium | 25-50 mg/kg | 2 g | IV, IO |
| Sodium bicarbonate (8.4%***) | 1 mEq/kg | N/A | IV, IO |

AHA, American Heart Association; CICU, cardiac intensive care unit; ET, endotracheal; IO, intraosseous; IV, intravenous.

*For supraventricular tachycardia. **Recommended for CICU patients. ***Not supported by AHA.

the absence of recurring or refractory ventricular fibrillation or ventricular tachycardia, history of a toxic drug exposure, or a primary hypothermic insult, resuscitative efforts may be discontinued if there is no return of spontaneous circulation despite advanced life support. In general, this requires no more than 30 minutes.⁹⁰ This acknowledges the futility of prolonged resuscitative efforts and empowers clinicians to feel *permitted to stop* resuscitative efforts. The guideline does not mandate stopping at a specific duration of CPR, but clinicians should recognize that the chance of survival with lifelong severe disabilities correlates with the duration of CPR, although prolonged CPR may benefit some children.

Surveys indicate that most family members would like to be present during resuscitation attempts of a loved one¹⁰⁹⁻¹¹²; presence during resuscitation can help family members adjust to the death.^{113,114} Although allowing family presence during resuscitation requires planning and additional resources, when done properly it is worth the effort.

Status Epilepticus

Status epilepticus is a pediatric emergency traditionally defined as either a continuous seizure of at least 30 minutes or more than two discrete seizures without complete recovery of consciousness. *Refractory status epilepticus* is defined as failure of two first-line antiepileptic medications to treat this condition for greater than 60 minutes. Many children with refractory status epilepticus have new or established CNS lesions.¹¹⁵

Epidemiology and Etiology

The incidence of pediatric status epilepticus from a prospective, population-based study is 40 cases/100,000 per year. Infants younger than 1 year of age have the highest incidence at 150 cases/100,000 per year.¹¹⁶ More than 90% of cases are convulsive status epilepticus. The first episode of status epilepticus occurs at a mean age of 4.2 years.¹¹⁷ There is a slight male predominance in status epilepticus.^{116,118}

There are five etiologic categories of status epilepticus that have a bearing on treatment and prognosis. A child with *idiopathic or cryptogenic* status epilepticus has no prior history of seizures and no known risk factors. *Atypical febrile* status epilepticus occurs during fever in children with no prior history of seizures without fever. Children with *acute symptomatic* status epilepticus have new CNS lesions such as encephalitis, trauma, tumor, stroke, or anoxia. Children with *remote symptomatic* status epilepticus have preexisting CNS lesions and therefore a lowered seizure threshold. In these children, status epilepticus can occur without provocation, sometimes even years after the initial insult. Finally some children have status epilepticus resulting from *progressive encephalopathy*, including neurodegenerative diseases, malignancies, and neurocutaneous syndromes (Box 60-1).^{116,118,119}

In one study, status epilepticus accounted for 1.6% of total pediatric ICU admissions, and etiology varied with age. In children younger than 2 years of age, *acute symptomatic* status epilepticus from meningitis and encephalitis accounted for 51% of cases, whereas *remote symptomatic* status epilepticus in children with a prior diagnosis of epilepsy was seen in 16% of children. Older children were more likely than younger children to have a history of epilepsy.¹¹⁸ Mortality rates for status epilepticus in children are between 3% and 6%.^{116,119} Mortality is dependent on etiology, age, and duration of status epilepticus. Mortality rates of 0% and 12.5% were seen when patients were divided into either unprovoked or febrile status epilepticus versus acute CNS insult or progressive encephalopathy groups, respectively.¹²⁰ Morbidity risk varies from 11% to 25%. Infants are at great risk for morbidity because the etiology in this group is commonly *acute symptomatic* status epilepticus. Neurologic sequelae of status epilepticus include epilepsy, recurrence, mental retardation, and motor disorders. However, many of the morbidities can be attributed to the underlying disease and not status epilepticus per se. Risk of recurrence in the category of *idiopathic* status epilepticus is less than 5%. In contrast, recurrence of status epilepticus in children in the *acute symptomatic* groups can be as high as 60%.^{116,120} Systemic complications occur with increasing frequency in

BOX 60-1 Etiology of Status Epilepticus

| |
|---------------------------------|
| Idiopathic/cryptogenic (24%) |
| Atypical febrile (24%) |
| Previously normal |
| Previously abnormal |
| Acute symptomatic (23%) |
| CNS infection |
| Anoxia |
| Trauma |
| Stroke/hemorrhage |
| Intoxication |
| Metabolic |
| Anticonvulsant withdrawal |
| Remote symptomatic (23%) |
| Progressive encephalopathy (6%) |
| Neurocutaneous syndrome |
| Neoplasm |
| Genetic/metabolic |

proportion to the duration of status epilepticus, the most important being respiratory failure, cardiovascular compromise, and autonomic and metabolic disturbances.¹²¹

There has also been considerable interest in the importance of diagnosis and treatment of subclinical status epilepticus that is commonly seen in children with neurologic insults requiring critical care, such as cardiac arrest and TBI, and is associated with an unfavorable outcome.^{122,123}

Diagnosis

As indicated, status epilepticus can be convulsive or nonconvulsive, the latter perhaps seen only on EEG. Convulsive seizures either begin as generalized seizures or progress from partial seizures. Nonconvulsive seizures are characterized as having subtle clinical signs such as nystagmus, irregular clonic twitches along with decreased consciousness, and/or ictal discharges on EEG. Included under the subheading of nonconvulsive seizures are complex and simple partial and absence seizures.¹²⁴

Treatment

The goals in treating status epilepticus are to provide respiratory and cardiovascular support, terminate clinical and electrical seizure activity, identify and treat precipitating factors, and prevent systemic complications.¹²⁴ Recognizing that a prolonged duration of seizure increases the risk of morbidity and mortality, recent guidelines and international surveys support initiating antiepileptic drugs for treatment within 5 minutes after the onset of an episode of status epilepticus. IV lorazepam is the recommended first-line therapy.^{125,126} A timetable for treatment of status epilepticus in children is provided in Table 60-2.

History of present and past illness may be useful in determining the cause of status epilepticus and in choosing therapy, but obtaining the history should not delay resuscitation. Initial treatment includes basic life support—airway, breathing, and circulation (ABCs). Prevention of hypoxemia and hypotension, which exacerbate neuronal injury, is important. The airway should be kept open with simple maneuvers and 100% oxygen applied with a nonbreathing mask. The airway should also be kept clear of secretions. Efficacy of oxygenation efforts should be monitored by pulse oximeter. Ventilation efforts are assessed clinically or by arterial blood gas determinations. If the patient is unable to maintain adequate oxygenation or ventilation, tracheal intubation using a rapid sequence technique is indicated. Circulation is monitored by assessment of ECG, BP, and perfusion. Ideally, a large-bore peripheral IV catheter should be placed for fluid and drug administration. A bedside blood glucose determination should be obtained. Serum electrolyte levels, renal and liver function tests, and anticonvulsant levels should be assessed. A serum and urine toxicology screen should be obtained. Fever and hypoglycemia should be treated as quickly as possible. The neurologic examination follows, focusing on

TABLE 60-2 Suggested Timetable for Emergency Diagnosis and Treatment of Status Epilepticus

| TIME | EXAM/INTERVENTION | TESTING |
|--|--|---|
| Initial presentation: 0 min | Airway, breathing, circulation, IV access, monitoring | Glucose, oxygenation via pulse oximetry \pm blood gas analysis |
| Primary survey: 5 min | Neurologic exam Administer antiepileptic drugs Lorazepam, 0.1 mg/kg IV Phenobarbital, 20 mg/kg IV Normal saline maintenance IV Reduce fever | Electrolytes, renal and liver function, ammonia, anticonvulsant levels, toxicology, complete blood cell count, urinalysis |
| Secondary survey: 15-30 min | Evaluate treatment results Second-line antiepileptic drug if seizure persists Fosphenytoin, 20 mg/kg IV, or phenytoin, 20 mg/kg IV | Patient-specific: cranial imaging (CT vs. MRI), lumbar puncture, EEG, ECG |
| Status epilepticus: >30 min | Intubation and mechanical ventilation | |
| Refractory status epilepticus: >60 min | Titrate antiepileptic drug to burst suppression Pentobarbital, 10 mg/kg IV given over 30 min, then 5 mg/kg every hour for 3 doses, then 1 mg/kg/h; titrate to effect Midazolam, 0.15 mg/kg IV, then 1-2 μ g/kg/min, titrate to effect Phenobarbital, 5-10 mg/kg IV every 20 minutes to achieve burst suppression, then every 12 hours Evaluate need for vasopressors | Continuous EEG Neurologic consultation Consider anesthesia consultation for treatment with inhaled anesthetic |

CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; IV, intravenous; MRI, magnetic resonance imaging.

GCS score, signs of raised ICP, focal deficits, and pupil size. In patients receiving neuromuscular blockade, electrical seizure activity should be monitored with continuous EEG.

First-line antiepileptic drugs for pediatric status epilepticus include benzodiazepines, phenytoin or fosphenytoin, and phenobarbital. Drug choice depends on the route available (IV is preferred), the patient's maintenance anticonvulsants (a different class is recommended), and patient characteristics. Evidence-based studies of anticonvulsants in children are rare. Recommendations are extrapolated from studies in adults. The optimal first-line treatment of status epilepticus in children is controversial.

As previously indicated, guidelines for the management of status epilepticus recommended IV lorazepam as the preferred first-line agent¹²⁵ for emergent initial therapy. Also, in an emergency, midazolam can be given IM or diazepam rectally.¹²⁵ Lorazepam can be administered rapidly, has a long duration of effect, and is effective even when administered rectally. Lorazepam produced less respiratory failure requiring intubation than diazepam in retrospective¹²⁷ and prospective studies.¹²⁸ The incidence of respiratory depression in these studies varied widely—between 3% and 76%. Support for selection of lorazepam over diazepam was also shown in a recent Cochrane review.¹²⁹

For subsequent urgent control, fosphenytoin or phenobarbital are reasonable choices, along with IV valproate, levetiracetam, or a continuous infusion of midazolam.¹²⁵ In a study in adults comparing lorazepam, phenytoin, phenobarbital, and diazepam, phenytoin had the highest success rate in stopping status epilepticus.¹³⁰ Phenytoin is not commonly associated with respiratory depression and produces less impairment of consciousness than either benzodiazepines or barbiturates. Fosphenytoin has the advantage of having a faster infusion rate, shorter onset of action, and fewer cardiovascular side effects than phenytoin but is more expensive.

Phenobarbital is also a very effective anticonvulsant, but it is often not the first choice in the treatment of status epilepticus because of its side effects of respiratory depression and cardiovascular disorders, especially when used in combination with benzodiazepines. Infants metabolize phenobarbital more rapidly than older children and often require higher doses adjusted for body weight. Nevertheless, the pharmacokinetics of phenobarbital are more predictable than those of phenytoin in infants.

Additional Diagnostic Workup

Lumbar puncture is best performed early after presentation, but not in unstable patients or those who may have increased ICP or coagulopathy or thrombocytopenia. The decision to perform lumbar puncture should be guided by head computed tomography (CT). Otherwise, the type of neuroimaging used in infants and children with status epilepticus should be individualized, depending on history and physical findings. Both ECG and EEG are useful to investigate the cause of status epilepticus (e.g., long QT syndrome or identifiable EEG patterns). EEG is also useful in titrating therapy (see the next section).¹²⁴

Drug Treatment for Refractory Status Epilepticus

Refractory status epilepticus is generally considered to be present when a patient fails treatment with a benzodiazepine and one other antiepileptic drug. This diagnosis is made with either EEG or clinical observation. Treatment should then proceed. Monitoring in a pediatric ICU or intermediate unit is recommended and neurologic consultation should be considered. These patients are mechanically ventilated, and seizures are typically treated with a variety of therapies, generally to induce burst suppression on continuous EEG. Most commonly, pentobarbital is used as a continuous infusion to treat refractory status epilepticus. Pentobarbital is given initially as a slow IV loading dose of 5 to 15 mg/kg, followed by an infusion rate of 1 mg/kg/h titrated to effect. There are differing opinions on when to begin to wean therapy, but it is generally recommended that about 12 hours of seizure cessation be attained before weaning the infusion.¹³¹ In children, placement of either a central venous pressure or pulmonary artery catheter is indicated to titrate fluid, inotropic, and pressor support. Pentobarbital use often requires the addition of inotropes or pressors. A midazolam infusion has also been shown to be effective in refractory status epilepticus in some children (0.15 mg/kg IV bolus followed by infusion of 1-2 μ g/kg/min). The infusion can be increased every 15 minutes if seizures are still present on continuous EEG or if burst suppression is not achieved. With this approach in one series, inotropic support was not required.¹³² As an alternative to continuous barbiturate or midazolam infusion, phenobarbital can be administered every 20 minutes (5-10 mg/kg IV) to achieve burst suppression and then as a chronic therapy every 12 hours.

Stroke

Epidemiology

Stroke in children is becoming increasingly recognized and now exceeds an incidence of 8 cases per 100,000 children per year.¹³³ Neonates account for about 25% of these cases. The increasing incidence is believed to result from improvements in diagnostic tools (MRI, CT, magnetic resonance angiography [MRA]) applied to the pediatric population and to increasing survival rates in infants and children with stroke risk factors (e.g., complex congenital heart disease, malignancies).

Etiology

Atherosclerosis is a key risk factor for stroke in adults. In pediatric and neonatal stroke, extracerebral risk factors contribute to about 75% of cases, but the spectrum of risk factors differs from those seen in adults. DeVeber¹³³ grouped the most common risk factors for childhood ischemic stroke into vascular, intravascular, and embolic categories (Box 60-2). The most common vascular risk factor has been reported to be transient cerebral arteriopathy.¹³⁴ Post-varicella arteriopathy, migraine, traumatic carotid dissection, vasculitis, and moyamoya syndrome are important examples in this category. Intravascular occlusion can occur in disorders such as sickle cell anemia, sinus thrombosis,

leukemias, and both acquired and congenital prothrombotic states. Dehydration and intravascular volume depletion increase stroke risk in these settings, which are of special importance in the pediatric ICU. There is an 84% incidence of an acute systemic illness and a 30% incidence of dehydration reported in infants and children with cerebral sinovenous thrombosis.¹³⁵ Congenital and acquired heart disease are the most important underlying causes of embolic stroke.¹³³ The risk of stroke in children after surgery for congenital heart disease is about 1 in 250 cases.¹³⁶

Diagnosis

The clinical presentation of stroke in infants and children is age related. Infants typically present with seizures and lethargy, whereas older children may present with acute focal neurologic deficits or diffuse symptoms (headache, lethargy, or seizures).^{133,137} It is often difficult to differentiate migraine, Todd paralysis, and stroke in children. Complicating this problem, CT may be normal within the initial 12 hours.¹³³ MRI is a more sensitive technique for diagnosing stroke, and advanced MRI modalities such as perfusion, diffusion, and MRA are important adjuncts to making the diagnosis. These methods are discussed in Chapter 58. Because of the impact of making a specific vascular diagnosis on the management strategy, angiography is often recommended in children with idiopathic stroke.¹³³

BOX 60-2 Most Common Risk Factors for Childhood Ischemic Stroke

VASCULAR

Arteriopathies

Transient cerebral arteriopathy of childhood
Postvaricella angiopathy
Fibromuscular dysplasia
Moyamoya syndrome
Postradiation vasculopathy

Vasospastic Disorders

Migraine
Ergot poisoning
Vasospasm with systemic arterial hypertension

Vasculitis

Meningitis
Systemic lupus erythematosus
Polyarteritis nodosa
Granulomatous angiitis
Takayasu arteritis
Dermatomyositis
Inflammatory bowel disease
Drug abuse (cocaine, amphetamines)

Systemic Vascular Disease

Early atherosclerosis
Diabetes
Ehlers-Danlos syndrome
Pseudoxanthoma elasticum
Homocystinuria
Fabry disease

Trauma

Brain herniation and arterial compression
Posttraumatic dissection
Intraoral trauma
Carotid ligation (e.g., extracorporeal membrane oxygenation)
Arteriography

INTRAVASCULAR

Hematologic Disorders

Hemoglobinopathies (sickle cell anemia)
Thrombocytosis
Polycythemia
Leukemia or other hematologic neoplasms

Acquired Prothrombotic States

Prothrombotic medications
Pregnancy and the postpartum period
Lupus anticoagulant
Anticardiolipin antibodies
Lipoprotein abnormalities
Hyperhomocysteinemia

Congenital Prothrombotic States

Antithrombin deficiency
Protein S deficiency
Protein C deficiency
Plasminogen deficiency
Factor V Leiden
Prothrombin gene mutation
Methylenetetrahydrofolate reductase

Metabolic Disorders

Hyperhomocysteinemia
Hyperlipidemia

EMBOLIC

Congenital Heart Disease

Complex congenital heart defect
Ventricular/atrial septal defect
Coarctation of the aorta
Patent foramen ovale
Patent ductus arteriosus

Acquired Heart Disease

Rheumatic heart disease
Prosthetic heart valve
Bacterial endocarditis
Cardiomyopathy and myocarditis
Atrial myxoma
Cardiac rhabdomyoma
Cardiac arrhythmia

Trauma

Amniotic fluid or placental embolism
Fat or air embolism
Foreign body embolism
Cardiac catheterization

In addition to cardiac surgery or catheterization, endocarditis, cardiomyopathy, and other occult cardiac abnormalities are important risk factors for embolic stroke. Echocardiography is thus essential in the diagnostic workup for stroke in children.^{138,139} The reader is referred to an outstanding state-of-the-art guidelines approach to the acute management of children with stroke, which was recently published by Rivkin et al.^{140a} and includes description of an emergent diagnostic protocol.

Treatment

In the acute setting, antithrombotic therapy has been increasingly used in the therapy for pediatric stroke. Strater and colleagues¹⁴⁰ compared treatment with low-molecular-weight heparin versus aspirin in 135 children with stroke across a variety of causes (including idiopathic, cardiac, vascular, and infectious) and found no difference in efficacy or safety when used to prevent stroke recurrence. This is a controversial area, however.¹⁴¹ DeVeber¹³³ states that neonates do not require antithrombotic treatment because of negligible recurrence risk, whereas older children require aspirin (2-3 mg/kg/d).¹⁴² In dissection, high-grade stenosis, or a severe prothrombotic state, low-molecular-weight heparin or warfarin is recommended for several months. In endocarditis, anticoagulation is not recommended because of the risk of rupture of occult mycotic aneurysms. Thrombolytic therapy has been subjected to very limited study in children, although cases describing the use of tissue plasminogen activator and cerebral balloon angioplasty in acute stroke in children with dramatic results are being reported.¹⁴³ Table 60-3 compares key management issues across three sets of guidelines in acute ischemic stroke, as summarized by deVeber and Kirkham.¹⁴⁴

Since the last edition of this textbook, there has been a revolutionary change in the management of acute ischemic stroke in adults with the advent of clot retrieval. This includes numerous successful clinical trials as compared with thrombolytic therapy. Over 500 articles on this topic have been published in the past 2 years. Although these studies

are beyond the scope of this chapter, they are reviewed by Campbell et al.¹⁴⁵ To date there have been a small number of publications on clot retrieval in children. Ellis et al.¹⁴⁶ reviewed this topic and identified 34 cases of clot retrieval. More recently, Hu et al.¹⁴⁷ and Bodey et al.¹⁴⁸ presented six additional cases. Several clot retrieval systems are available including the Solitaire, Merci, and Revive. This is a promising approach, but at this juncture it can only be suggested that there may be a role for clot retrieval in children in selected patients managed by a highly experienced team.¹⁴⁸ Complications with these devices have been reported in children.¹⁴⁹ Finally, in addition to clot retrieval, as discussed in the section on stroke diagnostics, the acute management approach in pediatric stroke is also evolving rapidly on multiple fronts and additional recommendations regarding imaging and intravenous tPA treatment are available in excellent single center protocols.¹⁴⁰

Supportive Care in the Pediatric Intensive Care Unit

An evidence-based approach for care in the pediatric ICU of children with stroke is lacking. Nevertheless, intensive care for the child with stroke must be at a level commensurate with that provided for other critical pediatric neurologic disorders such as severe TBI¹⁵⁰ and ruptured arteriovenous malformation.¹⁵¹

Careful attention to the ABCs with a neurointensive care approach is essential. If the GCS score is 8 or less or the airway or ventilation is compromised, intubation is indicated and should be performed using a neuroprotective, rapid-sequence approach. Normal values for both P_{aCO_2} and P_{aO_2} should be ensured. Arterial blood pressure must be adequate to optimize cerebral perfusion. The management of systemic hypertension in the setting of pediatric stroke can be complicated by the variety of underlying disorders (e.g., status post cardiac surgery, underlying hypertension) and the presence or absence of hemorrhage. In adults with thrombotic or hemorrhagic stroke and systemic hypertension, it is generally recommended that mean arterial blood pressure not be aggressively reduced below 130 mm Hg.¹⁵² Age-appropriate guidelines for this question are not available for children.

TABLE 60-3 Comparison of Guidelines for Acute Management of Ischemic Stroke in Children by Subtype*

| | UK GUIDELINES: 2004 RECOMMENDATIONS | G | S | CHEST GUIDELINES: 2008 RECOMMENDATIONS | G | S | AMERICAN HEART ASSOCIATION: 2008 RECOMMENDATIONS | G | S |
|--------------------------------|--|-----|----|--|----|---|--|------------|--------|
| General | Aspirin 5 mg/kg | WPC | 1 | UFH or LMWH or aspirin 1-5 mg/kg/d until cardioembolic and dissection subtypes excluded | 1B | 1 | UFH or LMWH (1 mg/kg q 12 h) up to 1 week until cause determined | 2B-C | 3 |
| Sickle cell disease | Exchange transfusion to HbS <30% | WPC | 1 | Intravenous hydration and exchange transfusion to HbS <30% | 1B | 1 | Optimal hydration, correction of hypoxemia and hypotension Exchange transfusion to HbS <30% | 1C 2A-B | 1 2 |
| Cardiac | Anticoagulation should be discussed by senior pediatric neurologist and pediatric cardiologist | WPC | 1 | LMWH for over 6 weeks | 2C | 3 | Therapy for heart problem | 1C | 1 |
| Dissection of neck vessels | Anticoagulation for extracranial dissection with no hemorrhage | WPC | 1 | LMWH for over 6 weeks | 2C | 3 | UFH or LMWH as a bridge to oral anticoagulation | 2A-C | 3 |
| Alteplase in children | Not recommended | — | 1 | Not recommended | 1B | 1 | Not recommended | 3C | 1 |
| Alteplase in teenagers | Not addressed | — | — | Not addressed | — | — | No consensus on use | — | 3 |
| Cerebral sinovenous thrombosis | Anticoagulation until recanalization for up to 6 months | — | C3 | Initial UFH or LMWH, then LMWH for 3 months plus another 3 months if not fully recanalized | 1B | 1 | Initial UFH or LMWH followed by warfarin for 3-6 months | 2A-C | 3 |

From DeVeber G, Kirkham F. Guidelines for the treatment and prevention of stroke in children. *Lancet*. 2008;7:983-5. Reproduced with permission.

*Childhood is defined as 28 days to 18 years (*Chest*) or 1 month to 16 years (UK). Comparison of guidelines for acute management of ischemic stroke in children by subtype of stroke.

G, grade of evidence or recommendation; HbS, sickled hemoglobin; LMWH, low-molecular-weight heparin; S, strength of evidence or recommendation; UFH, unfractionated heparin; WPC, working party consensus.

In infants and children with severe stroke with infarction and cerebral swelling, signs and symptoms of raised ICP can develop. Standard protocols for monitoring ICP and treatment of raised ICP in stroke in infants and children have not been developed. Nevertheless, intracranial hypertension can develop. Should signs and symptoms of intracranial hypertension be observed, even in the absence of controlled trials in severe pediatric stroke, ICP monitoring and ICP-directed therapy should be considered. Anecdotal reports of successful treatment with a variety of therapies including mild hypothermia and decompressive craniectomy have been reported.^{153,154} Plasticity in the pediatric brain, particularly in the recovery from focal lesions, should prompt the consideration of an aggressive approach.¹⁵⁵⁻¹⁵⁷ However, long-term morbidity remains substantial after childhood stroke.¹⁵⁸

Other aspects of contemporary pediatric neurointensive care should include maintenance of euglycemia and careful fluid management both to maintain a euvoletic state and avoid hyponatremia. In children, normal saline or 5% dextrose in normal saline should be used in the initial 24 hours, carefully monitoring blood glucose concentration, followed by the addition of dextrose or initiation of hyperalimentation after 24 hours. In infants, either 5% or 10% dextrose in normal saline should be used, with insulin titrated to treat hyperglycemia. A glucose value of 200 mg/dL is a reasonable threshold in the absence of clear-cut evidence. Appropriate nutritional support should also be instituted as soon as possible. Rehabilitation services should be consulted during the pediatric ICU admission.

CRITICAL CENTRAL NERVOUS SYSTEM INFECTIONS

Any microbe may cause CNS infections; age and immune status of the host and epidemiology of the pathogen help suggest the specific pathogens. Regardless of the etiology, most children with CNS infection present with nonspecific symptoms including fever, headache, nausea, vomiting, anorexia, and irritability. Photophobia, neck pain and rigidity, seizures, mental status change, and focal neurologic deficits are common signs, depending on the specific pathogen and area of the CNS infected.

Bacterial Meningitis

Epidemiology

The etiology of bacterial meningitis and its treatment differ in neonates (0-28 days of life) versus older infants and children. During the first 2 months of life, the bacteria that cause meningitis in normal infants reflect the maternal flora and the environment to which the infant is exposed. The most common pathogens include groups B and D streptococci, gram-negative enteric bacilli, and *Listeria monocytogenes*. Occasionally, *Haemophilus influenzae* (both type B and nonencapsulated strains) and other pathogens—more typically found in older patients—can be the etiologic agent. Bacterial meningitis in children between 2 months and 12 years of age is usually caused by *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *H. influenzae* type B. After the implementation of immunization against *H. influenzae*, the incidence of *H. influenzae* meningitis decreased rapidly. Subsequent to the universal recommendation for the use of conjugated pneumococcal vaccine at 2 months of age in 2000, the incidence of meningitis caused by this pathogen is also decreasing. A recent multicenter study reported Group B streptococci as the most common causative agent (86%) in children younger than 2 months, *N. meningitidis* (46%) in children 11 to 17 years, and *S. pneumoniae* in all other pediatric age groups.¹⁵⁹ Anatomic abnormalities, surgical procedures, neurotrauma, or immune deficiency often underlie meningitis caused by other agents.

Bacterial meningitis most commonly results from hematogenous dissemination of microorganisms from a distant site of infection. Colonization of the nasopharynx with a pathogenic microorganism is the usual source of bacteremia. Bacteria gain entry to the CSF through the choroid plexus of the lateral ventricles and the meninges and then circulate to the extracerebral CSF and the subarachnoid space.

Bacterial cell wall lipopolysaccharides of gram-negative bacteria and pneumococcal cell wall components stimulate a marked inflammatory response, with local production of tumor necrosis factor alpha, interleukin-1 β , prostaglandin E, and other mediators, leading to neutrophil infiltration, increased vascular permeability, and thrombosis. Inflammation of spinal nerves and roots produces meningeal signs, and inflammation of the cranial nerves produces optic, oculomotor, facial, and auditory neuropathies. Intracranial hypertension can produce oculomotor and abducens nerve palsy. Intracranial hypertension in meningitis is believed to result from a combination of cell death (cytotoxic cerebral edema), cytokine-induced increased capillary vascular permeability (vasogenic edema), and increased hydrostatic pressure after obstruction of CSF reabsorption or flow. Rarely, meningitis may follow bacterial invasion from a contiguous focus of infection such as paranasal sinusitis, otitis media, mastoiditis, orbital cellulitis, or cranial or vertebral osteomyelitis or may occur after introduction of bacteria via penetrating head trauma or meningomyelocele.¹⁶⁰

Diagnosis

The clinical presentation may be as fulminant as rapidly progressing shock, purpura, disseminated intravascular coagulation, and altered consciousness, frequently resulting in death within 24 hours. More often, however, children present with several days of fever with upper respiratory tract or gastrointestinal symptoms, followed by nonspecific signs of CNS infection such as lethargy and irritability. The presence of headache, emesis, bulging fontanelle, widening of the sutures, oculomotor or abducens nerve paralysis, hypertension with bradycardia, apnea, or hyperventilation suggests intracranial hypertension. Papilledema is uncommon in uncomplicated meningitis and suggests a more chronic process, such as intracranial abscess, sinus thrombosis, or subdural empyema. Seizures can result from cerebritis, infarction, or electrolyte abnormalities and occur in between 20% and 30% of cases. Seizures that occur at presentation or within the first 4 days of onset are usually of no prognostic significance. Seizures that persist beyond day 4 and those that are difficult to treat are associated with a poor prognosis.¹⁶¹

The diagnosis of acute bacterial meningitis is confirmed by analysis of CSF. Contraindications for an immediate lumbar puncture are (1) evidence of increased ICP (other than a bulging fontanelle), (2) presence of severe cardiopulmonary compromise or likelihood that positioning for the procedure would significantly compromise cardiopulmonary function, (3) infection of the skin overlying the needle insertion site, and (4) coagulopathy. If lumbar puncture is delayed, empirical antibiotic treatment should be started after a blood culture is obtained. Blood culture reveals the causative bacteria in 80% to 90% of cases of meningitis. The need for a cranial CT scan for signs and symptoms of increased ICP or brain abscess should not delay therapy. Table 60-4 summarizes the CSF findings in CNS infections. Pleocytosis with lymphocyte predominance may be seen early in bacterial meningitis; conversely, neutrophilic pleocytosis may be present in patients during the early stages of acute viral meningitis. The shift to lymphocytic-monocytic predominance in viral meningitis invariably occurs within 8 to 24 hours. A traumatic lumbar puncture complicates the diagnosis. If the CSF is bloody, it should be collected in three or more tubes. If it clears in successive tubes, it suggests a traumatic puncture. Blood that does not clear is more suggestive of intracranial bleeding. The CSF leukocyte-to-erythrocyte ratio in CSF from a traumatic lumbar puncture is generally similar to that in a concurrently obtained peripheral blood sample (usually 1:500 to 1:1000).¹⁶²

The mortality rate of bacterial meningitis after the neonatal period is less than 10%. Severe neurodevelopmental sequelae occur in between 10% and 20% of pediatric patients. The most common sequelae include hearing loss, mental retardation, epilepsy, delay in language acquisition, visual impairment, and behavioral problems. Sensorineural hearing loss occurs in 30%, 10%, and 5% to 10% of patients with pneumococcal, meningococcal, and *H. influenzae* type B meningitis, respectively.¹⁶³

TABLE 60-4 Cerebrospinal Fluid Findings in Central Nervous System Infections

| TYPE OF INFECTION | PRESSURE (cm H ₂ O) | LEUKOCYTES (mm ³) | PROTEIN (mg/dL) | GLUCOSE (mg/dL) |
|---|--------------------------------|--|---------------------------------|--|
| Normal | 5-8 | <5, ≥75% lymphocytes <30 for neonates | 20-45 Up to 180 for neonates | >50 (or 75% serum glucose) |
| Acute bacterial | ↑ (10-30) | 300-2000 PMNs predominate | 100-500 | ↓ (<40 or <50% serum glucose) |
| Partially treated bacterial meningitis | Normal or ↑ | 5-10,000 Usually PMNs | 100-500 | Normal or ↓ |
| Viral meningitis or meningoencephalitis | Normal or slightly ↑ (8-15) | Rarely >1000 PMNs early, then mononuclear cells | 50-200 | Normal (decreased in some mumps cases) |
| Tuberculous meningitis | ↑ | 10-500 PMNs early, lymphocytes predominate through most of the course | 100-3000 | <50 |
| Fungal meningitis | ↑ | 5-500 PMNs early, lymphocytes predominate through most of the course | 25-500 | <50 |
| Syphilis | ↑ | 50-500 Lymphocytes predominate | 50-200 | Normal |
| Amebic (<i>Naegleria</i>) meningoencephalitis | ↑ | 1000-10,000 or more PMNs predominate | 50-500 | Normal or slightly ↓ |

PMNs, polymorphonuclear leukocytes.

Treatment

The initial empirical choice of antibiotic treatment in immunocompetent infants and children is primarily determined by the antibiotic susceptibilities of *S. pneumoniae*. In the United States, between 25% and 50% of strains of *S. pneumoniae* are currently resistant to penicillin, and up to 25% of isolates are resistant to cefotaxime or ceftriaxone. Thus, empirical therapy is with vancomycin (60 mg/kg/24 h, divided, every 6 h) and cefotaxime (200 mg/kg/24 h, divided, every 6 h) or ceftriaxone (100 mg/kg/24 h, given either as a single daily dose or every 12 h). Patients allergic to beta-lactam antibiotics can be treated with chloramphenicol (100 mg/kg/24 h, divided, every 6 h). If *L. monocytogenes* infection is suspected, as in infants between 1 and 2 months of age or patients with T-lymphocyte deficiency, ampicillin (200 mg/kg/24 h, divided, every 6 h) should be administered with either cefotaxime or ceftriaxone. In addition, empirical acyclovir therapy for herpes simplex virus should be considered, especially in febrile neonates with rash, seizure, maternal history, or ill appearance, since delayed therapy of neonatal herpes simplex virus disease has been associated with increased mortality. If a patient is immunocompromised and gram-negative bacterial meningitis is suspected, ceftazidime and an aminoglycoside may be used as initial therapy. The duration of treatment should be either 10 or 14 days, depending on the bacteria; gram-negative bacillary meningitis should be treated for 3 weeks or for at least 2 weeks after sterilization of CSF. Repeat lumbar puncture may be indicated in some neonates and in children with gram-negative meningitis or infection caused by beta-lactam-resistant *S. pneumoniae*. Of the adjunctive treatments that might limit CNS inflammation, only corticosteroids have been properly assessed in clinical trials. Adjuvant corticosteroid use was associated with lower case fatality and lower rates of both severe hearing loss and long-term neurologic sequelae in acute bacterial meningitis. Corticosteroids administered either before or with the first dose of antibiotic reduced severe hearing loss in bacterial meningitis caused by *H. influenzae* as well as in meningitis caused by *S. pneumoniae*.¹⁶⁴ The recommended dose of dexamethasone is 0.6 mg/kg/24 h, divided every 6 hours for 4 days.¹⁶⁰ A recent meta-analysis of individual patient data from 25 randomized, placebo-controlled trials in both adults and children addressing corticosteroid use in meningitis showed that corticosteroid administration decreased the rate of hearing loss in children with meningitis due to *H. influenzae* (4% versus 12%) but not in children with meningitis due to other bacteria. Dexamethasone did not

significantly reduce the death rate.¹⁶⁴ Two randomized controlled trials (RCT) of dexamethasone alongside standard antibiotic therapy in neonatal bacterial meningitis suggest some reduction in death and hearing loss; however, they were deemed to contain very low-quality data in a recent systematic review. There are no data about the role of corticosteroids in patients with nosocomial or CSF shunt-associated meningitis. Thus, the role of dexamethasone in prevention of death or neurologic sequelae needs reevaluation.

Peltola et al.¹⁶⁵ reported improved outcomes in 654 children with meningitis with oral glycerol therapy (6 mL/kg/d divided in 4 doses; maximum 25 mL/dose). However, another study did not demonstrate benefit from oral glycerol on hearing impairment in pediatric meningitis.¹⁶⁶ Nevertheless, glycerol has been recommended for pediatric meningitis, albeit not at a guidelines level.¹⁶⁷ Recent reviews, however, state that osmotic diuretics, including glycerol, should be given to children with bacterial meningitis only as part of RCTs. A recent RCT that compared CPP- vs. ICP-targeted therapy in acute bacterial meningitis in children warrants mentioning in this update of the chapter.¹⁶⁸ In this study 110 comatose children (aged 1-12 yr) with acute CNS infection undergoing invasive ICP monitoring were randomized to a target level of ICP (<20 mm Hg) or to target level of CPP (>60 mm Hg). CPP-targeted therapy necessitated frequent use of vasopressors and less use of hyperventilation and osmotherapy. It was superior to ICP-targeted therapy in reducing mortality and morbidity.

Patients who (1) manifest poor perfusion, cutaneous signs of disseminated intravascular coagulation (purpura, petechiae), irregular respiratory pattern, altered mental status, cranial nerve involvement, and other signs potentially indicative of raised ICP and patients who (2) have a rapid clinical presentation, significant metabolic acidosis, hypoxemia, hypercapnia, neutropenia, hyponatremia, anemia, or abnormal liver or renal function should be admitted to the pediatric ICU. At least until the course of illness can be determined, the first several doses of antibiotics are administered and a tentative bacteriologic diagnosis is made. Early recognition of complications such as shock or raised ICP and initiation of treatment in a timely fashion may improve the outcome in fulminant meningitis.

Acute CNS complications during the treatment of meningitis include seizures, intracranial hypertension, cranial nerve palsies, stroke, herniation, and thrombosis of the dural venous sinuses.¹⁶⁹ Subdural effusions develop in between 10% and 30% of pediatric patients

and are more common in infants. They are asymptomatic in 85% to 90% of cases. Aspiration of subdural effusions is indicated in the presence of raised ICP; fever alone is not an indication for aspiration. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) with hyponatremia and reduced serum osmolality occurs in between 30% and 50% of children. Cerebral salt wasting can also be seen. Attention to maintaining a normal serum sodium concentration using either normal saline or judicious titration of hypertonic saline is important for preventing exacerbation of brain edema. Prolonged fever (>10 days) occurs in 10% of patients. It is usually due to intercurrent viral infection, secondary or nosocomial bacterial infection, thrombophlebitis, drug reaction, pericarditis, or arthritis.

Supportive Care in the Pediatric ICU

The issues in ICU care for infants and children with bacterial meningitis are similar to ones mentioned under encephalitis. The reader is referred to the following section for details.

Viral Encephalitis

Epidemiology

Enteroviruses are the most common etiologic agent of encephalitis in children. Severity ranges from mild illness to severe encephalitis with death or long-term morbidity. Enterovirus infections spread directly from person to person, with an incubation period of between 4 and 6 days. Most cases occur in summer and fall in temperate climates. Arboviruses are responsible for some cases of encephalitis. The most common arboviruses causing CNS infection in the United States are St. Louis and California encephalitis and West Nile virus.¹⁷⁰

Several members of the herpesvirus family can cause encephalitis. Herpes simplex virus (HSV) type 1 is an important cause of severe encephalitis in children. The cerebral cortex, especially the temporal lobe, is often severely affected by HSV. Neonatal herpes infections are usually caused by HSV type 2 contracted at delivery via vertical transmission. Three forms of the disease develop in neonates: (1) skin, eye, mouth disease (45% of cases), (2) encephalitis (35%), and (3) disseminated intravascular coagulation (20%). The transmission rate from mother to infant is between 30% and 40% with a primary genital infection and 3% for reactivated herpes infection. The mean age at onset of cutaneous or systemic disease is 6 days after birth, with the mean onset of encephalitis at 11 days. The diagnosis of HSV infection in neonates can be difficult to make unless skin lesions are present. Cultures of conjunctiva, nasopharynx, and rectum between 48 hours and 72 hours of age may identify early infection. In neonates, the mortality rates are about 50% and 14% for HSV-disseminated disease and encephalitis, respectively.¹⁷⁰

A number of other viruses are important causes of pediatric encephalitis. Varicella-zoster may cause CNS infection in close proximity to chickenpox. The most common manifestation of CNS infection by varicella-zoster is cerebellar ataxia. Cytomegalovirus infection of the CNS may be either part of congenital infection or disseminated disease in an immunocompromised host. CNS diseases caused by Epstein-Barr virus may present with perceptual distortions of sizes, shapes, and spatial relationships known as "Alice in Wonderland syndrome." There may be meningitis, seizures, ataxia, facial palsy, transverse myelitis, and encephalitis.¹⁷⁰ During the influenza A (H1N1) pandemic, neurologic sequelae were significant. As reported by Baltagi et al.,¹⁷¹ these findings in children included altered mental status, seizures, and encephalopathy, even without significant respiratory symptoms.

Infectious agents can enter the brain via a hematogenous route or by neuronal tracts. Many hematogenous pathogens cause direct endothelial damage to arteries, arterioles, and capillaries, resulting in vasculitis, hemorrhage, and thrombosis. Postinfectious encephalitis is an autoimmune process characterized by a perivenulitis with demyelination. It is uncommon in children younger than 1 year of age.¹⁷² The mortality rate of herpes infection even with early acyclovir treatment is 20% to 30%, and there is substantial morbidity.¹⁷³

Diagnosis

The onset of illness is generally acute and often preceded by a nonspecific febrile illness of a few days' duration. The manifestations of viral encephalitis in older children are headache and hyperesthesia, whereas in infants, irritability and lethargy predominate. Adolescents frequently complain of retrobulbar pain, fever, nausea, vomiting, photophobia, and pain in the legs, back, and neck. Exanthems often precede or accompany the CNS signs. Seizures occur in 60% of cases of HSV encephalitis. The CSF usually shows a mild mononuclear predominance. It should be cultured for viruses, bacteria, fungi, and mycobacteria. Detection of viral DNA or RNA by polymerase chain reaction is useful for diagnosis of HSV, varicella-zoster, cytomegalovirus, Epstein-Barr virus, and enteroviral meningoencephalitis. Polymerase chain reaction in CSF is 100% specific and more than 90% sensitive for HSV.¹⁷⁴ About 50% of patients with HSV encephalitis have focal abnormalities on nonenhanced CT. MRI is the imaging modality of choice and should ideally be the first step after the clinical exam. The EEG is abnormal in almost all cases of HSV encephalitis and may show periodic lateralized epileptiform discharges.¹⁷⁵

Immune-mediated encephalitis, most commonly acute disseminated encephalomyelitis, can be triggered by viral encephalitis. Recurrences of neurologic symptoms after HSV encephalitis can be due to recurrence of HSV or the appearance of autoantibodies. Immune-mediated encephalitis is diagnosed by detecting antibodies directed against specific cell-surface proteins.¹⁷⁶ In some cases the diagnostic work up should include (1) anti-NMDA receptor antibodies, usually immunoglobulin IgG, in serum or CSF (for NMDA-receptor encephalitis); (2) antithyroid peroxidase IgG in serum or occasionally CSF (for steroid-responsive encephalopathy associated with autoimmune thyroiditis); and (3) leucine-rich glioma-inactivated protein 1 IgG in serum, voltage-gated potassium channel complex antibodies in serum, anti-glutamic acid decarboxylase IgG in CSF, and anti-GABA_B receptor IgG in serum (for limbic encephalitis). Diagnosis of immune-mediated encephalitis is important since it changes therapy. Apart from requiring additional laboratory tests, immune-mediated encephalitis can also manifest with different or additional symptoms compared with viral encephalitis, such as movement disorders, cataplexy, hallucinations, and paranoia in NMDA-receptor encephalitis; coreas, tics, and focal neurologic deficits in autoimmune thyroiditis-associated encephalopathy; and memory dysfunction in limbic encephalitis. Although rare in children, teratomas, most commonly in the ovary, can trigger anti-NMDA receptor encephalitis; thus MRI of the pelvis and abdomen should be considered in girls with this disorder.

Treatment

Antiviral therapy with acyclovir is indicated for HSV encephalitis. Acyclovir has a relatively short half-life in plasma, and more than 80% is excreted unchanged in the urine, so renal impairment can exacerbate toxicity. The standard dose of acyclovir for HSV encephalitis is 30 mg/kg/24 h, divided every 8 hours for 14 days. The dose in neonates is 60 mg/kg/d. The duration of treatment is 21 days for immunocompromised patients. Acyclovir is effective in encephalitis due to HSV types 1 and 2 and varicella-zoster. The dose of acyclovir for varicella-zoster encephalitis is similar to that for HSV.¹⁷⁴ Antiviral therapy with oseltamivir is indicated in H1N1 encephalopathy.¹⁷¹ Immunotherapy (most commonly methylprednisolone, IV immunoglobulin and plasmapheresis, or rituximab and cyclophosphamide in patients refractory to first-line therapy) has a major role in the treatment of immune-mediated encephalitis. Immunotherapy also has a role in the management of children or adolescents with recurrence of neurologic symptoms after recovery from HSV encephalitis.¹⁷⁶

Supportive Care in the Pediatric Intensive Care Unit

Data supporting an evidence-based approach to pediatric ICU care of children with meningitis and encephalitis is lacking. Careful attention to the ABCs with a neurointensive care approach is essential. If the GCS score is less than 8 or the airway or ventilation is compromised,

intubation should be performed using a neuroprotective rapid-sequence approach. Normal values for both PaCO_2 and PaO_2 should be ensured. Bacterial meningitis and encephalitis can be associated with severe septic shock that should be treated according to published guidelines.¹⁷⁷ Arterial blood pressure must be adequate to optimize cerebral perfusion.

In infants and children with meningitis and encephalitis, increased ICP may develop. The most important cause of morbidity and mortality in CNS infections is herniation of brain tissue secondary to intracranial hypertension. While the study of Kumar et al. described above suggested that CPP-targeted therapy might be superior to ICP-targeted therapy,¹⁶⁸ available evidence supports the association of intracranial hypertension with poor neurologic outcome in infants and children.¹⁷⁸⁻¹⁸⁰ In addition, ICP monitoring and aggressive treatment of intracranial hypertension showed reduction in the expected mortality rate in pediatric and adult patients with meningitis and encephalitis.¹⁸¹⁻¹⁸⁴ ICP monitoring and ICP-directed therapy should be considered if signs and symptoms of intracranial hypertension develop. ICP monitoring in patients with known or suspected CNS infection with a GCS score less than 8 may be considered at the discretion of the physician. An external ventricular drain is the preferred method of ICP monitoring if there is hydrocephalus or therapeutic CSF drainage is required.

Other aspects of contemporary pediatric neurointensive care should be addressed as noted above, including maintenance of euglycemia and euolemia and avoidance of hyponatremia. This is important because SIADH is common. Nutritional support as outlined in Chapter 44 should also be instituted as soon as possible.

Brain Abscess

Epidemiology and Diagnosis

Brain abscesses are most common in children between the ages of 4 and 8 years. The underlying causes of brain abscess include chronic otitis media and sinusitis, orbital cellulitis, dental infections, penetrating head injury, infection of ventriculoperitoneal shunts, immunodeficiency states, embolization due to congenital heart disease with left-to-right shunts, and meningitis. About 80% of brain abscesses in children occur in the frontotemporal and parietal lobes, and 30% involve multiple sites. Table 60-5 summarizes the relationships between predisposing conditions and site of brain abscess, likely pathogens, and suggested initial empirical treatment. In the early stages, the clinical presentation of brain abscess includes low-grade fever, headache, and lethargy. Vomiting, papilledema, focal neurologic signs, and seizures may develop as the inflammation proceeds. Nystagmus, ipsilateral ataxia and dysmetria, headache, and vomiting are characteristic signs of cerebellar brain abscess. If the abscess ruptures into the ventricular cavity, severe shock may develop rapidly, and death may result.¹⁸⁵

Contrast-enhanced head CT and MRI are the most reliable methods of identifying brain abscess. An abscess cavity shows a ring-enhancing

lesion with enhanced CT. MRI with gadolinium administration may reveal a capsule. Blood cultures are positive in about 10% of cases. Lumbar puncture should not be undertaken in a patient with suspected brain abscess. Examination of CSF is seldom useful, and this procedure may precipitate herniation.

Treatment

Treatment is initiated with an antibiotics based on the probable pathogenesis and most likely organism. An encapsulated abscess should be treated with antibiotics and aspiration, which is also the best diagnostic approach. Surgery is indicated when the abscess (1) is larger than 2.5 cm in diameter, (2) contains gas, (3) is multiloculated, (4) is located in the posterior fossa, or (5) when fungus is identified. The duration of treatment depends on the organism and response but usually ranges between 4 and 6 weeks. Other aspects of neurointensive care in the pediatric ICU for infants and children with brain abscess should mirror those presented for meningitis and encephalitis.¹⁸⁶

POSTOPERATIVE NEUROSURGICAL CASES

Epidemiology

Neurosurgical procedures for children vary widely and include elective and emergent operations at all ages for a variety of illnesses, most commonly brain tumors, hydrocephalus, and arteriovenous malformations.

Diagnosis

The need for admission to a pediatric ICU is largely determined by the potential complications associated with the surgery involved. The most common complications that require intensive monitoring include hydrocephalus, airway compromise, bleeding, vascular complications, fluid and electrolyte abnormalities, and seizures. Persistent hydrocephalus is an obvious concern in patients treated for this problem, either with shunting, ventriculostomy, or a decompressive procedure. Patients with congenital hydrocephalus require ICU monitoring as determined largely by their preoperative status. A child with slowly progressive hydrocephalus with few clinical symptoms may not require ICU admission, whereas preoperative symptoms that raise a concern of potential herniation will require close observation and monitoring. Patients with Chiari malformations, tumors impinging on CSF drainage, or ventricular hemorrhages all carry a significant risk of developing postoperative hydrocephalus.

Airway compromise is a potentially life-threatening complication that is of particular concern after neurosurgical procedures involving the brainstem, because vocal cord paralysis or cranial nerve damage is possible. Patients with congenital facial abnormalities are also at risk for respiratory compromise. A third scenario that predisposes neurosurgical patients to airway problems is a procedure requiring

TABLE 60-5 Predisposing Conditions, Etiologic Agents, and Empirical Treatment in Brain Abscess

| PREDISPOSING CONDITION | SITE OF ABSCESS | ETIOLOGIC AGENTS | TREATMENT |
|---|-------------------------------------|--|---|
| Sinusitis Orbital cellulitis Dental infection | Frontal lobe | Streptococci, <i>Bacteroides</i> , Enterobacteriaceae, <i>Staphylococcus aureus</i> , <i>Haemophilus</i> spp. | Vancomycin + third-generation cephalosporin + metronidazole |
| Otitis media Mastoiditis | Temporal lobe/cerebellum | Streptococci, <i>Bacteroides</i> , Enterobacteriaceae, <i>S. aureus</i> , <i>Haemophilus</i> spp., <i>Pseudomonas aeruginosa</i> | Vancomycin + third-generation cephalosporin + metronidazole |
| Head trauma Postsurgical infection | Site of injury or surgery | <i>S. aureus</i> , streptococci, Enterobacteriaceae, <i>Clostridium</i> | Vancomycin + third-generation cephalosporin + metronidazole |
| Congenital cyanotic heart disease | Middle cerebral artery distribution | <i>Streptococcus viridans</i> , anaerobic and microaerophilic streptococci | Penicillin + metronidazole |
| Ventriculoperitoneal shunt | Site of shunt | <i>P. aeruginosa</i> , streptococci, Enterobacteriaceae | Vancomycin + ceftazidime |

prone positioning during surgery, because significant facial swelling can result.

Although the potential for bleeding is always a concern after surgical procedures, several diseases carry more than the typical risk for hemorrhage. Surgical resection of a vascular malformation is of concern for bleeding if resection is incomplete. However, all procedures carry some risk for postoperative bleeding, including procedures that do not involve a craniotomy. Surgical procedures near major arteries can cause vasospasm with resultant cerebral ischemia or infarct. Subarachnoid hemorrhage from aneurysmal or vascular malformation rupture is another well-known cause of vasospasm.

Electrolyte abnormalities can result from three disturbances in normal regulatory mechanisms: diabetes insipidus, SIADH, and cerebral salt wasting (see later discussion for management). Other complications from neurosurgical procedures include CSF leak, aseptic meningitis, and pseudomeningocele.

Physical Examination

The immediate examination should include an evaluation of the ABCs. Specific to neurosurgical patients, however, a rapid neurologic examination is important to evaluate for baseline deficits after surgery. This is essential for evaluation of subsequent changes in neurologic status. For example, unequal pupillary size may be a result of surgical intervention and would be present immediately after the surgery. However, development of unequal pupils in a patient who previously had equal pupillary size may be the first sign of impending herniation. The initial neurologic examination should include a gross evaluation of mental status. Patients routinely have a depressed level of consciousness after anesthesia, but repeated examinations are necessary to ensure that mental status continues to improve. Measurement of the GCS score is one means of objectively quantifying a child's level of consciousness. Cranial nerve examination is limited by the child's ability to cooperate but should include pupillary response (cranial nerve II), observation of extraocular movements (cranial nerves III, IV, and VI), jaw deviation during sucking in an infant (cranial nerve V), facial asymmetry while crying or laughing (cranial nerve VII), gag reflex (cranial nerves IX and X), and shoulder droop (cranial nerve XI). The motor exam relies on careful observation of movements, because few patients will be able to cooperate with a formal exam early after surgery. The sensory examination involves observing gross responses to stimuli. A full evaluation of deep tendon reflexes is usually possible. Neurologic evaluation should be repeated frequently during the first 24 hours, evaluating for new or progressing deficits.

Treatment

All patients in the pediatric ICU should have cardiorespiratory monitoring. Respiratory monitoring should be designed to warn of impending airway compromise, including measurement of respiratory rate, pulse oximetry, and repeated examinations evaluating work of breathing, air entry, and evidence of stridor. Hemodynamic monitoring is useful for evaluating both hemodynamic and neurologic status. Increases in heart rate and BP can be an indication of pain or of seizure activity. Increased BP with a low heart rate is worrisome as it suggests raised ICP and impending herniation, although herniation is not always signaled by Cushing's triad in children. Tachycardia with prolonged capillary refill or hypotension may indicate excessive fluid losses, either from bleeding, third space losses, or excessive urine output. Tachycardia and hypotension can also result from loss of vasomotor tone, from infection, medications, or loss of neurologic regulation after spinal surgery. Invasive BP monitoring is necessary when patients are at high risk for any of the complications listed earlier. Strict measurement of fluid intake and output is essential to monitor fluid balance and interpret disturbances in fluid and electrolyte regulation. When the surgical procedure carries a high risk of inducing fluid regulation abnormalities, as in craniopharyngioma resections, serum and urine electrolytes should be tested every 4 to 6 hours, along

with continuous monitoring of urine output and central venous pressure. Temperature control is important and should therefore be monitored closely. Aggressive measures to prevent hyperthermia are warranted because neurologic injury may be exacerbated by high brain temperature.

Fluid management for the postoperative neurosurgical patient differs from that for other postoperative patients. Although maintenance of circulating volume is important, it is critical to avoid excessive hydration to limit cerebral edema. In general, neurosurgical procedures do not result in the large third-space losses seen with other surgeries. Once adequate volume status is achieved to maintain perfusion, fluid requirements will usually be met with a maintenance fluid rate.

Euglycemia is important after neurologic surgery, because both hypo- and hyperglycemia can exacerbate neurologic injury. Based on recommendations in adults, initial IV fluids in older children should generally be normal saline or 5% dextrose in normal saline, and serum glucose levels should be monitored closely. The duration for dextrose restriction in older children is controversial because ketosis develops even with euglycemia. Generally this is maintained for the initial 24 hours. Hyperglycemia, however, should probably be avoided throughout the entire acute period after CNS insults. Infants, on the other hand, do not have the same capacity for maintaining serum glucose levels if given no source of carbohydrate intake. Initial dextrose concentration in fluid for the infant with a CNS insult should probably be 5% (in normal saline). When higher dextrose concentrations are used, such as with hyperalimentation, hyperglycemia should be carefully managed with insulin infusion. The risk of exacerbation of brain injury by hyperglycemia in infants and children is likely but somewhat theoretical. In contrast, it is clear that hypoglycemia can be harmful to the injured brain and should be avoided.

Hyponatremia is of particular concern in neurosurgical patients, because the osmotic effects can result in increasing cerebral edema. The incidence of hyponatremia has been reported to be as high as 31% at 48 hours in pediatric surgical patients.¹⁸⁷ The use of isotonic fluids in the pediatric ICU can reduce the incidence of iatrogenic hyponatremia.¹⁸⁸ Thus, normal saline is the preferred IV fluid to avoid this complication. When hyponatremia occurs in conjunction with a decreasing urine output, a high specific gravity, and a high sodium concentration in the urine, it is likely the result of SIADH. In this case, fluid restriction is indicated. Neurosurgical patients also have two unique possible sources for excessive sodium loss: CSF loss from extraventricular drainage and urine loss from cerebral salt wasting. Both require correction of sodium loss.

Mild hypernatremia is generally not detrimental and is usually a result of excessive sodium intake or osmotic diuresis. A progressively increasing serum sodium concentration in the presence of an increasing volume of hypo-osmolar urine, however, suggests diabetes insipidus. This complication is unusual except with surgeries that have the potential for pituitary injury. Management of diabetes insipidus requires careful titration of fluids, with a maintenance rate to cover insensible losses (300 mL/m²/d) plus total replacement of urine output with a fluid that matches the urine electrolyte concentrations. Vasopressin or desmopressin therapy may be required to control the free water loss.

A few medications should be considered for every neurosurgical patient. First, antiemetics are important to prevent postanesthesia nausea and vomiting, because vomiting can cause a dramatic increase in intracranial pressure. Ondansetron and droperidol are good choices for antiemetic therapy because they are minimally sedating.¹⁸⁹ Postoperative seizures can have serious consequences, so antiepileptics should be considered in all patients deemed to be at risk. Typically, phenytoin is the least sedating drug for seizure prophylaxis. Patients on chronic anticonvulsants should have their usual regimen restarted as soon as possible after the surgery. Dexamethasone is used to reduce edema around brain tumors and reduce tumor size.¹⁹⁰ The use of corticosteroids is controversial in most other settings. However, patients who received corticosteroids preoperatively may require stress-dose corticosteroids during the postoperative period. Prophylaxis with H₂ blockers

may reduce gastrointestinal hemorrhage in critically ill patients¹⁹¹ but may also increase the risk of nosocomial infections.¹⁹² Gastrointestinal bleeding is more common after resection of a posterior fossa tumor, and use of prophylaxis has been advocated in these patients.¹⁹³

Emergency Intervention

The postoperative problem of most concern, and sometimes the most difficult to evaluate in a child, is an altered mental status. Although anesthetics or narcotics can produce an altered sensorium, emergent evaluation is indicated if reversal of these medications does not yield a reassuring examination. If the patient's GCS score is less than 8, intubation should be performed before any transport or testing. If an extraventricular drain is in place, it should be open and low enough to allow CSF drainage. Mannitol or hypertonic saline should be given if signs of impending herniation exist and transient hyperventilation begun until a definitive surgical intervention is carried out. An emer-

gent head CT should then be performed. Further action will be guided by the CT findings.

OTHER CRITICAL CENTRAL NERVOUS SYSTEM DISORDERS IN INFANTS AND CHILDREN

There are other critical CNS disorders in infants and children, including hepatic encephalopathy, hypertensive encephalopathy, and Reye syndrome. Discussion of these and other less common disorders is beyond the scope of this chapter, and the reader is referred to the appropriate primary references or other textbooks focused on pediatric critical care medicine. Reye syndrome was once a key disorder in the field of pediatric neurointensive care, reaching a peak of 555 cases in the United States in 1980. In the past decade, fewer than 2 cases per year have been reported.¹⁹⁴

KEY POINTS

1. There are important age-related differences in both CNS insults and the response to these insults in infants and children.
2. Neurointensive care for infants and children should focus on preventing secondary extracerebral insults and optimizing brain-directed therapies. Optimization of cardiopulmonary physiology, maintenance of euglycemia, and prevention of hyperthermia and hyponatremia are important for best outcomes. Pediatric neurocritical care services can help standardize and optimize care.
3. Cardiopulmonary arrest in infants and children results from asphyxia in the majority of cases.
4. The goals of treating status epilepticus are to provide respiratory and cardiovascular support, terminate seizure activity, identify and treat the precipitating factors, and prevent systemic complications. Continuous EEG monitoring is gaining acceptance.
5. Congenital and acquired heart diseases are the most important underlying causes of embolic stroke in infants and children. Clot retrieval is revolutionizing adult stroke care but is still exploratory in pediatric neurocritical care.
6. The etiology and treatment of bacterial meningitis differ between neonates and older infants and children.
7. Herpes simplex virus is an important cause of severe encephalitis in children.
8. Treatment of impending herniation includes immediate airway control, mannitol or hypertonic saline administration, hyperventilation, cerebrospinal fluid drainage (if available), and emergent CT evaluation.

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■ References for this chapter can be found at expertconsult.com

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The clinical management of patients with acute respiratory failure is based on the assumption that significant abnormalities in respiratory mechanics, respiratory muscle performance, and control of breathing are the underlying mechanisms responsible for acute respiratory failure.¹ The effects of mechanical ventilation on gas exchange, respiratory muscle load, and dyspnea depend on the matching between the ventilator settings and the patient's respiratory physiology. However, mechanical ventilation is rarely optimized, which would require ventilator settings based on accurate and reproducible measurements of lung and chest wall mechanics, respiratory muscle function, and respiratory drive.²⁻⁵

■ RESPIRATORY PHYSIOLOGY

The goal of the intrinsic ventilatory control system is to integrate the timing and intensity of the phrenic nerve signal, inputs from chemoreceptors and pulmonary stretch receptors, and variations in metabolic demands. Contraction of the respiratory muscles leads to the generation of flow and volume to provide adequate alveolar ventilation with minimal work of breathing.⁶ During spontaneous breathing,⁷ the respiratory muscles generate pressure (P_{mus}) to produce flow against the resistive properties (R_{RS}) and volume against the elastic properties (E_{RS}) of the respiratory system and to eventually overcome intrinsic positive end expiratory pressure (PEEPi). Under these circumstances, the act of spontaneous breathing can be described at any instant as follows:

$$P_{\text{mus}} = P_{\text{res}} + P_{\text{el}} + \text{PEEPi} \quad (\text{Equation 1})$$

where P_{res} represents the resistive pressure and is a function of flow ($P_{\text{res}} = \text{Flow} \times R_{\text{RS}}$), and P_{el} represents the elastic recoil pressure and is a function of volume ($P_{\text{el}} = \text{Volume} \times E_{\text{RS}}$). Assuming that R_{RS} and E_{RS} are linear, the equation becomes:

$$P_{\text{mus}} = (\text{Flow} \times R_{\text{RS}}) + (\text{Volume} \times E_{\text{RS}}) + \text{PEEPi} \quad (\text{Equation 2})$$

In patients with acute respiratory failure requiring ventilatory support, pressure generated by the ventilator (P_{appl}) is added to the pressure generated by the contraction of the respiratory muscles according to the following equation:

$$P_{\text{mus}} + P_{\text{appl}} = (\text{Flow} \times R_{\text{RS}}) + (\text{Volume} \times E_{\text{RS}}) + \text{PEEPi} \quad (\text{Equation 3})$$

The complex interaction among all the variables in Equation 3 can be summarized by the concept of neuroventilatory coupling (Fig. 61-1).⁸ Under normal conditions, as well as at the onset of acute respiratory failure, the spontaneous contraction of the respiratory muscles suddenly generates flow and volume; the slope of the relationship between effort and ventilatory output is conditioned by the contractile properties of the respiratory muscles and the impedance of the respiratory system. When positive pressure is applied to assist the action of breathing in most common modes of mechanical ventilation, the coupling between the effort and output may be compromised.

During volume-targeted assist-control ventilation (ACV), flow and volume remain constant despite changes in muscle contraction. During pressure-targeted flow-cycled (pressure support ventilation [PSV]) or time-cycled (assist-control pressure-targeted ventilation [AC/PCV]) ventilation, despite better coupling between inspiratory effort and ventilatory output, any increase in respiratory impedance decreases the amount of delivered flow and volume.⁸ During noninvasive ventilation (NIV), air leaks may further compromise the coupling between the patient effort and ventilatory output.⁹

■ PATIENT AND VENTILATOR VARIABLES

Patient Variables

The patient interacts with the ventilator based on three physiologic variables^{2,10,11}:

1. Respiratory drive¹²
2. Ventilatory requirements⁵
3. Timing of the breathing pattern¹⁰

Ventilator Variables

The ventilator interfaces with the patient's physiology based on three technologic variables:

1. The delivery mechanisms (control variable); that is, the algorithm used by the ventilator to assist ventilation through the delivery of flow, volume, or pressure¹³⁻¹⁸
2. The inspiratory trigger (phase trigger variable), or when the ventilator starts to deliver flow, volume, and pressure^{19,20}
3. The cycling off criteria (phase cycling variable), or when the ventilator stops assisting inspiratory effort and lets the patient exhale spontaneously^{16,17}

Features of ventilators, such as blowers and inspiratory, expiratory, and positive end-expiratory pressure (PEEP) valves, are also important in determining the interaction between patient and ventilator.²¹⁻²⁴

To unload the respiratory muscles, restore sufficient gas exchange, and relieve the patient from dyspnea, the clinician has two options: 1) total ventilator-controlled mechanical support; or 2) partial patient-controlled support.

Total Ventilator-Controlled Mechanical Support

In this mode, the patient's breathing pattern is totally controlled by the ventilator. The pressure generated by the respiratory muscles is abolished. Although this condition can be achieved in some conscious patients (i.e., patients with neuromuscular diseases), it usually requires sedation and/or paralysis. Flow, volume, and pressure are imposed by the ventilator, and the patient's breathing pattern is totally replaced by that of the ventilator. The risk of patient-ventilator asynchrony is therefore abolished, but there are potential risks associated with sedation and paralysis,²⁵ including respiratory muscle atrophy,²⁶ lung damage due to overdistention,²⁷ patient discomfort,²⁸ and difficulty weaning after prolonged controlled mechanical ventilation.¹

Partial Patient-Controlled Mechanical Support

With this mode, spontaneous breathing activity is partially preserved,²⁹ with a decreased need for sedation and paralysis.³⁰ The ability to restore gas exchange, unload respiratory muscles, and relieve patient dyspnea with partial patient-controlled mechanical support, therefore, depends on the absence of patient-ventilator asynchrony.³¹

Although there are no well-accepted definitions, patient-ventilator asynchrony is common, albeit often unrecognized, underestimated, and inappropriately treated.^{3-5,18,31-33} Patient-ventilator asynchrony appears whenever a mismatch between the three physiologic variables characterizing spontaneous breathing (ventilatory drive, ventilatory requirements, and the duration and ratio of inspiratory time to total breath cycle duration) and the three technologic variables

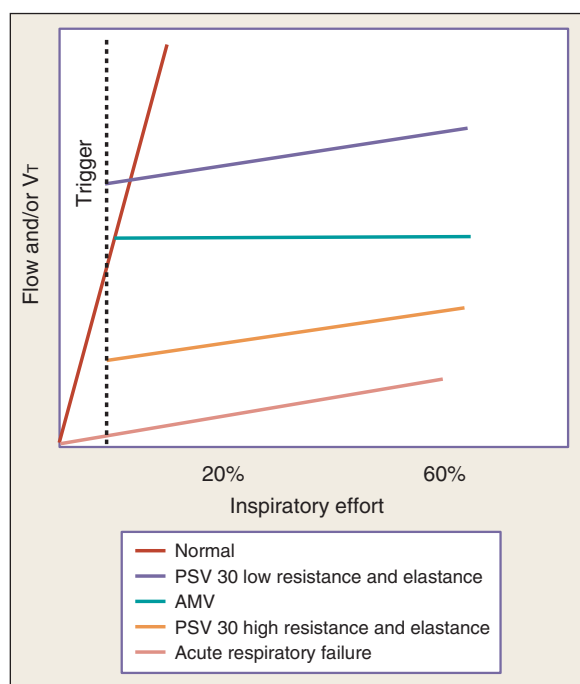


FIGURE 61-1 ■ Neuroventilatory coupling. Under normal conditions, as well as at the onset of acute respiratory failure, spontaneous contraction of respiratory muscles suddenly generates flow and volume. The slope of the relationship between effort and ventilatory output is conditioned by the contractile properties of the respiratory muscles and impedance of the respiratory system. When positive pressure is applied to assist the action of breathing in the most common modes of mechanical ventilation, the coupling between effort and output is compromised. During volume targeted assist-control ventilation (ACV), flow and volume remain constant despite changes in muscle contraction. During pressure support ventilation (PSV), despite a sort of coupling between inspiratory effort and ventilatory output, any increase in respiratory impedance decreases the amount of delivered flow and volume. VT, tidal volume.

characterizing ventilator function (trigger function, the gas delivery algorithm [controlled variable], and cycling criteria) occurs.

RESPIRATORY DRIVE-VENTILATOR TRIGGER ASYNCHRONY

During partial ventilatory assistance, the inspiratory synchronization system (inspiratory trigger) detects any patient inspiratory effort and activates a mechanical act. Therefore, inspiratory effort is tracked to couple the patient's effort with the delivery of pressure, flow, or volume. The goal of a good inspiratory trigger is to reduce the duration and intensity of the muscular effort as much as possible prior to the initiation of a mechanically supported breath.³⁴ It has been suggested that a trigger (independent of the algorithm) must have a response time of less than 100 ms. However, the inspiratory effort necessary to trigger a breath may be a significant part of the total inspiratory effort, representing 17% and 12% of the total inspiratory effort during pressure and flow triggering, respectively.^{19,20,13,14,15,16,17,18,21,32,33} Aslanian and coworkers found that although the time required for triggering was 43% shorter and the effort during the time of triggering was 62% less with flow triggering than with pressure triggering, effort for the post-triggering phase was equivalent for both these modalities.³⁵ Therefore, the clinical benefit of flow triggering appears to be much less relevant than commonly stated.³

Inspiratory phase asynchrony may be due to problems with inspiratory triggering, and this can be correlated with the respiratory drive.

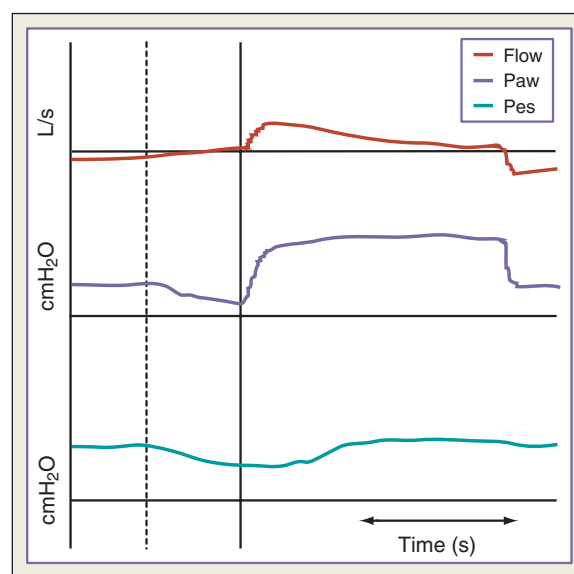


FIGURE 61-2 ■ Representative tracings show the interaction between patient effort and triggering of the ventilator. The delay between the beginning of inspiratory muscle activity (dotted line) and the beginning of mechanical inflation (solid line) can cause an inspiratory phase asynchrony. Flow: flow generated at airway opening; Paw: the pressure applied at airway opening; Pes: esophageal pressure.

Phase lag quantifies the delay between the start of inspiratory muscle activity and the beginning of mechanical inflation (Fig. 61-2).^{3,10,11} The presence of a threshold load, such as dynamic intrinsic PEEP, may further complicate the patient-ventilator interaction during the triggering phase.¹⁹ Giuliani et al. suggests that effort during triggering determines patient effort during the remaining portion of inspiration.³⁶ Leung and coworkers demonstrated that the higher the level of ventilator-applied pressure, the lower the respiratory drive, but the longer the time required to trigger the ventilator. As a result, respiratory muscles generate smaller inspiratory swings in intrathoracic pressure but over a longer inspiratory time.² Another problem is related to the fact that pressure is mostly detected inside the ventilator. Therefore, any resistive load (e.g., endotracheal tube or upper airways during NIV) reduces the ventilator trigger sensitivity in response to patient effort.¹⁸

Auto-triggering can be defined as a mandatory breath delivered in the absence of a patient's inspiratory effort.²² Monitored breaths on the ventilator are higher than those initiated by the patient. Auto-triggering can be generated by too sensitive inspiratory triggers, air leaks, or an external signal, such as heart rate or water in the respiratory circuit.

Ineffective triggering is due to the ventilator's inability to detect the patient's "request" for an assisted breath despite substantial inspiratory effort (Fig. 61-3). This phenomenon usually occurs with high levels of ventilator assistance and short expiratory times. Mechanical characteristics that may induce ineffective triggering include low elastance, high resistance, and intrinsic PEEP. Ineffective triggering is not correlated to an increase in the patient's inspiratory effort.⁴ The application of external PEEP below the intrinsic PEEP level can reduce the inspiratory effort required to trigger the ventilator.³⁷

Double triggering is defined as the presence of two inspiratory cycles separated by a very short expiratory time and may result in breath stacking. Double triggering can be elicited by a high patient ventilatory demand causing two breaths with a limited expiratory phase due to a too short of a ventilator inspiratory time (Ti) compared to the patient's neural time. This problem can be addressed by increasing Ti in time-cycled mode, by adjusting the expiratory threshold time in the flow-cycled mode, or optimizing pressure rise time (i.e., the time taken to reach the pressure set on the ventilator).³⁸

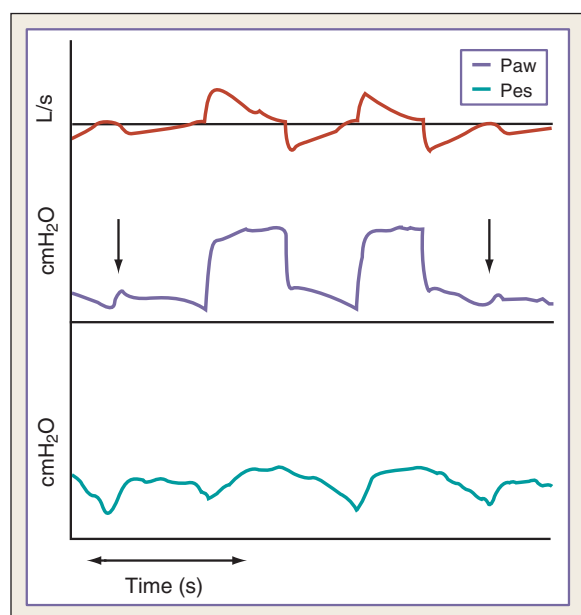


FIGURE 61-3 ■ Representative tracings show ineffective triggering due to ventilator's inability to detect patient's "request" for an assisted breath. A substantial inspiratory effort (arrows) generates only a bump in the flow and pressure tracings instead of a mandatory assisted breath. Flow: flow generated at airway opening; Paw: the pressure applied at airway opening; Pes: esophageal pressure.

Reverse-triggering is a recently discovered form of neuromechanical coupling with potentially important clinical consequences in heavily sedated patients.³⁹ In this case, contrary to the usual triggering sequence (patient's effort switching on the ventilator-driven breath), diaphragmatic muscle contractions are triggered by ventilator insufflations.

New trigger algorithms aim to improve the patient-ventilator interaction during sudden changes in flow or respiratory rate and the presence of air leaks during NIV. Volume triggers, triggers linked to flow waveform algorithms, combining pressure and flow signals in the same trigger algorithm, or using both pressure and flow triggers have been developed. However, all inspiratory trigger drawbacks may be overcome by using a neural trigger obtained using a dedicated nasogastric tube with multiple arrays of electrodes placed in the distal esophageal portion.^{8,40,41}

VENTILATORY REQUIREMENT-GAS DELIVERY ASYNCHRONY

Gas delivery asynchrony occurs when ventilator-delivered flow, volume, and pressure are insufficient to meet the patient's ventilatory demand. Ward and coworkers demonstrated that increasing the flow rate could be used as a means of reducing the patient's respiratory drive and active respiratory muscle work,¹³ although this may exert an excitatory effect on the respiratory rate and the rate of rising of inspiratory muscle activity.^{3,16,17,42-48} Laghi and colleagues demonstrated that the imposed inspiratory time during mechanical ventilation determined respiratory frequency independent of inspiratory flow and tidal volume.¹⁶ Pressure-targeted breaths may more effectively match the patient's ventilatory requirements because the flow is the dependent variable during constant pressure delivery. In addition, rapid pressurization of the airways is coupled with high inspiratory flow only at the beginning of inspiration, thus reproducing the physiologic flow profile.⁴⁹ However, during a pressure-targeted breath, the setting for the time of pressure increase may influence the patient-ventilator interaction because its modification determines the dependent flow output.^{50,51}

INSPIRATORY TIMING-VENTILATOR CYCLING ASYNCHRONY

A breath can be pressure, time, volume, or flow-cycled.⁵¹ While volume and pressure cycling are no longer used, a breath is defined as time-cycled when it is terminated after a given preset inspiratory time is reached (e.g., pressure- or volume-controlled time-cycled breaths) or as flow-cycled when the generated inspiratory flow decays from its peak of a fixed percentage (e.g., PSV mode).

Ventilator-patient asynchrony occurs when the patient is trying to exhale, but the ventilator is still delivering gas.^{35,52,53} Parthasarathy and coworkers demonstrated that prolonging mechanical inflation into neural expiration reduces the time available for unopposed exhalation, resulting in the need for a greater inspiratory effort to trigger the ventilator.⁵² Younes and colleagues showed that the delayed opening of the exhalation valve in ventilator-dependent patients exacerbates dynamic hyperinflation.⁵⁴

In patients ventilated with a time-cycled breath, expiratory phase asynchrony occurs when the patient's neural inspiratory time is shorter or longer than the ventilator inflation time. For proper cycling of the ventilator and optimal patient-ventilator synchrony, the patient's inspiratory flow and ratio of inspiratory time-to-total breath cycle duration must be tracked.

During flow-cycled breaths as in pressure-support mode, inspiratory time is determined exclusively by the time taken for the exponentially declining flow to reach the flow threshold value (when cycling between inspiration and expiration occurs).^{32,55} The inspiratory flow threshold value, also called the *expiratory trigger*, thus controls the inspiration-to-expiration switch in these modalities under the postulate that the very end of patient inspiration is tracked by inspiratory flow decay.^{50,56}

The goal of these ventilatory modes is to optimize the synchronization between spontaneous patient inspiratory time and ventilator inspiratory time. However, for proper cycling-off and optimal patient-ventilator synchrony, the ventilator must always track the patient's inspiratory flow.^{52,57,58}

PATIENT-VENTILATOR ASYNCHRONY DURING PRESSURE SUPPORT VENTILATION

Three phases may influence patient-ventilator interaction during PSV: 1) the threshold value of inspiratory flow decay (expiratory trigger); 2) the pressure ramp (pressure slope); and 3) the level of PSV.

(1) The expiratory trigger sensitivity can be fixed (default at 25% of peak flow) or can vary from 1% to 90% or 5 to 25 L/min in some old ventilator software (Fig. 61-4).⁵⁹ It can also be linked to algorithms where there is a ranking logic of expiratory cycling criteria that links cycling to expiration. Setting the expiratory trigger at a higher percentage of peak inspiratory flow (i.e., 40% to 70% of decay of the peak inspiratory flow) in patients with obstructive pulmonary disease improves patient-ventilator synchrony and reduces inspiratory muscle effort.⁶⁰ In addition, the modification of the cycling-off criteria may have a beneficial effect on reducing the dynamic hyperinflation and inspiratory effort in chronic obstructive pulmonary disease patients, especially at low levels of pressure support.⁶¹

The proper adjustment of the expiratory trigger threshold may be important in improving patient-ventilator synchrony and in decreasing the work of breathing during acute lung injury. Unlike in obstructive pulmonary disease, setting the threshold at 5% of the peak inspiratory flow might be the optimal value for patients with acute respiratory distress syndrome or acute lung injury.⁶² Indeed, Chiumello et al. found that in patients recovering from acute lung injury during PSV at 15 cm H₂O, the lowest cycling-off criteria reduced the respiratory rate and increased the tidal volume without modifying the work of breathing.⁶³

The expiratory sensitivity setting is crucial when ventilators are used to deliver NIV since air leaks may cause an abnormal prolongation of the mechanical inspiratory time at the expense of a patient's expiration that results in shortened and hampered expiration (inspiratory hang-up) (Fig. 61-5).⁶⁴⁻⁶⁹

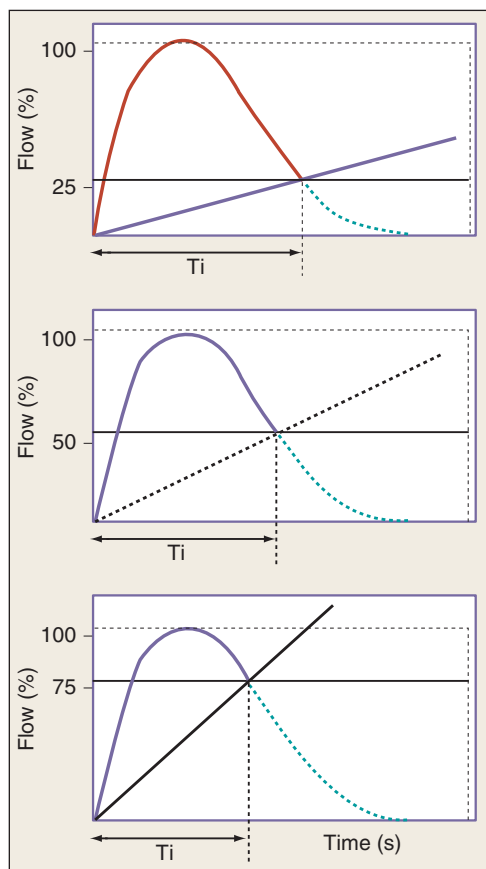


FIGURE 61-4 ■ Representative tracings show different settings for expiratory trigger sensitivity on a flow-time plot. *Top to bottom*, Expiratory trigger set at 25%, 50%, and 75% of peak flow. Ventilator inspiratory time is influenced by preset flow expiratory trigger sensitivity, at which point the ventilator switches to expiration.

(2) The setting of the pressure rise time (pressure slope) can affect the expiratory threshold by modifying the dependent inspiratory flow.^{63,70-73} Although there is some evidence that rapid pressure rise times might reduce a patient's work of breathing,⁷¹ a fast pressure increase may lead to particularly high peak inspiratory flow, which may then cause premature termination of inspiration when the fixed percentage criterion for expiratory cycling is reached (Fig. 61-6).^{18,61,73}

Prinianakis et al. assessed the effects of varying the rate of pressure change during noninvasive PSV on the breathing pattern of patients with COPD, as well as inspiratory effort, arterial blood gases, tolerance to ventilation, and the amount of air leakage. No significant changes were observed in breathing pattern and arterial blood gases between the differing amounts of pressure change, but the pressure-time product of the diaphragm, an estimate of its metabolic consumption, significantly decreased with increasing the rate of pressurization. Interestingly, air leaks increased, and the patients' tolerance of ventilation was significantly poorer with the fastest rate of pressure change.⁷⁴

(3) During NIV, the pressure support level affects patient-ventilator interactions, mainly through effects on the generation of air leaks.^{9,65} Since air leaks may determine modifications in the inspiratory flow profile (see above), their reduction by lowering to a PSV level of 1 or 2 cm H₂O has been demonstrated to improve patient-ventilator asynchrony.⁹

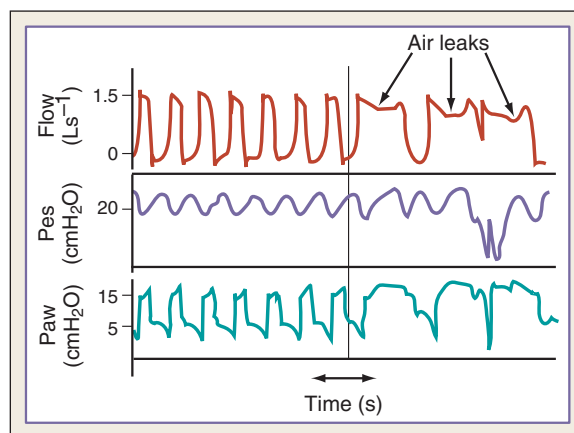


FIGURE 61-5 ■ Representative record of air leaks during noninvasive face mask pressure support ventilation. The presence of air leaks causes prolonged ventilator inspiratory time (arrows). Flow, flow generated at airway opening; Paw: the pressure applied at airway opening; Pes: esophageal pressure.

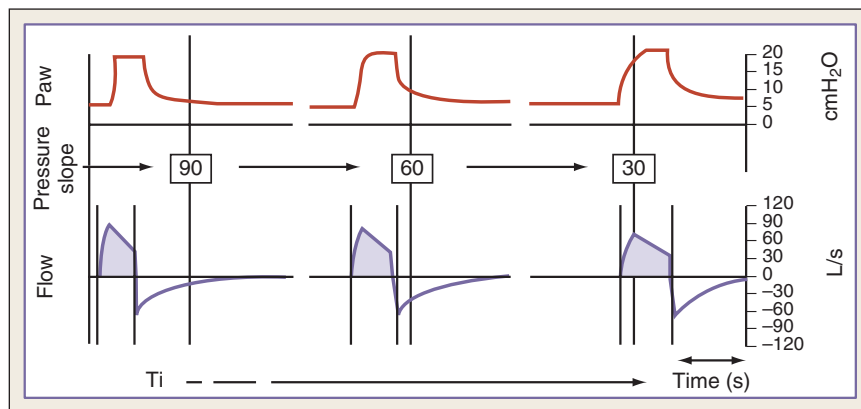


FIGURE 61-6 ■ Representative tracings show different pressure rise time sensitivities on a flow-time plot. *Left to right*, Pressure rise time set at 90%, 60%, and 30% of maximal pressurization time. Ventilator inspiratory time (shaded area) is influenced by preset pressure-slope sensitivity that generates a different peak inspiratory flow. Paw, the pressure applied at airway opening; Flow, flow generated at airway opening.

In conclusion, dyssynchrony at the termination of a PSV breath can be corrected by varying the cycling-off criteria (e.g., the expiratory trigger threshold) or modulating the inspiratory flow (e.g., modifying the pressure slope or varying the set pressure level).⁹ Automated modes designed to achieve an optimal expiratory cycling during PSV are available but deserve further investigation.⁷⁵⁻⁷⁶

TOTAL PATIENT-CONTROLLED MECHANICAL SUPPORT

Optimization of patient-ventilator interactions can be obtained only by continuous matching between the triggering, flow delivery, cycling functions of the ventilator and the patient's ventilatory drive, spontaneous inspiratory flow demand, and ratio of inspiratory time to the total breath cycle. This implies a continuous measurement of physiologic variables and continuous adaptation of the ventilator to the spontaneous variations in these variables. Future development in ventilator technology should be oriented toward systems with the capability to automatically interface between physiologic parameters and ventilator output. Such technology will be based on closed-loop algorithms able to achieve total patient-controlled mechanical support.⁴

The design features of an automatic control system in a mechanical ventilator include (1) what activates the system (the input); (2) what the system produces (the output); and (3) the protocol used to link input and output (the controlling algorithm). In a closed-loop system, the output will activate and condition the input. When changes in output are opposite to changes in input, the closed loop is said to be negative. The closed loop is positive when variations in output mirror variations in input. The most common example of a negative closed-loop control system in a clinical setting is the ventilator humidifier. In this case, the input is the temperature inside the chamber, and the output is the temperature of the gas being delivered to the patient. The controlling algorithm is designed to keep the latter constantly above a value set by the operator. If the output (i.e., the temperature of gas delivered to the patient) is lower than the preset level, the algorithm will increase the input (i.e., the temperature in the chamber). If the output is higher than the preset level, the algorithm will decrease the input. Closed-loop systems are hence able to stabilize and limit the performance of a mechanical system.

In the case of acute respiratory failure, the patient is unable to provide sufficient output (i.e., minute ventilation). Therefore, the ventilator should be able to detect the input from the patient and continuously adapt the output. If the input is increasing (i.e., ventilatory requirements are increasing), the ventilator will increase the output (i.e., apply more positive pressure). If the input is decreasing (i.e., ventilatory requirements are decreasing), the ventilator will decrease the output (i.e., apply less positive pressure). The controlling closed loop eventually applied by the ventilator must be positive. Positive closed-loop control systems are inherently unstable in the sense that they tend to: (1) "run away" with ventilatory assistance. If the pressure generated by the ventilator is higher than the pressure required to offset the passive properties of the respiratory system, the ventilator will continue to deliver flow and volume while the patient stops his or her inspiratory effort and tries to initiate expiration; and (2) "extinguish" ventilatory assistance. If the patient does not produce any inspiratory effort, the ventilator will not produce any ventilatory support.

Based on closed-loop algorithms, new modes of mechanical ventilation have been proposed. Such approaches represent modifications of PSV and are characterized by the patient's ability to control the amount of assistance provided by the ventilator. They are differentiated by the patient-related variables used to close the loop.

PROPORTIONAL ASSISTED VENTILATION (PAV), PROPORTIONAL PRESSURE SUPPORT (PPS), AND PROPORTIONAL ASSISTED VENTILATION PLUS (PAV+)

During PAV and PPS, the ventilator generates pressure in proportion to the patient-generated flow and volume^{77,78}; the ventilator amplifies

patient effort without imposing any ventilatory or pressure targets; and ventilator-generated pressure rises as long as inspiratory muscle effort is produced by the patient. During these modes of mechanical support, the clinician adjusts the percentage of flow-assisted or volume-assisted ventilation after determining the patient's resistance and elastance with the goal of reducing the load imposed by the patient's inspiratory workload.^{79,80,81} Despite the exciting potential of these techniques⁸¹⁻⁸⁴ applied either invasively or noninvasively,⁷⁵⁻⁹³ no large-scale studies have demonstrated an improvement in patient outcome with PAV or PPS compared with other modes of ventilation. Several studies performed during invasive ventilation showed that PAV improves patient-ventilator synchrony at the start of inspiration^{32,86,88} but not necessarily at the end.⁷⁸⁻⁸⁶

Compared with PAV, PAV+ provides a continuous measurement of the patient's elastance and resistance according to the method described by Younes and coworkers.^{79-81,89-93} This option requires that the physician set only a given percentage of the overall pressure gain level. During invasive ventilation, PAV+ appears to reduce the incidence of patient-ventilator asynchronies considerably compared to conventional PAV⁹⁴ (Fig. 61-7). When compared to PSV, PAV+ decreases the setting time and fastens changes in sedative doses.⁹⁵

NEURAL-ADJUSTED VENTILATORY ASSISTANCE (NAVA)

With NAVA, the electrical activity of the diaphragm is measured using an electrode array inserted into a nasogastric tube placed in the lower esophagus; this information is then used to control the ventilator to generate flow, volume, and pressure by applying pressure in proportion to diaphragm electrical activity.^{8,38,39,96,97} A representative tracing of NAVA is shown in Fig. 61-8. With NAVA, therefore, the patient retains full control of the breathing pattern.⁹⁸ Unlike with the proportional mode described earlier, estimates of respiratory mechanics are not needed. With NAVA, the patient's respiratory center controls the assisted positive breaths in all phases of the ventilation cycle, from triggering to cycling-off of inspiration. Any change in patient ventilatory output is matched breath by breath by the ventilator, even in the presence of variations in respiratory mechanics.

NAVA has been shown to decrease ineffective efforts (trigger asynchrony) and premature and delayed cycling (cycle asynchrony) compared to a pressure-controlled flow-cycled ventilation (i.e., PSV).⁹⁹⁻¹⁰¹ Furthermore, Vignaux et al. demonstrated that, compared to pressure support NIV, NAVA improves patient-ventilator synchrony both by reducing trigger delay and the number of asynchrony events.¹⁰² NAVA also appears to improve patient-ventilator synchrony during helmet ventilation.¹⁰³ Finally, NAVA has one major advantage compared to PAV since air leaks do not interfere with its correct functioning.¹⁰⁴

ADAPTIVE SUPPORT VENTILATION

Compared to PAV and NAVA, adaptive support ventilation is an assist time-limited, pressure-targeted mode of ventilation (pressure-controlled ventilation) that relies on a negative closed-loop system of regulating ventilator settings in response to changes in both respiratory impedance (elastance and resistance) and the patient's spontaneous efforts.¹⁰⁵ The basic principle relies on the work of Otis and coworkers¹⁰⁶ and Mead,⁶ demonstrating that for a given level of minute alveolar ventilation, there is a respiratory rate that is least costly regarding respiratory work. With adaptive support ventilation, the operator enters the patient's body weight and sets the desired minute ventilation. The expiratory time constant is determined by analysis of the expiratory flow-volume curve.¹⁰⁷ Adaptive support ventilation thus adjusts for inspiratory pressure, inspiratory-expiratory time ratio, and the mandatory respiratory rate to maintain the target minute ventilation and respiratory rate within a framework designed to avoid both rapid, shallow breathing and excessive inflation volumes. Spontaneous breathing triggers either a pressure-controlled or a spontaneous breath with inspiratory pressure support, the level of which is adjusted to meet the target respiratory rate-tidal volume combination.

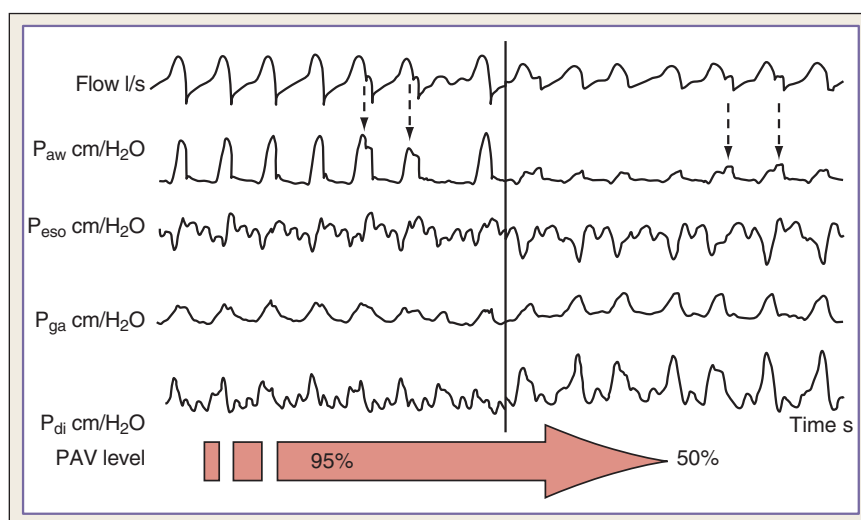


FIGURE 61-7 ■ Representative tracing of flow (Flow), airway pressure (P_{aw}), esophageal pressure (P_{eso}), gastric pressure (P_{ga}), and transdiaphragmatic pressure (P_{di}) during PAV+ ventilation. Directional arrow (bottom) going from left to right shows that the gain is reduced from 95% to 50% with a subsequently increased inspiratory effort. Dotted arrows (top) indicate the measurement of respiratory mechanics automatically computed by the ventilator.

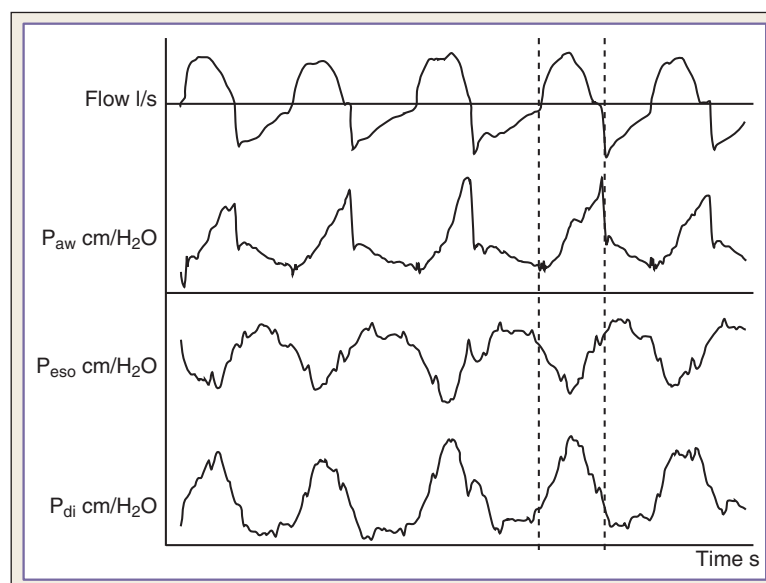


FIGURE 61-8 ■ Representative tracing of flow (Flow), airway pressure (P_{aw}), esophageal pressure (P_{eso}), and transdiaphragmatic pressure (P_{di}) during NAVA ventilation. The two dotted lines define the beginning and end of the patient's inspiratory effort.

KEY POINTS

1. Patient-ventilator asynchrony is common during mechanical ventilatory support. It is often unrecognized, underestimated, and inappropriately treated in a clinical setting.
2. Patient-ventilator asynchrony occurs when the three physiologic variables of the patient's breathing pattern, ventilatory drive, driving, and timing components of the breathing cycle, do not match ventilator trigger, ventilator-delivered flow, and ventilator cycling criteria.
3. Clinical optimization of patient-ventilator interactions can be obtained only by continuously matching the triggering, flow delivering, and cycling functions of the ventilator with the patient's physiologic variables.
4. Optimization of patient-ventilator interactions during invasive or noninvasive ventilation implies a continuous measurement of physiologic variables and continuous adaptation of the ventilator to the spontaneous variations in these physiologic variables.
5. Future developments in ventilator technology should be oriented toward a system with the capability to interface automatically between physiologic parameters and ventilator outputs. Such technology will be based on closed-loop algorithms able to achieve total patient-controlled mechanical support.

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This study found that in difficult-to-wean patients with chronic obstructive pulmonary disease, proportional assisted ventilation (PAV) improves ventilation and decreases inspiratory muscle effort. It also found that the combination of PAV and continuous positive airway pressure can unload the inspiratory muscles to values close to those in normal subjects.
- Beck J, Sinderby C, Lindström L. Effects of lung volume on diaphragm EMG signal strength during voluntary contractions. *J Appl Physiol* 1998;85(3):1123-34.
These authors found that variations in end-expiratory lung volume between breaths can affect the transformation of respiratory muscle activation into mechanical output (neuromechanical coupling).
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This article describes the loose patient-ventilator synchrony in the presence of air leaks and noninvasive pressure support ventilation.
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These authors found that during the assist-control mode, ventilator inspiratory time can determine respiratory frequency independently of inspiratory flow and tidal volume.
- Leung P, Jubran A, Tobin MJ. Comparison of assisted ventilator modes on triggering, patients' effort, and dyspnea. *Am J Respir Crit Care Med* 1997;155(6):1940-8.
This study found that when receiving assist-control ventilation or high levels of pressure support, one-quarter to one-third of a patient's inspiratory efforts may fail to open the inspiratory valve triggering the machine. The number of ineffective triggering attempts increases in proportion to the level of ventilatory assistance and is not correlated with the magnitude of inspiratory effort at a given level of assistance.
- Parthasarathy S, Jubran A, Tobin MJ. Cycling of inspiratory and expiratory muscle groups with the ventilator in airflow limitation. *Am J Respir Crit Care Med* 1998;158(5):1471-8.
These authors found that the continuation of a mandatory mechanical breath into neural expiration was associated with a waste of inspiratory effort, defined as failure of the subsequent inspiratory attempt to trigger the ventilator.
- Parthasarathy S, Tobin JM. Effect of ventilator mode on sleep quality in critically ill patients. *Am J Respir Crit Care Med* 2002;166(11):1423-9.
These authors found that inspiratory assistance during pressure support causes hypoxemia, which combined with a lack of a backup rate and wakefulness drive can lead to central apneas and sleep fragmentation, especially in patients with heart failure. A backup rate, as during assist-control volume-targeted ventilation, prevents the development of apneas and perhaps decreases arousals.
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Noninvasive ventilation is defined as the provision of ventilatory assistance to the lungs without an invasive artificial airway. Noninvasive ventilators consist of a variety of devices, including negative- and positive-pressure ventilators. Until the early 1960s, negative-pressure ventilation in the form of tank ventilators was the most common type of mechanical ventilation outside of the anesthesia suite.¹ However, during the Copenhagen polio epidemic of 1952, it was observed that the survival rate improved when patients with respiratory paralysis were treated with invasive positive-pressure anesthesia devices. Subsequently, invasive positive-pressure mechanical ventilation gradually became the preferred means of treating acute respiratory failure.² Negative-pressure and other so-called body ventilators remained the mainstay of ventilatory support for patients with chronic respiratory failure until the mid-1980s.¹

With improving mask and ventilator technology and the many advantages over negative-pressure ventilation,¹ noninvasive positive-pressure ventilation (NIPPV) displaced negative-pressure ventilation as the treatment of choice for chronic respiratory failure in patients with neuromuscular and chest wall deformities.³ Over the past 30 years, noninvasive ventilation has spread from the outpatient to the inpatient setting, where it is used to treat acute respiratory failure. Studies involving large clinical databases show that NIPPV use for patients with acute respiratory failure (ARF) due to COPD, as well as non-COPD diagnoses, increased several fold during the first decade of the millennium.⁴ A recent survey in Massachusetts found that NIPPV is used very frequently in the acute care setting, constituting up to 40% of initial ventilator starts.⁵ This chapter discusses the rationale for the increased use of NIPPV in critical care, as well as appropriate indications, practical applications, and monitoring.

RATIONALE

The most important advantage of noninvasive ventilation is the avoidance of complications associated with invasive mechanical ventilation. These include upper airway trauma, the bypass of the upper airway defense mechanisms, increased risk of nosocomial pneumonia, and interference with upper airway functions, including the ability to eat and communicate normally.⁶ By avoiding airway intubation, noninvasive ventilation leaves the upper airway intact, preserves airway defenses, and, during breaks, allows patients to eat and vocalize normally, as well as expectorate secretions. Compared with invasive mechanical ventilation, noninvasive ventilation reduces infectious complications, including pneumonia, sinusitis, and sepsis.⁷⁻⁹ Strengthening the rationale for its use is evidence that noninvasive ventilation lowers the morbidity and mortality rates of selected patients with acute respiratory failure and may shorten hospital length of stay or avoid hospitalization altogether,¹⁰ thus reducing costs.

The main indication for mechanical ventilatory assistance is to treat respiratory failure, either type 1 (hypoxemic), type 2 (hypercapnic), or both. [Figure 62-1](#) shows that airspace collapse, surfactant abnormalities, and airway narrowing and closure contribute to ventilation-perfusion abnormalities and shunt, which cause hypoxemia. By opening the collapsed air spaces and narrowed airways, positive airway pressure reduces shunt and improves ventilation-perfusion relationships, ameliorating hypoxemia. In addition, positive airway pressure can reduce the work of breathing by improving lung compliance as a

consequence of opening collapsed air spaces. Another potential benefit of positive airway pressure is enhanced cardiovascular function via the afterload-reducing effect of increased intrathoracic pressure. Conversely, deleterious cardiovascular effects may occur if the preload-reducing effect outweighs the afterload-reducing effect, as may be observed in patients with reduced intravascular fluid volume.

MECHANISMS OF ACTION

[Figure 62-2](#) shows the pathophysiologic mechanisms that contribute to ventilatory failure. Increased airway resistance, reduced respiratory system compliance, and intrinsic positive end-expiratory pressure (PEEP) contribute to the increased work of breathing, predisposing patients to respiratory muscle fatigue. In patients with chronic obstructive pulmonary disease (COPD), the increased radius of the diaphragmatic curvature, which increases muscle tension and thereby increases impedance to blood flow, exacerbates the situation. By counterbalancing intrinsic PEEP with extrinsic PEEP and by augmenting tidal volume with intermittent positive-pressure ventilation, NIPPV reduces the work of breathing and avoids the vicious circle leading to respiratory failure. Work of breathing measurements, including transdiaphragmatic pressure, diaphragmatic pressure-time product, and diaphragmatic electromyographic amplitude, are all decreased when NIPPV is delivered to patients with exacerbations of COPD. In such patients, continuous positive airway pressure (CPAP) and pressure-support ventilation (PSV) both reduce the work of breathing, but the combination of the two (PSV + PEEP) is more effective than either alone.¹¹

INDICATIONS

A number of causes of acute respiratory failure are now considered appropriate for noninvasive ventilation therapy and are listed in [Box 62-1](#). Evidence supporting these indications is rated and briefly discussed here; guidelines for patient selection are discussed later.

Airway Obstruction

Chronic Obstructive Pulmonary Disease

A number of randomized controlled trials^{12,13} and meta-analyses¹⁴ have consistently shown that compared with conventional therapy, NIPPV improves vital signs, gas exchange, and dyspnea scores; reduces the rates of intubation, morbidity, and mortality; and shortens hospital length of stay in patients with moderate to severe exacerbations of COPD. Thus, NIPPV is considered the ventilatory mode of choice in selected patients with acute exacerbations of COPD. Some studies suggest that the addition of heliox to NIPPV further improve the work of breathing and gas exchange during COPD exacerbations,¹⁵ but a subsequent multicenter trial found no improvement in other outcomes compared with noninvasive ventilation alone.¹⁶

Asthma

Uncontrolled studies have reported improvements in gas exchange and low rates of intubation after the initiation of NIPPV in patients with severe asthma attacks. Two controlled trials have demonstrated a more rapid improvement in expiratory flow rates with NIPPV,^{17,18} and one

BOX 62-1**Indications for Use of Noninvasive Ventilation in the Acute Care Setting****AIRWAY OBSTRUCTION**

COPD (A)*
 Asthma (B)
 Cystic fibrosis (C)
 Obstructive sleep apnea or obesity hypoventilation (B)
 Upper airway obstruction (C)
 Facilitation of weaning in COPD (A)
 Extubation failure in COPD (B)

HYPOXEMIC RESPIRATORY FAILURE

ARDS (C)
 Pneumonia (C)
 Trauma or burns (B)
 Acute pulmonary edema (use of CPAP) (A)
 Immunocompromised patients (A)
 Restrictive thoracic disorders (C)
 Postoperative patients (B)
 Do-not-intubate patients (C)
 During bronchoscopy (C)

*Letters in parentheses indicate the level of evidence supporting the use of noninvasive ventilation: A, multiple randomized, controlled trials; recommended; B, at least one randomized, controlled trial; weaker recommendation; C, case series or reports; can be attempted, but with close monitoring.

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure.

showed a decreased hospitalization rate in acute asthma patients treated with noninvasive ventilation compared with a sham mask.¹⁸ Neither study was powered adequately to assess intubation or mortality rates. Nonetheless, these data support a trial of NIPPV in asthmatics responding poorly to initial bronchodilator therapy. Noninvasive ventilation can be combined with continuous nebulization and heliox, although the added value of these latter therapies has not been established in controlled trials.

Cystic Fibrosis

Uncontrolled studies indicate that noninvasive ventilation is useful to stabilize gas exchange in the treatment of acute episodes of respiratory failure in end-stage cystic fibrosis patients and can serve as a bridge to transplantation.¹⁹

Obesity Hypoventilation Syndrome

Acute hypercapnic respiratory failure related to obesity hypoventilation is becoming more prevalent given the increasing obesity rates in the general population. A single-center prospective observational study was conducted to examine the use of NIV in these patients. Using COPD patients with acute hypercapnic respiratory failure for comparison, the authors found no change in the rate of NIV failure between the two groups and found lower rates of late NIV failure, readmission to the ICU, and ICU and hospital mortality in the OHS group. Their conclusion was that NIV can be safely and efficaciously used in acute hypercapnic respiratory failure related to OHS in the ICU.²⁰

Upper Airway Obstruction

Anecdotally, noninvasive ventilation can be used to treat patients with upper airway obstruction, such as that caused by glottic edema following extubation. In this situation, noninvasive ventilation can be combined with aerosolized medications or heliox, but no controlled trials have demonstrated the efficacy of this approach. If therapy with noninvasive ventilation is considered, patients should be selected with great caution and monitored closely, because upper airway obstruction can lead to precipitous deterioration. The use of noninvasive ventilation in patients with tight, fixed upper-airway obstruction is inappropriate because it delays the institution of definitive therapy.

Hypoxemic Respiratory Failure

Hypoxemic respiratory failure is defined as severe hypoxemia (arterial oxygen partial pressure-inspired oxygen fraction ratio <200) combined with a respiratory rate above 35 breaths per minute and a non-COPD diagnosis including acute pneumonia, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), pulmonary edema, or trauma. Controlled trials of noninvasive ventilation to treat patients with acute hypoxemic respiratory failure have shown statistically significant reductions in the rate of intubation, the length of hospital stay, the incidence of infectious complications,^{8,21} and in one study, ICU mortality.²¹ However, because of the heterogeneity of causes, these studies fail to demonstrate that all patient subgroups with hypoxemic respiratory failure benefit equally from noninvasive ventilation. Furthermore, when patients are stratified according to the acuity of illness, patients with a simplified acute physiologic score (SAPS II) less than 35 fare considerably better with NIPPV than do those with higher scores.²² Thus, the selection of patients with less severe disease is likely to enhance the success of NIPPV in treating hypoxemic respiratory failure, and studies that examine individual subgroups within the larger category are likely to be more useful clinically.

Pneumonia

One controlled trial showed that noninvasive ventilation in patients with severe community-acquired pneumonia lowers the rate of endotracheal intubation and shortens the length of ICU stay compared with conventional therapy; however, a subgroup analysis revealed that the benefits occurred only in patients with underlying COPD.²³ No benefit was apparent in the non-COPD patients with severe pneumonia. A subsequent uncontrolled trial in non-COPD patients with severe pneumonia found that two-thirds of such patients treated with noninvasive ventilation eventually required intubation.²⁴ Although the latter authors deemed a trial of noninvasive ventilation in non-COPD patients with severe pneumonia to be a reasonable approach, controlled data to support such a recommendation are currently lacking.

Immunocompromised States

The dismal prognosis of invasively ventilated immunocompromised patients makes noninvasive ventilation an appealing ventilatory mode, with its demonstrated ability to decrease the rate of nosocomial infection.⁷ Earlier studies in both solid organ transplantation patients²⁵ and neutropenic patients (most of whom had hematologic malignancies)²⁶ who developed acute hypoxemic respiratory failure, noninvasive ventilation reduced the rate of intubation, nosocomial infection, and ICU mortality compared with conventional therapy. However, more recent studies suggest that the benefit of NIPPV is difficult to demonstrate, and one adequately powered randomized controlled study comparing NIPPV to oxygen therapy showed no reduction in intubation or mortality rate or length of hospital stay.²⁷ In immunocompromised patients with *Pneumocystis carinii* pneumonia due to the acquired immunodeficiency syndrome (AIDS), noninvasive ventilation yields benefits compared to invasive mechanical ventilation in physiologically and demographically matched patients.²⁸ Thus, current recommendations suggest reserving NIPPV for milder cases of acute respiratory failure in immunocompromised patients and resorting to intubation without undue delay if progressive deterioration occurs.^{29,30}

Acute Respiratory Distress Syndrome

ARDS patients with severe oxygenation defects and multiple organ system dysfunctions should undergo prompt intubation and invasive ventilation as the preferred modality. A prospective cohort study³¹ using noninvasive ventilation as a “first-line” intervention for ARDS found that ventilator-associated pneumonia and mortality were greatly reduced when patients succeeded rather than failed noninvasive ventilation, and a simplified acute physiology score of 34 or less and PaO_2/FiO_2 above 175 within the first hour predicted the success of noninvasive ventilation. Thus, noninvasive ventilation could be considered in

ARDS patients meeting these criteria, but such patients must be monitored closely to avoid any delay in intubation if deterioration occurs.

Acute Cardiogenic Pulmonary Edema

Meta-analyses of randomized, controlled trials demonstrated that compared with oxygen therapy, CPAP (though not a true mode of ventilatory support) is highly effective at relieving respiratory distress, improving gas exchange, and averting intubation when used to treat patients with acute cardiogenic edema.^{32,33} Inspiratory assistance combined with expiratory pressure can reduce the work of breathing and alleviate respiratory distress more effectively than CPAP alone. Moreover, several uncontrolled trials and two controlled trials found that noninvasive ventilation and CPAP are equally effective in improving vital signs and avoiding intubation. The current recommendation is to use CPAP alone or noninvasive ventilation as an initial therapy; if CPAP is used initially, inspiratory pressure support should be added if the patient has persistent hypercapnia or dyspnea.³³

Postoperative Respiratory Failure

NIPPV and CPAP alone have been studied in postoperative patients who develop respiratory failure following various kinds of surgeries. In particular, it reduces extravascular lung water and improves lung mechanics and gas exchange following coronary artery bypass surgery.³⁴ Controlled trials show that CPAP or NIV averts postoperative complications compared to oxygen supplementation after high-risk procedures like thoracoabdominal aortic procedures³⁵ or abdominal surgery.³⁶ Noninvasive ventilation improves oxygenation, reduces the need for reintubation, lowers the mortality rate after lung resectional surgery,³⁷ and enhances pulmonary function after gastropasty.³⁸ Thus, noninvasive ventilation should be considered in selected postoperative patients at a high risk of pulmonary complications or with frank respiratory failure, especially in the setting of underlying COPD or pulmonary edema.

Trauma and Burns

Trauma patients develop respiratory failure for a multitude of reasons, but some have chest wall injuries, such as flail chest or mild acute lung injuries that might respond favorably to NIPPV. In a retrospective survey of 46 trauma patients with respiratory insufficiency that had been treated with NIPPV, Beltrame and coworkers found rapid improvements in gas exchange and a 72% success rate; however, patients with burns responded poorly.³⁹ More recently, a randomized trial of NIPPV versus high-flow oxygen in thoracic trauma patients with $\text{PaO}_2/\text{FiO}_2$ less than 200 was stopped early after the enrollment of 50 patients because of significant reductions in the intubation rate (12% versus 40%) and hospital length of stay (14 versus 21 days) in the NIPPV group.⁴⁰ These promising results justified a cautious trial of NIPPV in carefully selected and monitored thoracic trauma patients, but the data are too limited to draw firm conclusions.

Restrictive Lung Disease

The use of noninvasive ventilation in patients with underlying restrictive disease and acute deterioration of respiratory status has not been studied extensively because they constitute only a small portion of patients admitted to acute care hospitals. Patients with restrictions related to an underlying neuromuscular disease and superimposed acute respiratory failure may benefit from a trial of NIPPV. Small case series have reported that using NIPPV in patients with myasthenic crises may avoid intubation.^{41,42}

Patients with end-stage pulmonary fibrosis in respiratory extremis have been reported to respond poorly to mechanical ventilation.⁴³ However, in selected patients with interstitial lung diseases, NIV may play a role in preventing intubation and improving survival. A prospective observational study revealed that patients with Apache II scores < 20 and mixed interstitial lung disease requiring noncontinuous NIV had a higher survival rate than those requiring continuous NIV or invasive ventilation.⁴⁴ Similarly, a small retrospective observational study in patients with acute respiratory failure secondary to idiopathic

pulmonary fibrosis showed a poor overall prognosis, but, for those who survived, NIV helped to shorten the ICU stay and improve the 90-day survival rate.⁴⁵ Interestingly, this study also found that patients with an IPF and higher NT-proBNP at baseline appeared to have a higher chance of NIV failure.

Do-Not-Intubate Patients

Although controversial, noninvasive ventilation may be a useful tool in patients with acute respiratory failure who do not wish to be intubated. There are several reports of good outcomes (>50% survival to discharge) with noninvasive ventilation in this subset of patients, especially those with COPD and congestive heart failure.⁴⁶ Noninvasive ventilation may also be used as a palliative technique to reduce dyspnea, preserve patient autonomy, and provide time for the finalization of affairs for some terminal patients.⁴⁷ However, there is concern that this may merely prolong the dying process, and patients and their families must be informed that noninvasive ventilation is being used as a form of life support in this setting and should be given the option to refuse it.

Facilitation of Weaning and Extubation

Patients who require invasive mechanical ventilation initially and fail to wean promptly are potential candidates for noninvasive ventilation to facilitate extubation, thus reducing the complications related to prolonged intubation. Several randomized controlled trials and subsequent meta-analyses have demonstrated that noninvasive ventilation significantly shortens the duration of invasive mechanical ventilation, reduces the length of ICU stay, and improves survival compared with patients weaned in the routine fashion.⁴⁸⁻⁵⁰ The benefit of NIV in ventilator weaning seems to be highest in patients intubated for acute exacerbations of COPD.^{51,52}

Another potential application of noninvasive ventilation in the weaning process is to avoid reintubation in patients with extubation failure, a complication of invasive mechanical ventilation associated with a high mortality rate. Data for this use of NIPPV are variable and inconclusive. Earlier studies investigating the role of NIPPV in this situation showed promise, but one randomized trial found that NIPPV may delay required intubation in this setting, resulting in an increased ICU mortality rate.⁵³ More recent studies have demonstrated that patients at a high risk for extubation failure,⁵⁴ especially those with hypercapnia,⁵⁵ have a reduced need for reintubation and mortality if treated with noninvasive ventilation as opposed to oxygen supplementation alone. Subsequent meta-analyses have demonstrated that NIV, used prophylactically after planned extubation, has decreased reintubation rates.^{56,57} However, its effect on ICU and hospital mortality remains unclear. Thus, although the use of noninvasive ventilation to facilitate weaning and extubation appears to benefit hypercapnic patients with COPD or congestive heart failure, its overzealous application could lead to delayed reintubation and other adverse consequences.

Bronchoscopy

Both CPAP and NIPPV have been studied as methods of supporting oxygenation and ventilation during bronchoscopy. Using a specially designed open CPAP system during bronchoscopy in patients with marginal oxygenation, Maitre et al. observed the maintenance of adequate gas exchange and avoidance of respiratory failure.⁵⁸ In a controlled trial, Antonelli et al. demonstrated equivalent oxygenation and complication rates in patients undergoing bronchoscopy and supported with either noninvasive or invasive mechanical ventilation.⁵⁹ Thus, NIPPV is an effective way of providing ventilatory support to patients undergoing bronchoscopy.⁵⁹

PRACTICAL APPLICATION

Patient Selection

Noninvasive ventilation should be viewed as a “crutch” that assists patients through a period of acute respiratory failure while reversible

BOX 62-2**Predictors of Noninvasive Ventilation Success in Patients with Acute Respiratory Failure**

Lower acuity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] score)
 Ability to cooperate; better neurologic score
 Ability to coordinate breathing with ventilator
 Less air leakage; intact dentition
 Hypercarbia, but not too severe (PaCO_2 between 45 and 92 mm Hg)
 Acidemia but not too severe (pH between 7.1 and 7.35)
 Improvements in gas exchange and heart and respiratory rates within first 2 hours

factors are being treated, helping them avoid invasive mechanical ventilation and its attendant complications. To optimize the chance of success, noninvasive ventilation should be used early, when patients first develop signs of incipient respiratory failure. In addition, predictors of success are useful in identifying patients most likely to benefit (Box 62-2). The selection process might be viewed as taking advantage of a “window of opportunity”: the window opens when the patient first requires ventilatory assistance and closes when the patient becomes too unstable.

Based on the predictors of success and criteria used in prior controlled trials, we recommend the following three-step selection process: (1) to ensure that the patient has an etiology of respiratory failure likely to respond favorably to noninvasive ventilation; (2) to identify patients in need of ventilatory assistance by using clinical and blood gas criteria. Patients with mild respiratory distress and only those with mild gas exchange derangement are likely to do well without ventilatory assistance and should not be considered. Good candidates are those with moderate to severe dyspnea, tachypnea, and impending respiratory muscle fatigue, as indicated by the use of accessory muscles of breathing or abdominal paradox. The level of tachypnea used as a criterion depends on the underlying diagnosis. Those with COPD are considered candidates for noninvasive ventilation when the respiratory rate exceeds 24 breaths per minute; with hypoxemic respiratory failure, higher respiratory rates are used in the range of 30 to 35 breaths per minute; and (3) to exclude patients for whom noninvasive ventilation would be unsafe. Those with obvious or imminent respiratory arrest should be promptly intubated because the successful initiation of noninvasive ventilation requires some time for adaptation. Patients who are medically unstable with hypotensive shock, uncontrolled upper gastrointestinal bleeding, unstable arrhythmias, or life-threatening ischemia are better managed with invasive mechanical ventilation. Additionally, noninvasive ventilation should not be used for patients who are uncooperative, unable adequately to protect their upper airway or clear secretions, intolerant of masks, or for recipients of recent upper gastrointestinal or airway surgery.

Initiation of Noninvasive Ventilation

Once an appropriate candidate for noninvasive ventilation has been selected, a ventilator and interface must be chosen, initial settings must be selected, and the patient must be monitored closely in an appropriate location until stabilized. The roles of physicians, respiratory therapists, and nurses are of paramount importance in explaining the process to and gaining the confidence of the patient. Noninvasive ventilation can be initiated wherever the patient presents with acute respiratory distress, but he or she should be transferred to a location with sufficient monitoring (usually an ICU or step-down unit) until stabilized. During transfers, ventilatory assistance and monitoring should be continued.

Ventilator Selection

Selection of a ventilator is based largely on availability, practitioner experience, and patient comfort. Pressure-limited modes, including pressure support and pressure control, are available on most critical care ventilators. Pressure control ventilation (PSV) delivers time-cycled, preset inspiratory and expiratory pressures with adjustable inspiratory/expiratory ratios at a controlled rate. The majority of such models also permit patient triggering and the selection of a backup rate. PSV delivers preset inspiratory and expiratory pressures to assist spontaneous breathing efforts. Nomenclature and the specific characteristics of these modes may differ among ventilators, and this must be taken into account to avoid errors. For example, with some ventilators, pressure support is the amount of inspiratory assistance added to the preset expiratory pressure. Others require the independent selection of inspiratory and expiratory positive airway pressures, with the difference between the two determining the level of pressure support.

PSV is a flow-triggered and flow-cycled mode, and patient effort determines tidal volume and duration of inspiration. Pressure-support modes have the potential to match breathing pattern quite closely, and they have been rated by patients as more comfortable for NIPPV than volume-limited ventilation.⁶⁰ However, leaks during noninvasive ventilation can interfere with the detection of reduced inspiratory flow at the termination of inspiration, causing expiratory asynchrony. Noninvasive pressure-limited modes of ventilation are usually administered using either standard critical care ventilators or bilevel portable ventilators.

Traditional bilevel devices designed for home use have limited pressure-generating capability (≤ 30 cm H_2O) and lack oxygen blenders or sophisticated alarm or battery backup systems, precluding their use in patients who require high oxygen concentrations or inflation pressures. Newer versions designed for the acute setting are equipped with sophisticated alarm and monitoring capabilities, graphic displays, and oxygen blenders. These devices are capable of enhancing synchrony by offering ways to limit the inspiratory duration and an adjustable “rise time”—the time to reach the targeted inspiratory pressure. Many critical care ventilators now include an “NIV” mode that enhances leak compensation capabilities and silences “nuisance” alarms; however, these may have difficulty maintaining performance in the face of variable air leaks.⁶¹ If desired, volume-limited ventilation can be delivered using critical care ventilators, but a higher tidal volume than that commonly used for invasive mechanical ventilation is recommended to compensate for air leakage.

Initial ventilator pressure settings are usually low to facilitate patient acceptance, but they can be set higher if necessary to alleviate respiratory distress. Typical starting pressures are an inspiratory positive airway pressure of 10 to 12 cm H_2O and a PEEP (or expiratory positive airway pressure) of 4 to 5 cm H_2O . L’Her et al.⁶² demonstrated that increases in inspiratory pressure are helpful to alleviate dyspnea, whereas increases in expiratory pressure are preferable to improve oxygenation. For volume ventilation, initial tidal volumes range from 6 to 7 mL/kg. The ventilator is set in a spontaneously triggered mode, with or without a backup rate. Pressures commonly used to deliver CPAP in patients with acute respiratory distress range from 5 to 12.5 cm H_2O . CPAP can be applied using compressed air with a regulator system, blower-based CPAP devices, bilevel devices, or critical care ventilators.

Interfaces

The major difference between invasive and noninvasive ventilation is that with the latter, pressurized gas is delivered to the airway via a mask rather than via an invasive conduit. The open breathing circuit of noninvasive ventilation permits air leaks around the mask or through the mouth, rendering the success of noninvasive ventilation dependent on ventilators designed to deal effectively with air leaks and to optimize patient comfort and acceptance. Interfaces, the devices that connect the ventilator tubing to the nose, mouth, or both, enable pressurized

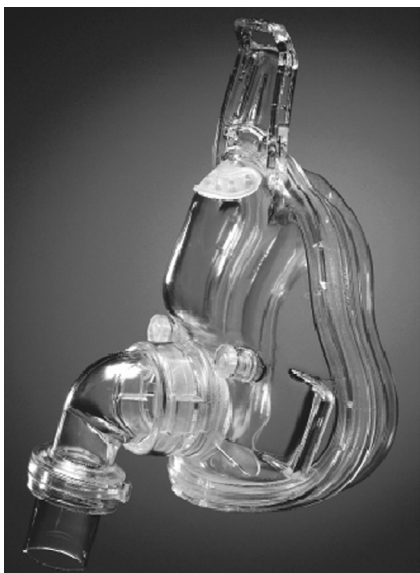


FIGURE 62-3 ■ Full facemask with soft silicon seal to minimize pressure on the nasal bridge. A disposable version of this mask is widely used in the acute care setting.

gas to enter the upper airway during noninvasive ventilation. Commonly used interfaces in the acute setting include nasal and full-face (or oronasal) masks.

Nasal masks are widely used for the administration of CPAP or NIPPV, particularly for chronic applications. Nasal masks are usually better tolerated than full-face masks for long-term applications because they cause less claustrophobia, increased comfort, and allow eating, conversation, and expectoration. The standard nasal mask is a triangular or cone-shaped clear plastic device that fits over the nose and uses a soft cuff that forms an air seal over the skin. The mask exerts pressure over the nasal bridge, often causing skin irritation and redness, and occasionally ulceration. Many modifications are available to avoid complications, such as the use of forehead spacers or masks with ultra-thin silicon seals or heat-sensitive gels that minimize skin trauma.

Full-face masks cover both the nose and the mouth (Fig. 62-3) and are preferable to nasal masks in the acute setting. The efficacy of both nasal and oronasal masks in lowering PaCO_2 and avoiding intubation is similar in the acute setting, but a randomized controlled trial⁶³ observed better patient tolerance with full-face masks because of reduced air leakage through the mouth. More recently, “total” face masks have become available; they seal around the perimeter of the face and resemble a hockey goalie’s mask or a snorkel mask. Made of optical-grade plastic, they are easy to apply and cause no more claustrophobia than standard face masks.⁵ Mouthpieces are seldom used to administer noninvasive ventilation in the acute setting but are occasionally used during initiation when the patient holds the mouthpiece in place to adapt to the sensation of positive-pressure ventilation. Helmets are clear plastic bucket-shaped devices that fit over the entire head and seal over the shoulders and neck.⁶⁴ These have achieved popularity in some European countries but are not available for NIV in the United States.

Selection of a comfortable mask that fits properly is the key to the success of noninvasive ventilation. The full-face mask should be tried first in the acute setting, and if possible, the patient should be allowed to hold the mask in place initially. The mask straps are then tightened with the least amount of tension necessary to avoid excessive air leakage. Some leakage is acceptable and even obligatory with bilevel ventilators, because of the need to flush carbon dioxide from the single-channel ventilator circuit. However, excessive air leakage can lead to noninvasive ventilation failure with any ventilator.

BOX 62-3

Monitoring of Patients Receiving Noninvasive Ventilation in Acute Care Settings

LOCATION

Critical care or step-down unit
Medical or surgical ward if able to breathe unassisted for >20-30 min

“EYEBALL” TEST

Dyspnea
Comfort (mask, air pressure)
Anxiety
Asynchrony
Leaks

VITAL SIGNS

Respiratory and heart rates
Blood pressure
Continuous electrocardiography

GAS EXCHANGE

Continuous oximetry
Arterial blood gasses (baseline, after 1-2 h, and as clinically indicated)

Head straps hold the mask in place and are important for patient comfort. Straps attach at two to five points, depending on the type of mask. More points of attachment add to stability.

Oxygenation and Humidification

Oxygen is titrated to achieve the desired oxygen saturation, usually greater than 90% to 92%, either by using oxygen blenders in critical care and some bilevel ventilators or by adjusting the liter flow (up to 15 L/min) delivered via oxygen tubing connected directly to the mask or ventilator circuit. Bilevel ventilators have limited oxygenation capabilities (maximal inspired oxygen fraction, 0.45-0.5), so ventilators with oxygen blenders should be used for patients with hypoxemic respiratory failure. A heated humidifier should be used to prevent drying of the nasal passage and oropharynx when the duration of application is anticipated to be more than a few hours.

Monitoring

Once noninvasive ventilation is initiated, patients should be closely monitored in a critical care or step-down unit until they are sufficiently stable to be moved to a regular medical floor. The aim of monitoring is to determine whether the main goals are being achieved, including the relief of symptoms, reduced work of breathing, improved or stable gas exchange, good patient-ventilator synchrony, and patient comfort (Box 62-3). A drop in the respiratory rate with improved oxygen saturation or improving pH with a lower PaCO_2 within the first 1 to 2 hours indicates a successful outcome.⁶⁵ Abdominal paradox, if present initially, subsides, and the heart rate usually falls. The absence of these propitious signs indicates a poor response to noninvasive ventilation and the need to make further adjustments. Leaks should be sought and corrected, patient-ventilator synchrony should be optimized, and pressures may need to be adjusted upward to relieve respiratory distress and achieve a reduction in PaCO_2 . If these adjustments fail to improve the response within a few hours, noninvasive ventilation should be considered a failure, and the patient should be promptly intubated if it is still clinically indicated. Excessive delay in intubation may precipitate a respiratory crisis and add to the morbidity and mortality.

ADVERSE EFFECTS AND COMPLICATIONS

When applied by experienced caregivers to appropriately selected patients, noninvasive ventilation is usually well tolerated and is

associated with minimal complications. The most frequent adverse effects and complications are related to the mask, ventilator airflow or pressure, patient-ventilator interaction, or airway secretions.

Common adverse effects related to the mask include discomfort and erythema or skin ulcers, usually on the nasal bridge, related to pressure from the mask seal. Proper fitting and attachment, consistent use of artificial skin over the nose, and newer masks with softer silicone seals help minimize these problems. Adverse effects related to airflow or pressure include conjunctival irritation caused by air leakage under the mask into the eyes and sinus or ear pain related to excessive pressure. Refitting the mask or lowering the inspiratory pressure may ameliorate these problems. Nasal or oral dryness caused by high airflow is usually indicative of air leaking through the mouth. Measures to minimize leakage may be useful, but nasal saline or emollients and heated humidifiers are often necessary to relieve these complaints. Nasal congestion and discharge are also frequent complaints and can be treated with topical decongestants or steroids and oral antihistamine-decongestant combinations. Gastric insufflation occurs commonly, may respond to simethicone, and is usually tolerated.

Patient-ventilator asynchrony is a common occurrence during NIPPV. Failure to adequately synchronize compromises the ventilator's ability to reduce the work of breathing and may contribute to NIPPV failure. The asynchrony may be related to patient agitation, which can be treated with the judicious use of sedatives. Failure to synchronize can also result from inadequate ventilator triggering or the inability to sense the onset of patient expiration because of air leakage. This can be corrected by minimizing air leaks and using ventilator modes that permit a limitation of maximal inspiratory duration. Even with the best efforts to optimize settings and comfort, a minority of patients still fail. This may be partly due to the progression of the underlying disease process or the patient's inability to tolerate NIPPV, but every effort should be made to ascertain that it is not due to technologic problems that could be corrected by mask or ventilator adjustments. Therefore, intubation should not be delayed if improvement is not apparent within a few hours.

KEY POINTS

1. The use of noninvasive positive-pressure ventilation (NIPPV) in patients with certain forms of acute respiratory failure is becoming established, mainly because of increasing evidence for efficacy and advances in noninvasive interfaces and ventilators.
2. NIPPV delivered by nasal or oronasal mask reduces the need for endotracheal intubation, decreases the length of stay in the ICU and hospital, and reduces mortality when used in selected patients with exacerbations of chronic obstructive pulmonary disease (COPD).
3. The efficacy of NIPPV has been demonstrated for acute pulmonary edema, for mild to moderate respiratory failure in immunocompromised patients, and to facilitate extubation in COPD patients.
4. Patients who develop respiratory failure and who refuse intubation are potentially good candidates for NIPPV, but all patients must be selected carefully.
5. Several factors are vital to the success of NIPPV: careful patient selection; properly timed initiation; comfortable, well-fitting interface; coaching and encouragement; and careful monitoring.
6. Noninvasive ventilation should be used to avert endotracheal intubation rather than as an alternative to it. One should not persist in the use of NIPPV if it leads to a delay in necessary intubation.
7. A trial of noninvasive ventilation should be instituted in properly selected patients with acute respiratory failure before a respiratory arrest is imminent, to provide ventilatory assistance while the factors responsible for the respiratory failure are aggressively treated.
8. Noninvasive ventilation is an important addition to the methods available to assist patients with acute respiratory failure and, if properly applied, improves patient outcome in the critical care setting.

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THE CONCEPT OF LIBERATION AND EXTUBATION

Weaning from mechanical ventilation represents the period of transition from total ventilatory support to spontaneous breathing. About 70% of intubated mechanically ventilated patients are extubated on the first spontaneous breathing trial (SBT) attempt, whether by disconnection from the ventilator or after breathing at low levels of pressure support for short periods of time, such as 30 to 120 minutes.^{1,2} The remaining patients (about 30%) require progressive withdrawal from artificial ventilatory support.

Early liberation from mechanical ventilation and removal of the endotracheal tube is clinically important. Unnecessary prolongation of mechanical ventilation increases the risks of complications, including infections (particularly of bronchopulmonary origin), barotrauma, cardiovascular compromise, tracheal injuries, and muscle deconditioning. Clinicians should hasten the process that ultimately leads to removal of the endotracheal tube to maximize patient outcome.³

Liberation and extubation are different issues.⁴ Liberation refers to weaning from mechanical ventilation and means that a patient no longer requires ventilatory support. When this step is achieved, the clinician has to consider a different question, i.e.: "Is the patient able to breathe spontaneously without the endotracheal tube?" Removal of the endotracheal tube is referred to as extubation. Regarding magnitude, the extubation failure rate (i.e., the need to replace the endotracheal tube and reinstitute mechanical ventilation) is variable and ranges from 5% to 20% of extubated patients.^{1,5-7}

MECHANISMS EXPLAINING LIBERATION FAILURE

Respiratory Pump Failure

The most common reason for weaning failure is respiratory pump insufficiency and is caused by an imbalance between the patient's capabilities and respiratory demands.⁸⁻¹¹ Jubran and Tobin¹² investigated the progression of respiratory mechanics during SBT in patients with chronic obstructive pulmonary disease (COPD). At the very beginning of the trials, patients who subsequently failed had a slightly higher airway resistance, respiratory system elastance, and intrinsic positive end-expiratory pressure (PEEP) compared to those who succeeded. However, during the trials, respiratory mechanics progressively worsened in patients who failed to be liberated from the ventilator. Subjects who failed developed rapid, shallow breathing and most developed an increase in PaCO₂. Together, these abnormalities resulted in increased inspiratory muscle effort, which in some patients was likely close to the threshold of muscle fatigue.

Laghi et al.¹³ studied 19 intubated patients during weaning from mechanical ventilation, of which 11 patients failed and 8 succeeded. Several physiologic indices were measured before and 30 minutes after SBT. The transdiaphragmatic twitch pressure, elicited by magnetic bilateral phrenic stimulation, did not differ before the SBT between the patients that failed or succeeded at ventilator liberation, and this variable did not decrease after the trial in either group. Patients failing the SBT were reconnected to the ventilator due to clinical signs of intolerance. It was concluded that weaning failure was not accompanied

by low-frequency diaphragmatic fatigue, although weaning failure patients exhibited severe diaphragmatic weakness since twitch pressures were always low.

Common Disorders That Alter the Balance of Capacity and Load in Critical Illness

Reduced Neuromuscular Capacity. Previous studies have shown that diaphragmatic injury and atrophy are associated with the use of passive assisted control ventilation^{14,15} and are significantly correlated with longer periods of ventilator support.¹⁶ Critical illness polyneuropathy and myopathy, which are frequent complications of sepsis and multiple organ system failures, may also impede weaning.¹⁷ In addition, respiratory muscle weakness is associated with delayed extubation.¹⁸ Finally, malnutrition and deconditioning due to prolonged bed rest during critical illness can induce severe muscle dysfunction.¹⁹

Increased Muscle Loads. The increased work of breathing results from increased mechanical loads (elastic and/or resistive). Increased elastic workloads occur when lung and chest wall compliance are reduced (e.g., pulmonary edema, extreme hyperinflation during an acute asthmatic attack, pulmonary fibrosis, abdominal distension, obesity, trauma, or thoracic deformities).¹³ The presence of intrinsic PEEP is another example of increased elastic workload and is a relatively common phenomenon, especially in patients with COPD.^{20,21} Resistive work for breathing during critical illness may increase as a result of bronchospasm, excessive secretions, endotracheal tube resistance (which augments with kinking and deposition of secretions), and ventilator valves/circuits and humidifiers, especially when conditioning of inspired gases is provided with heat and moisture exchangers. The latter also increases the instrumental dead space.

Cardiovascular Dysfunction

The presence of cardiovascular dysfunction can contribute to weaning failure by augmenting the loads on the respiratory system and by reducing neuromuscular capacity.^{22,23} Cardiovascular dysfunction can result from physiologic changes that occur during the resumption of unassisted spontaneous breathing.²⁴ When spontaneous breathing resumes, the intrathoracic pressure during inspiration is negative. This becomes a situation that results in increased left ventricular preload and afterload. Increased heart loads augment myocardial oxygen demand and may precipitate myocardial ischemia in patients with coronary artery disease.²⁵

Jubran et al.²⁶ examined hemodynamics and mixed venous saturations in patients during weaning trials. Successfully weaned patients demonstrated increases in cardiac index and oxygen transport compared to values during mechanical ventilation. Patients who failed weaning did not increase oxygen delivery to the tissues due in part to the elevated right and left ventricular afterloads. Consequently, these abnormalities can jeopardize respiratory muscle function.

In intensive care unit (ICU) patients, congestive heart failure may occur as a consequence of an increase in venous return, volume overload, or catecholamine release induced by physiologic stress, such as weaning.^{24,27,28} Impairment of cardiovascular function can be magnified in the setting of a positive fluid balance.^{29,30}

It has been recently shown that performing an SBT using a T-tube (instead of pressure support and PEEP) is difficult to wean patients elicits a different cardiovascular response and when support is added

(in the form of pressure support and PEEP), respiratory and cardiovascular function both improve.³¹

In the ICU, there are noninvasive tools (e.g., echocardiography and measurement of plasma B-type natriuretic peptide [BNP]) that help to make the diagnosis of cardiovascular dysfunction. Mekontso-Desap et al.³² measured BNP levels during weaning trials. In this study, 41% of patients failed the weaning process and high BNP levels were identified as an independent risk factor for weaning failure. In addition, 9 of the 42 patients in whom weaning failed were successfully weaned after the administration of diuretics.

PREDICTION OF WEANING AND EXTUBATION OUTCOMES

Yang and Tobin³³ studied the predictive power of several weaning indices and showed that the rapid shallow breathing index (f/VT) had the best predictive value. In their study, 95% of patients with a ratio f/VT greater than 105 failed during a test of spontaneous breathing. The rapid shallow breathing index appears to be the most useful method at the bedside to screen a patient for liberation readiness. If the value is less than 105, then 30-120 minutes of an SBT should be used as a confirmation of the capability of breathing spontaneously without assistance. However, since the f/VT has a low specificity (there is a relatively large proportion of weaning failure subjects in whom the test is positive), the f/VT alone is not sufficient to predict weaning failure. From a practical point of view, the information conveyed by weaning indices and clinical judgment should be considered together in making clinically important decisions regarding extubation.

Patients incapable of protecting their airway and clearing secretions with an effective cough are at an increased risk of extubation failure. Traditional assessment has consisted of demonstrating a cough reflex when the airways are stimulated with a suction catheter and by the absence of excessive secretions. Smina et al.³⁴ found that patients with a peak expiratory flow equal to or below 60 L/min were five times more likely to have an unsuccessful extubation than patients with expiratory flows greater than 60 L/min.

EXTUBATION FAILURE

Extubation failure can be defined as reintubation and the reinstitution of ventilatory assistance within 24-48 hours of extubation. Data by Esteban et al.^{5,35} indicate that the reintubation rate is about 13%-19%.

Mechanisms explaining extubation failure include impending abnormalities not diagnosed at the time that extubation was performed (e.g., pneumonia or ongoing cardiac failure) and the inability to keep the tracheobronchial tree free of copious secretions.^{7,36,37} Extubation failure results in a marked increase in the duration of mechanical ventilation, ICU and hospital stay, need for tracheostomy, and hospital mortality.^{5,7,38-40} Further studies are needed to understand the pathophysiological mechanisms of extubation failure.

PROGRESSIVE WITHDRAWAL OF MECHANICAL VENTILATION

When patients fail SBTs, pressure support ventilation (PSV) is the modality most often used for the progressive withdrawal of mechanical ventilation.⁴¹ Two prospective multicenter randomized clinical trials have shown that the use of synchronized intermittent mandatory ventilation (SIMV) is less efficacious than other techniques.^{1,2}

Sedation and analgesia are important components of care for mechanically ventilated patients. An important study revealed that the daily interruption of sedation significantly reduced the duration of mechanical ventilation.⁴² Since sedation and weaning from mechanical ventilation cannot be separated from one another, when these two strategies are combined (i.e., daily interruption of sedation and the systematic use of SBTs) to hasten liberation from the ventilator, the results are more effective than if the two strategies are used separately.⁴³

PSV

Clinical experience^{1,2} and data obtained from clinical trials^{44,45} suggest that the "optimal" initial levels for PSV are those that provide respiratory rates between 25 and 30 breaths/min. In this setting, it is particularly important to rule out the existence of asynchronous breathing or ineffective respiratory effort. A ventilator setting with a high level of pressure support can be the cause of patient-ventilator asynchrony. The patients who show ineffective triggering exhibit a longer time on mechanical ventilation and tracheostomy is more frequent in these patients.⁴⁶ A subsequent study found a decrease in the number of ineffective respiratory efforts without changes in the work required for breathing and without modifications in the respiratory rate when pressure support levels were reduced.⁴⁷ These studies^{46,47} indicate that some patients are receiving excessive levels of mechanical ventilation during the weaning process.

The level of external PEEP used in patients with clinically suspected dynamic hyperinflation and dynamic airway collapse should be adjusted with great caution since the measurement of dynamic intrinsic PEEP in spontaneously breathing patients is not easily performed. To that end, it has been suggested that external PEEP can be titrated according to the changes in airway occlusion pressure.⁴⁸

During weaning, the PSV levels are decreased according to the patient's clinical tolerance, usually by steps of 2-4 cm H₂O at least twice a day. In general, clinical tolerance to a level of PSV of about 8 cm H₂O without PEEP is required before performing extubation, although this level may vary according to a given patient's overall clinical status.

Spontaneous Breathing with T-Tube

Tolerance to breathing through a T-tube represents a good test to evaluate patients' capacity to maintain autonomous, spontaneous breathing.⁴⁹ The optimal duration of a T-tube trial is at least 30 minutes and no more than 120 minutes.

The main disadvantage of the T-tube trial is related to the absence of a connection to a mechanical ventilator. Since the patients are not monitored by the alarms on the ventilator, they need to be closely supervised.

SBTs with pressure support or a T-tube are suitable methods for evaluating the capacity for spontaneous breathing.⁵ However, the use of T-tube weaning trials in difficult-to-wean patients should be considered since PSV modifies the breathing pattern, inspiratory muscle effort, and cardiovascular response compared to the T-tube in this group of patients.³¹

Noninvasive Ventilation

Noninvasive ventilation (NIV) could be used in some clinical scenarios during weaning:

1. Preventive NIV in patients considered high-risk candidates for reintubation.⁵⁰ Examples of such patients include those who have hypercapnia at the end of the weaning test and patients with a history of heart problems or chronic hypercapnic respiratory failure.⁵¹⁻⁵³ One study demonstrated a reduction in the reintubation rate when NIV was used postextubation.⁵¹ Another study showed both a reduction in reintubation and mortality rates with the use of NIV.⁵² Finally, the study of Girault et al.⁵³ found that NIV could improve weaning results in chronic hypercapnic respiratory failure patients by shortening the duration of intubation and reducing the risk of postextubation acute respiratory failure. However, no differences in reintubation and mortality rates were found.
2. NIV for respiratory failure after extubation. A Canadian study examined the use of NIV for respiratory failure after extubation but found no difference regarding reintubation or mortality.⁵⁴ In 2004, a study was published questioning the use of NIV for postextubation respiratory failure.⁵⁵ The patients were randomized to receive treatment with oxygen and usual care versus NIV treatment and intubation if needed. Although the rate of reintubation was similar

to the Canadian study, the group treated initially with NIV had a higher mortality rate. These results have ended the indiscriminate use of NIV so that NIV is only recommended for specific populations, including those with chronic respiratory problems⁵⁶ and selected postoperative patients.^{57,58}

The high-flow nasal cannula (HFNC) is a relatively new system that delivers heated and humidified oxygen via nasal prongs with a maximum flow of 60 L/min. HFNC provides a low level of positive airway pressure (<4 cm H₂O), which is highly dependent on mouth closing.⁵⁹ Several studies have found that HFNC can be used in weaning period. Maggiore et al.⁶⁰ conducted a randomized trial on 105 patients with a PaO₂/FiO₂ ratio < 300 mm Hg immediately before they were extubated. A total of 52 patients were conventionally treated with Venturi mask, and 53 patients were treated with HFNC during the initial 48 hours after extubation. The HFNC group as compared to those patients randomized to a Venturi mask resulted in significantly better oxygenation, significantly less discomfort associated with the respiratory device, and a significantly lower reintubation rate. Adequately powered randomized studies are needed to confirm or refute the hypothesis for the benefits associated with HFNC.

New Modalities

Several novel weaning modalities have been examined, including those using closed-loop PSV^{61,62} and that provide a continuous adaptation of ventilator assistance to the patient's needs 24 hours a day.⁶³ Lellouche et al. examined this modality in two groups of patients during the weaning period.⁶⁴ In the control group, weaning was performed as per usual care based on written weaning guidelines. In the study group, weaning was performed using a computer-driven weaning protocol. In the study group, weaning time was significantly reduced in comparison to usual weaning (3 days vs. 5 days; $P = 0.01$). The reduction in the weaning time was associated with a decrease in both the total duration of mechanical ventilation (7.5 days vs. 12 days; $P = 0.003$) and the ICU length of stay (12 days vs. 15.5 days; $P = 0.02$).

A subsequent study by Rose et al.,⁶⁵ comparing weaning duration with a closed-loop mode versus usual care (weaning managed by experienced critical care specialty nurses using a 1:1 nurse-to-patient ratio) found no differences between the two strategies. Schadler et al.⁶⁶ found

that the closed-loop system decreased the duration of mechanical ventilation in a specific subgroup of patients (cardiac surgery). Finally, a study by Burns et al.⁶⁷ compared automated weaning with closed-loop mode versus a standardized protocol in critically ill patients and found that automated weaning patients had significantly shorter median times to first successful SBT (1 day vs. 4 days; $P < 0.001$) and to successful extubation (4 days vs. 5 days; $P = 0.01$).

CLASSIFICATION OF WEANING

A Consensus Conference classification⁶⁸ defined 3 groups of patients who were weaned: (1) simple weaning (i.e., those patients who proceed from initiation of weaning to successful extubation on the first attempt); (2) difficult weaning (i.e., those patients who fail initial weaning and require up to 7 days from the first SBT to achieve successful weaning); and (3) prolonged weaning (i.e., those patients who require more than 7 days from the first SBT to achieve successful weaning).

The objective of this classification was to provide greater epidemiologic insight in the weaning process and its relationship with outcomes.⁶⁸ The simple weaning group represents 60%-70% of ventilated patients, the difficult group includes 20%-25% of patients, and the prolonged group includes the remaining 5%-15% of patients.⁶⁹ Several studies⁷⁰⁻⁷⁴ have evaluated this classification and the distribution among groups is shown in Fig. 63-1, outcomes are shown in Table 63-1, and an overall summary of results shown in Fig. 63-2. These data confirm that simple weaning is the most common scenario and that prolonged weaning is associated with poorer outcomes.

SUMMARY

The vast majority of intubated mechanically ventilated patients can be successfully liberated from the ventilator after passing an SBT. The best strategy to shorten the total time of mechanical ventilation is based on a simple and daily clinical approach that determines the ability of patients to tolerate unassisted spontaneous breathing. This approach requires that a screening test is performed as early as possible each day and if positive, the patient is continued a confirmatory SBT of 30 to 120 minutes of duration. When patients fail SBTs, techniques for progressive withdrawal of mechanical ventilation can be used. PSV is the

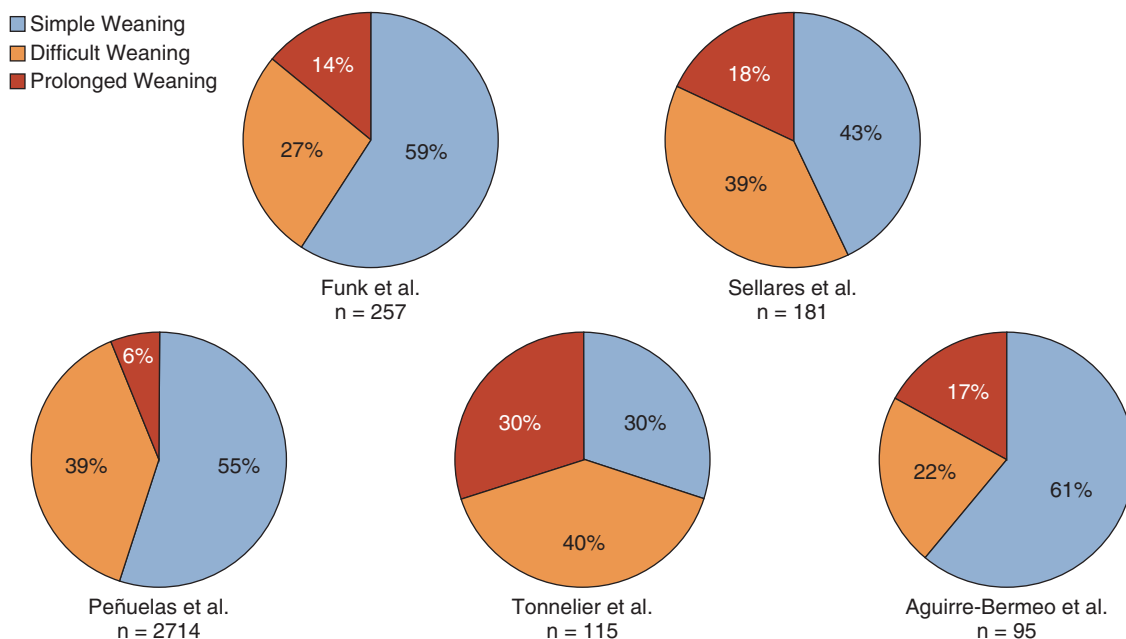


FIGURE 63-1 ■ Patient's distribution in different studies according to the Conference classification.

TABLE 63-1 Outcomes of the Different Studies According to the Conference Classification

| VARIABLE | STUDY | SIMPLE WEANING | DIFFICULT WEANING | PROLONGED WEANING |
|-------------------|--------------------------------|----------------|-------------------|-------------------|
| Reintubation | Funk et al. (n = 257) | 13% | 7% | 5% |
| | Sellares et al. (n = 181) | 15% | 19% | 33% |
| | Peñuelas et al. (n = 2714) | 10% | 10% | 16% |
| | Tonnelier et al. (n = 115) | 0% | 6% | 15% |
| | Aguirre-Bermeo et al. (n = 95) | 7% | 19% | 73% |
| Tracheotomy | Funk et al. (n = 257) | 7% | 15% | 68% |
| | Sellares et al. (n = 181) | 8% | 9% | 39% |
| | Peñuelas et al. (n = 2714) | 6% | 6% | 10% |
| | Aguirre-Bermeo et al. (n = 95) | 3% | 10% | 50% |
| ICU stay, (days)* | Funk et al. (n = 257) | 4 (1-9) | 11 (7-20) | 27 (18-37) |
| | Sellares et al. (n = 181) | 11 ± 12 | 12 ± 8 | 21 ± 13 |
| | Peñuelas et al. (n = 2714) | 6 (3-10) | 9 (6-15) | 18 (14-25) |
| | Tonnelier et al. (n = 115) | 10 ± 9 | 16 ± 15 | 30 ± 25 |
| | Aguirre-Bermeo et al. (n = 95) | 10 ± 7 | 17 ± 13 | 24 ± 15 |
| ICU mortality | Funk et al. (n = 257) | 3% | 1% | 22% |
| | Sellares et al. (n = 181) | 13% | 11% | 42% |
| | Peñuelas et al. (n = 2714) | 7% | 7% | 13% |
| | Tonnelier et al. (n = 115) | 0% | 2% | 18% |
| | Aguirre-Bermeo et al. (n = 95) | 3% | 5% | 38% |

*Data are presented as median (percentiles 25%-75%) or means ± SD.

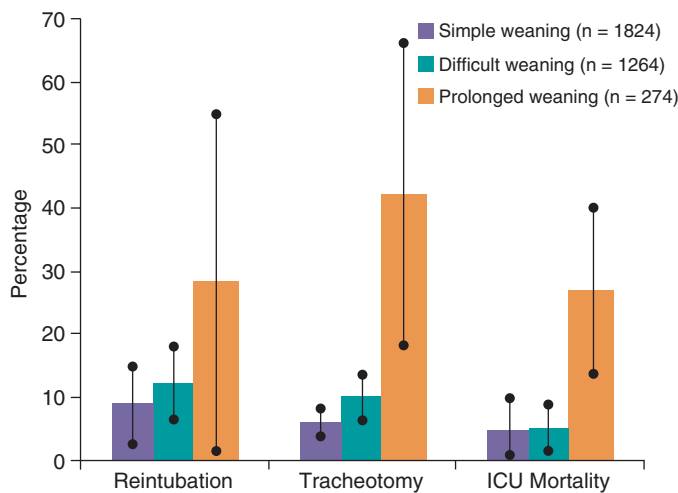


FIGURE 63-2 ■ Overall summary of study outcomes according to the Conference classification. Data are presented in mean percentage and standard deviation.

modality most often used in this scenario. Automated systems seem to perform at least as well as usual care and perhaps even better. NIV may be useful to hasten the weaning process and avoid reintubation in selected populations. Patients with a long weaning duration (>7 days from the first SBT) have poorer outcomes. Extubation failure is poorly understood and is associated with a high mortality rate.

KEY POINTS

1. In the vast majority of patients, weaning from mechanical ventilation is a simple process. Patients are extubated at the first SBT attempt. This is associated with favorable outcomes.
2. The implementation of a weaning strategy based on solid clinical and pathophysiologic knowledge improves outcomes regarding the duration of mechanical ventilation and length of stay in the ICU. This effect can be attributed primarily to the fact that patients are screened daily for the capability to maintain spontaneous breathing.
3. A relatively small group of patients require prolonged weaning. This is associated with worsened outcomes. These patients need to be carefully evaluated for neuromuscular and cardiovascular dysfunction and could benefit from adjunctive therapy.
4. Mechanisms explaining extubation failure are still poorly understood and much research is needed in this area. Patients with extubation failure have an increased mortality rate that varies depending on the specific cause of the failure.
5. Noninvasive ventilation is used to facilitate weaning and extubation but with some reservations. Patients should be carefully selected and the NIV administration should be tailored in a patient per patient basis.

ANNOTATED REFERENCES

Brochard L, Rauss A, Benito S, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1994;150(4):896-903.

This is the first randomized trial comparing three different methods of weaning. They conclude that the outcome of weaning is influenced by the modality chosen during this period. The weaning duration was shorter with pressure support compared with SIMV or T-tube when pooled together.

Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *N Engl J Med* 1995;332(6):345-50.

This is a randomized multicenter study comparing four different methods of weaning. They show that a once daily spontaneous breathing trial is twice as fast as pressure support and three times more rapid than SIMV. Multiple trials of spontaneous breathing do not reduce the time of weaning compared with the once daily trial.

Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008;371(9607):126-34.

This study demonstrated that a strategy combining cessation of sedation followed by spontaneous breathing shortens the duration of mechanical ventilation and improves patient outcome.

Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1997;155(3):906-15.

This is a physiologic study to determine the mechanisms of acute respiratory distress. They show that COPD patients who failed the spontaneous breathing trial developed rapid shallow breathing with worsening pulmonary mechanics, resulting in an increased PaCO₂.

Thille AW, Richard JC, Brochard L. The decision to extubate in the intensive care unit. *Am J Respir Crit Care Med* 2013;187(12):1294-302.

This is a clinical review of extubation in the ICU with an analysis of risk factors and impact of extubation failure. This review discusses the weaning tests and the optimal strategies for weaning in patients at high risk for extubation failure.

■ References for this chapter can be found at expertconsult.com.

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Many critically ill patients are unable to effectively clear secretions that accumulate in the central and peripheral airways. This can be due to factors such as increased secretion production, impaired cough reflex, weakness, and pain. An endotracheal tube prevents closure of the glottis to generate high expiratory pressures necessary for an effective cough, thereby promoting the retention of secretions. In addition, in critically ill patients, cilia in the pulmonary tree are impaired in function and reduced in number.^{1,2} This leads to an increased risk of aspiration, atelectasis, and pneumonia, which are all detrimental to a critically ill patient.

Adjunctive respiratory therapies aim to prevent and treat respiratory complications that are encountered in critically ill patients (Table 64-1).

METHODS TO IMPROVE PULMONARY MUCOCILIARY CLEARANCE

Percussion

Percussion of the chest can aid in secretion clearance. By using clapping cupped hands over the thorax in a rhythmic fashion or using mechanical devices that mimic the same action, the energy of the force generated is transmitted through the thorax to dislodge any secretions. When used in conjunction with postural drainage, this is an effective method to mobilize secretions from the pulmonary tract.³

High-Frequency Chest Compression

High-frequency chest compression (HFCC) enhances mucus clearance. Using an automated vest device worn by the patient that is attached to an air-pulse generator, small volumes of gas are introduced at a rapid rate ranging from 5 to 25 Hz, producing pressures up to 50 cm H₂O. This technique, primarily used in cystic fibrosis patients, is equivalent to conventional chest physiotherapy techniques of percussion and postural drainage.^{4,5} In an observational study comparing HFCC to percussion and postural drainage in nine long-term mechanically ventilated patients, no difference was seen in the amount of sputum production, oxygen saturation, or patient comfort.⁶ HFCC was determined to be safe and felt to save staff time. In a small randomized trial of patients extubated after being ventilated for more than 21 days, the addition of HFCC improved sputum clearance but did not have a significant impact on weaning success rates.⁷ It is difficult to apply this technique to most critically ill patients because of the size of the vest, as covering the thorax may prevent adequate monitoring.

Manual Hyperinflation

Manual hyperinflation with an inflation bag aims to inflate the lungs slowly to 1.5 to 2 times the tidal volume or to peak airway pressures of 40 cm H₂O. An inspiratory pause allows for filling of alveoli with slow time constants. This is followed by a quick release to allow for rapid expiration. The goal is to recruit atelectatic lung regions to improve oxygenation and improve clearance of secretions. Similar to recruitment maneuvers described with mechanical ventilators, manual hyperinflation leads to only transient improvements in oxygenation. Thus, it may facilitate secretion clearance but without any long-term

clinically significant improvement in patient outcome.⁸⁻¹² It also has the disadvantage of requiring a ventilator disconnect and this method can be mimicked by a mechanical ventilator.¹³

Contraindications to manual hyperinflation include hemodynamic compromise and elevated intracranial pressure. There is also a risk of barotrauma due to preferential inflation of open lung regions that are highly compliant compared to the collapsed regions.

Positioning and Mobilization

Mobilization of patients in the intensive care unit (ICU) either through active or passive limb exercises may improve overall patient well-being and, in the long term, may lead to better patient outcomes. The addition of early physiotherapy and occupational therapy to daily interruption of sedation resulted in slightly more ventilator-free days and improved functional capacity.¹⁴

Positioning of the patient with the head of the bed elevated at least 30 degrees significantly reduces the risk of aspiration and ventilator-associated pneumonia.¹⁵ Upright positioning of patients in whom there is no contraindication improves lung volumes and therefore gas exchange and work of breathing, especially in those where the supine or semirecumbent position leads to increased work of breathing. In some individuals with unilateral lung disease, positioning with the affected side up can lead to improved ventilation/perfusion (\dot{V}/\dot{Q}) matching by increasing perfusion to the dependent “good” side.^{16,17} If atelectasis secondary to retained secretions is the cause, having the affected side up leads to improved postural drainage.

Postural drainage involves positioning the body to allow gravity to assist in the movement of secretions and is indicated in patients with sputum production of more than 25 to 30 mL/day and who have difficulty clearing their secretions.¹⁸

Tracheal Suction

Used in conjunction with other techniques to mobilize secretions from the peripheral to the central airways, suctioning is an effective way of removing secretions to improve bronchial hygiene. Using an open method, the patient is disconnected from the ventilator and a disposable suction catheter is inserted. A closed system involves a suction catheter placed in a protective sheath and directly connected to the ventilator circuit. No disconnect is required and the risk of environmental cross-contamination is reduced. Routine changes of the in-line suction catheters are not required and are cost-effective.^{21,22} Overall, the risk of nosocomial pneumonia between the two systems is not different.²³⁻²⁵

Due to the anatomic arrangement of the large central airways, a suction catheter most often preferentially enters the right main bronchus over the left side. Specially designed curved-tipped “left sided” suction catheters increase the likelihood of suctioning from the left mainstem bronchus.

Nasotracheal suctioning has fallen out of favor over direct tracheal suctioning and should only be considered in patients who are able to protect their airway and in conjunction with assisted coughs and other forms of chest physiotherapy.

Complications with suctioning include hypoxemia (especially in the setting of a ventilator disconnect), increased intracranial pressure,

TABLE 64-1 Adjunctive Respiratory Therapies**METHODS TO IMPROVE PULMONARY MUCOCILIARY CLEARANCE**

Chest physiotherapy:

- Percussion
- Postural drainage
- Chest vibration

Suctioning:

- Oropharyngeal suctioning
- Nasopharyngeal suctioning
- Endotracheal suctioning

Continuous lateral rotation

Positive expiratory pressure devices

Forced expiration

Closed chest oscillation

Bronchoscopy

Manual hyperinflation

Bronchodilators

Mucoactive agents

METHODS TO IMPROVE LUNG EXPANSION

Deep breathing

Incentive spirometry

Intermittent positive ventilation

Optimum body position

CPAP therapy

METHODS TO IMPROVE OXYGENATION AND VENTILATION

Inhaled vasodilators:

- Nitric oxide
- Prostaglandins

Helium-oxygen (heliox)

mechanical trauma to the trachea, bronchospasm, and bacterial contamination. All patients should be preoxygenated with 100% oxygen for 1 or 2 minutes prior to suctioning. To reduce the risk of agitation, the patient should be informed before tracheal suctioning is performed. The suctioning should be limited to 15 to 20 seconds, and the suction port on the catheter should be opened and closed intermittently, but not closed for more than 5 seconds at a time.

Continuous Rotation Therapy

Continuous rotational or kinetic therapy extends the practice of regular twice hourly repositioning of patients from one side to the other by placing the patient on a bed that moves to preprogrammed angles on a more frequent basis or through the use of air mattresses that deflate alternatively from side to side to provide postural position changes. Most studies demonstrate a lower incidence of nosocomial pneumonia or atelectasis.²⁶⁻³² A systematic review did not demonstrate improvements in mortality or the duration of mechanical ventilation with kinetic therapy.³³

Bronchoscopy

Fiberoptic bronchoscopy has the advantage of providing direct visualization of the airways and permits suctioning of specific segments where secretions may be retained. As a recent review highlighted,³⁴ bronchoscopy is a moderately effective technique for the treatment of atelectasis in critically ill patients, with success rates ranging from 19% to 89% depending on the extent of the atelectasis (lobar atelectasis responds better than subsegmental atelectasis). When compared with aggressive multimodal chest physiotherapy in the only randomized trial, no

difference in the rate of resolution was observed between the two methods.³⁵ Since bronchoscopy is an invasive procedure, it is not without associated risks and complications: the sedation required for the procedure, transient increases in intracranial pressure, hypoxemia, and hemodynamic consequences or arrhythmias. Therefore bronchoscopy is not recommended except in situations, such as extensive unilateral atelectasis leading to significant difficulties in oxygenating or ventilating that have not resolved with other methods (e.g., suctioning).

Chest Physiotherapy

Chest physiotherapy is a multimodal therapy with the goals of improving pulmonary function (gas exchange, improved lung compliance, and improved pulmonary mucus clearance). Techniques include percussive therapies (manual or mechanical chest percussion), postural drainage, chest vibration, manual hyperinflation, mobilization, suctioning, and rotational therapy. Overall, chest physiotherapy provides transient improvements in oxygenation and lung compliance, likely secondary to airway clearance and the recruitment of atelectatic regions. In specific situations, it may improve outcome and clinical course, such as preventing ventilator-associated pneumonia³⁶ or acute lobar atelectasis.³⁷

Aerosol Therapies**Aerosolization**

Aerosolization of medications allows direct delivery and activity at the site of pathology and the ability to deliver high concentrations with minimal systemic absorption and toxicity.

The two most common methods of delivery by aerosolization are via: 1) nebulization; or 2) metered-dose inhalers (MDIs). *Nebulization*, commonly with a pneumatic jet, uses a high flow of gas (usually 6-8 L/min) to produce small particles of the liquid medium with the medication of interest. In the spontaneously breathing patient, approximately 50% of the nebulized liquid is in the respirable range, with a mass median aerodynamic diameter (MMAD) of 1 to 5 μm . Approximately 10% reaches the lower respiratory tract and small airways. In mechanically ventilated patients, 1% to 15% of the nebulized liquid and medication is delivered to the lower respiratory tract. Ultrasonic nebulization uses high-frequency ultrasonic waves on the surface of the liquid medium to generate respirable particles.

MDIs are pressurized canisters with the drug suspended as a mix of propellants, preservatives, and surfactants. Upon activation, particles ranging in size from 1 to 2 μm are produced. An MDI used in conjunction with a chamber or spacer device significantly increases drug delivery in both spontaneously breathing patients and when attached to the ventilator circuit either directly to the endotracheal tube or as part of an in-line device in the inspiratory limb of the Y-piece.

Factors that influence the efficacy of aerosol delivery in mechanically ventilated patients include³⁸:

1. Administration position in the circuit: an MDI should be closer to the endotracheal tube at the Y-piece and used with a spacer. A pneumatic nebulizer should be at least 30 cm from the Y-piece.
2. Humidification: can decrease aerosol delivery to the respiratory tract due to greater deposition in the ventilator circuit. Higher doses may be required to achieve the desired effect.
3. Timing of delivery: delivery should occur during the inspiratory phase to maximize drug delivery.
4. Flow rates: slower inspiratory flow rates (and therefore longer inspiratory time) increase the delivery of nebulized medications. A decelerating flow pattern can also increase the delivery to the lower airways.
5. Tidal volumes: larger tidal volumes (greater than 500 mL) ensure optimal delivery.
6. Endotracheal tube size: tube sizes less than 7 mm reduce delivery.
7. Density of inhaled gas: low-density gases, such as helium-oxygen mixtures, increase deposition to the lower airways by increasing the laminar flow and producing a smaller respirable particle size.

Bronchodilators

Bronchodilators are the most frequently administered aerosolized therapy in critically ill patients. Inhaled β_2 -agonists, such as albuterol or fenoterol, are generally well tolerated in a critically ill patient and improve lung mechanics particularly in patients with reversible airflow obstruction. In acute lung injury, β_2 -agonists may improve lung edema clearance and have additional antiinflammatory properties. However, the clinical significance of such therapy has yet to be established.³⁹⁻⁴² Adverse effects (e.g., arrhythmias, hypokalemia) can occur in patients receiving excessive doses where significant systemic absorption is likely. Other bronchodilators, including ipratropium bromide, can also be effective in patients with increased airway reactivity, especially when used in conjunction with a β_2 -agonist. Bronchodilators administered via MDI are equally as effective as a nebulizer in spontaneously breathing patients.³⁸ In mechanically ventilated patients, the use of nebulization is either equally as good⁴³ or less effective^{44,45} than an MDI with a spacer. MDI administration has the advantage of easier use without the risk of bacterial contamination and the need to adjust flow rates.³⁸

Antibiotics

Theoretical advantages of aerosolized antibiotics include direct therapy to the site of infection at higher concentrations with a lower risk of systemic absorption and side effects. In chronic pulmonary infective states (e.g., cystic fibrosis and severe bronchiectasis),⁴⁶⁻⁴⁸ aerosolized antibiotics have a role in reducing bacterial concentrations in the sputum, but they have only been shown to provide clinical long-term benefits in cystic fibrosis.⁴⁸ In the acute infective state, aerosolized antibiotics have no additional benefit compared to parenteral antibiotics.⁴⁹⁻⁵¹

In the intubated or tracheostomized patient, the risk of colonization of the airway is high, with a significant increase in the risk for nosocomial pneumonia. As a preventive measure, a recent meta-analysis of prospective clinical trials of aerosolized aminoglycosides suggested a significant reduction in the development of ventilator-associated pneumonia but no difference in overall mortality.⁵² As an adjuvant for the treatment of ventilator-associated pneumonia, a recent review⁵³ and a meta-analysis of five randomized controlled trials suggested a significant improvement in the clinical resolution of pneumonia.⁵⁴ Despite these findings, limitations of these analyses must be considered, given the heterogeneity of the trials. Bacterial resistance must also be considered. Side effects reported in spontaneously breathing patients treated with inhaled tobramycin include increased cough, dyspnea, and chest pain.⁴⁶

Mucoactive Agents

In chronic inflammatory lung conditions such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, and intubation/tracheostomy, the overproduction of mucus and impaired clearance results in complications such as airflow obstruction, atelectasis, and infection. Mucus is primarily composed of water, mucin glycoprotein, cellular debris, neutrophil-derived filamentous actin and DNA, and bacteria.⁵⁵

Mucolytic agents reduce the viscosity of mucus by breaking down the mucin glycoprotein network or free DNA strands, thereby improving mucus rheology to improve clearance. Aerosolized *N*-acetylcysteine (NAC) breaks down the disulfide bonds of the mucin glycoprotein network and is associated with improved mucus clearance. However, due to the increased incidence of bronchospasm with its use, therapy with NAC is not frequently initiated but may be used in conjunction with an inhaled bronchodilator.⁵⁵ Recombinant human DNase (rhDNase, dornase alpha) improves mucus viscosity and pulmonary function in the cystic fibrosis patients but has no significant effect in acute exacerbations of cystic fibrosis.^{56,57} In bronchiectasis not due to cystic fibrosis, rhDNase is not effective and may be potentially harmful.⁵⁸ In mechanically ventilated patients with atelectasis, there is no significant improvement in clinical outcome.^{59,60}

Other Aerosol Therapies

Additional aerosol therapies include hypertonic saline, racemic epinephrine (for acute upper airway obstruction due to inflammation), corticosteroids, and surfactant.

METHODS TO IMPROVE LUNG EXPANSION

Lung expansion techniques that mimic normal sigh maneuvers may help reverse and prevent atelectasis. These techniques are often used in postoperative patients at high risk for pulmonary complications, such as those undergoing thoracic and upper abdominal surgery, as well as patients with neuromuscular or chest wall disorders.

Deep breathing and incentive spirometry involve coached inspiratory maneuvers to voluntarily increase lung volumes greater than the vital capacity of the patient. Both are equally effective in reducing postoperative pulmonary complications compared to chest physiotherapy.⁶¹

A recent systematic review of continuous positive airway pressure (CPAP) in the postoperative setting for upper abdominal surgery suggested a reduction in atelectasis and the need for reintubation but no improvement in mortality or need for ICU admission.⁶²

Intermittent positive pressure breathing to improve lung expansion has fallen out of favor as a preventive measure in postoperative patients due to the expense, lack of a difference in outcomes compared to deep breathing or incentive spirometry, and complications such as abdominal distension.⁶³

METHODS TO IMPROVE OXYGENATION AND VENTILATION

Nitric Oxide

Nitric oxide (NO) is a vascular-derived relaxing factor that causes vasodilation via vascular smooth muscle relaxation. The main action of NO is mediated by activating guanylate cyclase, increasing intracellular cyclic guanylate monophosphate (cGMP), thereby causing smooth muscle and subsequent vasomotor relaxation.⁶⁴ The beneficial effects observed with inhaled NO are mediated primarily through pulmonary vasodilation. Additional observed benefits include a reduction in platelet aggregation and neutrophil adhesion/sequestration in the lungs.⁶⁵⁻⁶⁷ NO is rapidly inactivated by binding to the heme moiety of hemoglobin. Due to its short half-life, NO does not enter the systemic circulation, making it an ideal selective pulmonary vasodilator.

The most common use of NO in the ICU is in the setting of acute respiratory distress syndrome (ARDS). Randomized control trials of varying sample size in ARDS have demonstrated improvement in oxygenation by improving the \dot{V}/\dot{Q} mismatch. NO improved the P_{aO_2} and $P_{aO_2}:F_{iO_2}$ ratios acutely but was no different than control by 24 to 72 hours.^{68,69} A reduction in mean pulmonary artery pressure was also observed in these trials with the use of NO. A beneficial trend was observed in a post hoc analysis in one trial in the more severe forms of ARDS.⁶⁸ However, a meta-analysis of controlled trials did not support the routine use of inhaled NO in ARDS and even suggested a possible increase in renal dysfunction.⁷⁰⁻⁷³ It can be considered as a treatment option in refractory cases of severe ARDS.⁷²

NO can be considered a "rescue" therapy to possibly allow for the institution of more protective forms of ventilation, with decreases in F_{iO_2} and mean airway pressures to maintain acceptable oxygenation. It might also be used in situations in which secondary pulmonary hypertension leads to compromised hemodynamic function from right ventricular failure.

Almitrine bismesylate enhances pulmonary vasoconstriction in areas of hypoxic vasoconstriction, thereby enhancing the redistribution of blood flow from shunt areas to lung units with normal \dot{V}/\dot{Q} ratios.^{74,75} This effect of almitrine therefore potentiates the effects of inhaled NO on gas exchange. Almitrine is not readily available in North America.

TABLE 64-2 Clinical Conditions Where Inhaled Nitric Oxide May Be Used

| |
|--|
| Acute respiratory distress syndrome |
| Severe primary and secondary pulmonary hypertension |
| Congenital cardiac syndromes |
| Right ventricular failure in acute pulmonary embolism or after cardiac surgery |
| Pulmonary ischemic-reperfusion injury after a heart-lung or lung transplant |
| Sickle cell crisis |

In addition to ARDS, other clinical conditions where NO use may be beneficial are listed in Table 64-2. Inhaled NO has been used following heart and lung transplants as a method to reduce right ventricular afterload in the setting of elevated pulmonary artery pressures.⁷⁶ In lung transplants, NO has been described to reduce the risk of ischemia-reperfusion injury. However, this effect was not supported by a randomized clinical trial in which NO was instituted early after lung transplantation.⁷⁷

Inhaled NO is typically initiated at low doses ranging from 1 to 2 ppm and gradually increased until the desired effect is achieved. One method recommended in the United Kingdom based on American-European Consensus Conference on ALI/ARDS guidelines is to perform a dose/response test starting at 20 ppm and reduce the concentrations to 10, 5, and 0 ppm to determine the lowest effective dose.⁷⁸ A significant response should be considered a 20% increase in the $\text{PaO}_2:\text{FiO}_2$ ratio or at least a 5 mm Hg decrease in the mean pulmonary artery pressure (PAP). Improvements in gas exchange are usually observed at lower doses than the reductions in PAP. The usual dose of inhaled NO ranges from 10 to 40 ppm. Doses greater than 80 ppm are associated with a higher risk for adverse effects.

Adverse effects of NO include the formation of methemoglobin and spontaneous oxidation to nitrogen dioxide (NO_2). NO_2 is toxic and causes airway irritation and hyperreactivity with levels as low as 1.5 ppm, as well as pulmonary edema and pulmonary fibrosis after exposure to higher levels. Despite these adverse effects, the development of methemoglobinemia or other toxicities related to NO_2 during acute or prolonged NO inhalation are unusual, especially when NO has been administered at concentrations less than 80 ppm.⁷⁹

To reduce the risk of exposure to NO_2 , NO should be stored at concentrations no higher than 1000 ppm in a pure nitrogen environment and only exposed to oxygen at the time of administration. NO should be delivered into the ventilator circuit as close to the patient as possible. NO and NO_2 levels should be monitored closely on the inspiratory side of the Y-piece when using doses above 2 ppm. Rebound pulmonary vasoconstriction can occur with sudden discontinuation, leading to a rapid worsening of \dot{V}/\dot{Q} mismatch and pulmonary hypertension with a significant hemodynamic collapse.⁸⁰

An absolute contraindication to NO therapy is a methemoglobinemia reductase deficiency (congenital or acquired). Relative contraindications include bleeding diathesis (secondary to reports of altered platelet function and bleeding time with iNO), intracranial hemorrhage, and severe left ventricular failure (NYHA grade III or IV).⁷⁸

Inhaled Prostaglandins

Inhaled prostaglandins I₂ (PGI₂) and E₁ (PGE₁) have similar effects to inhaled nitric oxide, with minimal systemic effects.⁸¹ PGE₁ has the advantage of more rapid degradation by pulmonary endothelial cells, providing a selective advantage over PGI₂ at higher doses.⁸² A recent meta-analysis did not find an improvement in the outcome for the routine use in ARDS⁸³ but they can be considered as alternatives for rescue therapy when used for conditions similar to those treated with iNO. As with iNO, care must be taken to avoid the abrupt discontinuation of PGI₂ or PGE₁ because pulmonary hypertension and cardiovascular collapse can rebound as a result.

Heliox

Helium is an inert gas with a significantly lower density than room air (1.42 g/L for oxygen versus 0.17 g/L for helium). By substituting helium for nitrogen, the degree of reduction in the density of the gas is directly proportional to the fraction of the inspired oxygen concentration in the mix. Heliox reduces the Reynolds number, increasing the laminar flow and reducing airflow resistance. Consequently, the work of breathing and dynamic hyperinflation associated with high airway resistance are reduced. Clinical situations where heliox may be used include conditions with high airflow resistance, such as severe acute asthma or COPD exacerbations, bronchiolitis, bronchopulmonary dysplasia, and extrathoracic or tracheal obstruction. Heliox has been used to improve lung compliance during noninvasive ventilation in COPD patients, to reduce the work of breathing, to avoid intubation, and to improve aerosolized drug delivery. In the management of moderate to severe asthma exacerbations, routine use of heliox is not supported by systematic reviews of the literature but can be considered as an adjuvant in severe cases. In COPD exacerbation, two multicentered trials found no difference in intubation rate or length of stay in the ICU when heliox was added to noninvasive ventilation.^{84,85} However, there appeared to be a cost benefit resulting from a shorter overall hospital length of stay.⁸⁴ Most studies utilize helium/oxygen mixes of 80:20 or 70:30 to achieve a therapeutic benefit. At higher concentrations of oxygen, the effect of helium declines and therefore heliox is limited to patients who are not severely hypoxemic. When used in conjunction with nebulized medications, higher flows of heliox may be required to ensure adequate delivery of the medication, though this may be offset by the smaller particle size generated in a heliox mixture. Ventilators also require a recalibration for measured FiO_2 , flows, and tidal volumes when using heliox.

SUMMARY

Pulmonary disease and complications are common in critically ill patients, especially those undergoing mechanical ventilation. It is important for the clinician to recognize these potential complications and the many forms of adjunctive respiratory therapies available to prevent further morbidity. Simple therapies, such as chest physiotherapy, suctioning, and positioning should be utilized in most patients, with more advanced procedures and therapies used on a selective basis based on the underlying clinical condition.

KEY POINTS

1. Inability to effectively clear secretions is common in critically ill patients, increasing the risk of aspiration, atelectasis, and pneumonia.
2. Chest physiotherapy, positional therapy, and early mobilization should be considered in all critically ill patients.
3. Other adjunctive forms of respiratory therapy should be considered on an individual basis based on the underlying clinical condition.
4. Aerosolization of medications is an effective way of direct delivery to the lungs.
5. Metered-dose inhalers (MDIs) are preferred over nebulization for the delivery of bronchodilators in both the spontaneously breathing and mechanically ventilated patient.
6. Inhaled nitric oxide is associated with improved pulmonary and cardiac physiologic parameters when administered in a variety of clinical conditions encountered in the ICU.
7. Heliox can be considered as adjuvant therapy in severe cases of airflow obstruction.

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Hyperbaric oxygen (HBO₂) treatment involves intermittent breathing of pure oxygen at greater than ambient pressure (>1.4 atmospheres absolute [ATA]). Over the past 20 years, HBO₂ has undergone refinement, with an increased understanding of the mechanisms of action and clinical applications.

■ APPLICATIONS

HBO₂ treatment is carried out in either a monoplace (single person) or multiplace (typically 2 or more) chamber. Pressures applied while in the chamber are usually 2 to 3 ATA, representing the sum of the atmospheric pressure plus additional hydrostatic pressure equivalent to 1 or 2 atmospheres. Treatments are usually for 2 to 8 hours, depending on the indication and may be performed between 1 to 3 times daily. Monoplace chambers are usually compressed with pure oxygen. Multiplace chambers are pressurized with air and patients breathe pure oxygen through a tight-fitting face mask, hood, or endotracheal tube. During treatment, the PaO₂ typically exceeds 2000 mm Hg and levels of 200 to 400 mm Hg occur in tissues.¹

HBO₂ should be viewed as a drug and the hyperbaric chamber as a dosing device. Elevating tissue oxygen tension is a primary effect. Although this may alleviate physiologic stress in hypoxic tissues, lasting benefits of HBO₂ must relate to an abatement of the underlying pathophysiologic processes. The accepted indications comprise a heterogeneous group of disorders (Box 65-1), thus implying that there are several mechanisms of action for HBO₂ (Box 65-2).¹⁻³

Arterial Gas Embolism and Decompression Sickness

Among the earliest application of hyperbaric therapy was to treat disorders related to gas bubbles in the body. Compressed air construction work required exposure to elevated ambient pressure within compartments (caissons) for many hours to excavate tunnels or bridge foundations in muddy soil that otherwise would flood. In the 19th century, workers were noted to frequently experience joint pain, limb paralysis, or pulmonary compromise when they returned to ambient pressure. This condition—decompression sickness (DCS), caisson disease, or bends—was later attributed to nitrogen bubbles in the body and recompression was found to relieve symptoms. Recompression to treat DCS, based purely on Boyle's law with a reduction of gas bubble volume due to pressure, was later improved by adding supplemental oxygen to hasten inert gas diffusion out of the body. Similar observations were made at later times for scuba divers who are also prone to develop arterial gas embolism (AGE) due to pulmonary overpressurization on decompression.

Iatrogenic AGE has been reported in association with cardiovascular, obstetric/gynecologic, neurosurgical, and orthopedic procedures and generally whenever disruption of a vascular wall occurs. Nonsurgical processes reported to cause AGE include overexpansion during mechanical ventilation, hemodialysis, and after accidental opening of central venous catheters.⁴

Treatment of gas bubble disorders include standard support of airway, ventilation, and circulation plus prompt application of HBO₂. Gas bubbles have been reported to persist for several days, and although delays should be avoided, HBO₂ may be beneficial even when begun

after long delays.⁵⁻⁹ Controlled animal trials support the efficacy of HBO₂, but randomized clinical trials have not been conducted.¹⁰ In their review of 27 case series, Moon and Gorman described the substantial benefit of HBO₂ treatment, in which 78% of 441 cases receiving HBO₂ fully recovered and 4.5% died, whereas only 26% of 74 cases not undergoing HBO₂ treatment fully recovered and 52% died.⁴

Mechanisms of action of HBO₂ in AGE and DCS treatment include the reduction of gas bubble size according to Boyle's law, hyperoxygenation to hasten inert gas diffusion, and an additional effect related to inhibition of leukocyte adherence to injured endothelium. Endothelial dysfunction occurs in association with mechanical interactions of bubbles at vessel walls and lumen occlusion.¹¹⁻¹⁵ Neutrophil activation and perivascular adherence occur and are associated with functional deficits post decompression.^{16,17} Animals depleted of leukocytes before experimental cerebral air embolism suffer a less severe reduction in cerebral blood flow and better neurologic outcome.¹⁸ HBO₂ has been shown to temporarily inhibit human β_2 -integrin adhesion function.¹⁹ Inhibition of neutrophil β_2 -integrin adhesion by HBO₂ has been described in a number of animal models, including skeletal muscle ischemia-reperfusion, cerebral ischemia-reperfusion, pulmonary smoke inhalation injury, and brain injury after carbon monoxide (CO) poisoning.²⁰⁻²³ The mechanism for this effect involves S-nitrosylation of cytoskeletal β -actin, which impedes the coordinated cell-surface β_2 -integrin migration required for firm adherence.²⁴

CO Poisoning

CO is the leading cause of injury and death by poisoning in the world.²⁵ The affinity of CO for hemoglobin to form carboxyhemoglobin (COHb), is more than 200-fold greater than that of O₂. CO-mediated hypoxic stress is a primary insult, but COHb values correlate poorly with clinical outcome.²⁶⁻³² Pathologic mechanisms, in addition to elevations of COHb, include intravascular platelet-leukocyte aggregation, leukocyte-mediated oxidative injury to brain, the excessive release of amino acids (e.g., glutamate), impaired mitochondrial oxidative phosphorylation, and possible myocardial calcium overload.³³⁻³⁹

Survivors of acute CO poisoning are at risk for developing delayed neurologic sequelae (DNS) that include cognitive deficits, memory loss, dementia, parkinsonism, paralysis, chorea, cortical blindness, psychosis, personality changes, and peripheral neuropathy. DNS typically occurs from 2 to 40 days after poisoning and the incidence is from 25% to 50% after severe poisoning.

Administration of supplemental oxygen is the cornerstone of treatment for CO poisoning. Oxygen inhalation will hasten the dissociation of CO from hemoglobin, as well as provide enhanced tissue oxygenation. HBO₂ causes COHb dissociation to occur at a rate greater than that achievable by breathing pure oxygen at sea level. Additionally, HBO₂, but not ambient pressure oxygen treatment, has several actions that have been demonstrated in animal models to be beneficial in ameliorating pathophysiologic events associated with central nervous system (CNS) injuries mediated by CO. These include an improvement in mitochondrial oxidative processes,⁴⁰ inhibition of lipid peroxidation,⁴¹ and impairment of leukocyte adhesion to injured microvasculature.²² Animals poisoned with CO and treated with HBO₂ have been found to have more rapid improvement in cardiovascular status,⁴² lower mortality,⁴³ and diminished incidence of neurologic sequelae.⁴⁴

BOX 65-1**Accepted Indications for Hyperbaric Oxygen Therapy**

- Air or gas embolism
- Carbon monoxide poisoning
- Clostridial myositis and myonecrosis
- Crush injury, compartment syndrome, acute traumatic ischemia
- Decompression sickness
- Enhancement of healing in selected problem wounds
- Severe anemia
- Intracranial abscess
- Necrotizing fasciitis
- Refractory osteomyelitis
- Radiation necrosis
 - Delayed radiation injury
- Compromised skin grafts and flaps
- Thermal burns
 - Central retinal artery occlusion
 - Idiopathic sudden sensorineural hearing loss

Data from Weaver, LK, editor. Hyperbaric oxygen therapy indications. 13th ed. Durham, NC: Undersea and Hyperbaric Medical Society; 2014.

BOX 65-2**Mechanisms of Action of Hyperbaric Oxygen****RELATED TO HYPEROXYGENATION OF TISSUES**

- Angiogenesis/neovascularization/osteogenesis/epithelialization in ischemic tissues (mechanisms likely include O₂ behaving as intracellular signal transducer, leading to augmentation of one or more growth factors and mobilization of vasculogenic stem cells)
- Bacteriostatic/bactericidal actions
- Carboxyhemoglobin dissociation hastened
- *Clostridium perfringens* α toxin synthesis inhibited
- Phagocytic bacterial killing improved
- Temporary inhibition of neutrophil β_2 -integrin adhesion
- Vasoconstriction
 - Induction of growth factors and growth factor receptors
 - Inhibition of neutrophil adhesion
 - Reduction of ischemia reperfusion injury
 - Reduction in inflammation and edema

RELATED TO PRESSURIZATION

- Reduction of gas bubble volume (Boyle's law)

Despite online criticisms of their analysis, a meta-analysis by the Cochrane Library concluded that it is unclear whether HBO₂ reduces the incidence of adverse CO-mediated neurologic outcomes.⁴⁵ There are five prospective, randomized trials that have assessed the clinical efficacy of HBO₂ for acute CO poisoning.^{30,31,32,46,47} Several studies failed to find a benefit,^{30,47} but methodological weaknesses discussed by several authors^{39,48} diminish their clinical impact. Only one clinical trial satisfies all items deemed to be necessary for the highest quality of randomized controlled trials.⁴⁹ HBO₂ treatment also appears to diminish acute mortality based on a retrospective analysis.⁴⁸

In patients exposed to smoke and fire, careful attention needs to be paid to the patient's airway, and early intubation should be strongly considered. Some patients being treated for CO toxicity become more alert during HBO₂ therapy and therefore, in vented patients, adequate sedation should be prioritized due to the risk of dislodging the endotracheal tube and patient safety. Some burn centers employ adjunctive HBO₂ for severe burns. Animal models have documented benefits with HBO₂ in reducing partial to full-thickness skin loss, hastening epithelialization, and lowering mortality.¹ Randomized clinical trials, albeit with small patient numbers, have reported improved rates of healing of burns with shorter hospitalization stays and, therefore, reduced costs.⁷⁹⁻⁸² The rationale for treatment has been based on reducing tissue edema and increasing neovascularization.

Clostridial Myonecrosis (Gas Gangrene)

Successful treatment of gas gangrene depends on prompt recognition and aggressive intervention. Early treatment with HBO₂ is recommended to inhibit the production of alpha-toxin by *C. perfringens*. Mortality rates with conventional therapy from 11% to 52% have been reported. There are five retrospective comparisons using HBO₂ and 13 case series in the literature. These have been discussed in several reviews.^{1,54,55} Because of difficulties with comparison among patient groups, impartial assessment of HBO₂ efficacy based on mortality or "tissue salvage" rates is difficult. Most authors comment on clinical benefits associated with treatment. Temporal improvement of vital signs in patients with gangrene can be among the most dramatic observations in day-to-day practice.

Progressive Necrotizing Infections

The use of HBO₂ for treatment of necrotizing fasciitis and Fournier's gangrene, which are mixed aerobic-anaerobic infections, has been reported in six nonrandomized comparisons and four case series.⁶²⁻⁷¹ As with gas gangrene, variations in time of diagnosis and clinical status on admission compromise assessment of the existing literature. Most studies have reported that when HBO₂ is added to surgery and antibiotic therapy, mortality is reduced versus surgery and antibiotics alone. Animal trials have been difficult to assess because synergistic bacterial processes are difficult to establish. One report has found HBO₂ to potentiate antibiotics in streptococcal myositis,⁷² and several animal models of polymicrobial bacteremia and sepsis have reported increased survival with HBO₂.⁷³⁻⁷⁵ Mechanisms of action may include the suppressed growth of anaerobic microorganisms and improved bactericidal action of leukocytes (that function poorly in hypoxic conditions).^{11,76-78}

CRITICAL CARE IN HYPERBARIC MEDICINE

Plans for treatment begin while the patient is still in the intensive care unit, before transport to the hyperbaric chamber is initiated. Issues to be addressed include informed consent, a determination that all intravenous/arterial lines and nasogastric tubes/Foley catheters are secured, capping all unnecessary intravenous catheters, placing chest tubes to one-way Heimlich valves, and adequately sedating or paralyzing the patient as clinically indicated.

The environment of the hyperbaric chamber imposes limitations on equipment, including space restrictions, fire codes, and the effect of pressure on equipment function. Electrical components of equipment are located outside the hyperbaric chamber. Cables penetrate the chamber bulkhead to make a connection to the pneumatic portion of ventilators, internal cardiac pacer wires, electrocardiogram attachments, and arterial line transducers. The patient is attached to equipment at ambient pressure before treatment. Once the treatment pressure is achieved, all settings are checked and transducers recalibrated. It is especially important to remember to check the cuff pressure of endotracheal tubes. Many centers make it a practice to replace the air in these cuffs with an equivalent volume of sterile saline before treatment to avoid volume changes related to pressurization.

There are several intravenous infusion pumps that operate normally in the multiplace chamber environment. If glass bottles, pressure bags, or any other gas-filled equipment is used inside a hyperbaric chamber, it must be adequately vented and closely monitored during treatment. There are limited numbers of ventilator brands approved for the high-pressure environment and, generally, pressure cycle mode functions more reliably than volume cycle. Furthermore, patients with severe lung disease and high mean airway pressures often cannot be treated under hyperbaric conditions until pulmonary function improves.

Bed type, size, and timing of treatment around other procedures and diagnostic testing can limit the number of HBO₂ treatments the patient receives. The recent trend to place very ill patients with elevated

creatinine on continuous dialysis has also hindered the ability to treat patients at regular intervals.

ADVERSE EFFECTS

The inherent toxicity of O₂ and potential for injury due to elevations of ambient pressure must be addressed whenever HBO₂ is used therapeutically. Middle ear barotrauma is the most common adverse effect of HBO₂ treatment.⁹¹ As the ambient pressure within the hyperbaric chamber is increased, a patient must be able to equalize the pressure within the middle ear by auto-insufflation. Standard protocols include the instruction of patients on auto-insufflation techniques and adding oral or topical decongestants when needed. When these interventions fail, tympanostomy tubes must be placed. Intubated patients have difficulty with equalization, and the tympanic membrane must be examined after each treatment. The incidence of tube placement has been reported to be approximately 4% in one series.⁹² Others report an overall incidence of aural barotrauma to be between 1.2% and 7%.^{93,94}

Pulmonary barotrauma during HBO₂ treatment is extremely rare but should be suspected when any significant chest or hemodynamic symptoms occur during or shortly after decompression. Since the off-gassing of gas in virtually all cases will be pure O₂, absorption within the body may occur. If symptoms do develop, however, decompression should be prevented and the patient evaluated. If the pneumothorax is suspected, placement of a chest tube is appropriate. Preexisting pneumothorax should be treated with chest tube drainage before initiating therapy.

Biochemical toxicity due to O₂ can be manifested by injuries to the lungs, CNS, and eyes. Pulmonary insults can impair mechanics (elasticity), vital capacity, and gas exchange.⁹⁴ These changes are typically observed only when treatment duration and pressures exceed typical therapeutic protocols. CNS O₂ toxicity is manifested as a grand mal seizure. This occurs at an incidence of approximately 1 to 4 in 10,000 patient treatments.^{93,99,100} The risk is higher in hypercapnic patients and possibly those who are acidotic or compromised due to sepsis, because an incidence of 7% (23 in 322 patients) was reported in case series of HBO₂ treatment of gas gangrene.⁵⁴ Anecdotally, intubated patients seem to be at higher risk of seizures due to the greater amount of

oxygen to which they are exposed. Seizures are managed by reducing the inspired O₂ tension while leaving the patient at the same ambient pressure (to avoid pulmonary overexpansion injury when a patient is in tonic convulsion phase).

Progressive myopia has been reported in patients who undergo prolonged daily therapy, but this typically reverses within six weeks after termination of treatments.¹⁰² There is a risk for nuclear cataract development, most typically when treatments exceed a total of 150 to 200 hours, but they may arise with less provocative exposures.^{103,104} Although there is a theoretical risk of retrolental fibroplasia in neonates,¹⁰⁵ there are no reports of this having occurred. Currently, the experimental and clinical evidence does not indicate that typical HBO₂ therapy protocols have detrimental effects on neonates or the unborn fetus.¹⁰⁶ This is likely due to the relatively short duration of hyperoxia.

OTHER RISKS

Confinement anxiety may occur and is typically managed with the use of sedating agents. Any environment with an elevated concentration of O₂ presents a risk for fire. Scrupulous attention to avoiding an ignition source is standard in HBO₂ therapy programs.¹⁰⁷

KEY POINTS

1. Several therapeutic mechanisms of action for hyperbaric oxygen therapy stem from two fundamental effects: hyperoxygenation of perfused tissues and reduction of gas bubble volume.
2. Safe treatment of critically ill patients can be accomplished in either one-man "monoplace" or larger multiple-person hyperbaric chambers.
3. Efficacy of hyperbaric oxygen therapy has been documented by randomized clinical trials for a heterogeneous group of disorders.

ANNOTATED REFERENCES

Bennett MH, Feldmeier J, Hampson N, et al. Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database Syst Rev* 2012;(5):CD005005.

This meta-analysis surveyed 11 trials and concluded that for people with late radiation tissue injury affecting head, neck, anus, and rectum HBO₂ improved outcome.

Hampson NB, Piantadosi CA, Thom SR, et al. Practice recommendations in the diagnosis, management, and prevention of carbon monoxide poisoning. *Am J Respir Crit Care Med* 2012;186(11):1095-101.

The consensus opinion paper reviews current issues pertaining to acute CO poisoning. Based on data from the existing study with the best design that most closely addresses the actual practical handling of patients it concludes that HBO₂ should at least be considered in all cases of serious acute CO poisoning and normobaric 100% oxygen continued until the time of HBO₂ administration.

■ References for this chapter can be found at expertconsult.com.

Londahl M, Katzman P, Nilsson A, et al. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care* 2010;33(5):998-1003.

When clinicians discuss critical care, skin ulcers are rarely considered. However, the foot wound of a diabetic patient heightens the risk of cardiovascular and all-cause mortality beyond that associated with the metabolic derangements typically linked to diabetes. This blinded, prospective, randomized trial of 94 patients demonstrated that HBO₂ improved wound healing over 2-fold compared with placebo.

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Imaging of the chest in critically ill patients is necessary for obtaining accurate diagnoses, as well as for evaluating the response to therapy and monitoring the placement and position of supportive devices. However, imaging of intensive care unit (ICU) patients is challenging, both technically and diagnostically.

Portable radiographs and computed tomography (CT) are the primary modalities used to evaluate critically ill patients. Both have limitations, however, when patients are immobile and mechanically ventilated. For example, the quality of portable bedside chest radiographs is diminished secondary to multiple factors, including anteroposterior (AP) projection, supine or semi-upright patient positioning, overlying supportive lines, tubes, and other life support devices. AP projection and a shorter source-to-image distance result in the magnification of the heart and mediastinum (Figs. 66-1, A, and 66-1, B).¹ The supine positioning of the patient can also make the heart and anterior mediastinal structures appear larger, as well as obscure pneumothoraces and posteriorly layering pleural effusions. Pulmonary vascular engorgement can also be overestimated in a supine patient.

Computed tomography provides better anatomic detail and a higher degree of diagnostic accuracy than plain film radiographs but is more difficult to obtain since it is not portable. CT scan quality can be limited by ventilator-assisted respiratory motion artifacts and beam-hardening artifacts from devices. Many patients in the ICU have diminished renal function, so IV contrast frequently cannot be used.

Interventional radiology has become an increasingly integral part of the approach to critically ill patients. Image-guided placement of vascular lines and pleural catheters, especially in the case of loculated pleural effusions, is common. Additionally, tissue sampling for pathologic evaluation is often performed under image guidance by the interventional radiologist (Table 66-1).

SUPPORT DEVICES

Multiple devices are routinely utilized in critically ill patients for monitoring and support (Table 66-2). Malposition of these devices can lead to significant morbidity and possibly death. Knowledge of the radiographic appearance of the equipment along with their correct placement is essential. Moreover, being familiar with potential complications related to each particular device is important.

Tracheal Tubes

Mechanical ventilation is required for the treatment of respiratory failure and includes placement of a cuffed endotracheal tube (ETT) or tracheostomy tube (TT) of appropriate size to ensure an adequate airway. ETTs are usually designated by a thin radiodense line along its length. The proper location of the ETT tip should be 3 to 7 cm above the carina with the patient's chin in a neutral position. This corresponds to the tip being located at approximately the level of the T3/T4 vertebral bodies. There can be up to 2 cm of displacement of the tube tip if the neck is in flexion or extension. Keeping the tip at the level of the clavicular heads is a good landmark. Inadvertent displacement of the ETT can occur into the esophagus, but more commonly, it is too deeply advanced into the airway so that its tip resides in either the right or left main stem bronchus. With esophageal intubation, there is usually

gaseous distention of the stomach on chest x-ray (CXR), and at times, the tube can be visualized lateral to the tracheal air column. When intubation of the main stem bronchus occurs, it is usually right-sided because of the shallow angle between the trachea and right main stem bronchus compared with the left. The contralateral bronchus can become obstructed by the low tube resulting in atelectasis or collapse of that lung, and the ipsilateral lung can become hyperinflated with an increased risk of pneumothorax. Too high a location for an ETT is also undesirable with the risk of vocal cord damage (Figs. 66-2 and 66-3).

Tracheostomy tubes are inserted surgically at the cricoid level. The tip should always be several centimeters above the carina. After insertion, gas in the soft tissues of the upper mediastinum and neck is common but should resolve quickly. Widening of the upper mediastinum after TT placement should raise concern for complications, such as bleeding and hematoma.

Pneumothorax after ETT and TT placement can also occur and should be evaluated on each CXR (Fig. 66-4). A tracheal laceration is an uncommon complication. Tracheal stenosis is a chronic complication of TTs, which can occur at the stoma site or at the site of the cuff, which is approximately 1.5 cm distal to the stoma.

Central Venous Catheters

Central venous catheters (CVC) are most commonly placed via a subclavian vein or internal jugular vein approach. They are routinely used for venous access and for measuring central venous pressures in critically ill patients. They are typically 6-8F in diameter. Knowledge of thoracic venous anatomy is useful in determining proper catheter placement or misplacement. The optimal location of the catheter tip is within the superior vena cava (SVC), located along the right parame-diastinum, from the level of the right first anterior intercostal space (which is past the last venous valve) to the cavoatrial junction (which is 1.5 to 2 vertebral body heights inferior to the carina).

Too inferiorly positioned catheters within the right atrium can result in an increased risk of cardiac perforation and arrhythmias. If the catheter tip hooks posteriorly in the right parame-diastinal region, it is likely within the azygos vein (Figs. 66-5, A, and 66-5, B) and should be retracted slightly back into the SVC. In patients with a left SVC variant, the catheter will course along the left parame-diastinal region and usually enters the right atrium by way of the coronary sinus.

Inadvertent arterial catheterization is usually suspected clinically because of bright red, pulsatile blood return, but an arterial course on CXR will assist in confirmation (Fig. 66-6).

Pneumothorax occurs up to 5% of the time with central venous catheter insertion and is most commonly observed with the subclavian approach (Fig. 66-7). Therefore, an upright chest radiograph should be obtained after each line insertion and, just as importantly, after a failed insertion attempt.² If there is a new apical opacity, mediastinal widening, or an enlarging unilateral effusion seen on the postprocedure radiograph, a localized hematoma or a hemothorax from venous or arterial damage should be suspected. Additionally, a CT scan, preferably with contrast enhancement to detect any active bleeding, may be necessary for confirmation. Rarely, CVCs can fracture with the free fragment usually migrating through the central veins and right heart chambers into the pulmonary arterial branches (Fig. 66-8).

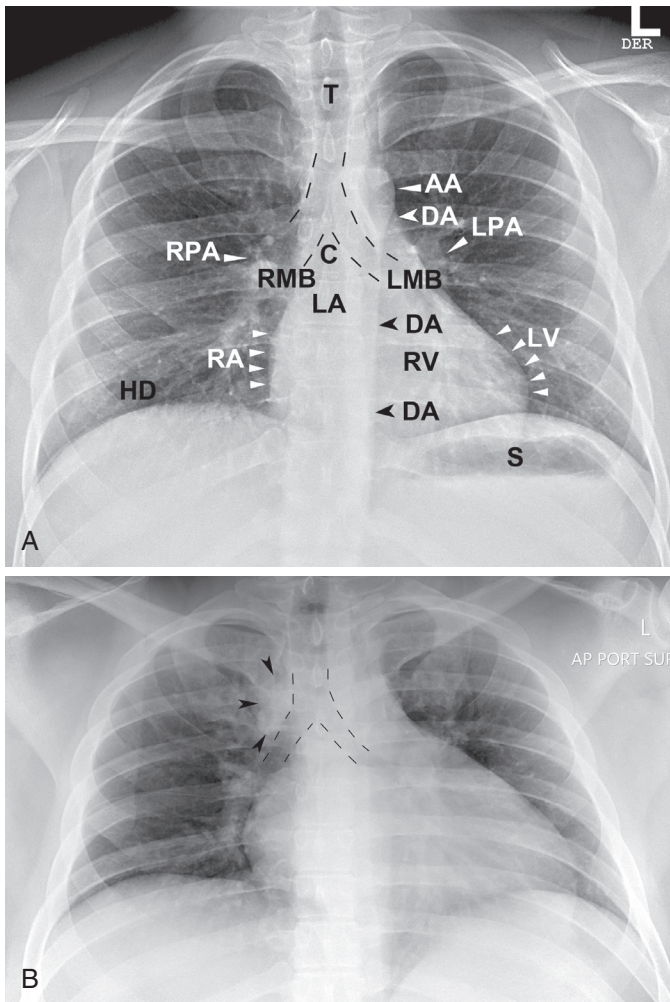


FIGURE 66-1 ■ **A**, Posteroanterior (PA) upright chest x-ray. **B**, Anteroposterior (AP) supine view of the same patient. Note magnification of heart and mediastinum. Shallow inspiration increases vascular resistance making the perihilar and interstitial markings (pulmonary vessels) more prominent, as well as the azygos vein (*outlined by arrowheads*). AA, aortic arch; C, carina; DA, descending aorta; HD, hemidiaphragm; LA, left atrium; LMB, left main stem bronchus; LV, left ventricular border; RA, right atrial border; RMB, right main stem bronchus; RV, right ventricular body; S, stomach; T, trachea.

TABLE 66-1

Systematic Approach to Chest X-ray Interpretation

- Note projection (anteroposterior vs. posteroanterior), patient position (supine vs. upright, and a number of views).
- Determine the nature and location of all supportive devices and postoperative equipment.
- Evaluate heart size, contour, and location.
- Evaluate pulmonary vasculature.
- Assess the lung parenchyma and expected silhouettes.
- Assess the pleura.
- Evaluate the mediastinum and hilar regions.
- Evaluate the osseous structures.
- Check the visualized upper abdomen.

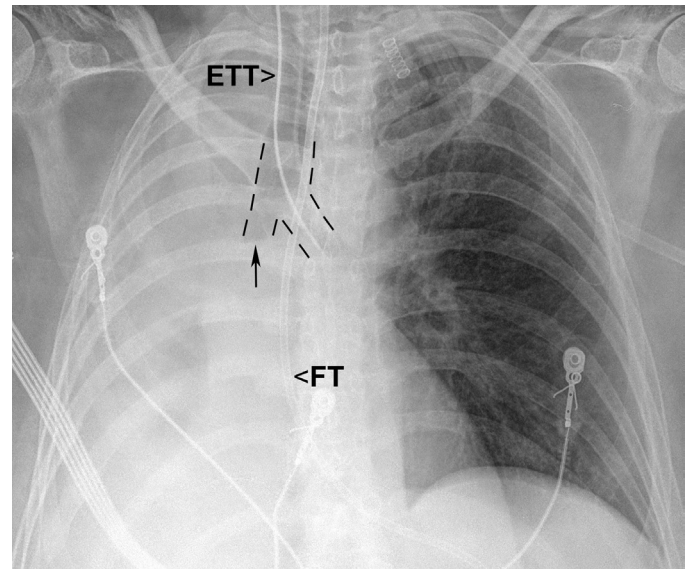


FIGURE 66-2 ■ Anteroposterior (AP) chest x-ray. Left MS (main stem) bronchus intubation with the collapse of the right lower lobe (RLL) and right middle lobe (RML) and rightward shift of the mediastinum. Arrow marks the “cutoff sign” of the distal right main stem bronchus. Note that with RML collapse, the hemidiaphragm and right atrial border are not seen as there is no longer an air interface. ETT, endotracheal tube; FT, feeding tube.

TABLE 66-2

Desired Location of Supportive Devices

ENDOTRACHEAL TUBE

- 3-7 cm above carina, ~T3/T4 vertebral body level, level of clavicular heads.

TRACHEOSTOMY TUBE

- Inserted at cricoid level; tip several cm above carina.

CENTRAL VENOUS CATHETERS TIP

- Distal superior vena cava to cavoatrial junction.

PULMONARY ARTERY CATHETERS TIP

- Right or left main pulmonary artery within 2 cm of pulmonary hilum.

CARDIAC PACEMAKERS AND AUTOMATIC IMPLANTABLE CARDIOVERTER DEFIBRILLATORS LEAD TIPS

- Right ventricle, right atrium, and through coronary sinus to cardiac vein.

THORACOSTOMY TUBE

- For effusion: Posteroinferior.
- For PTX: Anterosuperior.
- Side port inside lateral rib margin.

NASOGASTRIC TUBE TIP

- >10 cm past esophagogastric junction in left upper quadrant.

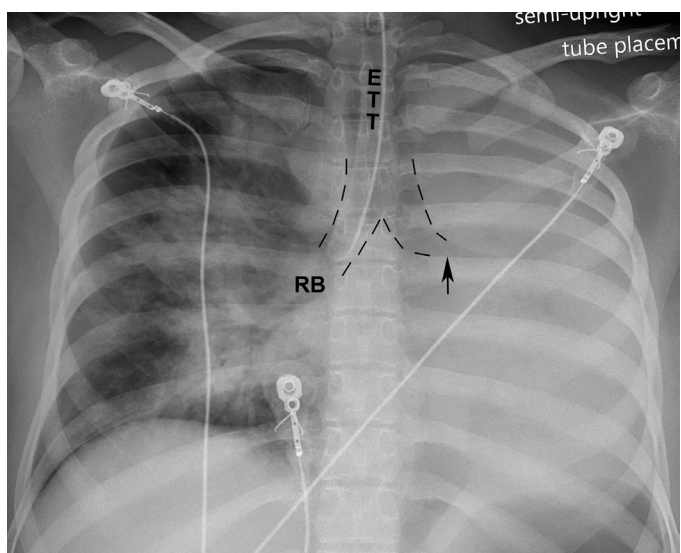


FIGURE 66-3 ■ Anteroposterior (AP) chest x-ray. Right main stem bronchus intubation with the collapse of the entire left lung and leftward shift of the mediastinum. In this case, the left hemidiaphragm and left ventricular border are no longer seen. The “collapse” is always opposite the side that is selectively intubated. Right perihilar air space opacities are due to “batwing” edema caused by acute myocardial infarction. Arrow marks the “cutoff” sign. ETT, endotracheal tube; RB, right main stem bronchus.

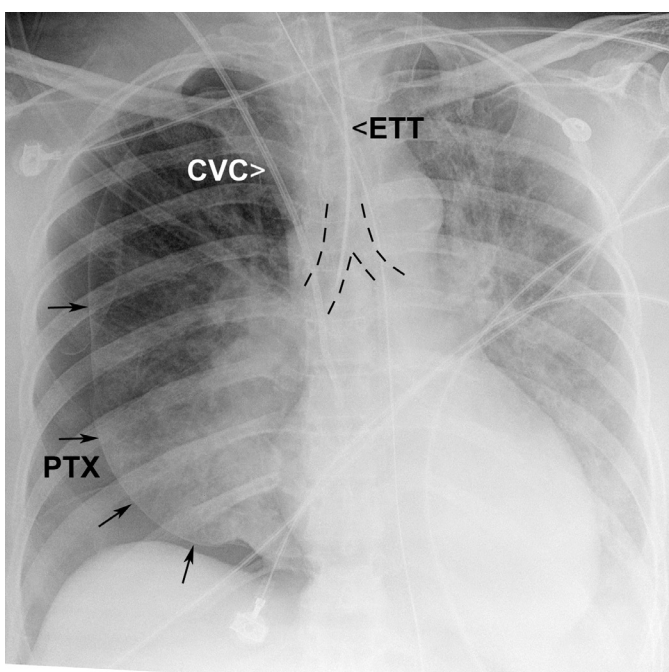


FIGURE 66-4 ■ Anteroposterior (AP) chest x-ray. Right main stem bronchus intubation resulting in a right pneumothorax (PTX), outlined by arrows. Background of interstitial pulmonary edema. Atelectasis and a pleural effusion obscure left hemidiaphragm and cause a “retrocardiac density.” CVC, central line; ETT, endotracheal tube.

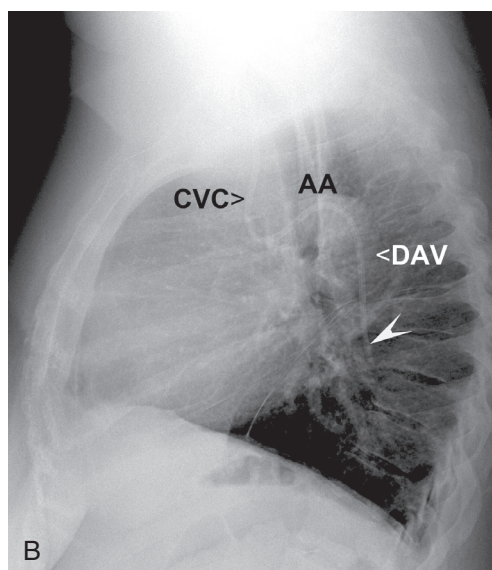
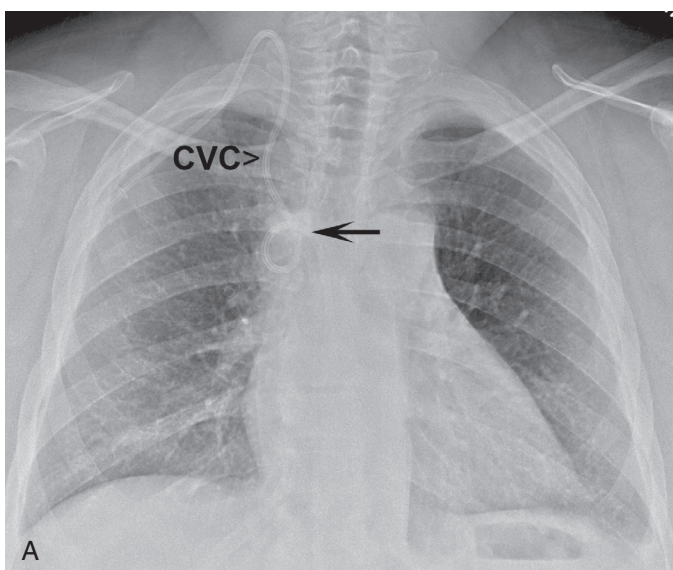


FIGURE 66-5 ■ **A**, Posteroanterior (PA) chest x-ray. Placement of a central line (CVC) in the azygos vein. Arrow depicts the coiled CVC in the region of the azygos vein. **B**, Corresponding lateral chest x-ray. Note how the CVC takes a 90-degree posterior turn into the azygos arch (AA) before taking a 90-degree inferior turn into the descending azygos vein (DAV).

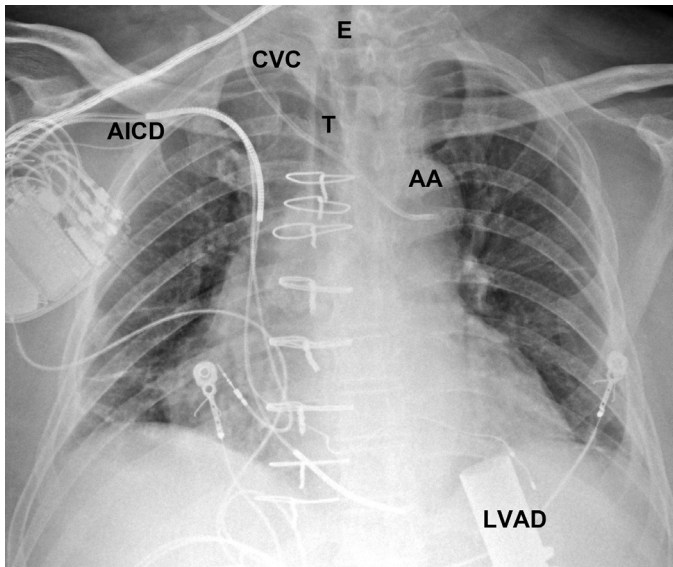


FIGURE 66-6 ■ Anteroposterior (AP) supine chest x-ray. Central line (CVC) that was placed in the right internal carotid artery instead of the right internal jugular vein. Instead of traveling straight downward along the right paramediastinum, the CVC courses obliquely across the superior mediastinum to the aortic arch (AA). AICD, automatic implantable cardioverter defibrillator; E, esophagus; LVAD, left ventricular assist device; T, trachea.

Percutaneous retrieval is necessary to prevent complications, such as vascular injury, occlusion, or cardiac arrhythmias.

Peripheral central venous catheters (PICC) frequently placed via an antecubital vein are smaller (2-5F) and more flexible. The risk of associated pneumothorax is, therefore, minimal. However, their increased flexibility leads to more frequent displacement, coiling, or kinking after placement, as well as to fractured fragments (Fig. 66-9).

Tunneled catheters are placed surgically, usually via a subclavian vein approach, and have a lower risk of infection. These catheters can become pinched between the clavicle and first rib resulting in difficult infusions, thrombosis, or fragmentation (Fig. 66-10). The tip position of PICCs and tunneled catheters is similar to that of standard CVCs.

Pulmonary Artery Catheters

Pulmonary artery catheters (PACs) (i.e., Swan-Ganz catheters) are used to monitor the cardiac and pulmonary hemodynamic status of critically ill patients. Proper placement is very important for accurate results. Usually inserted via an internal jugular (IJ) or subclavian approach, the tip is floated through the right heart chambers and into the main pulmonary arterial system, where it should remain when not in use (approximately 2 cm from the pulmonary hilum). When in use, the tip is advanced and “wedged” in a proximal interlobar artery where accurate pulmonary capillary pressures can be obtained that reflect left atrial pressure. Balloon inflation is required only at the time of measurement readings and should not be visualized on CXR as a ~1 cm round lucency at the catheter tip. A pulmonary infarct is not common but is the most frequent serious complication of PAC. This can result from a too peripheral location of the catheter (Fig. 66-11) or too prolonged inflation of the balloon. Pulmonary infarct on CXR presents as a new peripheral wedge-shaped or patchy airspace opacity corresponding to the lobe or segment in which the catheter was located. Pulmonary arterial pseudoaneurysm or perforation with hemorrhage and clinically presenting with hemoptysis are also rare complications of PACs.

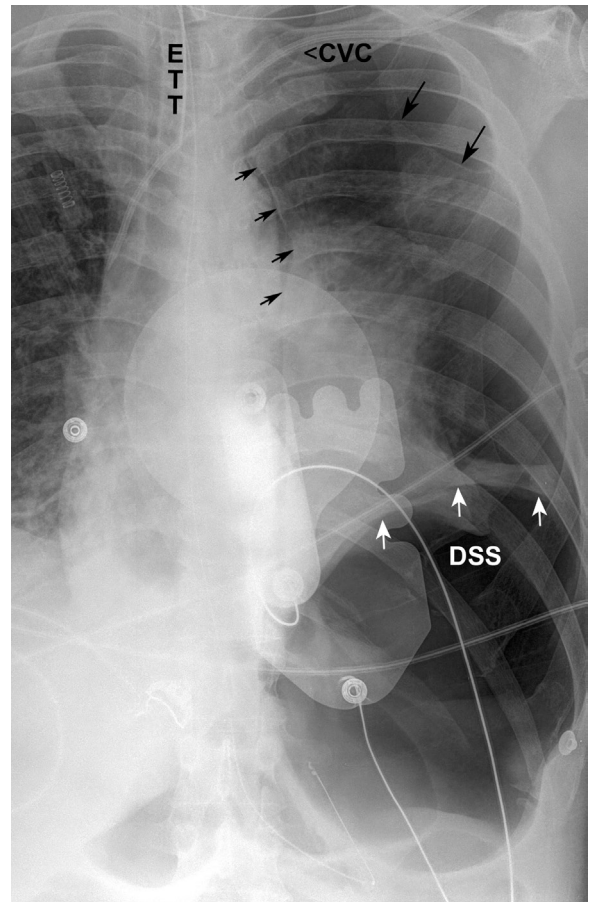


FIGURE 66-7 ■ Anteroposterior (AP) supine chest x-ray. Large left-sided pneumothorax (PTX) with air noted around the left lung apex (large arrows), medially along the mediastinum (small arrows), and inferiorly, under the lung (white arrows). The latter results in the so-called “deep sulcus sign” (DSS) because costophrenic and cardiophrenic angles can be seen.

ECMO Catheters

Extracorporeal membranous oxygenation (ECMO) can be used for critically ill adults with respiratory failure. The technology of ECMO is similar to cardiopulmonary bypass but can be instituted at the bedside by placing a large bore (19-24F) catheter into the venous system to remove deoxygenated blood. The extracted blood then undergoes extracorporeal oxygenation before being returned to either the venous or arterial system via another large bore catheter. Venous access is typically through the right IJ vein or a femoral vein. Arterial access is typically through the right carotid artery or a common femoral artery (Fig. 66-12).

Implanted Cardiac Devices

Cardiac pacemakers and automatic implantable cardioverter defibrillators (AICD) are used for a variety of conduction abnormalities and to prevent sudden death from ventricular fibrillation. Insertion is usually via a transvenous approach, most commonly through the subclavian or IJ veins. One lead tip is placed within the right ventricle and should be located to the left of the midline on the frontal CXR and anteriorly on the lateral CXR. Additional lead tips are usually positioned within the right atrium, which is to the right of midline or through the coronary sinus into the middle or great cardiac veins,

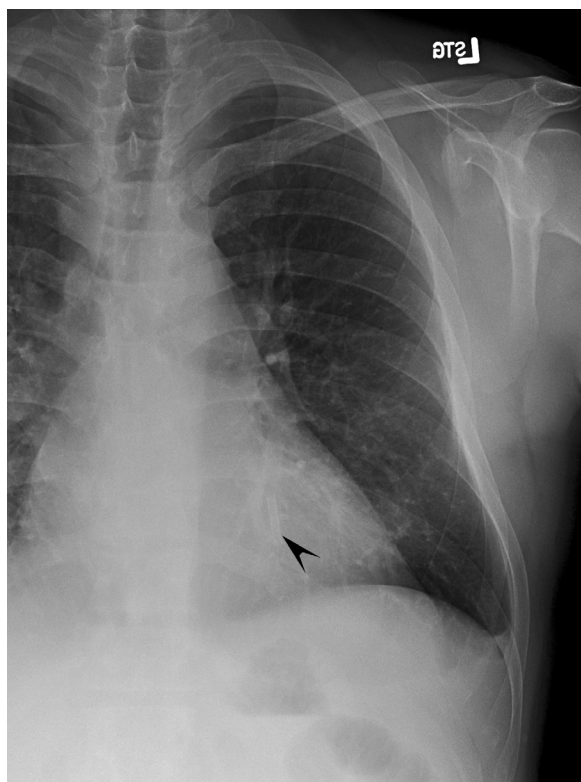


FIGURE 66-8 ■ Anteroposterior (AP) supine chest x-ray. Catheter fragment (*arrow*) in a left lower lobe pulmonary artery branch.

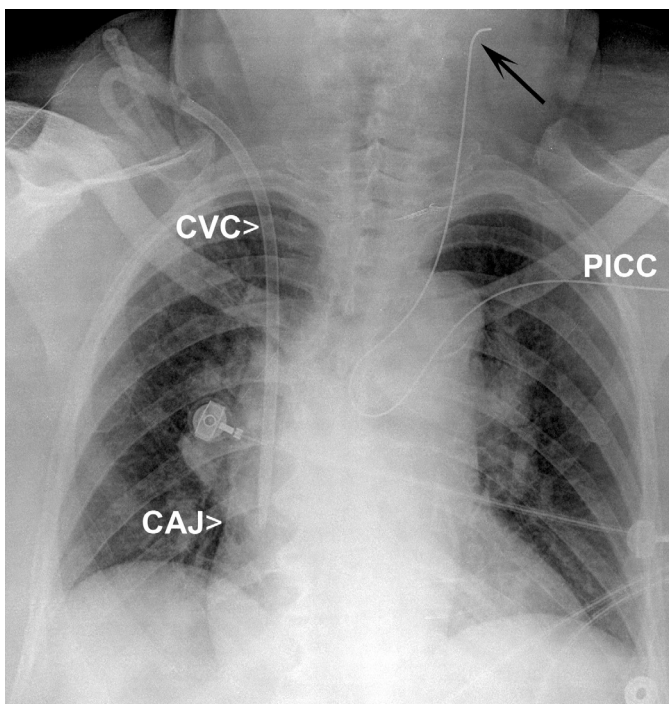


FIGURE 66-9 ■ Anteroposterior (AP) supine chest x-ray. Left peripheral central venous catheter (PICC) courses cephalad from the left brachiocephalic vein into the left internal jugular vein, with its tip (*arrow*) residing in the mid neck. Note that the guide wire is within the PICC, making it very easy to see. Right internal jugular CVC tip in a good position at the cavoatrial junction (CAJ).

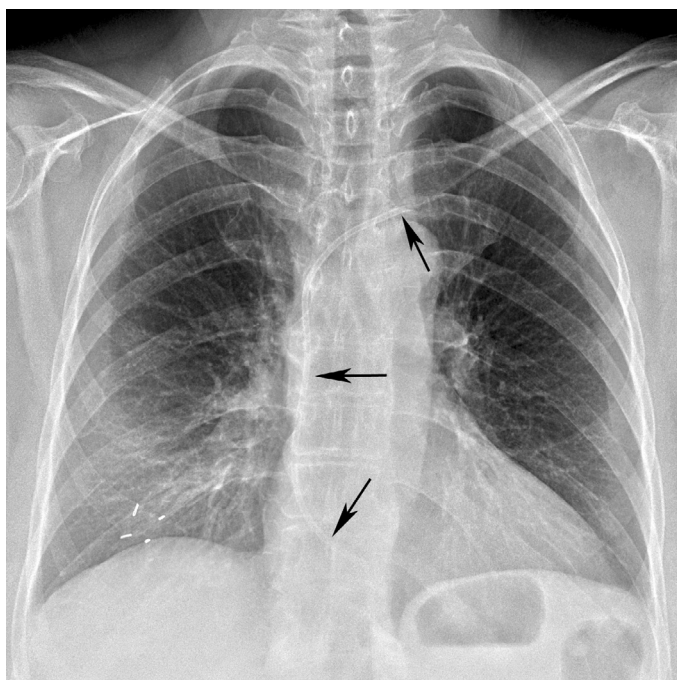


FIGURE 66-10 ■ Posteroanterior (PA) upright chest x-ray. Retained portacath fragment (*arrows*) within left brachiocephalic vein, superior vena cava, and right atrium is the result of shearing the catheter.

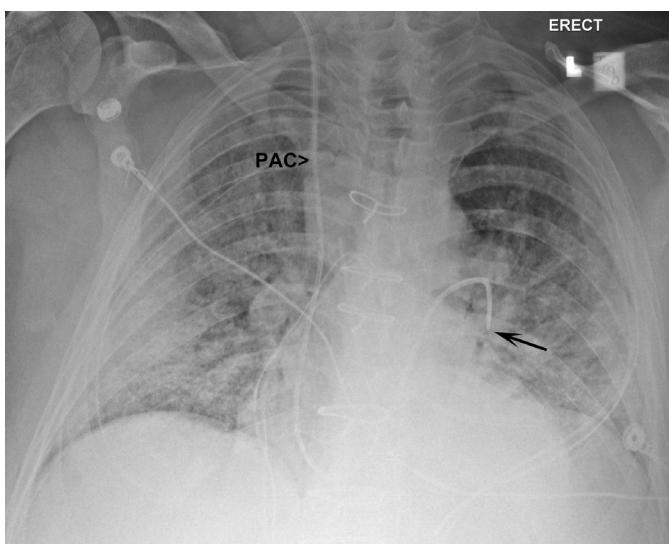


FIGURE 66-11 ■ Anteroposterior (AP) upright chest x-ray. Swan-Ganz catheter tip (*arrow*) is too distal, located in left lower lobe pulmonary artery. Background of cardiomegaly, interstitial and alveolar edema, and retrocardiac atelectasis.

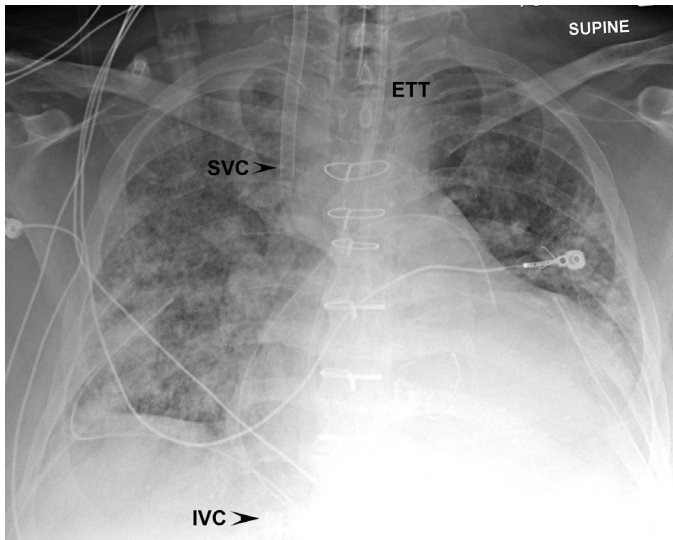


FIGURE 66-12 ■ Anteroposterior (AP) supine chest x-ray. Diffuse bilateral airspace opacities in a patient with diffuse alveolar disease (DAD). Dual caval ECMO catheters noted in the SVC (superior vena cava) and IVC (inferior vena cava, marked with arrows). Bilateral chest tubes, ET tube, feeding tube, mediastinal drains, and mitral valve prosthesis also noted.

draping over the surface of the left ventricle. The generator pack is placed subcutaneously in the anterior chest wall.

It is always important to evaluate lead integrity after placement of a cardiac pacemaker or AICD. Fractures of the leads occur most commonly at one of three locations: near the tip, at the generator pack, or at the site of venous access.³ Myocardial perforation is another complication, and radiographic evidence of associated hemopericardium is suspected with progressive enlargement of the pericardial silhouette. Tamponade is usually diagnosed clinically but can be seen radiographically, with temporal pulmonary artery enlargement and engorgement of the vena cava.

Implantable loop recorders are small devices that are inserted under the skin to monitor the electrical activity of the heart continuously in the form of electrocardiograms. They do not require the use of implantable cardiac wires. Arrhythmic episodes are recorded and stored for extended periods to assist in the diagnosis of patients with syncope, seizures, and palpitations. They are rectangular in shape and most often located to the left of the sternum⁴ (Fig. 66-13).

Thoracostomy Tubes

Thoracostomy tubes are available in multiple diameters and degrees of flexibility. They are used to evacuate air and/or fluid from the pleural space. Correct placement of the tube depends on the type of substance being drained. To drain pleural fluid, the tube typically needs to be located posteroinferiorly. To relieve a pneumothorax, an anterosuperior location is usually best.

Chest CT is superior to CXR in accurately determining the course of thoracostomy tubes and noting their relationship to pleural air and fluid collections (Figs. 66-14, A, and 66-14, B). When loculations or adhesions are present, CT or ultrasound may be necessary as guidance for optimal tube placement.

The thoracostomy tube's side port is distinguished as a focal disruption of the radiopaque linear marker that runs the length of the tube and should always be located inside the rib margin (Fig. 66-15). If the side port is not within the rib margin, a pneumothorax and/or subcutaneous emphysema may develop. Inadvertent intraparenchymal

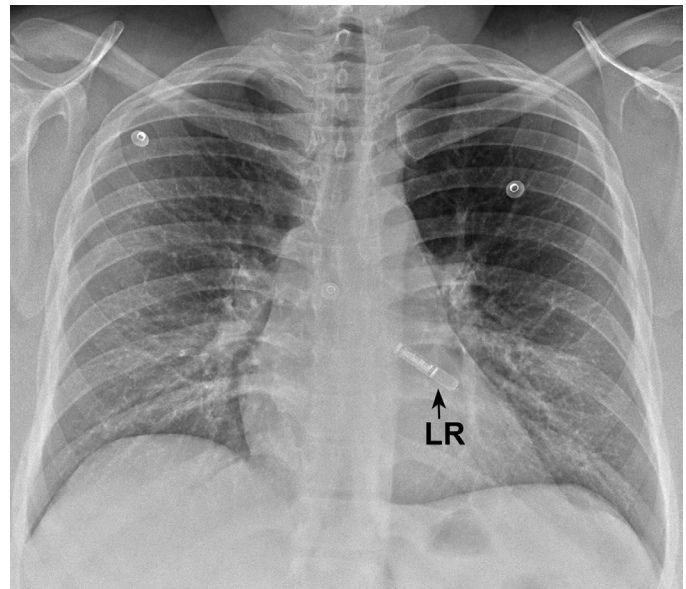


FIGURE 66-13 ■ Posteroanterior (PA) chest x-ray. Implantable loop recorder (LR) is in the soft tissues of the anterior left chest wall.

placement can result in laceration, hematoma, or bronchopleural fistula. Malfunction of the tube can occur when incorrectly positioned in a fissure or within the subcutaneous tissues, or when occluded by clot or debris.

Thoracostomy tubes are typically placed during thoracic surgery to be removed 1 to 2 days later. In postcardiac surgery patients, an anterior mediastinal drain that runs parallel to the sternum is common, as are pericardial and posterior-inferior mediastinal tubes, which usually are present at right angles to the sternum. Thin epicardial pacing wires placed through the chest and anchored in the myocardium are usually seen on the postoperative CXR. At the midline, thin epidural analgesic catheters or spinal neurostimulator wires can also be visualized (Fig. 66-16).

Enteric Tubes

Many critically ill patients who require gastric suction or enteric feedings are sedated or neurologically impaired, resulting in a depressed cough reflex. Inadvertent passage of enteric tubes into the tracheobronchial tree may be clinically unrecognizable. Radiographic confirmation of correct enteric tube position is, therefore, prudent before feeding or suction can begin. Nasogastric (NG) and feeding tubes (FT) each have a characteristic radiographic appearance. Gastric tubes are larger in diameter and have a linear radiopaque stripe along their entire length, apart from their side ports. Feeding tubes are thinner and longer without a radiopaque strip but instead contain a short cylindrical weighted metallic tip.

Enteric tubes can be displaced into the tracheobronchial tree or coiled within the hypopharynx, as well as being malpositioned (usually too proximally) within the enteric system (Fig. 66-17). The NG tube side hole is usually 10 cm from the tip and should be located well below the esophagogastric (EG) junction. A side hole proximal to or at the EG junction often leads to the aspiration of gastric contents (aspiration pneumonia), the postobstructive collapse of a lung or lobe, and to superimposed pneumonia. Feeding tube tips should be positioned in the duodenum or proximal jejunum to avoid reflux of feedings, which can also lead to increased risk of aspiration (Fig. 66-18). Since the enteric tubes are inserted over a wire, there is a potential risk of esophageal or gastric perforation. Displacement of the wire into the airway can result in pneumothorax.

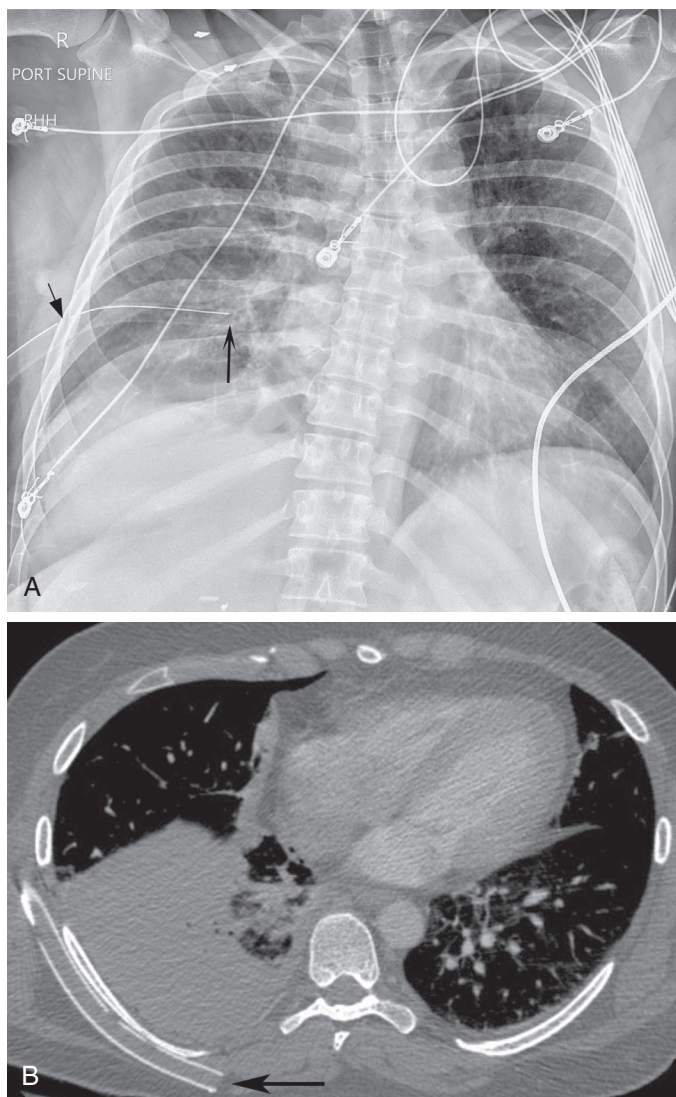


FIGURE 66-14 ■ **A**, Anteroposterior (AP) supine chest x-ray. Chest tube tip (*large arrow*) appears to be within the right chest cavity. Note that the side port (*small arrow*) overlies the right lateral ribs and does not appear within the hemithorax. Right pleural effusion obscures right hemidiaphragm. **B**, Axial computed tomography (CT) slice. Same patient showing chest tube tip (*small arrow*) is actually outside of chest cavity within the soft tissues of the back.

Left Ventricular Assist Devices

An intraaortic counterpulsation balloon (IACB) is used to assist with severe left ventricular dysfunction by reducing systolic afterload and augmenting coronary artery perfusion. It consists of a 16- to 20-mm long inflatable balloon surrounding the distal end of a vascular catheter. It is usually inserted percutaneously through the femoral artery or directly into the thoracic aorta.

At the distal tip of the IACB, there is a small radiopaque cylindrical marker to help locate and position the catheter. When properly positioned, the tip should be located distal to the left subclavian artery in the proximal descending thoracic aorta, just below the bottom of the aortic arch (Fig. 66-19). The balloon itself is not typically visible on the CXR because it is either deflated or sometimes filled with water.³

When the IACB is advanced too far, the catheter can obstruct or occlude the left subclavian or left common carotid artery. If not advanced far enough, the balloon will be too distal relative to the

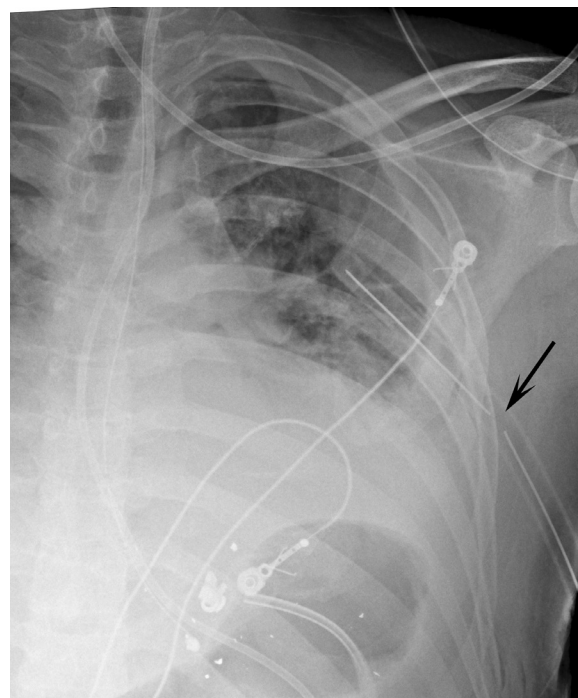


FIGURE 66-15 ■ Anteroposterior (AP) supine chest x-ray. Left chest tube has not been advanced adequately with the side hole outside of rib margin (*arrow*).

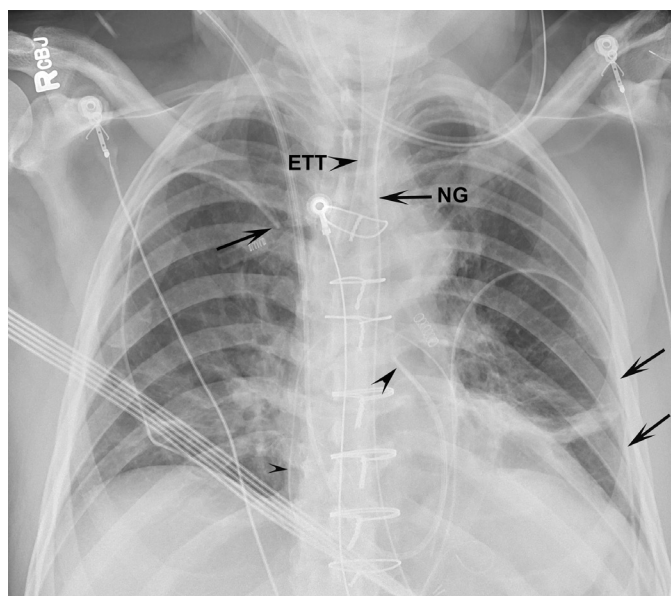


FIGURE 66-16 ■ Anteroposterior (AP) supine chest x-ray. Immediate postoperative coronary artery bypass graft chest x-ray with classic left lower lobe atelectasis, partially obscuring the left heart border and the left hemidiaphragm. Endotracheal tube (ETT), nasogastric tube (NGT), bilateral chest tubes (*black arrows*), and Swan-Ganz catheter (*black arrowhead*) are all in a good position.

proximal aorta, and counterpulsation will be less effective. There is also the risk of occluding the mesenteric and/or renal vessels, resulting in ischemia.

Aortic dissection following IACB insertion is another potential complication, especially in patients with pronounced aortic atherosclerotic

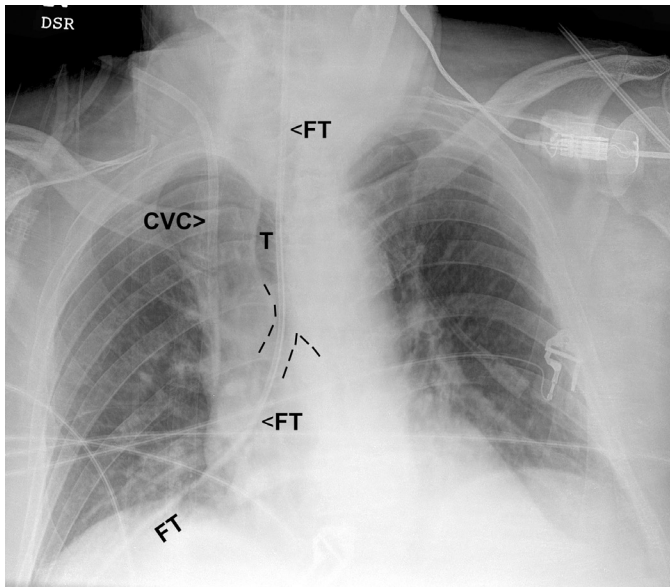


FIGURE 66-17 ■ Anteroposterior (AP) supine chest x-ray. Feeding tube (FT) courses through the trachea and then down the right bronchial tree to lodge in the peripheral lung.



FIGURE 66-18 ■ Anteroposterior (AP) supine abdomen x-ray. Feeding tube tip (white arrow) is at the level of the fourth distal portion of the duodenum.

disease or tortuosity, and should be considered when there is new mediastinal widening and/or loss of definition of the descending thoracic aorta on the CXR.

Left ventricular assist devices (LVAD) are typically implanted for three purposes: as a bridge to transplantation, as a therapy for patients ineligible to receive a transplant, and as a bridge to myocardial

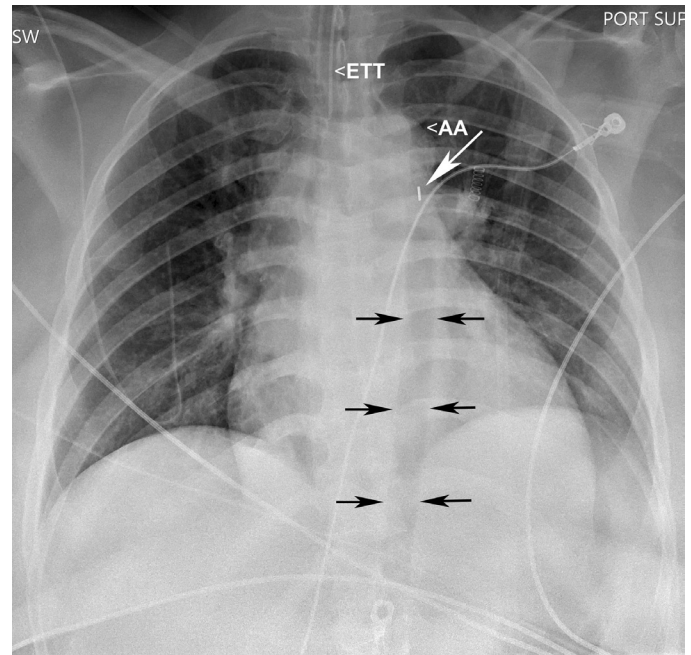


FIGURE 66-19 ■ Anteroposterior (AP) supine chest x-ray. Intraaortic balloon pump (IABP) is in proper position with a proximal cylindrical marker (white arrow) just below the aortic arch (AA). When the x-ray was taken, the balloon happened to be inflated and can be easily recognized (outlined by smaller black arrows). Endotracheal tube (ETT) is also present and in the proper position.

recovery. CT scan of the chest is currently used as a problem-solving tool when echocardiography for LVAD evaluation is inconclusive. electrocardiography-gated CT of an LVAD should show the inflow cannula entering the left ventricular apex and directed into the left ventricular cavity without obstruction or surrounding thrombus formation, a neutral intraventricular septum, closure of the aortic valve during systole and diastole, and minimal to no aortic valve regurgitation. The outflow cannula will attach to the ascending or descending thoracic aorta (Fig. 66-20).⁵

The Impella is a percutaneously inserted ventricular assist device which is placed via a retrograde approach across the aortic valve using femoral artery access or via mini-thoracotomy (Figs. 66-21, A, and 66-21, B). It pumps blood from the left ventricle into the ascending aorta and systemic circulation. The device should straddle the aortic valve with the inflow tip (distal end of the catheter) residing in the left ventricular cavity and the outflow end in the proximal aorta.^{6,7}

CARDIOVASCULAR SYSTEM

As was discussed in the introduction, the patient's position will affect the cardiac size, as well as the appearance of the vasculature. Additionally, the cardiac silhouette appears approximately 12.5% larger on AP vs. posteroanterior (PA) images.¹ The same is true if the patient is rotated or if the CXR is taken in a lordotic view. Similarly, the phase of the respiratory cycle, specifically if the radiograph is not acquired during end-inspiration, will change the appearance of the heart and vasculature. In all of these cases, the heart will appear larger and the vasculature "plumper" and more ill-defined. When standing, the lower lobe pulmonary vasculature is normally larger in diameter than the upper lobe vasculature. However when supine, due to gravity, the blood flow is normally redirected posteriorly, and the differential appearance between the upper and lower lobe vascularity is not present.

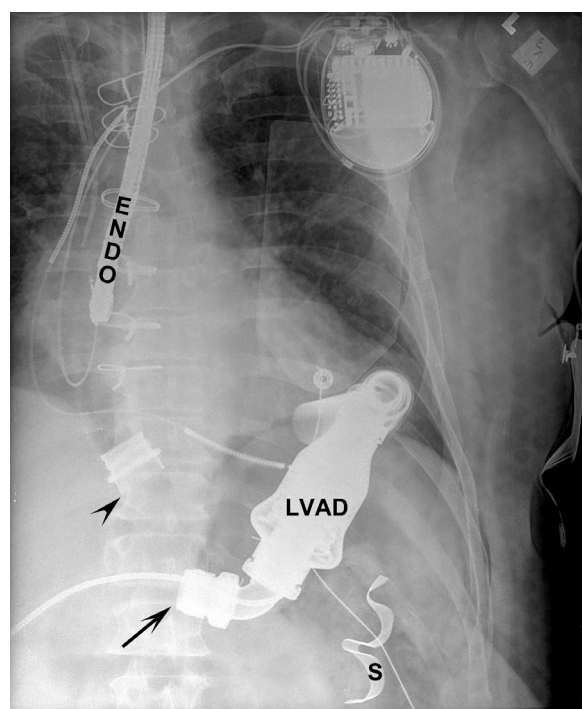


FIGURE 66-20 ■ Anteroposterior (AP) supine chest x-ray, intraoperative. Detached left ventricular assist device (LVAD) outflow cannula (gap between arrowhead and arrow). Also, note an esophageal probe (ENDO) and a left upper quadrant surgical sponge (S).

When evaluating the cardiovascular system, the cardiac silhouette should be less than 50% of the transverse dimension of the lower thorax in the end-inspiration. A big “heart” may in fact not be cardiomegaly but a normal size heart with surrounding pericardial effusion. Here is where temporal analysis with a baseline “well patient” CXR coupled with clinical history becomes critical.

If there is global enlargement of the heart, it is usually due to an ischemic cardiomyopathy (ICM), a dilated cardiomyopathy (DCM), or multivalvular disease. The presence of pulmonary edema, diastolic dysfunction, or stenotic or regurgitant murmurs, coupled with the patient’s history, almost always establishes the correct diagnosis. Focal enlargement of the heart, in which one or two chambers are enlarged, is most commonly seen with LV enlargement due to ischemic disease, with or without a true aneurysm, single valve disease, cardiac tumors, or congenital heart disease.

■ LUNG PARENCHYMAL OPACITIES

Pulmonary Edema

Serial CXRs provide an assessment of the changing pulmonary vascular blood volume; evaluation of the temporal pattern is helpful in regards to response to therapy and aiding in an accurate diagnosis. Additionally, differentiating cardiogenic from noncardiogenic pulmonary edema is important, but challenging, in the critical care setting.

Cardiogenic Edema

In cardiogenic edema, Swan-Ganz catheter measurements provide a reliable measurement of cardiac function. There are correlating CXR findings as capillary wedge pressure increases and transudation of fluid into the interstitium and alveoli occurs (Table 66-3).

Initially, there is central peribronchial cuffing/thickening with pulmonary capillary wedge pressure (PCWP) of 12 to 18 mm Hg in a patient with normal intravascular oncotic values. The upper lobe

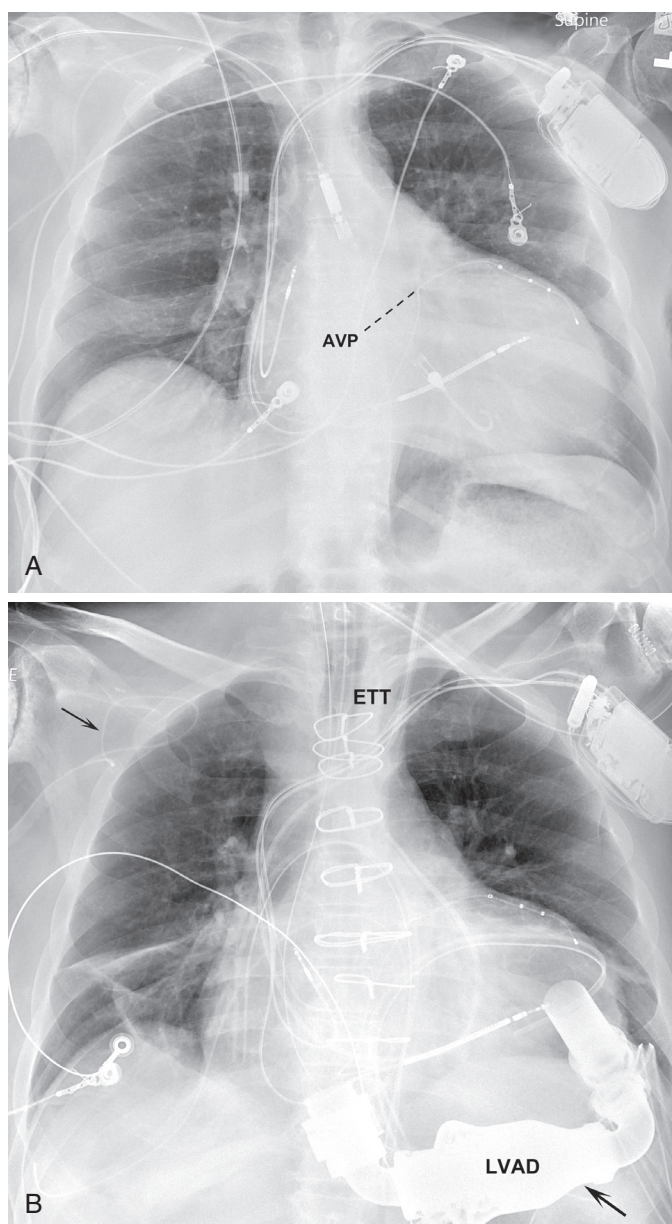


FIGURE 66-21 ■ **A**, Anteroposterior (AP) supine chest x-ray. Impella device properly positioned, straddling the aortic valve plane (AVP). **B**, Anteroposterior (AP) upright chest x-ray. Same patient after undergoing surgery via a sternotomy to replace the impella with an LVAD (bottom right arrow). Right, PICC line now coiled at right axillary vein level (top left arrow). Cardiomegaly and bibasilar subsegmental atelectasis.

TABLE 66-3 Cardiogenic Edema

PULMONARY CAPILLARY WEDGE PRESSURE (PCWP) = 12-18 MM HG

- Central peribronchial cuffing
- Cephalization/engorgement of central pulmonary arteries

PCWP = 18-25 MM HG

- Interstitial prominence with Kerley A and Kerley B lines

PCWP = >25 MM HG

- Alveolar opacities
- Cardiomegaly
- Pleural effusions

arteries become engorged (or “capitalized”) and appear to be the same or greater diameter than the respective inferior lobar vessels in a vertically obtained radiograph. To aid in establishing the volume of pulmonary blood flow, comparing the diameters of the central pulmonary arteries and the adjacent bronchus on end is useful. The normal ratio is 1:1 or less. An increase in this ratio reflects increased pulmonary flow/pressure. With further increasing PCW pressure to 18–25 mm Hg, fluid then accumulates within interlobular septa, as demonstrated by prominent horizontal linear opacities. These have been termed *Kerley A lines* when they are longer and perihilar in location and *Kerley B lines* when finer and extended to the pleural surface. Finally, when the wedge pressure exceeds 25 mm Hg, alveolar edema occurs, presenting as fluffy perihilar or basilar-dependent airspace opacities (Figs. 66-22, A, 66-22, B, and 66-22, C). The airspace opacities in cardiogenic edema can fluctuate rapidly, which can be a clue to diagnosis.⁸ Cardiomegaly and pleural effusions are also usually present with cardiogenic edema. Sometimes, there can be a lag in the radiographic improvement of cardiogenic edema relative to the pulmonary artery catheter pressures, which is thought to be related to the fact that it can take hours or days for large amounts of extracellular fluid to be reabsorbed.

The distribution of interstitial and airspace opacities in pulmonary edema is usually symmetric and dependent. However, opacities associated with pulmonary edema can be asymmetric, usually related to gravity and patient positioning. Underlying emphysema or chronic interstitial lung disease can also make edema appear patchy in its distribution.

Noncardiogenic Edema

Causes of noncardiogenic edema include neurogenic edema, renal disease, and global fluid overload, re-expansion edema, sepsis with increased capillary permeability, and rarer causes, such as fat embolism or other types of chemical pneumonitis⁹ (Table 66-4).

Neurogenic edema usually develops within hours to days after a neurologic insult, which can include trauma, stroke, seizure or intracranial hemorrhage, mass, or infection. The etiology of pulmonary edema in these settings is felt to be related to elevated microvascular pressure and increased pulmonary vascular permeability. It is postulated that a massive sympathetic discharge causes a surge of catecholamines resulting in cardiopulmonary dysfunction. The key to diagnosis is temporal, as there is usually a rapid clearance of bilateral airspace disease after the resolution of the cerebral edema/insult. Cardiomegaly and vascular engorgement are absent.^{10,11}

Edema from renal disease is related to an overall fluid overload state. Cardiomegaly, vascular cephalization, and effusions are commonly observed.

Re-expansion edema is due to the rapid re-expansion of a collapsed lung. It is unilateral and follows the drainage of pleural effusion or pneumothorax. It is more likely to occur when a large volume of pleural fluid or air is removed and if the affected lung has been chronically collapsed. Cardiomegaly is not an associated finding (Fig. 66-23).

Fat embolization is a rare complication of severe long bone fracture and is usually diagnosed clinically based on the trauma history. Dyspnea, altered mental status, and petechiae develop 12 to 72 hours after the initial injury. Chest imaging findings can be similar to pulmonary edema and organizing pneumonia (OP) with airspace geographic opacities, usually ground glass. This appearance is likely related to pneumonitis and increased capillary permeability (Figs. 66-24, A,

and 66-24, B). Cardiomegaly and vascular engorgement are absent. Low-density fat-filling defects in the pulmonary arteries are only very rarely seen.³

Pulmonary Contusion

Pulmonary contusion is a frequent complication following chest trauma and usually presents within six hours of the incident (Figs. 66-25, A, and 66-25, B). Radiographically, contusion (or focal hemorrhage/bruising of the lung parenchyma) presents as peripheral airspace opacities typically located deep to the site of chest wall impact. Associated adjacent rib fractures are also commonly seen. The opacities related to contusion usually clear rapidly; within 24 to 72 hours. Laceration, or disruption of the lung parenchyma, can accompany a contusion and present as focal ovoid radiolucencies within the contused portion of the lung.³ These are also referred to as traumatic pneumatoceles. Hemorrhage can fill the cavity, producing an opaque hematoma. Lacerations and associated hematomas usually resolve slowly over weeks to months (Table 66-5).

Diffuse Alveolar Disease/Organizing Pneumonia

The lung's response to injury, despite numerous offending agents, shows a similar radiographic pattern regardless of the underlying cause. Similarly, histologic features are similar with many insults leading to damage of the alveolar epithelial basement membrane and organization, characterized by fibroblast proliferation. This pattern is seen in diffuse alveolar damage (DAD) and OP (Table 66-6).¹² In most circumstances, the organization clears as part of the normal process of repair. However, in some instances, repair is self-reinforcing and leads to fibrosis.

The acute phase of DAD appears as diffuse or patchy geographic ground glass opacities (GGO) with areas of consolidation and septal thickening on CXR and CT. The distribution is most pronounced in the dependent portions of the lungs (Fig. 66-12). Fibrotic disease in the setting of chronic lung injury can progress to reticulation and traction bronchiectasis, which are most pronounced in the anterior, non-dependent portions of the lung. This distribution may be related to

TABLE 66-4 Noncardiogenic Pulmonary Edema

- Global fluid overload/renal disease
- Sepsis with increased capillary permeability
- Re-expansion edema
- Neurogenic edema
- Fat embolism
- Chemical pneumonitis

TABLE 66-5 Trauma

- Rib, sternal, clavicular, spinal fractures
- Pulmonary contusions, traumatic pneumatoceles, parenchymal hematoma
- Pneumothorax
- Hemothorax
- Aortic injury—transection, dissection
- Mediastinal hematoma and pneumomediastinum
- Diaphragmatic rupture

TABLE 66-6 Diffuse Alveolar Disease/Organizing Pneumonia

Infection
Drug reaction
Sepsis/shock
Toxic inhalation
Aspiration
Eosinophilic pneumonia
Collagen vascular disease
Radiation injury
Hypersensitivity pneumonitis
Idiopathic (cryptogenic organizing pneumonia)

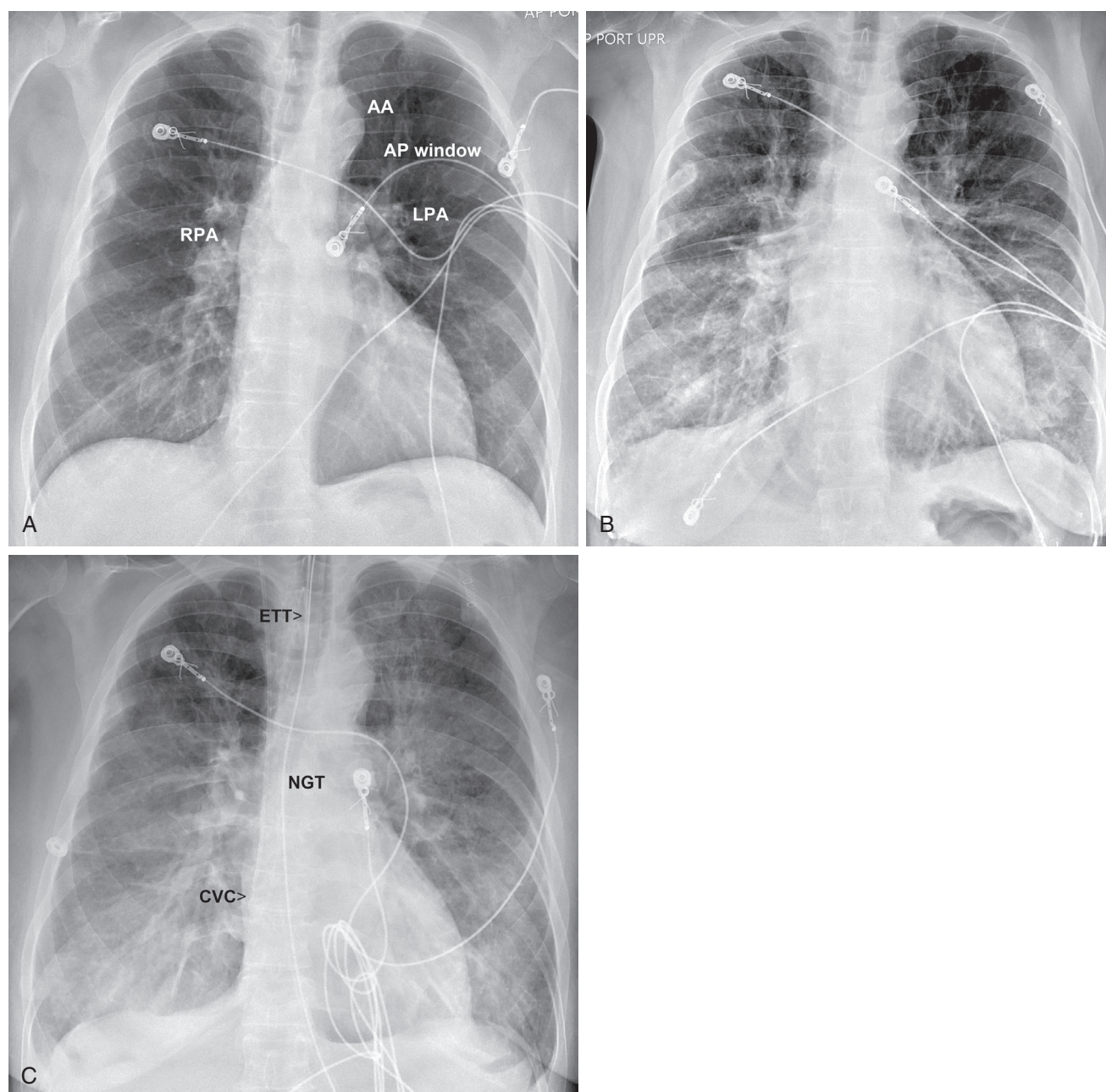


FIGURE 66-22 ■ **A**, Anteroposterior (AP) upright chest x-ray. Emphysema is evidenced by hyperexpansion and attenuation of the upper lobe pulmonary arteries and veins. AA, aortic arch; AP window, aortopulmonary window; LPA, left pulmonary artery; RPA, right pulmonary artery. **B**, Anteroposterior (AP) upright chest x-ray: +3½ hours. Same patient 3½ hours later with redistribution of the pulmonary vasculature to the upper lobes, interstitial pulmonary edema as evidenced by indistinctness of the pulmonary vessels and “peribronchial cuffing,” a small right pleural effusion, and developing cardiomegaly. **C**, Anteroposterior (AP) supine chest x-ray: +4½ additional hours. Same patient 4½ hours later with diffuse but symmetric airspace opacities consistent with fluid filling the alveoli. Increasing pleural effusions are now layering posteriorly, giving a “whiter” appearance to the mid and lower hemithoraces. CVC, right internal jugular vein central venous catheter; ETT, endotracheal tube; NGT, nasogastric tube.

barotrauma due to mechanical ventilation or oxygen toxicity, whereas the dependent lung is protected from collapse^{13,14} (Table 66-6).

Historically, “OP” was used to describe the lung responses to pulmonary infection, though many other cases are recognized now. In the absence of an identifiable cause, the clinical diagnosis of cryptogenic OP (COP) can be made.^{15,16}

In most OP cases, there are diffuse, bilateral consolidative, and ground glass infiltrates. These are typically peripheral or peribronchocentric and frequently with interspersing areas of normal, unaffected

lung. The “reverse halo” and “atoll” signs on CT can be seen with OP and are characterized by GGO surrounded by a rim of denser consolidated opacity.¹⁷

Cardiomegaly and pulmonary vascular engorgement/cephalization are absent. Otherwise, the radiographic features of DAD and OP can be indistinguishable from pulmonary edema. Effusions are uncommon. Barotrauma with pneumothorax is more common with DAD because of reduced lung compliance and prolonged mechanical ventilation.^{18,19}

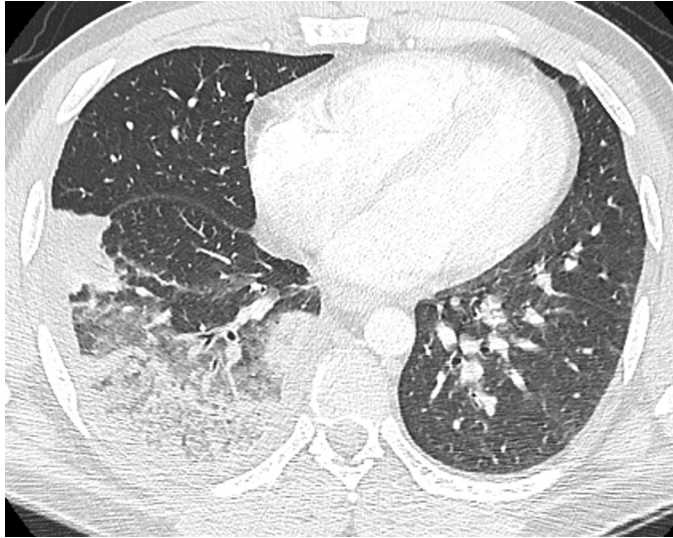


FIGURE 66-23 ■ Axial computed tomography (CT) slice through lower chest. Localized interstitial and airspace opacities in the right lower lobe after drainage of the pleural fluid collection. Small pleural effusion persists.

Pneumonia/Aspiration

The diagnosis of pneumonia is often clinical, based on the presence of fever and leukocytosis. However, new or progressive pulmonary opacification on CXR can aid in diagnosis. Nosocomial bacterial pneumonia can complicate the clinical course of up to 40% of ventilated patients.³ Proper antibiotic therapy with improvement in clinical symptoms may not alter the radiographic course of pneumonia for up to 48 hours after initiation. However, there should be a lack of progression, if not an improvement, in the radiographic abnormality after that point.

The risk of nosocomial pneumonia is much greater in patients who require intubation and mechanical ventilation than those who do not.²⁰ This is because the tracheal tube bypasses the usual upper airway defenses. Additionally, pharyngeal secretions and flora can leak around the cuff and enter the lower respiratory tract. Swallowing is impaired resulting in retention of secretions. The mechanical trauma to the tracheal epithelium also may predispose to opportunistic organisms. Aspiration can occur more easily in the presence of nasogastric tubes and ETTs, both of which are common in ICU patients.

The radiographic appearance of pneumonia includes the opacity of an entire lobe with or without air bronchograms (Figs. 66-26, A, and 66-26, B), confluent airspace opacities within a portion of a lobe, patchy and ground glass air space opacities, or endobronchial thickening with peribronchocentric opacities (Table 66-7).

Hospital-acquired pneumonia is more likely to be bilateral and multifocal than community-acquired pneumonia.²⁰ Cavitation and

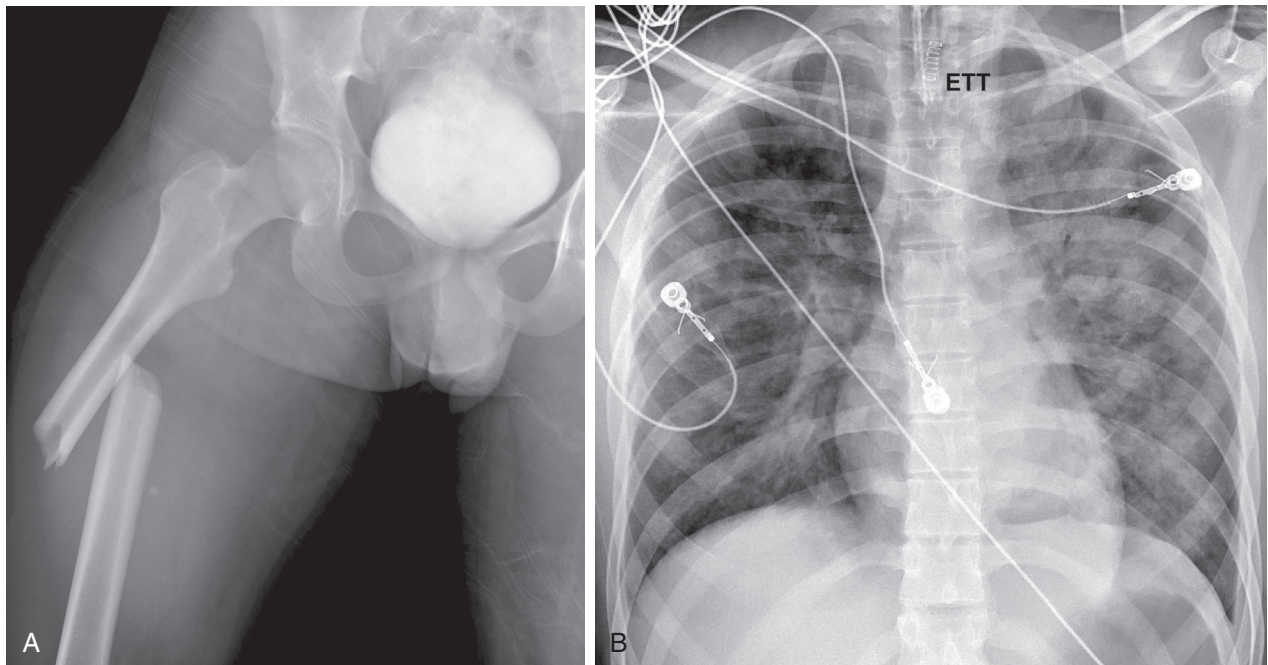


FIGURE 66-24 ■ **A**, Anteroposterior (AP) supine right femur x-ray. Proximal right femoral shaft fracture. **B**, Anteroposterior (AP) upright chest x-ray. Chest x-ray of the same patient demonstrates diffuse bilateral airspace opacities due to fat emboli, developed approximately 24 hours after femur fracture. ETT, endotracheal tube in proper position.

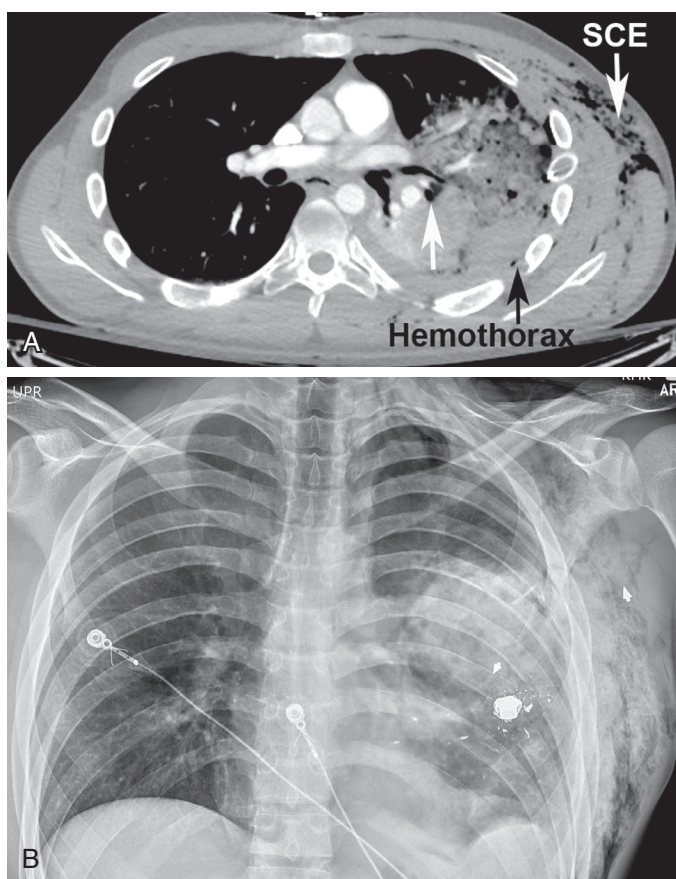


FIGURE 66-25 ■ **A**, Axial computed tomography (CT) slice at level of hila. Left lower and upper lobe airspace opacities, consistent with a contusion. Associated parenchymal laceration (*white arrow*), hemo-pneumothorax, and subcutaneous emphysema (SCE), all sustained by trauma from a gunshot. **B**, Corresponding anteroposterior (AP) chest x-ray. Small arrow in left axilla is a marker placed on the patient's skin to indicate the bullet entry site.

TABLE 66-7 Pneumonia

- Opacity of entire lobe, with or without air bronchograms
- Confluent airspace opacities
- Patchy and ground glass airspace opacities
- Endobronchial thickening with peribronchocentric opacities
- Cavitation and necrosis of parenchyma
- Pleural effusion and empyemas
- Interstitial or nodular pattern with atypical organisms
- Peripheral cavitary opacities with septic emboli
- Dependent location suggests aspiration

associated empyema can occur with bacterial and mycobacterial infections and are more common with nosocomial organisms than with community-acquired ones.

Atypical pneumonia includes viral, fungal, and mycobacterial etiologies, which are commonly seen in immunocompromised patients. Viral pneumonia can present as diffuse nodules or linear interstitial reticulation, as well as airspace consolidations. Fungal pneumonia can appear as nodules or as focal, patchy consolidations and ground glass opacities. Mycetomas, or fungus balls, can develop within preexisting cavities.

Septic emboli are typically present as multiple, bilateral, peripheral ill-defined or wedge-shaped opacities, some of which may cavitate

(Figs. 66-27, 66-28, and 66-29). Common sources of septic emboli include infected tricuspid and pulmonic valves or indwelling catheters, along with sepsis and urinary tract infections.

Aspiration pneumonia or pneumonitis is most common in patients with a decreased level of consciousness, those who have ETTs in place, and those with esophageal or swallowing disorders. Aspiration usually presents as airspace opacity within the dependent portions of the lungs, which in a supine patient are the posterior basilar and superior segments of the lower lobes and the posterior segments of the upper lobes (Fig. 66-30). The degree and location of the opacification are dependent on the volume and nature of the aspirate, in addition to the position of the patient. For example, when acidic gastric contents are aspirated, a chemical pneumonitis resembling pulmonary edema can occur. Whereas when infected mucoid material from the upper airway is aspirated, the appearance is a combination of volume loss and a denser opacity resembling pneumonia.^{3,20} Associated atelectasis can also occur secondary to bronchial obstruction by the aspirated material.

Atelectasis

Atelectasis is a common finding in critically ill and postoperative patients. It is often associated with general anesthesia and frequently occurs following thoracic and upper abdominal surgery. It represents areas of nonaerated lung with the extent ranging from subsegmental linear bands, platelike or patchy opacities, to full lobar collapse. Air bronchograms may or may not be present, and the appearance can be indistinguishable from pneumonia. When suspected atelectasis persists beyond the third or fourth postoperative day, pneumonia becomes more likely. However, atelectasis comes and goes more rapidly than pneumonia and aspiration pneumonitis, usually within hours rather than weeks or days. Secondary findings of volume loss, such as diaphragmatic elevation and tenting, displaced fissures, crowding of the bronchovascular structures, and in more severe cases, deviation of the heart and mediastinum toward the atelectatic side may occur. The left lower lobe is the most common location for atelectasis.²⁰ After cardiac surgery, left lower lobe atelectasis is a frequent finding secondary to phrenic nerve damage from stretching and cold-induced trauma (Fig. 66-16 and Table 66-8).

Thromboembolism

Acute pulmonary embolism (PE) is a potentially lethal condition and is more common in hospitalized patients due to immobility, postoperative status, chemotherapy and other medications causing hypercoagulability, and additional comorbidities. Conventional chest radiograph findings are inconsistently present and nonspecific. CT angiography of the pulmonary arterial system has, therefore, become the gold standard for detection of pulmonary emboli. Filling defects, partial or complete, within the pulmonary arteries, are diagnostic of PE. Associated findings include pleural effusion, atelectasis, wedge-shaped peripheral pulmonary infarction (Hampton's Hump), local oligemia (Westermarck sign), and reperfusion edema (Figs. 66-31, A, 66-31, B, and 66-32). Secondary pulmonary artery hypertension with enlargement of the main pulmonary artery and evidence of right heart strain with left convex bulging of the intraventricular septum and engorgement of the vena cava and hepatic veins can be present.

PLEURAL DISEASE

Pleural Fluid

In the ICU, pleural effusions are common but may go undetected on supine CXRs, even when moderately sized. Fluid usually settles dependently in the posterior base when supine and may present as a homogeneous increase in the overall density of the lower hemithorax, blunting of the costophrenic angle, and loss of diaphragmatic contour. On an upright CXR, pleural fluid collections that are uncomplicated

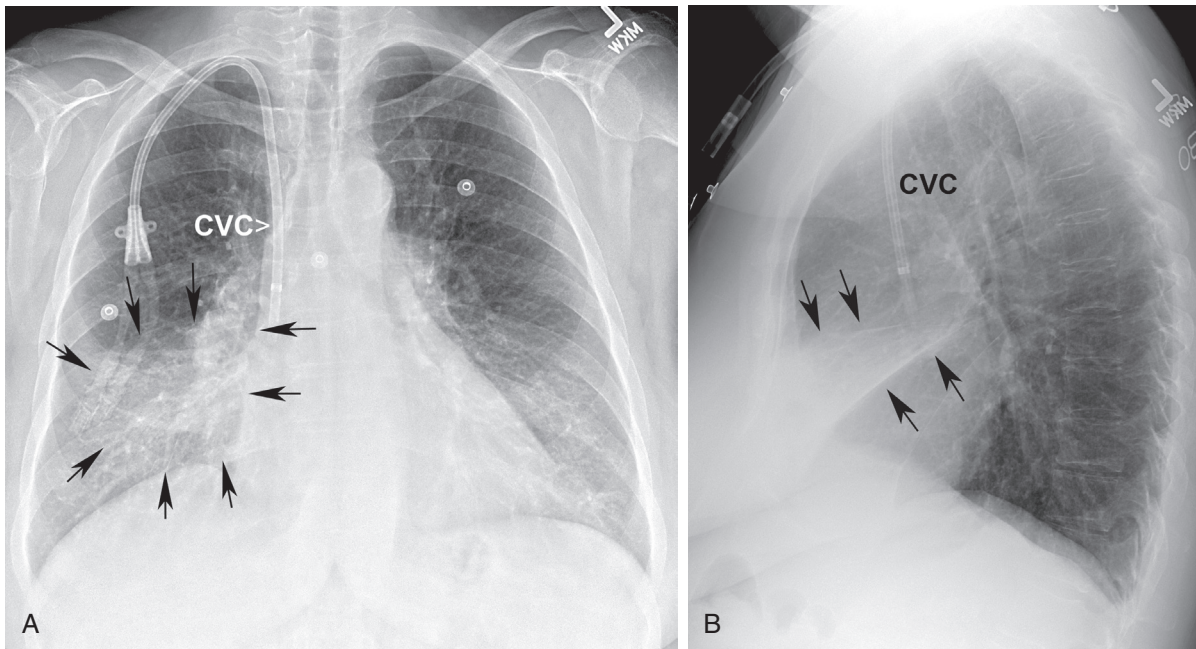


FIGURE 66-26 ■ **A**, Posteroanterior (PA) upright chest x-ray. Airspace opacity within the right middle lobe (RML) caused by pneumonia (*outlined by arrows*). Note indistinct right heart margin suggesting the involvement of the medial segment of the RML. **B**, Lateral upright chest x-ray. Airspace disease located between the minor fissure (*upper arrows*) and the right major fissure (*lower arrows*) caused by a right middle lobe pneumonia.

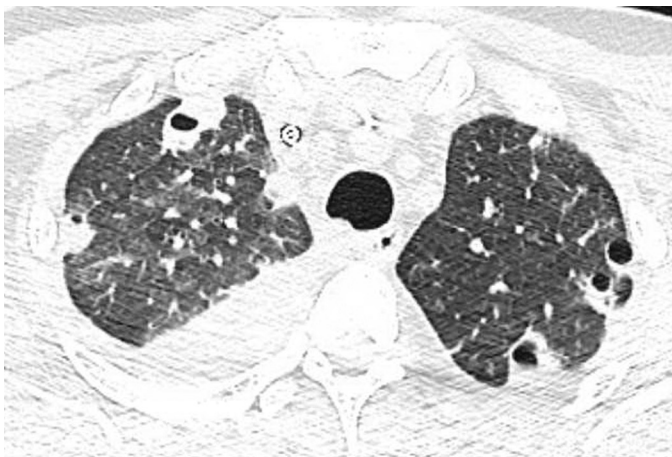


FIGURE 66-27 ■ Axial computed tomography (CT) slice. Multiple bilateral peripheral cavitary nodules due to septic emboli.

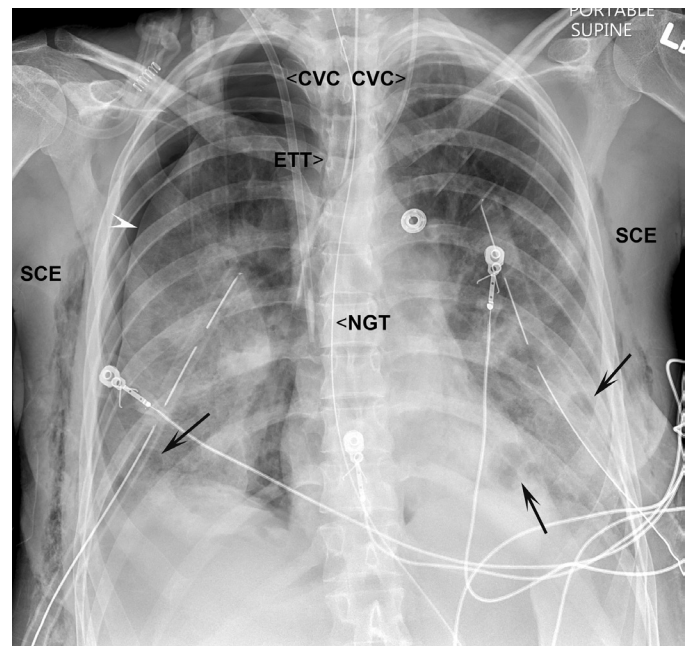


FIGURE 66-28 ■ Anteroposterior (AP) supine chest x-ray. Bilateral focal lucencies (*black arrows*) within areas of airspace opacity suggest septic emboli or parenchymal necrosis. There is an associated right pneumothorax (white arrowhead delineates lung edge). ETT, bilateral internal jugular CVCs (central venous catheters), bilateral chest tubes, and NGT (nasogastric tube) are in proper position. Subcutaneous emphysema (SCE) is secondary to recent chest tube insertion.

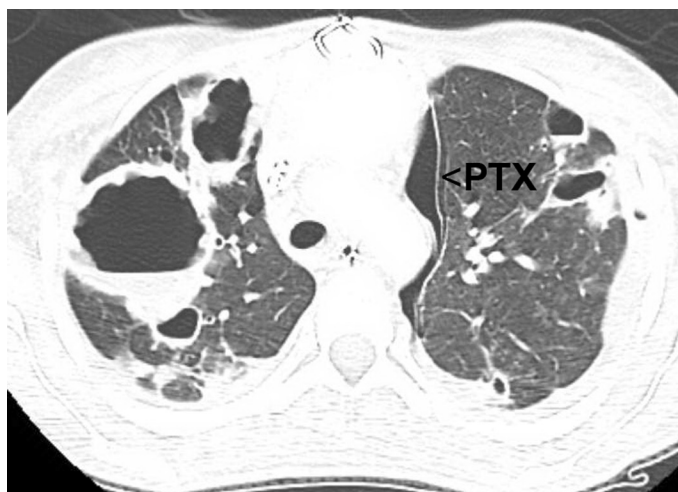


FIGURE 66-29 ■ Axial computed tomography (CT) slice at level of aortic arch. Large, thick wall cavities in the periphery of both lungs with associated left pneumothorax (PTX) in a patient with tricuspid endocarditis, consistent with septic emboli.

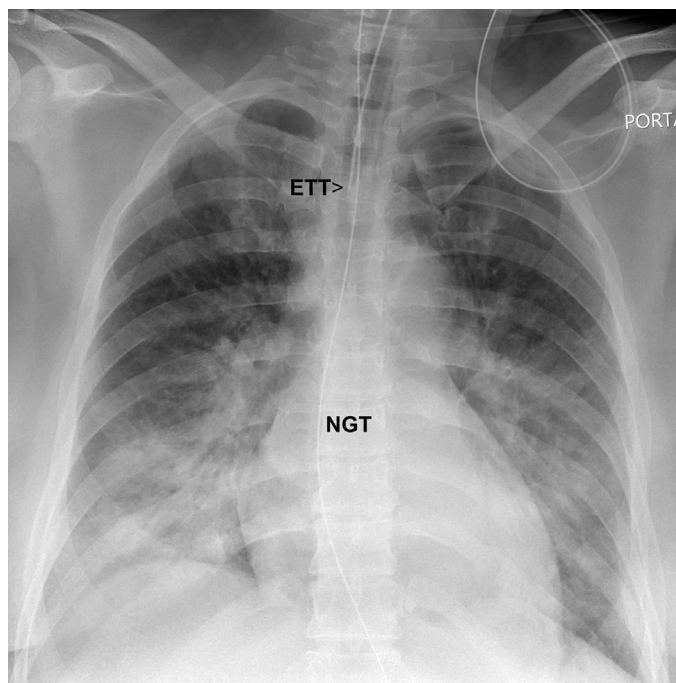


FIGURE 66-30 ■ Anteroposterior (AP) supine chest x-ray. Bilateral lower lobe patchy airspace opacities in an intubated patient are the result of aspiration pneumonia/pneumonitis. ETT, endotracheal tube; NGT, nasogastric tube.

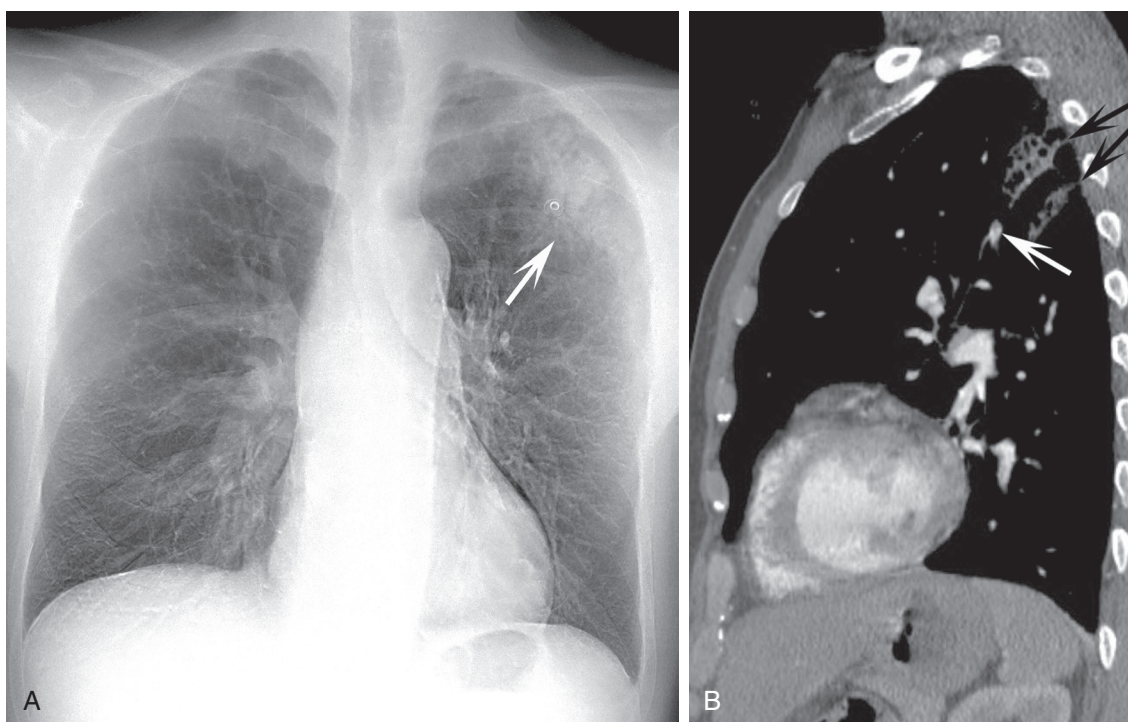


FIGURE 66-31 ■ **A**, Posteroanterior (PA) upright chest x-ray. Peripheral wedge-shaped opacity in the left upper lobe (*white arrow*). **B**, Sagittal computed tomography (CT) reconstruction. CT in same patient showing left upper lobe infarct and hemorrhage (*black arrows*) with an embolus in the left upper lobe segmental artery supplying this region (*white arrow*).

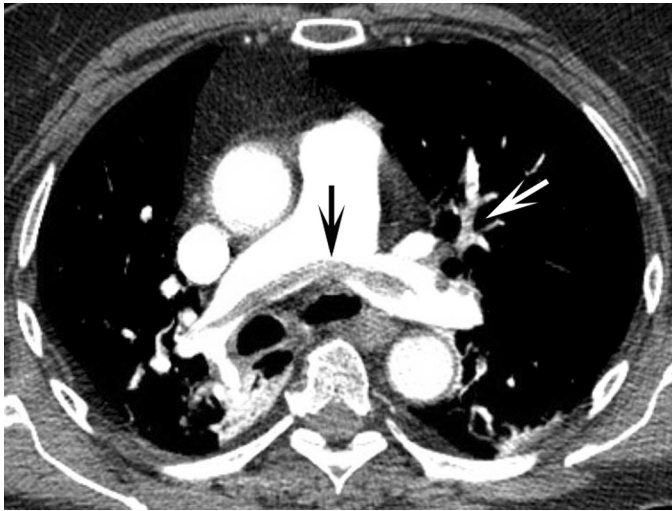


FIGURE 66-32 ■ Axial computed tomography (CT) slice at the level of the hila. Saddle embolus (*black arrow*) in the distal main pulmonary artery, straddling the entire length of the right and left main pulmonary arteries. Occlusive pulmonary embolism also noted in a left upper lobe segmental branch (*white arrow*).

TABLE 66-8 Atelectasis

- Subsegmental linear bands
- Platelike or patchy segmental opacities
- Lobar collapse
- +/- Air bronchograms
- Secondary signs of volume loss:
 - Diaphragmatic elevation
 - Displaced fissures
 - Crowding of bronchovascular structures
 - Mediastinal/cardiac ipsilateral deviation

and free flowing will present as a basilar opacity with a well-defined convex downward superior border and blunting of the costophrenic angle. As the effusion increases in size, it will track upwards resulting in a widening of the lateral pleural stripe and eventually apical “capping.” Bedside maneuvers, such as lateral decubitus films or cross table lateral films, can sometimes help determine the presence of pleural fluid and whether or not such fluid is free flowing vs. loculated (Fig. 66-33). A bedside ultrasound can also aid in detecting and characterizing pleural fluid collections and can assist with thoracentesis and pleural catheter guidance. CT is far superior to CXRs in evaluating complicated pleural fluid and gas collections.

Pleural effusions secondary to congestive heart failure and traumatic hemothorax are the most common etiologies of pleural fluid in the critical care unit. Other etiologies include pneumonia, pulmonary embolus, neoplasm, postoperative from median sternotomy or thoracotomy, and intraabdominal pathologies such as pancreatitis or hepatitis. Empyema is strongly suspected in the setting of pneumonia when the effusion is loculated and contains gas (Table 66-9).

Following trauma, pleural fluid collections are usually due to hemorrhage (hemothorax). Hemothorax from aortic rupture at the isthmus is left sided and can be associated with a left pleural cap. Vascular injury following central line placement or an attempt can also lead to pleural fluid accumulation. In these scenarios, there is a rapid accumulation of the fluid collections (Table 66-5).

Diaphragmatic rupture can occur after severe trauma and is usually left sided. It presents as an apparent elevation of the hemidiaphragm

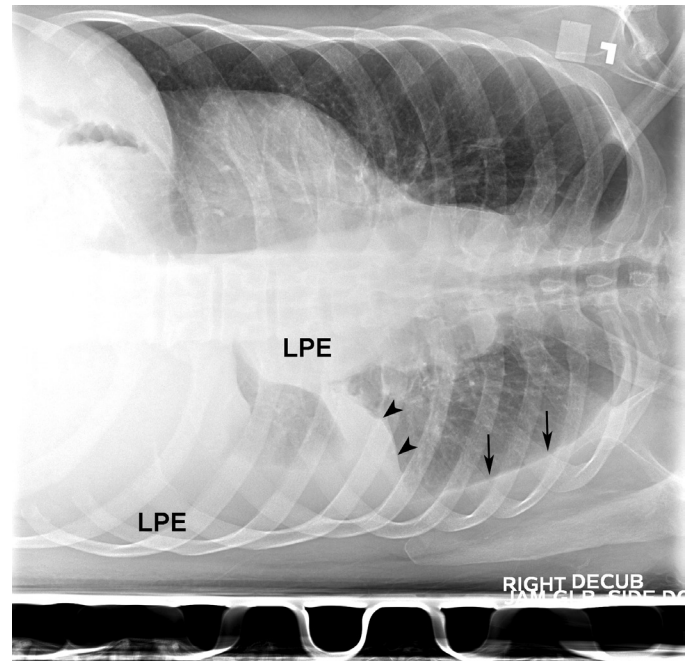


FIGURE 66-33 ■ Right lateral decubitus chest x-ray. Right lateral decubitus film showing right pleural effusion loculated inferiorly and medially (LPE), free flowing laterally (*arrows*), and extending into the minor fissure (*arrowhead*).

TABLE 66-9 Pleural Effusions

- Transudative—congestive heart failure, fluid overload most common; simple (0–32 HU) fluid density
- Exudative—cancer, infection, collagen vascular disease most common; slightly higher density (21–28 HU)
- Bloody—hemothorax after trauma, aortic rupture, line placement; higher density (21–28 HU)
- Purulent—empyema; can be loculated and contain gas (and may have enhancing rim)
- Chylous—milky; lower density than simple fluid (<0 HU)

from abdominal organs becoming displaced into the thoracic cavity or as a basilar lucency due to portions of gas containing colon or stomach projecting above the hemidiaphragm (Fig. 66-34). Diagnosis can be confirmed with CT, which can often reveal a discrete diaphragmatic defect.³ In patients receiving mechanical ventilation, there can be a delay in diagnosis because of the positive pressure gradient between the thoracic and abdominal cavities.

After pneumonectomy or lobectomy, the vacant space within the hemithorax should fill with fluid from chest wall bleeding, transudation from the plural surface, or lymphatic leakage. Ipsilateral diaphragmatic elevation, mediastinal shift, and hyperexpansion of the residual lung also helps to fill the residual space. Total obliteration of the pleural space usually takes several weeks. Small air leaks are not uncommon in the immediately postoperative period and usually close spontaneously with conservative management. However, one should be concerned that a bronchopleural fistula has developed with the following findings: progressive pneumothorax and failure of the hemithorax to fill with fluid; a drop of 2 cm or more in a preexisting air-fluid level; and a contralateral shift of the mediastinum or depression of the ipsilateral hemidiaphragm (Fig. 66-35).

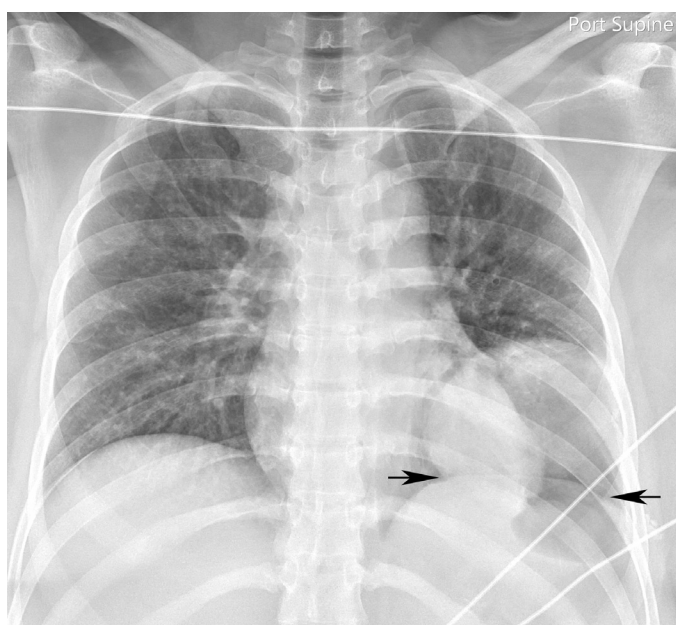


FIGURE 66-34 ■ Anteroposterior (AP) supine chest x-ray. Diaphragmatic rupture: “collar” sign with narrowing of the left juxtadiaphragmatic mass (*black arrows*) with the spleen and stomach protruding through the left hemidiaphragm defect into the left hemithorax.



FIGURE 66-35 ■ Posteroanterior (PA) upright chest x-ray. Persistent and increasing left pneumothorax (*white arrowheads*) 2 months after lobectomy, despite the presence of a small bore pigtail tube in lower left hemithorax, suggests the presence of a bronchopleural fistula.

Pleural Gas

Pneumothorax due to barotrauma is a common complication in patients supported by mechanical ventilation and is felt to be secondary to the direct rupture of alveoli into the pleural space. It can also be a complication of invasive procedures, such as a central venous catheter placement, endotracheal intubation, or feeding tube placement. Blunt chest trauma may result in pneumothorax even in the absence of rib fractures, as a result of a sudden increase in intraalveolar pressure. Following surgical procedures, such as coronary artery bypass and thoracotomy, pneumothorax is commonly encountered and should normally decrease over several days. Spontaneous pneumothorax can also occur with pneumonia, particularly *Pneumocystis* and other cavitary infections, such as *Staphylococcus* and *Klebsiella*.

The majority of air collections in supine patients are located in the basilar anteromedial portion of the hemithorax. Helpful radiographic features indicative of anterobasal pneumothoraces include a lateral or medial deep costophrenic sulcus sign (*Fig. 66-36*); diffuse hyperlucency of the lower hemithorax or the superior upper abdominal quadrant; and diaphragmatic, mediastinal, or cardiac contours that are too sharp compared to their normal appearance (*Table 66-10*).

TABLE 66-10

Pneumothorax on Supine Chest X-Ray

- Lateral or medial deep sulcus sign
- Diffuse hyperlucency of hemithorax or superior upper abdominal quadrant
- Too sharp diaphragmatic, mediastinal, or cardiac contours
- Apicolateral pleural line when upright or semi-upright
- Subcutaneous emphysema

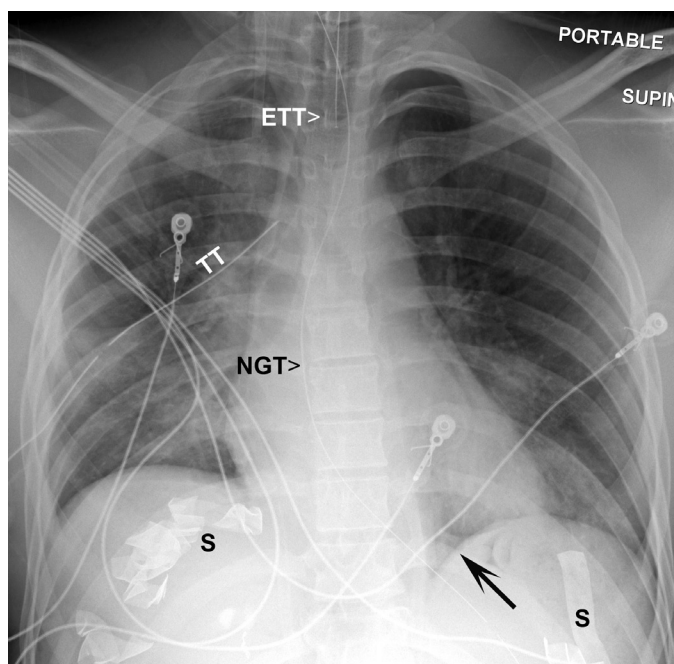


FIGURE 66-36 ■ Anteroposterior (AP) supine chest x-ray. Left medial “deep sulcus sign” (*black arrow*) is consistent with a pneumothorax on a supine chest x-ray. ETT, endotracheal tube, NGT, nasogastric tube, and TT, thoracostomy tube, are in proper good position. Postsurgical sponges/packing (S) are present in both upper abdominal quadrants.

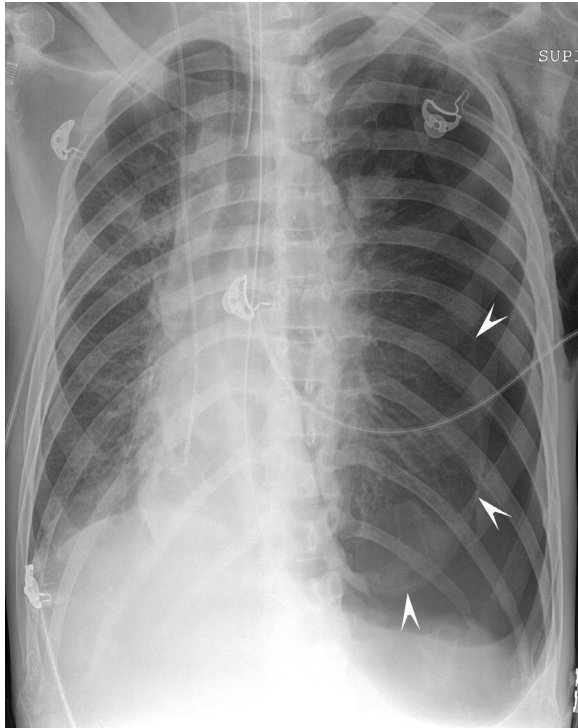


FIGURE 66-37 ■ Anteroposterior (AP) supine chest x-ray. The left hemithorax is hyperexpanded and lucent. Left tension pneumothorax (arrowheads) accounts for these findings as well as deviation of the heart and mediastinum to the right and depression of the ipsilateral hemidiaphragm.

TABLE 66-11

Tension Pneumothorax Characteristics

- Contralateral shift of mediastinum
- Depression of ipsilateral hemidiaphragm
- Flattening of heart border and vena cava (which reflects impairment of normal venous return)

Identification of a pneumothorax on an upright chest film is much easier than on supine films. Typically, there is an apicolateral pleural line with no lung markings beyond it. Decubitus views with the side of interest uppermost can aid in the diagnosis of a pneumothorax. Subcutaneous emphysema along the chest wall or neck should alert one to the presence of occult pneumothorax or pneumomediastinum. CT is much more sensitive for detecting pneumothoraxes, even minute ones, compared with plain radiographs.

Tension pneumothoraces occur when the pressure in the pleural space equals or exceeds the atmospheric pressure and are more common with continuous mechanical ventilation (Fig. 66-37 and Table 66-11).

■ MEDIASTINUM

In critically ill patients, portable supine AP chest radiographs are of limited utility in evaluating the mediastinum. Chest CT is extremely helpful in the mediastinal evaluation because even large mediastinal abnormalities may be hidden on chest radiographs.

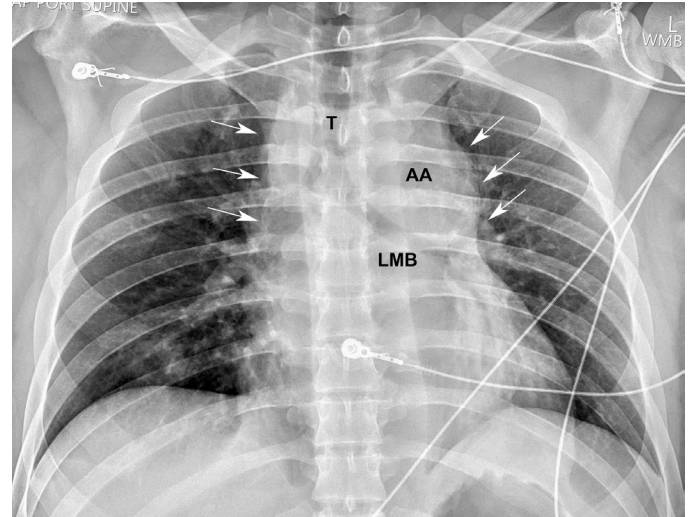


FIGURE 66-38 ■ Anteroposterior (AP) supine chest x-ray. Traumatic aortic transection or “tear,” resulting in a wide mediastinum (white arrows) with an indistinct aortic arch (AA), depression of left main stem bronchus (LMB), and deviation of the trachea (T) to the right.

Mediastinal Fluid

Aortic dissection and aortic transection (aortic rupture) are probably the most critical mediastinal abnormalities that need to be ruled out in the acute setting. Mediastinal findings on plain radiographs can include a dense, widened mediastinum (normal mediastinal width at the level of the aortic arch should be <8 cm with supine AP technique); an indistinct aortopulmonary window and descending aortic contour; displaced intimal atherosclerotic calcifications; rightward deviation of the trachea; and downward displacement of the left main stem bronchus (Figs. 66-38 and 66-39). If the acute aortic injury is suspected, a CT aortic angiogram before and after contrast administration should be obtained. On the precontrast images, a hyperdense acute intramural hematoma can be seen. After contrast, findings can include an intimal flap with both true and false lumens in the case of dissections or disruption of the aortic wall with an abrupt change in vessel caliber, pseudoaneurysm, periaortic hematoma, or gross extravasation of contrast material in the case of a transection²¹ (Table 66-12).

The most commonly observed location of traumatic aortic injury is at the aortic isthmus just distal to the left subclavian artery origin. Although the most common location of an aortic transection is at the aortic root, this is rarely seen as this injury is almost always fatal.

With Type I aortic dissections and aortic root transections, hemothorax or pericardial hematomas (Figs. 66-40, A, and 66-40, B) often occur and can result in a cardiac tamponade. With transection at the isthmus, there is usually a left-sided hemothorax with a left apical cap. Mediastinal hematomas in trauma patients can also be due to bleeding from mediastinal veins or sternal or spinal injuries. Esophageal rupture, adenopathy, and mediastinal abscesses after sternotomy can lead to a widened mediastinum.

Mediastinal Gas

In the critically ill patient, the air in the mediastinum is most often secondary to barotrauma. A sudden increase in intralveolar pressure with a rupture directly into the mediastinum rather than the pleural space can also result from blunt trauma, severe coughing, and chronic obstructive pulmonary disease. Other etiologies, such as rupture of the airway or esophagus and infection, can result in pneumomediastinum (Figs. 66-41, A, and 66-41, B). Mediastinal gas can dissect

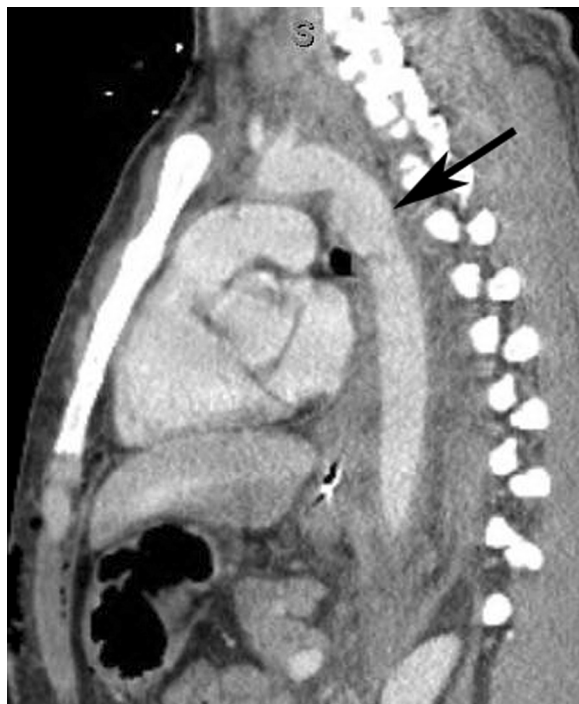


FIGURE 66-39 ■ Sagittal computed tomography (CT) reconstruction. Acute aortic transection near the level of the ligamentum arteriosum (black arrow).

TABLE 66-12 Acute Aortic Injury

- Dense, widened mediastinum
- Indistinct anteroposterior window and descending aortic contour
- Displaced intimal atherosclerotic calcifications
- Rightward deviation of trachea
- Downward displacement at left main stem bronchus
- Left pleural effusion or left apical cap
- Pericardial effusion

superiorly into the neck and subcutaneous tissues or inferiorly into the retroperitoneum.

Pneumomediastinum is detectable on a CXR when air outlines anatomic structures that are not normally visible, such as the medial border of the SVC and great vessels, or surrounds the central pulmonary arteries and thoracic aorta. Due to the continuity of the right and left sides of the mediastinum, air can outline the central portion of the diaphragm under the inferior heart margin.

Pneumopericardium (Fig. 66-42) can be suspected when the air is seen in the superior pericardial recess outlining the great vessels. Pneumomediastinum may lead to pneumopericardium from air tracking along the adventitia of the pulmonary veins and into the pericardial space.³

Upper Abdomen

Abnormalities in the upper abdomen can be seen on chest images. Potentially serious findings include pneumoperitoneum (Fig. 66-43), bowel obstruction, pneumatosis, portal venous gas, and pneumobilia. Unexpected foreign bodies from trauma or surgery (including retained needles or sponges) can also be identified.

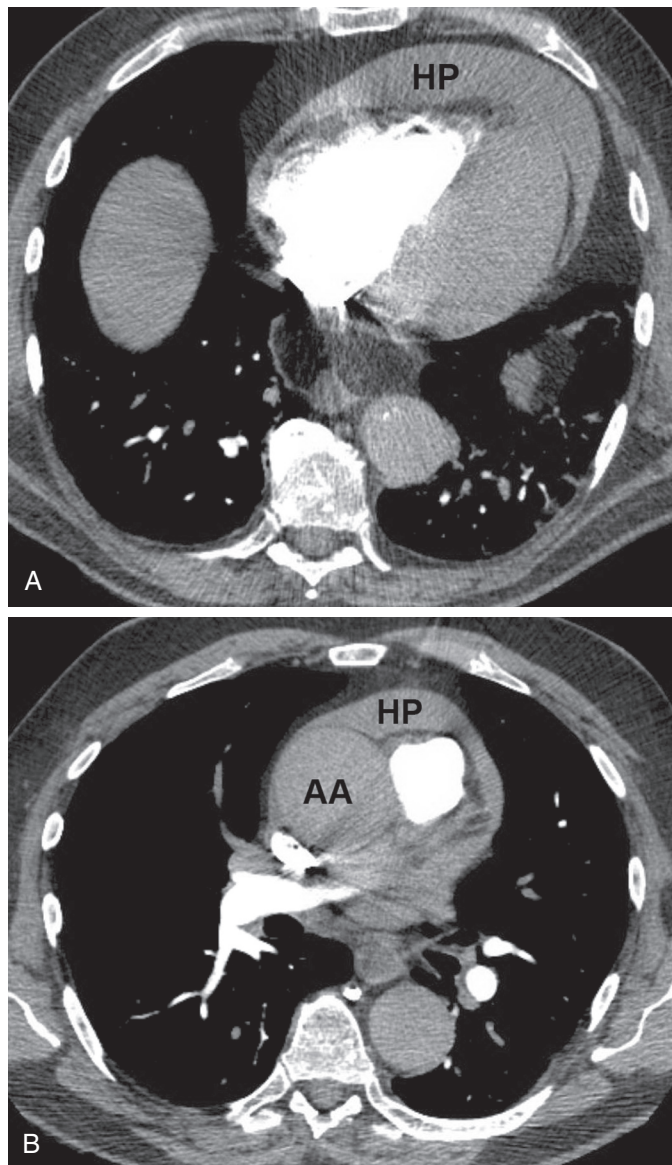


FIGURE 66-40 ■ **A**, Axial computed tomography (CT) slice. Large pericardial hematoma (HP) with narrowing of the right ventricle and straightening of the interventricular septum, findings of associated cardiac tamponade. **B**, Axial computed tomography (CT) slice. Etiology of the same patient's hemopericardium (HP) and cardiac tamponade is a "leaking or ruptured" ascending aorta aneurysm (AA).

CONCLUSION

To best serve the critically ill population of patients, integrating available clinical information with a comprehensive systemic analysis of imaging and obtaining appropriate studies are vital. The portable CXR remains the initial study of choice for evaluation of the chest in the ICU. However, CT is used as a problem-solving tool for "hidden" lung abnormalities when plain films are equivocal. Computed tomography provides better anatomic detail and a higher degree of diagnostic accuracy, though is more tedious to obtain in critically ill patients. Ultrasound is also a helpful bedside tool, aiding in the diagnosis of loculated pleural effusions and assisting in the placement of thoracostomy tubes and central lines.

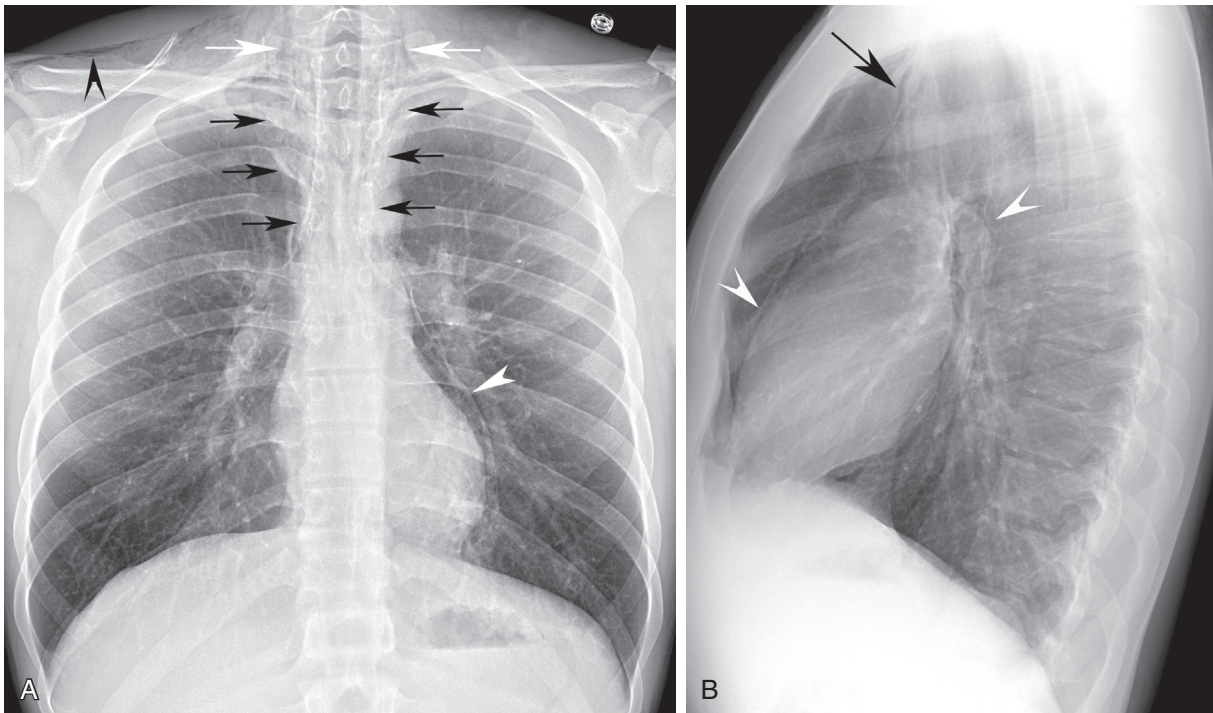


FIGURE 66-41 ■ **A**, Posteroanterior (PA) upright chest x-ray. Pneumomediastinum (*black arrows*) extending into the base of the neck (*white arrows*) and right supraclavicular soft tissues (*black arrowhead*). Lucency is surrounding the heart due to a pneumopericardium (*white arrowhead*). **B**, Lateral upright chest x-ray. Pneumopericardium is surrounding the heart and left pulmonary artery (*white arrowheads*). Pneumomediastinum (*black arrow*) tracking upwards along the anterosuperior mediastinum.



FIGURE 66-42 ■ Anteroposterior (AP) supine chest x-ray. Posttraumatic tension pneumopericardium (*white arrowheads*). Right medial “deep sulcus sign” indicates a pneumothorax (*black arrowheads*) on a supine chest x-ray.

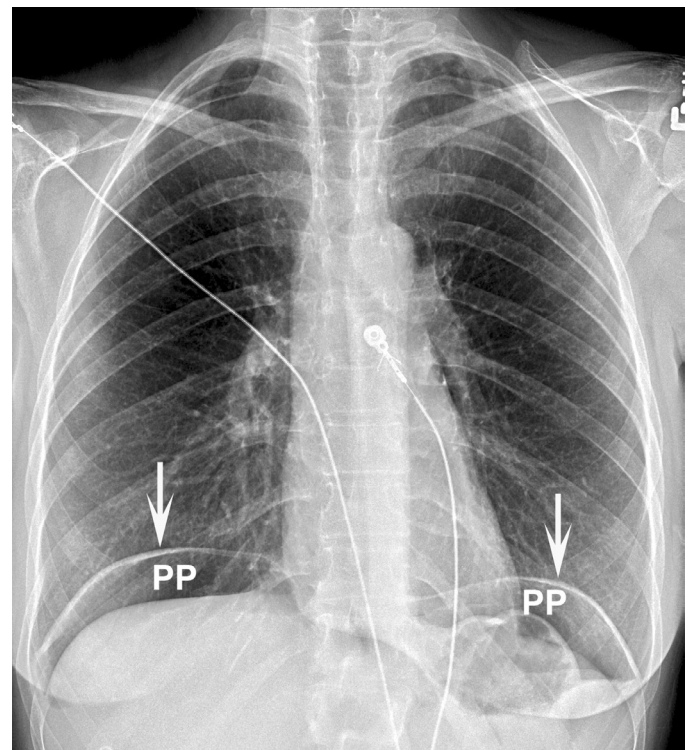


FIGURE 66-43 ■ Posteroanterior (PA) upright chest x-ray. Lucencies below and, importantly, outlining the hemidiaphragms (*white arrows*) indicate a pneumoperitoneum (PP).

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Acute respiratory distress syndrome (ARDS) is a common problem in the intensive care unit and can complicate a wide spectrum of critical illnesses. First described by Ashbaugh in 1967,¹ the syndrome was initially termed the *adult respiratory distress syndrome*, to distinguish it from the respiratory distress syndrome of neonates. However, with the recognition that ARDS can occur in children, the term *acute* has replaced *adult* in the nomenclature in recognition of the typical acute onset that defines the syndrome. Although specific treatments for ARDS have been slow to emerge, new strategies of mechanical ventilation that improve mortality, targeted treatments for severe ARDS that include prone positioning, and neuromuscular paralysis and fluid management strategies that reduce the length of mechanical ventilation emphasize the importance of identifying and treating all patients with ARDS. Although this point would seem to be straightforward, in practice, ARDS remains largely underdiagnosed,^{2,3} and expert practitioners may disagree on the diagnosis⁴ perpetuating inappropriate or inadequate treatment.

■ EPIDEMIOLOGY

The exact incidence of ARDS has been difficult to estimate for a variety of reasons, with estimates ranging from 7 to 85 cases per 100,000 people. In the past, variable definitions of the syndrome were used.⁵ The wide variety of causes and coexisting disease processes has also made identification of cases difficult both at the clinical and administrative coding level.⁶ The National Institutes of Health first estimated the incidence at 75 per 100,000 population in 1977,⁷ while a number of studies since then have reported lower incidences.⁶ Two prospective studies confirmed the higher original National Institutes of Health Estimate. The first used enrollment logs from the National Heart, Lung, and Blood Institute sponsored an ARDS Network of 20 hospitals and estimated that the incidence could be as high as 64 cases per 100,000 population. This dataset has the advantage of being prospectively collected from a large number of academic medical centers. The second was a large, prospective study of residents of King County, Washington. In that study, the crude incidence of ARDS in adults was 78.9 per 100,000 patient years.⁸ A large, prospective European study found that ARDS occurred in 7.1% of all hospital admissions.⁹ Several studies suggest a decline in the incidence of ARDS over time.¹⁰ For example, a large prospective cohort of trauma patients at risk for ARDS and multisystem organ failure collected from 1997 to 2004 showed that the incidence of ARDS decreased from 43% in 1997 to 12% in 2004, a finding that may reflect advances in posttrauma critical care.¹¹ In a population-based study in Olmstead County, Minnesota, the incidence of ARDS declined from 82.4 to 38.9 per 100,000 person-years from 2001 to 2008, despite concurrent increases in severity of acute illness and numbers of comorbidities and a higher prevalence of major predisposing conditions for ARDS.¹² A 1-year observational study in Spain reported an incidence of ARDS of 7.2 per 100,000 population in 2008 and 2009 during the era of routine application of low tidal volume ventilation.¹³ Regardless of the exact incidence, it is clear that ARDS is a major public health problem that will be encountered frequently by all physicians who care for critically ill patients.

■ RISK FACTORS

ARDS almost always occurs in the setting of a predisposing clinical risk factor (Table 67-1), with risk increasing with multiple risk

factors.^{14,15} The commonly associated clinical disorders can be separated into those that directly injure the lung and those that indirectly injure the lung. Although it is not always feasible to determine the exact cause of ARDS in a given patient, direct causes appear to account for approximately one-half of all cases of ARDS.¹⁶ Regardless of the underlying cause of ARDS, most patients with ARDS have a systemic illness with inflammation and organ dysfunction that is not confined to the lung.¹⁷

Sepsis is the most common cause of indirect lung injury, with an overall risk of progression to ARDS of approximately 30% to 40% among patients with severe sepsis requiring intensive care unit (ICU) admission.^{14,18-20} In addition to sepsis itself being a risk factor for ARDS development, the site of infection may also influence the risk of lung injury. In patients admitted to an ICU with sepsis, patients who had pneumonia as the source of sepsis had an increased risk of ARDS compared to those with infections at other sites (abdomen, skin, soft tissue, etc.).²¹ Severe trauma with shock and multiple transfusions also can cause indirect lung injury. Although the other causes of indirect lung injury are less common, many, such as blood transfusions,²² are commonplace events in the ICU setting. The most common cause of direct lung injury is pneumonia, which may be of bacterial, viral, or fungal origin. Secondary factors may also increase the risk. Such factors include chronic lung disease,²⁰ chronic or acute alcohol abuse,^{23,24} cigarette smoking,^{22,25,26} increasing age,²⁷ transfusion of blood products,²⁸⁻³⁰ lung resection,³¹ and obesity.²⁷ By contrast, several studies have shown that patients with diabetes are less likely to develop ARDS.³²⁻³⁴ To some extent, every patient in the ICU is at risk for developing ARDS, and vigilance is required to recognize the diagnosis and treat appropriately.

■ PATHOPHYSIOLOGY

The pathophysiology of ARDS is complex and remains incompletely understood.³⁵ Microscopically, lungs from afflicted individuals in the early stages typically show diffuse alveolar damage with alveolar flooding by proteinaceous fluid, neutrophil influx into the alveolar space, loss of alveolar epithelial cells, deposition of hyaline membranes on the denuded epithelial basement membrane, and formation of microthrombi (Fig. 67-1).³⁶ The alveolar flooding occurs as a result of injury to the alveolar-capillary barrier and is a major determinant of the hypoxemia and altered lung mechanics that characterize early ARDS. The alveolar-capillary barrier is formed of two separate cell layers, the microvascular endothelium, and the alveolar epithelium. Injury to the alveolar epithelium is a prominent feature histologically, with loss of alveolar epithelial barrier integrity and sloughing of alveolar epithelial type I cells. Alveolar epithelial apoptosis is widespread and likely contributes to the loss of epithelium seen ultrastructurally.^{37,38} Although endothelial injury is less obvious at the microscopic level, ultrastructural studies reveal that it is widespread^{39,40} and is accompanied by increased endothelial permeability.³⁵ Endothelial injury allows leakage of plasma from the capillaries into the interstitium and airspaces. The alveolar flooding in ARDS is characteristically with a protein-rich edema fluid due to the increased permeability of the alveolar capillary barrier, in contrast to the low-protein pulmonary edema that results from hydrostatic causes such as congestive heart failure or acute myocardial infarction.⁴¹⁻⁴⁴ Over time, the pathologic changes in ARDS evolve such that acute inflammation and pulmonary edema become less prominent and fibrosing alveolitis may appear. Recent autopsy

TABLE 67-1

Risk Factors Associated with the Development of Acute Respiratory Distress Syndrome

| DIRECT LUNG INJURY | INDIRECT LUNG INJURY |
|------------------------------------|-------------------------------|
| Pneumonia | Sepsis |
| Aspiration of gastric contents | Multiple trauma |
| Pulmonary contusion | Cardiopulmonary bypass |
| Fat, amniotic fluid, or air emboli | Drug overdose |
| Near-drowning | Acute pancreatitis |
| Inhalational injury | Transfusion of blood products |
| Reperfusion pulmonary edema | |

studies show that fibroproliferative changes can be seen even early in ARDS and may coexist with exudative changes.⁴⁵

Neutrophils play an important role in the initial inflammatory response in ARDS.⁴⁶ Early ARDS is characterized by migration of neutrophils into the alveolar compartment.^{39,40} Neutrophils can release a variety of injurious substances including proteases such as neutrophil elastase, collagenase, and gelatinases A and B and reactive nitrogen and oxygen species. In addition, they can elaborate proinflammatory cytokines and chemokines that amplify the inflammatory response in the lung. Recent evidence suggests that neutrophil extracellular traps (NETS) that contain DNA, histones, and other intracellular proteins may act as damage-associated molecular patterns in amplifying the immune response in ARDS.^{47,48} Resident alveolar macrophages are also involved in initiating and sustaining a proinflammatory cytokine cascade that leads to recruitment of neutrophils into the lung.⁴⁹

In addition to acute neutrophilic inflammation and elaboration of a proinflammatory cytokine cascade, a variety of other abnormalities contribute to the pathogenesis of ARDS. Surfactant dysfunction is characteristic, with abnormalities in both the protein and lipid components,⁵⁰⁻⁵³ and likely results from disruption of normal surfactant activity by the influx of plasma proteins into the airspaces, intraalveolar proteolysis, and injury to the alveolar epithelial type II cells. Surfactant dysfunction may have important implications both for lung mechanics and for host defense.⁵⁴ Activation of the coagulation cascade and impaired fibrinolysis are also apparent in patients with ARDS,^{55,56} both in the lung⁵⁷⁻⁵⁹ and systemically.⁶⁰ An alteration in the balance of endogenous oxidants and antioxidants with a fall in endogenous antioxidants⁶¹ despite the increased oxidant production has also been observed.⁶²

The contribution of ventilator-associated lung injury to the pathogenesis of ARDS has been increasingly recognized. There are several mechanisms by which mechanical ventilation can injure the lung. Ventilation at very high volumes and pressures can injure even the normal lung, leading to increased-permeability pulmonary edema due to capillary stress failure⁶³ and sustained elevations of circulating plasma cytokines.⁶⁴ In the injured lung, even tidal volumes that are well tolerated in the normal lung can lead to alveolar overdistension in relatively uninjured areas because the lung available for distribution of the administered tidal volume is greatly reduced and the distribution of inspired gas is uneven.^{65,66} In addition to alveolar overdistension, cyclic opening and closing of atelectatic alveoli can cause lung injury even in the absence of alveolar overdistension. The combination of alveolar overdistension with cyclic opening and closing of alveoli is particularly harmful and can initiate a proinflammatory cytokine cascade.⁶⁷ A ventilatory strategy that was designed to minimize alveolar overdistension and maximize alveolar recruitment ameliorated this proinflammatory cytokine release.⁶⁸ This fundamental insight into the pathogenesis of clinical ARDS has led to multiple clinical trials of novel ventilatory strategies for patients with ARDS, including the landmark ARDS Network trial of 6 mL/kg versus 12 mL/kg tidal volume ventilation⁶⁹ and several trials of higher levels of positive end-expiratory pressure

(PEEP) with or without recruitment maneuvers to maximize alveolar recruitment (see [Treatment](#) section below).

Although current treatment for all patients with ARDS is similar regardless of cause, emerging evidence indicates that there may be biologically and clinically distinct subphenotypes within ARDS that may respond differently to treatment. One such distinction is between patients who develop ARDS as a result of direct injury to the lung (secondary to pneumonia or aspiration) and those who have primarily indirect injury to the lung due to a systemic insult (secondary to sepsis or pancreatitis). Whether the distinction between direct and indirect lung injury is clinically useful is unclear.^{70,71} Some investigators have demonstrated reduced respiratory system compliance in patients with ARDS caused by direct pulmonary injury as compared to that of indirect cause,⁷² although total respiratory system compliance (including the chest wall) is similar.⁷³ Improvement in lung mechanics may be more likely in patients with direct lung injury with the application of PEEP and alveolar recruitment maneuvers.^{74,75} Biomarkers studies suggest that patients with direct lung injury have more evidence of lung epithelial injury, while those with indirect injury have more evidence of endothelial injury.⁷⁶ However, in the largest cohort of patients studied to date, there was no difference in mortality between those with direct (pulmonary) and indirect (extrapulmonary) causes of lung injury.¹⁶

A potentially more clinically useful distinction is between ARDS endotypes derived using statistical approaches. Calfee and colleagues used latent class analysis to discover two distinct ARDS endotypes among patients enrolled in two large clinical trials based on clinical, laboratory, and biomarker measurements.⁷⁷ One group was characterized by high levels of proinflammatory cytokines, higher use of vasopressors, a higher prevalence of sepsis, and lower serum bicarbonate (hyperinflammatory endotype). This group had higher mortality and fewer ventilator- and organ-failure-free days compared to the group that had a more hypoinflammatory endotype. Most interestingly, the same two classes with similar defining features were independently derived from two large, heterogeneous patient cohorts. Identification of biologically and clinically meaningful endotypes has the potential to alter therapeutic approaches to ARDS and will likely be the emphasis of many future studies.

DIAGNOSIS

Clinical Criteria

Several clinical definitions have been used for diagnosis of ARDS since it was first described in 1967. Before 1994, a variety of definitions were used, including the Murray Lung Injury Score.⁷⁸ In 1994, the American European Consensus Conference (AECC) published new clinical definitions for acute lung injury (ALI) and ARDS.⁵ These definitions were recently modified, and the modified version, referred to as the Berlin definition,⁷⁹ is currently the primary diagnostic tool for ARDS for both clinical diagnosis and research purposes ([Fig. 67-2](#)). It differs from the AECC definition in a few important ways. First, the new definition dispenses with the term *acute lung injury* (ALI) and only uses *ARDS*, which is now characterized as either mild, moderate or severe based on the degree of hypoxemia. Second, it specifies that the onset of ARDS, including bilateral infiltrates on chest radiograph, occurs within 1 week of a known precipitant. To meet the definition, patients must be receiving ≥ 5 cm H₂O of continuous positive airway pressure; for mild ARDS, this airway pressure can be delivered by noninvasive positive pressure ventilation. Severity is classified based on the degree of hypoxemia as mild, moderate, or severe. In all patients with suspected ARDS, an underlying cause of acute lung injury (see [Table 67-1](#)) should be sought. In the absence of an identifiable underlying cause, particular attention should be given to the possibility of other causes of pulmonary infiltrates and hypoxemia such as hydrostatic (cardiogenic) pulmonary edema. Finally, the Berlin definition recognizes that elevated vascular filling pressures and ARDS can coexist; there is no absolute requirement in the Berlin definition to rule out a cardiac cause

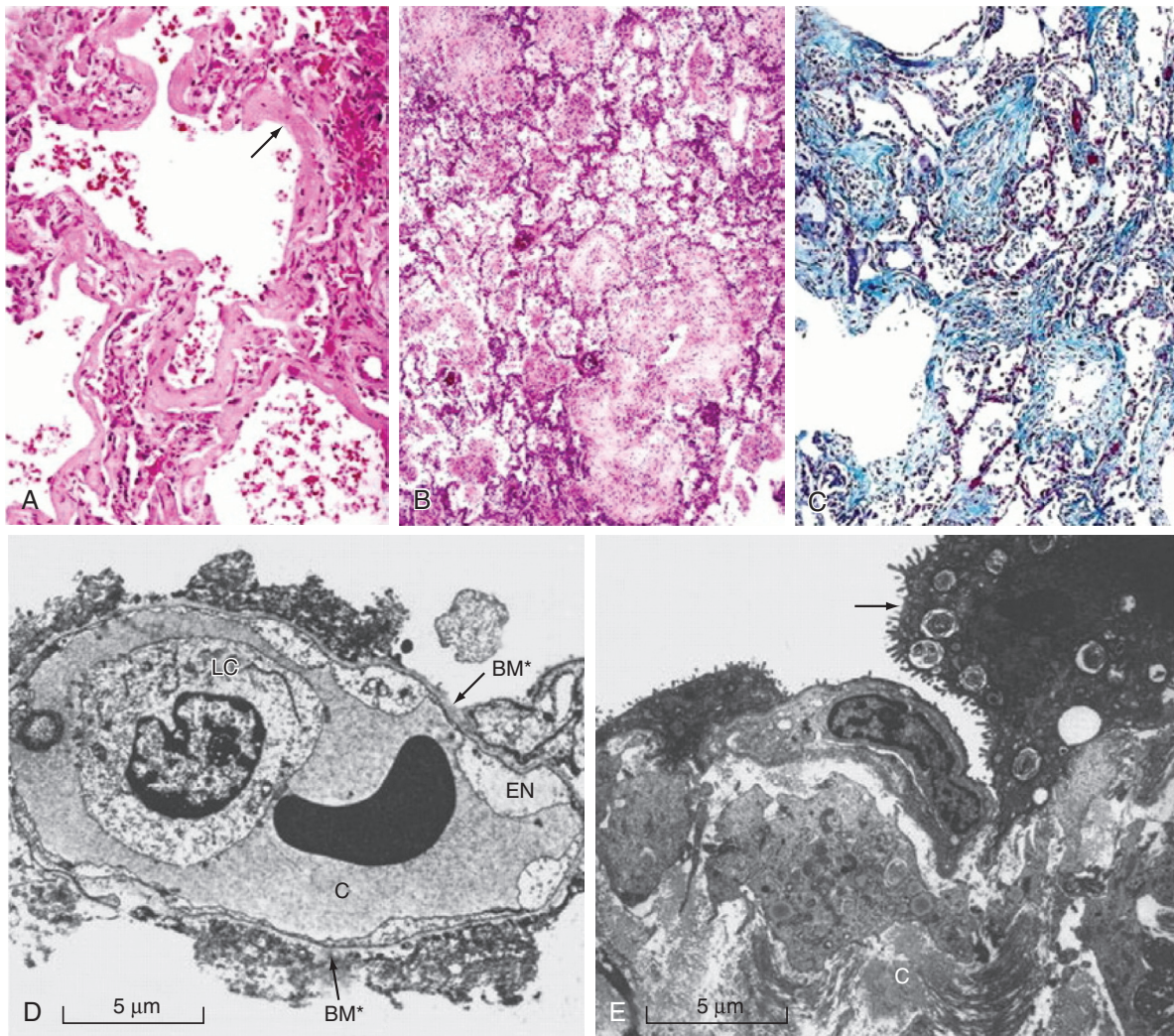


FIGURE 67-1 ■ Histologic findings in acute respiratory distress syndrome (ARDS). **A** shows a lung-biopsy specimen obtained from a patient 2 days after the onset of the syndrome as a result of the aspiration of gastric contents. Characteristic hyaline membranes are evident (*arrow*), with associated intraalveolar red cells and neutrophils, findings consistent with the pathological diagnosis of diffuse alveolar damage (hematoxylin and eosin, $\times 90$). **B** and **C** show lung biopsy specimens obtained 14 days after the onset of sepsis-associated ARDS. **B** shows granulation tissue in the distal air spaces with a chronic inflammatory-cell infiltrate (hematoxylin and eosin, $\times 60$). Trichrome staining in **C** reveals collagen deposition (*dark blue areas*) in the granulation tissue, a finding consistent with the deposition of extracellular matrix in the alveolar compartment ($\times 60$). **D** shows a specimen of lung tissue from a patient who died 4 days after the onset of ARDS; there is injury to both the capillary endothelium and the alveolar epithelium. An intravascular neutrophil (LC) can be seen in the capillary (C). Vacuolization and swelling of the endothelium (EN) are apparent. Loss of alveolar epithelial cells is also apparent, with the formation of hyaline membranes on the epithelial side of the basement membrane (BM*). **E** shows a specimen of lung tissue obtained from a patient during the fibrosing-alveolitis phase in which there is evidence of reepithelialization of the epithelial barrier with alveolar epithelial type II cells. The arrow indicates a typical type II cell with microvilli and lamellar bodies containing surfactant. The epithelial cell immediately adjacent to this cell is in the process of changing to a type I cell, with flattening, loss of lamellar bodies, and microvilli. The interstitium is thickened, with deposition of collagen (C). (Permission from Ware LB, Matthay MA. Medical progress: the acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1334-49.)

of pulmonary edema unless a patient's respiratory failure cannot be explained fully by an ARDS risk factor. In these instances, objective cardiac testing such as echocardiography or pulmonary artery catheterization can be used.

One potential limitation of the Berlin definition is the need for arterial blood gas sampling to calculate a $\text{PaO}_2/\text{FiO}_2$ ratio. Recent work

has shown good correlation between the $\text{SpO}_2/\text{FiO}_2$ ratio (measured by pulse oximetry) and the $\text{PaO}_2/\text{FiO}_2$ ratio,^{80,81} with an $\text{SpO}_2/\text{FiO}_2$ ratio of 235 corresponding to a $\text{PaO}_2/\text{FiO}_2$ ratio of 200 and an $\text{SpO}_2/\text{FiO}_2$ ratio of 315 correlating to a $\text{PaO}_2/\text{FiO}_2$ ratio of 300. These correlations are valid only when the SpO_2 is less than 98% because the oxyhemoglobin dissociation curve is flat above this level. As measurement of oxygen

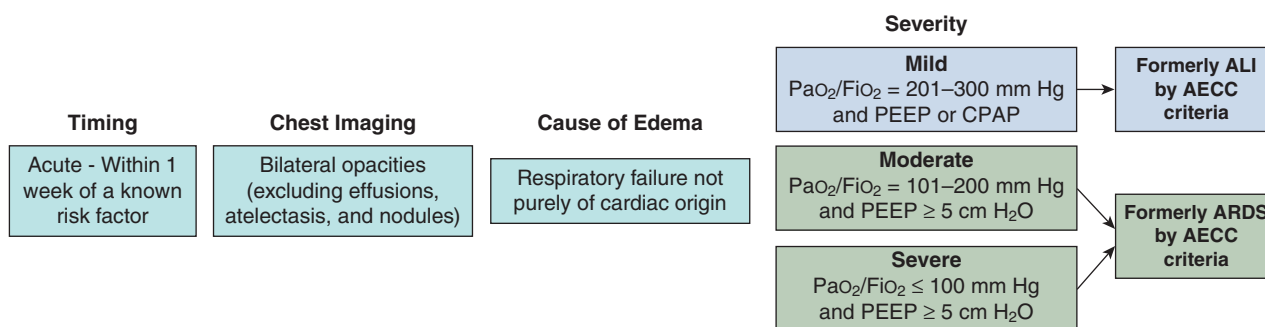


FIGURE 67-2 ■ The Berlin Definition of ARDS.

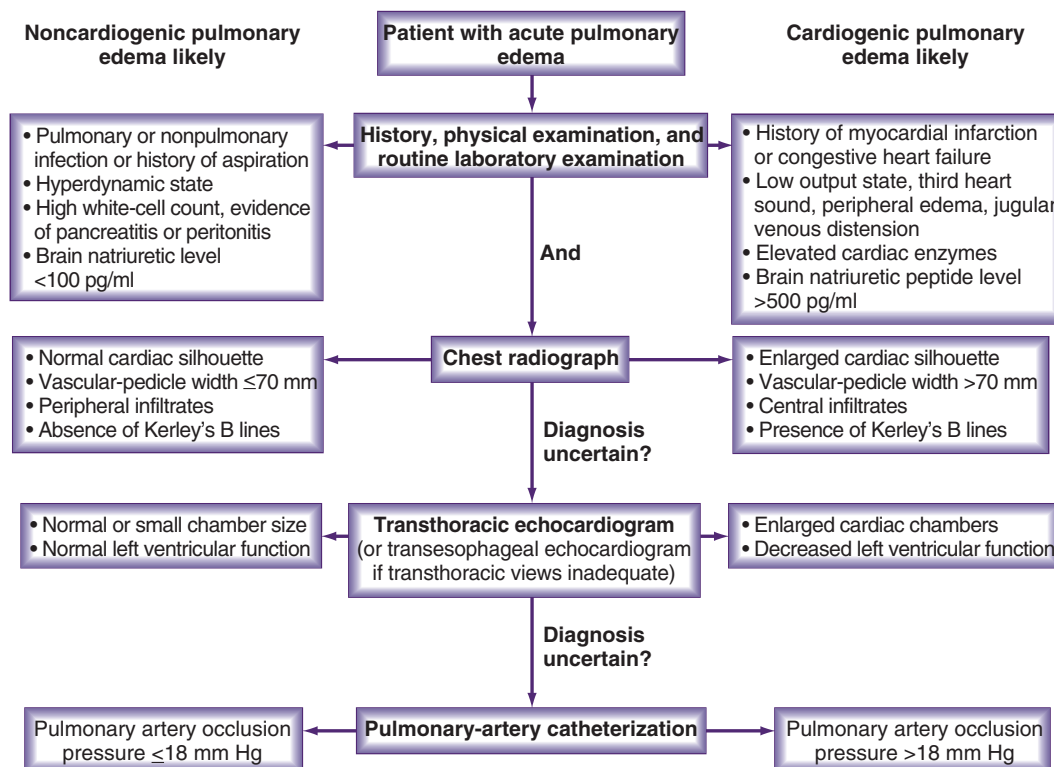


FIGURE 67-3 ■ Algorithm for differentiating between cardiogenic and noncardiogenic pulmonary edema. (With permission from Ware LB, Matthay MA. Clinical practice. Acute pulmonary edema. N Engl J Med. 2005;353[26]:2788-2796.)

saturation is noninvasive, continuous measurements and the use of the SpO₂/FiO₂ ratio in addition to the PaO₂/FiO₂ ratio may improve the ability of clinicians to diagnose ARDS.⁸² However, the SpO₂ has yet to be incorporated into formal definitions of ARDS.

Differentiation between ARDS and hydrostatic edema can be difficult, and there may be significant overlap in these syndromes (Fig. 67-3).⁸³ A multicenter trial of intravenous catheter directed fluid management strategies in patients with ARDS showed that 29% of those with clinically defined ARDS had a PAOP >18 mm Hg at the time of pulmonary artery catheter insertion but that 97% had a normal or elevated cardiac index, suggesting that they did not have clinical heart failure.⁸⁴ Other studies have shown similar rates of elevated PAOP in patients with ARDS.⁸⁵ There are no specific clinical or laboratory studies that can reliably distinguish between ARDS and hydrostatic edema. A study examining the diagnostic utility of serum levels of

B-type natriuretic peptide (BNP) showed that BNP measured at admission could not reliably differentiate between hydrostatic edema and ARDS. Furthermore, BNP levels in these patients did not correlate with invasive hemodynamic measurements.⁸⁶ N-terminal BNP levels are also elevated in ARDS⁸⁷ but do not necessarily correlate with PAOP.

Although the standardization of ARDS definitions has been of enormous value for both clinical diagnosis and clinical research, the nature of ARDS is such that any definition will have shortcomings. First, the Berlin definition is based solely on clinical criteria because currently there is no laboratory test that allows clinical assessment of the presence or absence of ARDS. Second, the presence or absence of multiorgan dysfunction, an important determinant of outcome, is not specified. Finally, although the presence of bilateral infiltrates has major prognostic significance and is clearly a hallmark of the syndrome, the radiographic findings are not specific for ARDS,^{4,88} and a

TABLE 67-2 Ventilator Management of Patients with ARDS**CALCULATE PREDICTED BODY WEIGHT (PBW)**

- Males: PBW (kg) = $50 + 2.3 [(height \text{ in inches}) - 60]$ or $50 + 0.91 [(height \text{ in cm}) - 152.4]$
- Females: IBW (kg) = $45.5 + 2.3 [(height \text{ in inches}) - 60]$ or $45.5 + 0.91 [(height \text{ in cm}) - 152.4]$

VENTILATOR MODE

Volume Assist/Control until weaning

TIDAL VOLUME (VT)

- Initial Vt: 6 mL/kg predicted body weight
- Measure inspiratory plateau pressure (Pplat, 0.5 sec inspiratory pause) every 4 hours AND after each change in PEEP or Vt.
- If Pplat > 30 cm H₂O, decrease Vt to 5 or to 4 mL/kg.
- If Pplat < 25 cm H₂O and Vt < 6 mL/kg PBW

RESPIRATORY RATE (RR)

- With initial change in Vt, adjust RR to maintain minute ventilation.
- Make subsequent adjustments to RR to maintain pH 7.30-7.45, but do not exceed RR = 35/min and do not increase set rate if PaCO₂ < 25 mm Hg.

I : E Ratio

Acceptable range, 1:1-1:3 (no inverse ratio)

FiO₂, PEEP, AND ARTERIAL OXYGENATION

Maintain PaO₂ = 55-80 mm Hg or SpO₂ = 88%-95% using the following PEEP/FiO₂ combinations:

| FiO ₂ | 0.3-0.4 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 | 1 |
|------------------|---------|------|------|-------|-------|-------|-------|-------|
| PEEP | 5-8 | 8-14 | 8-16 | 10-20 | 10-20 | 14-22 | 16-22 | 18-25 |

ACIDOSIS MANAGEMENT

- If pH < 7.30, increase RR until pH ≥ 7.30 or RR = 35/min.
- If pH remains < 7.30 with RR = 35, consider bicarbonate infusion.
- If pH < 7.15, Vt may be increased (Pplat may exceed 30 cm H₂O).

ALKALOSIS MANAGEMENT

If pH > 7.45 and patient not triggering ventilator, decrease set RR but not below 6/min.

FLUID MANAGEMENT

- Once patients are out of shock adopt a conservative fluid management strategy.
- Use diuretics or fluids to target a central venous pressure (CVP) of <4 or a pulmonary artery occlusion pressure (PAOP) of <8.

LIBERATION FROM MECHANICAL VENTILATION

- Daily interruption of sedation
- Daily screen for spontaneous breathing trial (SBT)
- SBT when all of the following criteria are present:
 - (a) FiO₂ < 0.40 and PEEP < 8 cm H₂O
 - (b) Not receiving neuromuscular blocking agents
 - (c) Patient is awake and following commands.
 - (d) Systolic arterial pressure > 90 mm Hg without vasopressor support
 - (e) Tracheal secretions are minimal, and the patient has a good cough and gag reflex.

SPONTANEOUS BREATHING TRIAL

- Place patient on 5 mm Hg pressure support with 5 mm Hg PEEP or T-piece.
- Monitor HR, RR, oxygen saturation for 30-90 minutes.
- Extubate if there are no signs of distress (tachycardia, tachypnea, agitation, hypoxia, diaphoresis).

variety of other conditions can mimic ARDS (Table 67-2).⁸⁹ For these reasons, diagnostic uncertainty in ARDS is common,⁹⁰ is a major barrier to initiation of appropriate therapy, and is one of the main reasons why clinicians fail to initiate lung protective ventilation in clinically appropriate patients.⁹¹

Invasive Methods

In the majority of patients, the initial diagnosis of ARDS is made clinically. Invasive procedures for diagnosis of ARDS are of limited clinical utility and the benefits often do not outweigh the risks.⁹² Among the potential invasive diagnostic methods available, bronchoscopy is the most frequently used. Bronchoscopy may be indicated in the early phases of ARDS in patients for whom there is no identifiable predisposing risk factor and in the immunosuppressed. Bronchoalveolar lavage for cultures and cytologic examination can identify the cause of pneumonia and is particularly useful in the diagnosis of opportunistic infections. Lavage fluid usually has a predominance of neutrophils, and there may be evidence of diffuse alveolar hemorrhage. Cytologic

examination can be used to confirm the presence of diffuse alveolar damage.⁹³ Rarely an alternate, treatable diagnosis is found such as acute eosinophilic pneumonia, pulmonary alveolar proteinosis, diffuse alveolar hemorrhage, or unsuspected infection.

In the past, open lung biopsy was obtained more frequently for diagnosis. Interestingly, the degree of histologic abnormality on lung biopsy does not correlate with ultimate outcome as measured by pulmonary function.⁹⁴ Open or thoracoscopic lung biopsy may still be useful in some cases where the diagnosis is uncertain and the underlying cause is not apparent. Although open lung biopsy can provide findings that lead to a change in treatment, a meta-analysis of published series indicated that postoperative complications occurred in 22% of patients.⁹⁵ Several pathologic studies have shown that biopsy or autopsy can identify unsuspected diagnoses requiring specific therapy such as miliary tuberculosis, pulmonary blastomycosis, aspergillosis, or bronchiolitis obliterans organizing pneumonia in 40% to 60% of cases⁹⁶⁻⁹⁸; however, the general applicability of these studies may be limited by the fact that they were retrospective case series. In a meta-analysis of published studies, open lung biopsy altered management in

73% of cases⁹⁵; biopsy findings that alter management may be associated with better survival.⁹⁹

In addition to familiarity with the Berlin definition of ARDS, the critical care clinician should be aware that ARDS also has been called by a variety of other terms, some of which are seen mainly in older literature but some that remain in clinical use. Some of the more common of these terms include adult hyaline membrane disease, post-perfusion lung or pump lung, shock lung, ventilator-associated lung injury, and adult respiratory insufficiency syndrome. The terms *reperfusion pulmonary edema*, *primary graft dysfunction*, *primary graft failure*, and *transplant lung* have been used to describe ARDS occurring immediately after lung transplantation. Regardless of the name applied, ARDS is a clinical syndrome that has prognostic and therapeutic implications above and apart from the underlying cause (i.e., infections, aspiration, trauma, etc.). This fact does not diminish the imperative to identify these underlying causes, if present, and treat them aggressively.

CLINICAL COURSE

Early ARDS

The Berlin definition aims to identify ARDS patients early in their course, in the acute or exudative phase. Clinically, the acute phase is manifested by the acute onset of radiographic infiltrates consistent with pulmonary edema, hypoxemia, and increased work of breathing. Radiographic infiltrates are bilateral (by definition) but may be patchy or diffuse, fluffy or dense (Fig. 67-4), and pleural effusions may occur.¹⁰⁰ Chest computed tomographic (CT) imaging, though rarely used clinically, has been employed extensively as an investigative tool to better define the nature of the radiographic infiltrates in patients with ARDS. The distribution of infiltrates by CT is surprisingly variable. Although some patients have evidence of diffuse alveolar edema on CT, many patients have more focal infiltrates with areas of alveolar filling and consolidation occurring predominantly in dependent zones, while nondependent regions are relatively spared.¹⁰¹⁻¹⁰³ However, even areas that appear spared in conventional radiographic images may have substantial inflammation when sampled using bronchoalveolar lavage¹⁰⁴ or imaged using FDG-PET.¹⁰⁵ Patients with more diffuse infiltrates may be more likely to respond to recruitment maneuvers¹⁰⁶; whether CT imaging could be helpful for guiding ventilator treatment is not yet known.

The hypoxemia that characterizes early ARDS is usually relatively refractory to supplemental oxygen. The increased work of breathing in the acute phase of ARDS is due to decreased lung compliance as a result of alveolar and interstitial edema combined with increased

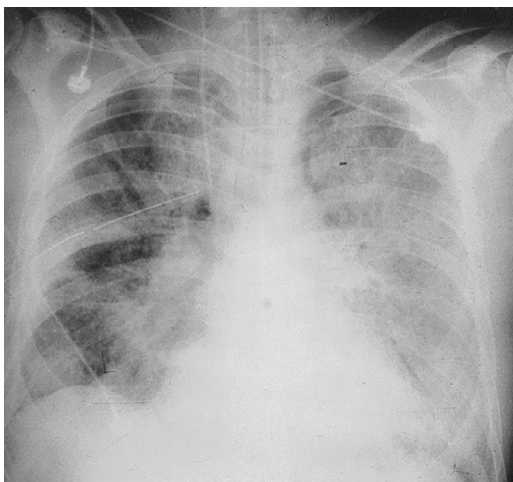


FIGURE 67-4 ■ Representative chest radiograph from a patient with acute respiratory distress syndrome.

airflow resistance¹⁰⁷ and increased respiratory drive.¹⁰⁸ The combination of hypoxemia and increased work of breathing usually necessitates endotracheal intubation and mechanical ventilation, although occasionally patients can be managed with noninvasive ventilation or very high-flow nasal cannula oxygen (see [Treatment](#) section below).

In addition to hypoxemia and increased work of breathing, many patients with ARDS also develop evidence of increased pulmonary vascular resistance, leading to pulmonary hypertension and acute right ventricular (RV) failure. The prevalence of pulmonary hypertension in patients presenting to the hospital with ARDS may be as high as 92%.¹⁰⁹ Even in the era of low tidal volume ventilation, transesophageal echocardiography showed evidence of acute right ventricular failure in 22% of 226 consecutive patients with moderate or severe ARDS¹¹⁰ that was associated with an almost two-fold increase in 28-day mortality. Attempts to reverse pulmonary hypertension and RV failure with pulmonary vasodilators such as sildenafil have led to decreased pulmonary artery pressure with treatment as well as concomitant increases in shunt fraction and decreases in oxygenation.¹¹¹ These findings suggest that although patients with ARDS have evidence of pulmonary hypertension, it may, in some cases, be a beneficial physiologic response to reduce blood flow to areas of severely compromised lung.

Late Fibroproliferative ARDS

In most patients, ARDS will substantially resolve after the acute phase. However, in others, the syndrome progresses to a fibrosing alveolitis. Fibrosing alveolitis usually becomes clinically apparent after 7-10 days, although evidence of deposition of extracellular matrix has been identified in alveolar lining fluid from patients as early as the first day after intubation,¹¹² and autopsy studies show early fibrotic changes in some patients.⁴⁵ Radiographically, linear opacities develop, consistent with the evolving fibrosis. Histologically, pulmonary edema and neutrophilic inflammation are less prominent. A severe fibroproliferative process fills the airspaces with granulation tissue that contains extracellular matrix rich in collagen and fibrin as well as new blood vessels and proliferating mesenchymal cells.^{113,114}

Clinically, the late fibroproliferative phase of ARDS is characterized by continued need for mechanical ventilation, often with persistently high levels of PEEP and FiO_2 . The lung compliance may fall even further, and pulmonary dead space is elevated. If it has not developed in the acute phase, pulmonary hypertension may develop now due to obliteration of the pulmonary capillary bed, and right ventricular failure may occur.¹¹⁵ This phase of the illness can be prolonged, lasting weeks, and can be very frustrating for the clinician, patient, and family, as small gains in pulmonary function are frequently offset by new problems such as hospital-acquired infections and nonpulmonary organ dysfunction. Progressive deconditioning can make eventual weaning from mechanical ventilation difficult if the fibrosing alveolitis stage is prolonged. Based on the improvement in the number of ventilator-free days through use of lower tidal volumes, it seems likely that the incidence of fibrosing alveolitis is falling. However, a recent autopsy study found more fibrotic changes in patients treated in the low tidal volume era than in patients treated with higher tidal volumes.⁴⁵ One possible explanation is that better supportive care has prolonged survival of some patients with more severe lung injury, allowing more time for fibrotic changes to develop and be detected at autopsy.

Resolution of ARDS

Lung biopsies from ARDS survivors typically show normal or near-normal lung histology. For such histologically complete resolution of ARDS to occur, a variety of processes must be reversed. Alveolar edema is actively reabsorbed by the vectorial transport of sodium and chloride from the distal airway and alveolar spaces into the lung interstitium where it can be cleared by the lymphatics or by reabsorption into the vasculature.¹¹⁶ Water is passively absorbed along the osmotic gradient, probably through water channels, the aquaporins.¹¹⁷ The majority of patients with early ARDS have impaired alveolar fluid

transport; in those with intact alveolar fluid transport, faster rates of alveolar epithelial fluid transport are associated with better outcomes.⁴¹ Soluble and insoluble protein must also be cleared from the airspaces. Soluble protein probably diffuses by a paracellular route into the interstitium, where it is cleared by lymphatics. Insoluble protein probably is cleared by macrophage phagocytosis or alveolar epithelial cell endocytosis and transcytosis.¹¹⁸

The denuded alveolar epithelium must be repaired. The alveolar epithelial type II cell serves as the progenitor cell for repopulating the alveolar epithelium. Type II cells proliferate, migrate, and differentiate to reconstitute a tight alveolar epithelial type I cell barrier. The inflammatory cell infiltrate must also resolve, but here the mechanisms are less clear. Resolution of neutrophilic inflammation may be predominantly via neutrophil apoptosis and phagocytosis by macrophages. However, one report suggests that neutrophil apoptosis is impaired in the lungs of patients with ARDS.¹¹⁹ The resolution of fibrotic changes is also not well understood. Clearly, substantial remodeling is necessary to restore a normal or near-normal alveolar architecture. In patients with advanced fibrosis, this process likely takes place over many months, as pulmonary function abnormalities continue to improve, sometimes remarkably so, out to the first year and beyond in survivors of ARDS (see below).^{120,121}

TREATMENT

Standard Supportive Therapy

The gradual decline in mortality attributable to ARDS over time^{122,123} likely reflects improvements in standard supportive therapy. Although detailed discussion of all aspects of supportive therapy is beyond the scope of this chapter, a few aspects will be considered.

Treatment of Predisposing Factors

First and foremost, a search for the underlying cause of ARDS should be undertaken. Appropriate treatment for any precipitating infection such as pneumonia or sepsis is critical to enhance the chance of survival. In the immunocompromised host, invasive diagnostic evaluation, including bronchoscopy, may be warranted to look for evidence of opportunistic infections. In a patient with sepsis and ARDS of unknown source, an intraabdominal process should be considered. Timely surgical management of intraabdominal sepsis is associated with better outcomes.¹²⁴ In some patients, the cause of lung injury will not be specifically treatable (such as aspiration of gastric contents) or will not be readily identifiable.

Fluid and Hemodynamic Management

Historically, patients with critical illness and ARDS received a pulmonary artery catheter (PAC) to manage fluid and hemodynamic status. A large, randomized European trial of PAC use compared to no PAC use in all patients admitted with ARDS¹²⁵ showed no difference in clinical outcomes on either group, suggesting that routine PAC use in ARDS without specified PAC-guided interventions is not beneficial. The ARDS Clinical Trials Network tested the value of pulmonary artery catheterization in the context of specific fluid management protocols and was unable to demonstrate the superiority of PAC over the central venous catheter in directing specific fluid management protocols in ARDS patients, and PAC use did not improve outcomes in these patients.⁸⁴ Some investigators have proposed that clinical outcomes in ARDS can be improved by delivery of supranormal levels of oxygen using vigorous volume resuscitation and positive inotropes. However, no benefit to supranormal levels of oxygen delivery has been demonstrated in patients with ARDS.^{126,127}

For decades there was disagreement as to the best fluid management strategy in patients with ARDS. Proponents of a liberal fluid strategy reasoned that increased circulating volume would preserve end organ perfusion and protect patients from the development of

nonpulmonary organ failures. Reductions in intravascular volume can have adverse effects on cardiac output and tissue perfusion, factors that could contribute to multisystem organ failure. This concern is legitimate, since mortality in ARDS is usually from nonpulmonary causes including other organ failures. Others support a conservative fluid strategy in an attempt to reduce circulating volume, thereby reducing the driving force for pulmonary edema formation. In experimental lung injury, lower left atrial pressures are associated with less formation of pulmonary edema.^{128,129} Some limited clinical evidence supports this approach.¹³⁰⁻¹³³ Because of this equipoise, the ARDS Network conducted a large, multicenter, randomized controlled trial of catheter (central venous catheter vs. pulmonary artery catheter)—driven fluid management in patients with ARDS.⁸⁴ Once patients were out of shock they were randomized to a liberal fluid treatment strategy that resulted in an average of 1 L of fluid accumulation per day or to a conservative fluid treatment strategy with aggressive use of diuretics to achieve a goal CVP <4 or a goal PAOP <8, resulting in an average of zero net fluid accumulation by day 7. Although there was no difference in mortality at 60 days (the primary outcome of the study), patients in the conservative group had improved oxygenation and significantly more ventilator-free days without the development of additional organ failures. In this study it did not matter whether treatment was guided by central venous pressure measurements (derived from a central venous line) or from pulmonary arterial occlusion pressure measurements (derived from a pulmonary artery catheter).¹³⁴

Despite the findings in support of a conservative fluid management strategy in patients with ARDS, there continues to be a great deal of uncertainty about the appropriate goals for hemodynamic therapy in ARDS. Currently, the recommended strategy is to aim to achieve the lowest intravascular volume that maintains adequate tissue perfusion as measured by urine output, other organ perfusion, and metabolic acid-base status using central venous pressure monitoring to direct therapy. If organ perfusion cannot be maintained in the setting of adequate intravascular volume, then administration of vasopressors and/or inotropes should be used to restore end organ perfusion.¹¹⁵ Available evidence does not support the use of one particular vasopressor or combination of vasopressors. Once shock has resolved, patients should be managed with a conservative fluid strategy with the goal of driving the CVP <4 to keep each patient's fluid balance net zero during the ICU stay.

Nutrition

Standard supportive care for the patient with ARDS includes the provision of adequate nutrition. The enteral route is preferred to the parenteral route and is associated with less infectious complications.¹³⁵ Enteral feeding may also have other beneficial effects. Experimentally, lack of enteral feeding promoted translocation of bacteria from the intestine.¹³⁶ In normal volunteers, administration of parenteral nutrition with bowel rest increased circulating levels of TNF- α , glucagon and epinephrine, and increased febrile responses compared to volunteers who received enteral nutrition.¹³⁷

The goals of nutritional support in any critically ill patient include the provision of adequate nutrients for the patient's level of metabolism and the treatment and prevention of any deficiencies in micro- or macronutrients.¹³⁸ Whether a particular dietary composition could be beneficial in patients with ARDS is unclear. Immunomodulation via dietary manipulation has been attempted by a number of investigators in critically ill patients using various combinations of omega-3 fatty acids, ribonucleotides, arginine, and glutamine. A meta-analysis of these trials suggested a beneficial effect on infection rate but not overall mortality.¹³⁹ However, a large, multicenter, randomized placebo-controlled study of omega-3 fatty acid and antioxidant supplementation in patients with ARDS was stopped early by the data safety monitoring board for a trend towards excess mortality in patients receiving the omega-3 fatty acid supplement.¹⁴⁰ Using a different approach, a high-fat, low-carbohydrate diet reduced the duration of mechanical ventilation in patients with acute respiratory failure.¹⁴¹

Although the mechanism of this beneficial effect was postulated to be due to reduction of the respiratory quotient and a resultant fall in carbon dioxide production, the most common cause of a high respiratory quotient in critically ill patients is not dietary composition but simply overfeeding.¹³⁸ A study of clinical outcomes in 1000 ARDS patients randomized to full calorie versus trophic (10 cc/hr) enteral feeds did not show any difference in mortality or other clinical outcomes.¹⁴² Overall, there is still no compelling evidence to support the use of anything other than standard (enteral) nutritional support, with avoidance of overfeeding, in patients with ARDS. How early to attempt institution of feeding remains an unanswered question.

Mechanical Ventilation

Lung Protective Ventilation

Although historically a tidal volume of 12 to 15 mL per kg was recommended in patients with ARDS, it is now clear that a low-tidal volume, plateau pressure-limited ventilatory strategy reduces mortality. In 2000, the NIH ARDS Network published the findings of their first randomized, controlled, multicenter clinical trial in 861 patients.⁶⁹ The trial was designed to compare a lower tidal volume ventilatory strategy (6 mL/kg predicted body weight, plateau pressure < 30 cm H₂O) with a higher tidal volume (12 mL/kg predicted body weight, plateau pressure < 50 cm H₂O). The rationale for the clinical trial was the growing body of clinical and experimental evidence suggesting that ventilation with high tidal volumes and high plateau pressures might be harmful to the injured lung (see [Pathophysiology](#) section above). In this trial, the inhospital mortality rate was 40% in the 12-mL/kg group and 31% in the 6-mL/kg group, a 22% reduction. Ventilator-free days and organ failure-free days were also significantly improved in the low-tidal volume group. These findings were truly remarkable, since no prior large randomized clinical trial of any specific therapy for ARDS had ever demonstrated a mortality benefit.

The current recommended treatment strategy for patients with ARDS is summarized in [Table 67-3](#). Predicted body weight is calculated based on measured height using the equations provided. This is a key point that is often overlooked by clinicians; use of actual rather than predicted body weight can result in the use of erroneously high

and potentially injurious tidal volumes, particularly if obesity is present. The tidal volume should initially be set at 6 mL/kg predicted body weight. Interestingly, a tidal volume of 6 mL/kg predicted body weight is similar to normal tidal volumes in spontaneously breathing adults at rest. So, although this particular tidal volume is often referred to as low tidal volume, it is really *normal* tidal volume ventilation. However, if the end-inspiratory plateau pressure (measured during a 0.5-second pause) is still >30 cm H₂O, then the tidal volume must be reduced in a stepwise fashion by 1 mL/kg to a minimum of 4 mL/kg. Ventilation with this tidal volume is generally well tolerated. Some patients may have breath stacking or significant dyssynchrony with the ventilator. Increasing the inspiratory flow rate, and if necessary, the level of sedation, is usually sufficient to manage these problems. Several studies have shown that, on average, patients receiving lower tidal volume ventilation do not require increases in dose or duration of sedatives compared to patients receiving higher tidal volume ventilation.^{143,144} Respiratory acidosis may develop but is usually not symptomatic. Raising the respiratory rate is usually sufficient to compensate for the decreased tidal volume; a rate as high as 35 was used in the clinical trial. As with any mode of ventilation in ARDS, patients occasionally will require neuromuscular blockade to alleviate severe dyssynchrony. Although many believe that neuromuscular blockade should be reserved for patients with severe hypoxemia, since the use of paralytics may increase the risk of critical illness polyneuropathy and myopathy, one randomized clinical trial showed a 28-day mortality benefit with use of neuromuscular paralysis with cisatracurium besylate for the first 48 hours in severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$).¹⁴⁵

In the ARDS Network protocol, the level of PEEP and FiO_2 is titrated according to a set of predetermined values (see [Table 67-3](#)). The optimal level of PEEP in ARDS has been controversial. Higher levels of PEEP may be beneficial in preventing alveolar collapse and minimizing injurious repeated opening and closing of alveoli. On the other hand, higher PEEP may overdistend and injure more compliant areas of the lung. Several studies have investigated the effects of different levels of PEEP in patients with ARDS.¹⁴⁶ One large multicenter trial conducted by the ARDS Network randomized patients with ARDS ventilated with low-tidal volume ventilation to receive lower (mean PEEP levels on days 1-4 were 8.3 ± 3.2) versus higher levels of PEEP (mean PEEP levels on days 1-4 were 13.2 ± 3.5).¹⁴⁷ In this study there were no differences between the groups in clinical outcomes including ventilator-free days and mortality. Two other studies of the effects of PEEP in ARDS had similar results,^{148,149} although one of the studies did show an increase in the number of ventilator-free days and organ failure-free days with application of higher PEEP.¹⁴⁹ None of these trials has shown significant increases in barotrauma related to higher PEEP levels. Although these three, large studies have not shown beneficial effects of higher PEEP in all patients with ARDS, there may be a subset of patients who would benefit from higher PEEP. In a small trial, a ventilator strategy that incorporated low tidal volume and titration of the PEEP level to above the lower inflection point on each individual patient's pressure volume curve improved mortality in ARDS.¹⁵⁰ However, measurement of the pressure volume curve in any given patient is not practical clinically. Given the lack of compelling data favoring either a high PEEP or low PEEP strategy, current recommendations are to adjust the PEEP within an acceptable range (see [Table 67-3](#)) to achieve adequate oxygenation at a given FiO_2 .

Prone positioning was initially studied in several small¹⁵¹⁻¹⁵³ and three large trials¹⁵⁴⁻¹⁵⁶ and was associated with improvements in oxygenation but no reduction in mortality. Subgroup analysis suggested potential benefit in severe ARDS, leading to a multicenter prospective randomized trial of prolonged prone position (>16 h/day) in patients with severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$) that showed a substantial reduction in 28-day mortality in the prone group.¹⁵⁷ Given the results of this trial, prone positioning should be considered in all patients with severe ARDS who do not have contraindications to prone positioning such as elevated intracranial pressure, severe hemoptysis, recent sternal surgery, pregnancy, new deep venous thrombosis or unstable fractures.

TABLE 67-3 Conditions That Mimic ARDS

| | FINDINGS ON CHEST IMAGING | POTENTIAL DIAGNOSTIC TESTS |
|---|---|--|
| Diffuse alveolar hemorrhage | Bilateral alveolar and ground glass infiltrates | Bronchoscopy with bronchoalveolar lavage |
| Pulmonary alveolar proteinosis | Central and lower lung zone alveolar infiltrates, "bat wing" appearance, "crazy paving" on CT | High-resolution computed tomography, bronchoscopy with bronchoalveolar lavage and PAS staining |
| Acute interstitial pneumonia | Bilateral alveolar and ground glass infiltrates, septal thickening, traction bronchiectasis | No alternative cause of ARDS identified, open or thoracoscopic lung biopsy |
| Cryptogenic organizing pneumonia | Peripheral distribution of alveolar infiltrates, migratory infiltrates | Bronchoscopy with transbronchial lung biopsy |
| Acute exacerbation of idiopathic pulmonary fibrosis | Ground glass opacities superimposed on peripheral, basilar fibrotic changes | Computed tomography demonstrating characteristic fibrotic changes |

Adapted from Janz DR, Ware LB. Approach to the patient with the acute respiratory distress syndrome. *Clin Chest Med* 2014;35(4):685-96.
PAS, periodic acid-Schiff.

Noninvasive Ventilation and High-Flow Nasal Cannula

Noninvasive positive pressure ventilation (NIV) delivered by nasal or full face mask has been highly successful in avoidance of intubation in patients with acute exacerbation of COPD.¹⁵⁸ Noninvasive ventilation is commonly used in pediatric patients with ARDS,¹⁵⁹ although there is only one, small randomized trial of 50 patients showing that NIV improved oxygenation and prevented the need for endotracheal intubation in children admitted with acute respiratory failure. The role for NIV in adults with ARDS is still unclear. A growing number of small studies suggest that bilevel NIV with pressure support ventilation and PEEP may reduce the need for intubation and improve outcomes in selected patients with ARDS.^{160,161} However, data from large, randomized controlled trials is still lacking. Furthermore, it seems likely that the majority of patients with ARDS will still require invasive mechanical ventilation. In one large multicenter study of 354 of 2770 patients with acute hypoxemic respiratory failure *who were not already intubated*, NIV failed in 30% of patients but failed in 51% of patients with ARDS.¹⁶² One group of patients in whom NIV is particularly appealing is those patients who are immunosuppressed for various reasons and are at highest risk for nosocomial infections. Encouraging results have now been reported in a variety of patients with acute respiratory failure and immunosuppression.¹⁶³⁻¹⁶⁵

More recently, very high-flow nasal cannulas oxygen delivery has been tested in patients with acute hypoxemic respiratory failure as an alternative to immediate intubation. In a study of 310 patients with acute respiratory failure including some patients with ARDS, treatment with high-flow nasal cannula increased ventilator-free days and reduced mortality compared to noninvasive or invasive mechanical ventilation.¹⁶⁶ One benefit of high-flow nasal cannula is that it can provide a significant level of PEEP noninvasively. Pending data from larger randomized clinical studies, a trial of noninvasive mechanical ventilation or high-flow nasal cannula oxygen could be considered in a patient with ARDS who does not have a severe oxygenation defect, hemodynamic instability, or altered mental status as long as the patient can be closely observed and readily intubated if needed.

Pharmacologic Therapy

There is no specific pharmacologic therapy for ARDS. A variety of treatment strategies have been investigated in large randomized trials including antiinflammatory strategies, surfactant replacement, vasodilation, novel anticoagulants, antioxidants, and strategies to enhance the resolution of pulmonary edema. Agents that appeared promising in experimental and early clinical studies but failed in large randomized trials include early glucocorticoids,^{167,168} anti-TNF antibody fragments,¹⁶⁹ alprostadil,¹⁷⁰⁻¹⁷² surfactant,¹⁷³⁻¹⁷⁵ ketoconazole,¹⁷⁶ N-acetylcysteine,¹⁷⁷ procysteine,¹⁷⁷ lisofylline,¹⁷⁸ statins,¹⁷⁹ albuterol,^{180,181} recombinant activated protein C,¹⁸² and site-inactivated recombinant factor VIIa.¹⁸³

Some investigators have suggested that glucocorticoid therapy, although not helpful for the acute phase of ARDS, might hasten the resolution of late fibroproliferative ARDS. One very small randomized study (plagued by crossovers such that only 4 patients remained in the placebo arm) suggested that glucocorticoid therapy might be beneficial in late ARDS.¹⁸⁴ This question was addressed in a randomized, multicenter study conducted by the ARDS Network of 14 days of methylprednisolone in patients who had persistent ARDS for 7 days.¹⁸⁵ Compared to patients treated with placebo, those treated with methylprednisolone had an increase in the number of shock-free days and ventilator-free days by day 28 as well as improvements in oxygenation but did not have improved survival and had higher rates of reintubation perhaps due to neuromuscular weakness. Given the serious concern about the safety of high-dose glucocorticoids in critically ill patients, including the possibility of increasing the risk of nosocomial infections or critical illness polyneuropathy/myopathy and the lack of improvement in mortality, routine use of glucocorticoids cannot be recommended.

Despite the dismal findings of the numerous studies of pharmacologic therapy for ARDS to date, new therapeutic strategies are under investigation and may yet be beneficial. Because of the failure of pharmacologic therapies in established ARDS, attention has turned to the prevention and early treatment of ARDS, and several trials are in the planning stages or ongoing. For established ARDS, cell-based therapy with intravenous mesenchymal stromal (stem) cells (MSCs) is currently being tested in a phase 2 clinical trial. In preclinical studies, MSCs have pleiotropic protective and reparative effects in the lung including secretion of antiinflammatory and antibacterial factors, secretion of epithelial and endothelial growth factors, and direct transfer of mitochondria to restore energy balance in the injured lung epithelium.¹⁸⁶ Another area under active investigation includes strategies to hasten or facilitate the resolution of ARDS. Such therapies might be targeted at increasing the rate of alveolar fluid clearance, modulating alveolar epithelial repair, or modulating immune regulation of the resolution of inflammation.

Rescue Therapies

Despite appropriate treatment, a fraction of patients with ARDS will have profound and refractory hypoxemia. The initial management of these patients includes increased sedation and neuromuscular paralysis to maintain adequate oxygenation. In patients who do not respond to conventional treatment with low-tidal volume ventilation and remain persistently hypoxemic, there are several nonproven rescue therapies that can be tried to improve oxygenation in the acute setting (summarized in Table 67-4). Although previously viewed primarily as a rescue therapy, prone positioning improved mortality in moderately severe ARDS in one study¹⁵⁷ and is now being used more frequently in routine care of patients with moderately severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$) in addition to its utility in improving oxygenation in the setting of refractory hypoxemia. Extracorporeal membrane oxygenation (ECMO) has been used in patients with ARDS and severe hypoxemia. In specialized centers ECMO has been used successfully to treat patients with severe ARDS.¹⁸⁷⁻¹⁸⁹ One large trial randomizing 180 patients with severe ARDS to ECMO versus conventional management showed improved survival without disability at 6 months in patients treated with ECMO.¹⁹⁰ In this study, patients randomized to ECMO were transferred to a specialty center to receive therapy. Upon arrival, only 75% of patients in the ECMO group were actually treated with ECMO. The study design makes it difficult to determine whether the transfer to a specialty center for care or the ECMO itself conferred benefit. Although the results of this study are encouraging, the need for transfer to a specialty center and the dropout rate of 25% upon transfer limit the generalizability of this study; additional clinical trials are under way. High-frequency oscillatory ventilation (HFOV) appeared to be promising in several small, randomized trials in patients with ARDS,¹⁹¹⁻¹⁹⁵ with improvements in oxygenation in patients with severe hypoxemia. However, two large, randomized clinical trials in severe ARDS failed to show a benefit,^{196,197} and in one of the trials, mortality was higher in the HFOV group.¹⁹⁶ For this reason, HFOV should only be used as a rescue therapy and only by experienced operators. Other rescue therapies include the use of a pulmonary vasodilator, such as inhaled nitric oxide (NO) or inhaled prostacyclin. There have been several small, randomized clinical trials of inhaled NO in ARDS; although none has shown improved mortality, its use has been associated with improvements in oxygenation.¹⁹⁸ Inhaled prostacyclin is another pulmonary vasodilator that may be used as a rescue therapy in severe, refractory ARDS, although there are no randomized trials showing a mortality benefit.¹⁹⁹

COMPLICATIONS

Complications are common in any critically ill patient population. Supportive care for all critically ill patients must include vigilance in both preventing and diagnosing common complications such as pulmonary embolus, acute myocardial infarction, gastrointestinal

TABLE 67-4 Summary of Rescue Therapies for Acute Lung Injury and Acute Respiratory Distress Syndrome

| RESCUE THERAPY | YEAR | HOW STUDIED | NUMBER OF PATIENTS | COMMENTS | REFERENCES |
|---|------|-------------|--------------------|---|------------|
| ECMO | 1979 | Phase III | 90 | In this multicenter trial there was no benefit with the use of ECMO. | 241 |
| | 2009 | Phase III | 180 | This large, randomized trial showed benefit to treatment with ECMO; however, 25% of patients assigned to ECMO did not receive this therapy, and the need for urgent transfer to specialized treatment centers limits general applicability of this trial. | 190 |
| ECCOR | 1994 | Phase III | 40 | This newer form of extracorporeal therapy did not improve mortality. | 204 |
| Prone positioning | 2001 | Phase III | 304 | Although prone positioning improved oxygenation, there was no mortality benefit | 155 |
| | 2009 | Phase III | 342 | Patients were randomized according to severity of hypoxemia to receive 20 hours of prone positioning vs. usual care and had no reduction in mortality at 28 days or 6 months. | 156 |
| | 2013 | Phase III | 466 | Patients with more severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$ mm Hg) were randomized to supine or prone position (>16 h/day). Patients in the prone group had improved 28-day mortality. | 157 |
| High-frequency oscillatory ventilation (HFOV) | 2002 | Phase III | 148 | HFOV group had improved oxygenation but no difference in mortality. | 191 |
| | 2005 | Phase III | 61 | No significant differences in any outcome between the groups | 195 |
| | 2013 | Phase III | 548 | HFOV had higher mortality and more hemodynamic instability. | 196 |
| | 2013 | Phase III | 795 | No difference in mortality | 197 |
| Inhaled nitric oxide | 1998 | Phase II | 177 | Although some patients will have improvement in oxygenation with inhaled nitric oxide, there was no mortality benefit in any of these large studies. | 242 |
| | 1999 | Phase III | 203 | | 243 |
| | 2004 | Phase III | 385 | | 244 |

PEEP, positive end expiratory pressure; ECMO, extracorporeal membrane oxygenation; ECCOR, extracorporeal CO₂ removal.

bleeding, and nosocomial infection. Certain complications are more common in ARDS patients and deserve special mention.

Barotrauma

Barotrauma occurs when air dissects out of the airways or alveolar space into surrounding tissues, leading to pneumothorax, pneumomediastinum, pneumatocele, or subcutaneous emphysema (Fig. 67-5). The exact incidence of pulmonary barotrauma in ARDS is unclear but appears to be declining. Data from two large, randomized trials of protective ventilatory strategies suggest an incidence of early pneumothorax of 12% to 13%.^{200,201} Higher incidences have been reported in the past, a finding that may have been the result of using mechanical ventilation with high tidal volumes and very high inspiratory plateau pressures.²⁰² In 861 patients enrolled in the NIH ARDS Network trial, approximately 10% developed some form of barotrauma, regardless of whether they were in the 6- or 12-mL/kg tidal volume arm. Further, PEEP level was the only factor that predicted the development of barotrauma in a multivariate analysis.²⁰³

Treatment of barotrauma depends on the location of the extravasated air. Pneumothorax can be life threatening, particularly if it is under tension; immediate diagnosis and tube thoracostomy are essential. Pneumothorax should be considered in any mechanically ventilated patient with ARDS who develops sudden, unexplained worsening of hypoxemia, respiratory distress, or hemodynamic instability. A chest radiograph (preferably upright) is usually sufficient to make the diagnosis, but in many cases there may not be time to obtain one (see Fig. 67-5). Pneumomediastinum and subcutaneous emphysema can be painful but do not require specific therapy other than analgesia. Air embolus is a potentially fatal complication of positive pressure mechanical ventilation that has been reported occasionally in patients with ARDS²⁰⁴⁻²⁰⁶ and usually occurs in conjunction with other evidence of pulmonary barotrauma, often simultaneously.

Nosocomial Pneumonia

The incidence of nosocomial pneumonia in patients with ARDS is difficult to quantify. Depending on the diagnostic definition and/or strategy employed, estimates range from 15% to 60%.^{207,208} There is no

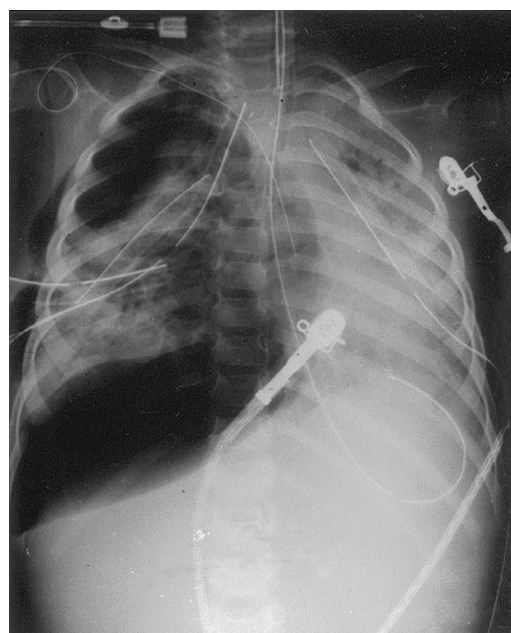


FIGURE 67-5 ■ Chest radiograph showing tension pneumothorax in a patient with acute respiratory distress syndrome.

consensus regarding the appropriate way to diagnose nosocomial pneumonia in the mechanically ventilated patient. Since patients with ARDS frequently die from uncontrolled infection, recognition (though notably difficult) and treatment of nosocomial pneumonia is an important part of caring for the ARDS patient. Clinical criteria commonly used in the diagnosis of nosocomial pneumonia include fever, elevated WBC count, purulent secretions, and pulmonary infiltrates. However, these signs are often present in patients with ARDS, even in the absence of nosocomial pneumonia.²⁰⁹ Autopsy studies of patients who died with ARDS show a high incidence of unsuspected pneumonia.²¹⁰⁻²¹² An

in-depth discussion of diagnostic strategies is presented elsewhere in this text. Regardless of the methods used for diagnosis, early, appropriate, and empiric therapy is the mainstay of treatment for nosocomial pneumonia. The adequacy and timeliness of initial empiric therapy are important determinants of outcome. Knowledge of local resistance patterns is crucial, and a high index of suspicion is required.

Multiorgan System Dysfunction

Although ARDS is often thought of as a primary pulmonary disorder, ARDS is often a systemic disorder with many similarities to sepsis or SIRS. Multiorgan system dysfunction is a common complication in ARDS. Organ dysfunction may result from the underlying cause of ARDS, such as sepsis, or occur independently. The exact incidence of multiorgan system dysfunction in ARDS is difficult to quantify. In the ARDS Network trial of low tidal volume ventilation, the mean number of nonpulmonary organ system failures per patient was 1.8.²⁰⁰ Given the simultaneous occurrence of multiple organ failures, it is often difficult to determine the exact cause of death in ARDS patients, and survival ultimately depends on successful support of the failing organs.

Neuromuscular Weakness

Patients with ARDS are at high risk for developing prolonged muscle weakness that persists after resolution of pulmonary infiltrates and can complicate weaning from mechanical ventilation and rehabilitation. This clinical syndrome is commonly called *critical illness polyneuropathy* but has components of neuropathy and myopathy that can coexist or occur separately.²¹³ Although little prospective data is available, several studies suggest that neuromuscular abnormalities are persistent in many survivors of critical illness, even when studied up to 5 years after ICU discharge.^{121,214} Prolonged muscle weakness is most common in critically ill patients who are treated with glucocorticoids. In one study, the use of corticosteroids was shown to be the best independent predictor of ICU-acquired paresis (odds ratio, 14.9; 95% CI, 3.2–69.8).²¹⁵ In the absence of a compelling clinical indication such as underlying connective tissue disease, the use of glucocorticoids should not be routine unless new clinical evidence in support of their clinical utility in ARDS becomes available. In other studies, neuromuscular blockade has also been implicated.

CLINICAL OUTCOMES AND PROGNOSIS

Once a patient develops ARDS, several prognostic factors can help clinicians to predict the outcome. An elevated pulmonary dead space fraction in ARDS is a reflection of extensive injury to the lung microcirculation, lung microvascular thrombi, and regional differences in pulmonary blood flow and is a predictor of death in patients with ARDS.^{216,217} Although the dead space fraction may predict mortality, it is not routinely measured in the ICU. For this reason, predictive models that use readily available clinical variables have been developed.²¹⁸ In addition to dead space fraction, a positive cumulative fluid balance at day 4 in patients with ARDS predicts increased mortality,²¹⁹ further supporting the use of a conservative fluid strategy in patients with ARDS.¹³⁴

The reported mortality from ARDS appears to be gradually declining,¹²² although this finding has not been consistent between retrospective studies.²²⁰ Before the 1990s, mortality in clinical trials was approximately 40% to 60%.²²¹ Several recent single-center studies

suggest that mortality rates measured in the same centers has declined over time.^{222–225} In an ARDS Network study that enrolled 861 ARDS patients in the late 1990s, aggregate mortality to hospital discharge was 31% in the 6-mL/kg tidal volume arm and 40% in the 12-mL/kg tidal volume arm. However, mortality data from this study may significantly underestimate overall ARDS mortality since many severely ill patients were excluded, including those with advanced liver disease, bone marrow transplantation, severe chronic respiratory disease, burns greater than 30% body surface area, or any other underlying condition with a likelihood of death greater than 50% within 6 months. As has been observed in other studies, the risk of in-hospital mortality in this study was highest in those with sepsis (43%), intermediate in those with pneumonia (36%) or aspiration (37%), and lowest in those with multiple trauma (11%).¹⁶ The low-tidal volume strategy was effective at reducing mortality across all causes of ARDS.¹⁶ Another study has shown that implementation of the ARDS Network low-tidal volume ventilator strategy is associated with lower hospital mortality compared to historical controls.²²⁶ In a more recent ARDS Network study published in 2012, the overall 60-day mortality was 23%.¹⁴²

Several recent multicenter studies in France,²²⁷ Sweden,²²⁸ Australia,²²⁹ and Argentina²³⁰ attempted to define mortality and prognostic variables in observational, population-based studies rather than from clinical trial participants. In these studies, mortality was variable, ranging from 32% for mild ARDS to 58% to 60% for moderate to severe ARDS. Factors independently associated with mortality from ARDS varied from study to study and included age, Acute Physiology Score, $\text{PaO}_2/\text{FiO}_2$ ratio, organ failures or septic shock, immunosuppression, cardiovascular failure, and chronic liver disease.^{30,227–230} Two other U.S. studies of patients with ARDS predominantly from medical intensive care units reported high overall mortality rates (58%).^{231,232} Mortality was associated with chronic liver disease and other underlying disease such as HIV infection or cancer. Although most studies have reported short-term mortality from ARDS, a recent study examined 1-year mortality.²³³ In a heterogeneous group of 641 patients with ARDS, 1-year mortality was substantially higher than hospital mortality (41% vs. 24%; $P < 0.0001$). In summary, these studies suggest that while some improvements in ARDS mortality have been made, mortality remains quite high in population-based studies, and improvements in short-term outcomes may not be reflected in better long-term outcomes.

ARDS survivors frequently have long-term functional disability, cognitive dysfunction, and psychosocial problems.²³⁴ Interestingly, pulmonary function frequently returns to normal or near-normal in survivors. In a report of 1-year follow-up in 109 survivors of ARDS,¹²⁰ lung volumes and spirometry had returned to normal by 6 months. However, carbon monoxide diffusing capacity was persistently low throughout the year. Six-minute walk distances were persistently low at 12 months, largely due to muscle wasting and weakness rather than pulmonary function abnormalities.¹²⁰ Treatment with any systemic corticosteroid, the presence of illness acquired during the ICU stay, and the rate of resolution of the lung injury and multiorgan dysfunction during the ICU stay were the most important determinants of the 6-minute walk distance during the first year of follow-up. In other studies, patients who survive ARDS are reported to have reduced health-related quality of life²³⁵ and pulmonary-disease-specific health-related quality of life^{236–238} and functional impairment that persists 2 years after ICU discharge.²³⁹ In addition to physical and social difficulties after ARDS, survivors have high rates of depression and anxiety.²⁴⁰

ANNOTATED REFERENCES

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■ References for this chapter can be found at www.expertconsult.com.

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Aspiration is defined as the misdirection of oropharyngeal or gastric contents into the larynx and lower respiratory tract.¹ The pulmonary syndromes that commonly follow aspiration depend on the quantity and nature of the aspirated material, frequency of aspiration, and the nature of the host's defense mechanisms. The most important syndromes include *aspiration pneumonitis*, or Mendelson syndrome, a chemical pneumonitis caused by the aspiration of gastric contents, and *aspiration pneumonia*, an infectious process caused by the aspiration of oropharyngeal secretions colonized by pathogenic bacteria.¹ There is some overlap between these two syndromes, but they are distinct clinical entities. Other aspiration syndromes include airway obstruction, lung abscess, exogenous lipoid pneumonia, chronic interstitial fibrosis, and *Mycobacterium fortuitum* pneumonia.

■ ASPIRATION PNEUMONITIS

Aspiration pneumonitis is best defined as acute lung injury following the aspiration of regurgitated gastric contents.¹ This syndrome usually occurs in patients with a marked disturbance of consciousness, such as drug overdose, seizures, coma due to acute neurologic insults, and massive cerebrovascular accident, following head trauma and during anesthesia. In clinical practice, drug overdose is the most common cause of aspiration pneumonitis, occurring in approximately 10% of patients hospitalized following a drug overdose. Historically the syndrome most commonly associated with aspiration pneumonitis is Mendelson's syndrome, reported in 1946 in obstetric patients who aspirated while receiving general anesthesia.²

Although aspiration is a widely feared complication of general anesthesia, clinically apparent aspiration in modern anesthesia practice is exceptionally rare, and in healthy patients the overall morbidity and mortality are low. Nevertheless, aspiration pneumonia is an important perioperative complication and remains the most common cause of anesthesia-related death. The risk of aspiration with modern anesthesia is reported to be between 2.9 and 4.7 per 10,000 general anesthetics (about 1 in 3000 anesthetics) with a mortality of approximately 1:125,000, accounting for between 10% and 30% of all anesthetic deaths.^{3,4} Emergency surgery (particularly, trauma and abdominal surgery with delayed gastric emptying) procedures performed at night, inadequate anesthesia, obesity, elderly immobilized patients, and patients with obstructive sleep apnea are considered to be at a higher risk of aspiration.^{4,5}

Pathophysiology

Mendelson emphasized the importance of acid when he showed that un-neutralized gastric contents introduced into the lungs of rabbits caused severe pneumonitis indistinguishable from that caused by an equal amount of 0.1 N hydrochloric acid.^{2,6,7} However, if the pH of the vomitus was neutralized before aspiration, the pulmonary injury was minimal. Experimental studies have demonstrated that the severity of lung injury increases significantly with the volume of the aspirate and indirectly with its pH, with a pH of less than 2.5 being required to cause aspiration pneumonitis. However, the stomach contains a variety of other substances in addition to acid that may be damaging when aspirated. Several experimental studies have revealed that aspiration of

small, particulate food matter from the stomach may cause severe pulmonary damage, even if the pH of the aspirate is above 2.5.^{8,9} These studies suggest that cell recruitment and expression of inflammatory mediators are most pronounced after injury with combined acid and small food particles. Such data are supported by findings in patients where the most severe lung injury was observed following aspiration with particulate food matter.^{10,11}

Clinical Presentation

Aspiration of gastric contents can present dramatically with a full-scale occurrence that includes gastric contents in the oropharynx, wheezing, coughing, shortness of breath, cyanosis, pulmonary edema, hypotension, and hypoxemia, which may progress rapidly to severe ARDS and death. However, after the aspiration of gastric contents, many patients may not develop such signs or symptoms, while others may develop a cough or wheeze. In some patients, aspiration may be clinically silent, manifesting only as arterial desaturation with radiologic evidence of aspiration. Warner and colleagues studied 67 patients who aspirated while undergoing anesthesia.⁷ Forty-two (64%) of these patients were completely asymptomatic, 13 required mechanical ventilatory support for more than 6 hours, and four died.

Management of Aspiration Pneumonitis

The upper airway should be suctioned following a witnessed aspiration. Endotracheal intubation should be considered in patients who are unable to protect their airway. While a common practice, the prophylactic use of antibiotics in patients with suspected or witnessed aspiration is not recommended. Similarly, the use of antibiotics shortly after an aspiration episode in a patient who develops a fever, leukocytosis, and a pulmonary infiltrate is discouraged as it may select for more resistant organisms in a patient with an uncomplicated chemical pneumonitis. However, empiric antimicrobial therapy is appropriate in patients who aspirate gastric contents in the setting of small bowel obstruction or other circumstances associated with the colonization of gastric contents. Antimicrobial therapy should be considered in patients with aspiration pneumonitis that fails to resolve within 48 hours. When antimicrobial agents are used, broad-spectrum coverage is recommended. Antimicrobials with anaerobic activity are not routinely required.

Corticosteroids have been used in the management of aspiration pneumonitis since 1955.¹² However, due to a limited amount of outcome data, it is not possible to make evidence-based recommendations on the use of these agents in patients with aspiration pneumonia.

■ ASPIRATION PNEUMONIA

Aspiration pneumonia refers to the development of a radiographic infiltrate in the setting of patients with risk factors for increased oropharyngeal aspiration. Approximately half of all healthy adults aspirate small amounts of oropharyngeal secretions during sleep. Presumably, the low virulent bacterial burden of normal pharyngeal secretions together with forceful coughing, active ciliary transport, and normal

humoral and cellular immune mechanisms result in clearance of the inoculum without sequelae. However, if mechanical, humoral, or cellular mechanisms are impaired or if the aspirated inoculum is large enough, pneumonia may follow. Any condition that increases the volume and bacterial burden of oropharyngeal secretions in the setting of impaired host defense mechanisms may lead to aspiration pneumonia. Indeed, in stroke patients undergoing a swallow evaluation, there is a strong correlation between the volume of the aspirate and the development of pneumonia.¹³ Factors that increase oropharyngeal colonization with potentially pathogenic organisms and increase the bacterial load may augment the risk of aspiration pneumonia.

The clinical setting in which pneumonia develops largely distinguishes aspiration pneumonia from other forms of pneumonia. However, there is a great deal of overlap. This is illustrated by the fact that otherwise healthy elderly patients with “community-acquired pneumonia” have been demonstrated to have a significantly higher incidence of silent aspiration when compared with age-matched controls.¹⁴

Epidemiology

The lack of specific and sensitive markers of aspiration makes the epidemiologic study of aspiration syndromes difficult. Furthermore, most studies do not make the distinction between aspiration pneumonitis and aspiration pneumonia. Nevertheless, several studies list “aspiration pneumonia” as the cause of community-acquired pneumonia (CAP) in 5% to 15% of cases.^{15,16} CAP is a major cause of morbidity and mortality in the elderly, and it is likely that aspiration is the major cause of pneumonia in these patients. Epidemiologic studies have demonstrated that the incidence of pneumonia increases with aging, with the risk being almost six times higher in those over the age of 75, compared to those less than 60 years of age.^{17,18} The attack rate for pneumonia is highest among those in nursing homes.¹⁹

Dysphagia in Patients with Aspiration Pneumonia

Dysphagia is a major risk factor leading to aspiration pneumonia. In addition, dysphagia contributes significantly to protein-energy malnutrition and dehydration. Impairment in any component of the swallow mechanism, including anatomic abnormalities of the upper airway or esophagus, can lead to dysphagia. Dysphagia has traditionally been associated with brainstem and bilateral cerebral infarction though it has more recently been shown also to occur in isolated cerebral infarctions. Furthermore, dysphagia is commonly associated with silent cerebral infarction.

Dysphagia is common in Westernized nations and is a major cause of morbidity and mortality. Indeed, aspiration pneumonia is likely the final common pathway by which many chronically ill patients die. It has been estimated that over 16 million senior citizens in the United States suffer from dysphagia.²⁰ Furthermore, an additional 300,000 to 600,000 patients develop dysphagia each year in the United States from neurologic disorders.²¹ Dysphagia affects more than 30% of patients who have had a cerebrovascular accident, 52% to 82% of patients with Parkinson's disease, 84% of patients with Alzheimer's disease, up to 40% of adults aged 65 years and older, and more than 60% of institutionalized elderly patients.²²

The efficiency of the swallow mechanism decreases with aging, thereby increasing the risk of aspiration and pneumonia in the elderly. Kikuchi and colleagues evaluated the occurrence of silent aspiration in otherwise “healthy elderly patients” with CAP and age-matched control subjects using indium chloride scanning.¹⁴ Silent aspiration was demonstrated in 71% of patients with CAP compared to 10% in control subjects. The impaired swallow mechanism in the elderly can be attributed to diminished sensation, silent cerebral infarction, cerebral atrophy, a delay in the synapse conduction in the afferent inputs to the central nervous system, and lingual weakness (sarcopenia) caused by aging.^{23,24}

TABLE 68-1

Risk Factors for Dysphagia and Aspiration Pneumonia

| |
|--|
| Cerebrovascular disease |
| • Ischemic stroke |
| • Hemorrhagic stroke |
| • Subarachnoid hemorrhage |
| Degenerative neurologic disease |
| Alzheimer's disease |
| Multi-infarct dementia |
| Parkinson's disease |
| Amyotrophic lateral sclerosis (motor neuron disease) |
| Multiple sclerosis |
| Head and neck cancer |
| Oropharyngeal malignancy |
| Oral cavity malignancy |
| Esophageal malignancy |
| Other |
| • Scleroderma |
| • Diabetic gastroparesis |
| • Reflux esophagitis |
| • Presbyesophagus |
| • Achalasia |

Risk Factors for Dysphagia

The major risk factors for dysphagia are listed in Table 68-1. In patients with an acute stroke, the incidence of dysphagia ranges from 40% to 70%.²⁵ Dysphagic patients who aspirate are at an increased risk of developing pneumonia.^{26,27} Although dysphagia improves in most patients following a stroke, in many the swallowing difficulties follow a fluctuating course with 10% to 30% continuing to have dysphagia with aspiration.^{28,29}

Factors That Increase the Risk of Pneumonia in Patients Who Aspirate

While the presence of dysphagia and the volume of the aspirate are key factors that predispose patients to aspiration pneumonia, a number of other factors also play an important role.¹³ Colonization of the oropharynx is an important step in the pathogenesis of aspiration pneumonia. The elderly have increased oropharyngeal colonization with pathogens, such as *Staphylococcus aureus* and aerobic gram-negative bacilli (e.g., *Klebsiella pneumoniae* and *Escherichia coli*). Although such increased colonization may be transient, it underlies the increased risk in the elderly of pneumonia due to these pathogens. Furthermore, colonization of dental plaque may be an important risk factor for aspiration pneumonia.³⁰ The defects in host defenses that predispose some individuals to enhanced colonization with these organisms are uncertain. However, dysphagia with a decrease in salivary clearance and poor oral hygiene may be major risk factors.³¹ Residents of long-term care facilities are prone to poor oral health due to lack of oral hygiene care, as well as conditions of periodontal and/or dental disease. In addition, proton pump inhibitors (PPIs) increase gastric and oropharyngeal colonization with potentially pathogenic organisms. Gulmez and colleagues reported that the concurrent use of PPI in patients over the age of 60 years increased the risk for community-acquired (aspiration) pneumonia.³²

Diagnosis and Management of Aspiration Pneumonia

There is no “gold standard” test to diagnose aspiration. Furthermore, unlike the case of aspiration pneumonitis, in patients with aspiration pneumonia the aspiration episode is not witnessed. The diagnosis is therefore inferred when a patient with known risk factors for aspiration has an infiltrate in a characteristic bronchopulmonary segment. In patients who aspirate in the recumbent position, the most common sites of involvement are the posterior segments of the upper lobes and

the apical segments of the lower lobes. In patients who aspirate in the upright or semirecumbent position, the basal segments of the lower lobes are favored. The typical picture is that of an acute pneumonic process, which runs a course similar to that of a typical CAP. Untreated, however, these patients also appear to have a higher incidence of cavitation and lung abscess formation.³³

Antimicrobial therapy is indicated in patients with aspiration pneumonia. The choice of antibiotics should depend on the setting in which the aspiration occurs, as well as the patient's premorbid condition. This includes such factors as whether the aspiration occurred in the community or a health care facility and patient characteristics such as alcoholism, oral hygiene, intravenous drug abuse, and the recent use of antibiotics or acid suppressive therapy.³⁴

Aspiration pneumonia most commonly occurs in the setting of a health care facility (HCAP) or an acute care hospital (HAP). Health care-associated aspiration pneumonia (HCAP) refers to pneumonia that develops in individuals receiving health care outside the hospital setting, including dialysis, nursing homes, and long-term acute care (LTAC) facilities. Patients with HCAP who have risk factors for infection with a drug-resistant pathogen should be treated with broad-spectrum agents.

Although commonly prescribed (and often considered the standard of care) antimicrobials with specific anaerobic activity are not routinely warranted. In the most rigorous study to date, El-Sohl and colleagues performed protected quantitative bronchial sampling in 95 patients with severe aspiration pneumonia.³⁵ Out of the 67 pathogens identified, gram-negative enteric bacteria were the predominant organisms isolated (49%), followed by anaerobic bacteria (16%), and *Staphylococcus aureus* (12%). A single anaerobic bacterium was isolated from 11 patients, usually in association with a gram-negative pathogen. Although seven cases with anaerobic isolates received initially inadequate antimicrobial therapy, six had an effective clinical response. Antimicrobials with specific anaerobic activity may only be indicated in patients with periodontal disease, patients expectorating putrid sputum, and patients with necrotizing pneumonia or lung abscess on a chest radiograph.^{1,34,36,37}

Assessment and Management of Dysphagia

All elderly patients with CAP and chronic idiopathic lung disease, as well as patients with a recent cerebrovascular accident and those with degenerative neurologic diseases, should be referred to a speech and language pathologist for a formal swallow evaluation.^{27,38} Patients with dysphagia require the formulation and implementation of an individualized management strategy. A clinician's bedside assessment of a cough and gag reflex is unreliable in screening for patients at risk of aspiration. Because objective swallowing evaluation can be performed with an nasogastric (NG) tube (or feeding tube) in place, it is not necessary to remove the NG tube (and interrupt enteral feedings) to evaluate dysphagia. Similarly, there is no contraindication to leaving an NG tube in place to supplement oral alimentation.³⁹

The management of patients with dysphagia requires the coordinated expertise of a number of health care professionals, including the patients' primary care physician, pulmonologist, speech and language pathologist, clinical dietician, occupational therapist, physiotherapist, nurse, oral hygienist, and dentist, as well as the patients' primary caregivers. The goal is to optimize the safety, efficiency, and effectiveness of the oropharyngeal swallow, to maintain adequate nutrition and hydration and improve oral hygiene. Enhanced quality of life, wherever possible, should direct management. Approaches to management should emphasize oral versus nonoral nutritional intake and hydration.

A fundamental principle of rehabilitation is that the best therapy for any activity is the activity itself; as swallowing may be considered the best therapy for swallowing disorders, rehabilitation should be aimed at identifying ways of ensuring safe and effective swallowing in individual patients. Current treatment for dysphagia includes the prevention of aspiration in the form of diet and fluid modifications,

compensatory maneuvers, position changes, and rehabilitation exercises.⁴⁰ Diet modification is also a common treatment for dysphagia. Modifications in food consistency are individually determined by means of the clinical swallow and videofluoroscopic swallow evaluation. A reduction in bolus volume and enhancement of bolus viscosity significantly improve the safety of swallowing and reduce the risk of aspiration.²³ In addition to changes in diet, maintenance of oral feeding often requires compensatory techniques to reduce aspiration or to improve pharyngeal clearance. A variety of behavioral techniques are used, including modifications in posture, head position, and respiration, as well as specific swallowing maneuvers.

Tube Feeding

Tube feeding is not essential in all patients who aspirate. However, short-term tube feeding, may be indicated in elderly patients with severe dysphagia and aspiration in whom improvement of swallowing is likely to occur. Nakajoh and colleagues demonstrated that the incidence of pneumonia was significantly higher in stroke patients with dysphagia who were fed orally compared to those who received tube feeding (54.3% vs. 13.2%, $P < 0.001$), despite the fact that the orally fed patients had a higher functional status (higher Barthel index).⁴¹ The FOOD trials consisted of two large randomized studies that enrolled dysphagic stroke patients.⁴² In the first trial, patients enrolled within 7 days of admission and were randomly allocated to early tube feeding or no tube feeding. Early tube feeding was associated with an absolute reduction in the risk of death to 5.8%. The second trial allocated patients to early NG feeding or early feeding via a percutaneous endoscopic gastrostomy (PEG) tube. PEG feeding was associated with an absolute increase in the risk of death to 1% and an increased risk of death or poor outcome of 7.8%. Patients with a PEG were less likely to be transitioned to oral feeding than the NG group and were more likely to be living in an institution. This difference in patient location may in part explain the higher mortality rate of the PEG-fed patients. Furthermore, PEG-fed patients were more likely to develop pressure sores, suggesting that these patients may have been nursed differently. The results of the FOOD trials suggest that dysphagic stroke patients should be fed early via a NG or feeding tube and transitioned to oral feeding as their dysphagia resolves. Those patients whose dysphagia does not resolve may be candidates for placement of a PEG tube.

Oral Hygiene

Dental plaque as well as "tongue coating" serves as a reservoir of potentially pathogenic organisms.³⁰ Occupants of residential homes have been shown to have poor oral hygiene and rarely receive treatment from dentists and oral hygienists.⁴³ An aggressive protocol of oral care will reduce colonization with potentially pathogenic organisms and decrease the bacterial load, measures which have been demonstrated to reduce the risk of aspiration pneumonia.⁴⁴⁻⁴⁷ Oral care should not be overlooked in edentulous patients, as "tongue cleaning" is associated with a decreased oropharyngeal bacterial load.^{48,49}

Pharmacologic Management

The neurotransmitter, Substance P, is believed to play a major role in both a cough and swallow sensory pathways. Angiotensin-converting enzyme (ACE) inhibitors prevent the breakdown of Substance P and may theoretically be useful in the management of patients with aspiration pneumonia. A number of studies have demonstrated a lower risk of aspiration pneumonia in stroke patients treated with an ACE inhibitor compared with other antihypertensive agents.^{50,51} This observation was initially noted in Japanese patients, and it has been suggested that this benefit was restricted to Asian populations.⁵² Furthermore, it has been postulated that lipophilic ACE inhibitors may be more beneficial than hydrophilic ACE inhibitors.⁵³ However, a population-based case-control study from the UK demonstrated that current prescription for an ACE inhibitor was associated with a reduction in the risk of pneumonia in the general population (odds ratio: 0.75; 95% confidence interval: 0.65 to 0.86).⁵⁴

CONCLUSIONS

Aspiration pneumonia and pneumonitis are common clinical syndromes. Aspiration pneumonitis follows the aspiration of gastric contents, usually in patients with a marked decreased level of consciousness. Treatment of aspiration pneumonitis is essentially

supportive. Aspiration pneumonia occurs in patients with dysphagia and usually presents as CAP or health care associated pneumonia with a focal infiltrate in a dependent bronchopulmonary segment. Patients with aspiration pneumonia require treatment with antibiotics selected on the basis of the risk of infection with a drug-resistant pathogen and management of the underlying dysphagia.

■ References for this chapter can be found at expertconsult.com.

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MAGNITUDE OF THE PROBLEM

Each year in the United States, acute asthma accounts for approximately 1.9 million emergency department (ED) visits, 480,000 hospitalizations, and 3400 deaths.¹ While failure to achieve outpatient control underlies many of these poor outcomes, a minority of patients present to the ED on oral corticosteroids or after a recent oral steroid taper.^{2,3} Factors underlying the exacerbation-prone phenotype include cigarette smoking, medication nonadherence, psychosocial factors, poverty, obesity, and alterations in host cytokine response to viral infections.⁴ The rate of asthma death is higher in blacks than whites and in patients aged 65 and older. Patients who require mechanical ventilation for asthma are at low risk for asthma death and pneumothorax, and the rate of asthma death in general has decreased each year since 2000.³ Risk factors for fatal or near-fatal asthma are listed in Table 69-1.

PATHOPHYSIOLOGY OF ACUTE AIRFLOW OBSTRUCTION

Fewer than 15% of asthmatics have rapid-onset exacerbations, which are predominantly bronchospastic events evolving over minutes to hours. They occur from exposure to allergens or irritants, stress, illicit drugs, or the use of nonsteroidal antiinflammatory agents or beta-blockers in susceptible patients. The trigger is generally not infectious.⁵ Asthma attacks more commonly evolve over 24 hours and are associated with increasing airway wall inflammation, bronchospasm, and mucous plugs. These exacerbations are commonly triggered by viral infections or mycoplasma and take longer to resolve.

Regardless of the tempo, critical airflow obstruction follows, and the time available for expiration is insufficient for full exhalation, resulting in gas trapping and dynamic lung hyperinflation (DHI). Trapped gas elevates the alveolar volume and pressure relative to mouth pressure at end expiration, a state referred to as *auto-PEEP*.⁶ Auto-PEEP must be overcome by forcefully lowering pleural pressure during inspiration, increasing inspiratory work. At the same time, DHI increases elastic work, and airway narrowing increases resistive work. Dynamic hyperinflation also places the diaphragm in a disadvantageous position, lowering force generation. In the end, an imbalance between increased work of breathing and decreased respiratory muscle strength can result in respiratory failure.⁷

Hypoxemia results from decreased ventilation (\dot{V}) to perfused (\dot{Q}) alveolar-capillary units. The severity of hypoxemia roughly tracks the severity of obstruction, but in recovering patients, airflow rates may improve faster than PaO_2 , and \dot{V}/\dot{Q} inequality, indicating that larger airways recover faster than smaller airways. Acutely ill asthmatics may also have small areas of high \dot{V} relative to \dot{Q} and increased physiologic dead space, perhaps from decreased blood flow to hyperinflated units. Elevated dead space and decreased alveolar ventilation in the fatiguing patient predisposes to hypercapnia.

Large swings in intrathoracic pressure accentuate the normal inspiratory fall in systolic blood pressure, a phenomenon called *pulsus paradoxus*. During vigorous inspiration, intrathoracic pressure falls, lowering right atrial and right ventricular (RV) pressures and augmenting RV filling. Enhanced right-sided filling shifts the intraventricular septum leftward, causing a conformational change in the left

ventricle (LV), LV noncompliance, and incomplete LV filling. Furthermore, DHI may impede LV filling by causing tamponade-like physiology. LV emptying is affected by large negative pleural pressures and increased LV afterload.

During forced expiration, high intrathoracic pressures impede right-sided filling. The net result of these cyclical changes in pleural pressure is *pulsus paradoxus*. Importantly, a dropping *pulsus paradoxus* does not always signal improvement, as fatigue limits the magnitude of pleural pressure swings.

CLINICAL FEATURES

Patients with moderate to moderately severe attacks are tachypneic and in respiratory distress. They have expiratory phase prolongation and difficulty speaking in long sentences. Arterial blood gases commonly reveal hypoxemia and respiratory alkalosis. Severe attacks lead to upright positioning, diaphoresis, monosyllabic speech, respiratory rate (RR) above 30/min, accessory muscle use, pulse above 120/min, *pulsus paradoxus* greater than 25 mm Hg, hypoxemia, and normo- or hypercapnia. Depressed mental status, paradoxical respiration, bradycardia, absence of *pulsus paradoxus* from fatigue, and a quiet chest signal an impending arrest. The emergence of wheezes in severe patients is generally a good sign that airflow has improved. Posture, speech, and mental status allow for quick appraisal of severity, response to therapy, and need for intubation.⁸ Sinus tachycardia is common, but other cardiac complications occur, including supraventricular and ventricular arrhythmias, right heart strain, and myocardial ischemia. "All that wheezes is not asthma" is an adage worth remembering, and Table 69-2 lists other diagnostic considerations.

PEAK FLOW MEASUREMENTS

Early measurement of the peak expiratory flow rate (PEFR) or forced expiratory volume in the first second of expiration (FEV_1) helps characterize the severity of an attack. As a general rule, a severe attack is characterized by a PEFR less than 200 L/min or an FEV_1 less than 1 L. Objective measures also point to alternate diagnoses when symptoms are not associated with the expected drop in lung function. Objective measurements should be deferred in patients with severe exacerbations because the maneuver can worsen bronchospasm even to the point of arrest.

The change in PEFR or FEV_1 predicts need for hospitalization. Several studies have demonstrated that failure of initial therapy to improve expiratory flow significantly after 30 to 60 minutes predicts a refractory course requiring continued treatment in the ED or hospital.

ACID-BASE STATUS

Arterial blood gases are recommended in patients with severe attacks, but serial gases are generally not necessary unless the patient is mechanically ventilated. Hypoxemia and respiratory alkalosis are common in mild to moderate exacerbations. Eucapnia and hypercapnia indicate a severe exacerbation but are in and of themselves not sufficient reasons for intubation because patients may still respond to pharmacotherapy.

TABLE 69-1 Risk Factors for Fatal or Near-Fatal Asthma

Frequent emergency department visits and hospitalizations
 Intensive care unit admission
 Intubation (prior or current)
 Hypercapnia
 Barotrauma
 Psychiatric illness
 Medical noncompliance
 Illicit drug use
 Poverty
 Inadequate access to medical care
 Use of >two canisters/month of an inhaled β_2 -agonist
 Poor perception of airflow obstruction
 Comorbidities (e.g., coronary artery disease)
 Sensitivity to *Alternaria* species

TABLE 69-2 Differential Diagnosis of Acute Asthma

Chronic obstructive pulmonary disease exacerbation
 Vocal cord dysfunction
 Intraluminal mass or foreign body
 Aspiration
 Tracheal stenosis
 Infectious bronchitis or pneumonia
 Heart failure ("cardiac asthma")

Renal compensation in response to acute respiratory alkalosis of sufficient duration manifests as a normal anion gap metabolic acidosis. Lactic acidosis occurs in patients with labored breathing, particularly in the setting of parenteral β -agonists.

CHEST RADIOGRAPHY

In classic cases of acute asthma, the chest x-ray rarely affects management. Indications for chest imaging include localizing signs on examination, concerns regarding barotrauma, and questions regarding the diagnosis and assessment of endotracheal tube position.

EMERGENCY DEPARTMENT DISPOSITION

Asthmatics with inadequate response to albuterol in the ED invariably require hospital admission or prolonged treatment in the ED.⁹ Approximately one-third of patients are nonresponders to albuterol (Fig. 69-1). These patients have negligible changes in PEFR after 30 to 60 minutes of therapy. Other markers of a severe attack such as a PEFR less than 40% of predicted or personal best, or deterioration despite treatment are indications for admission. Intensive care unit (ICU) admission is required for respiratory failure, the need for frequent albuterol treatments, fatigue, altered mental status, and cardiac toxicity. Patients with an incomplete response to treatment in the ED, defined by improved but persistent symptoms and a PEFR or FEV₁ between 40% and 69% of predicted, should be considered for admission, although select patients may return home safely with appropriate treatment and follow-up. Patients with a good response can be discharged with inhaled antiinflammatory therapy and instructions for follow up.

OXYGEN

Supplemental oxygen is provided to maintain the oxygen saturation above 90%. This improves oxygen delivery to tissues, including the respiratory muscles, and reverses hypoxic pulmonary vasoconstriction. Oxygen further protects against β -agonist-induced pulmonary vasodilation and increased blood flow to low \dot{V}/\dot{Q} units.

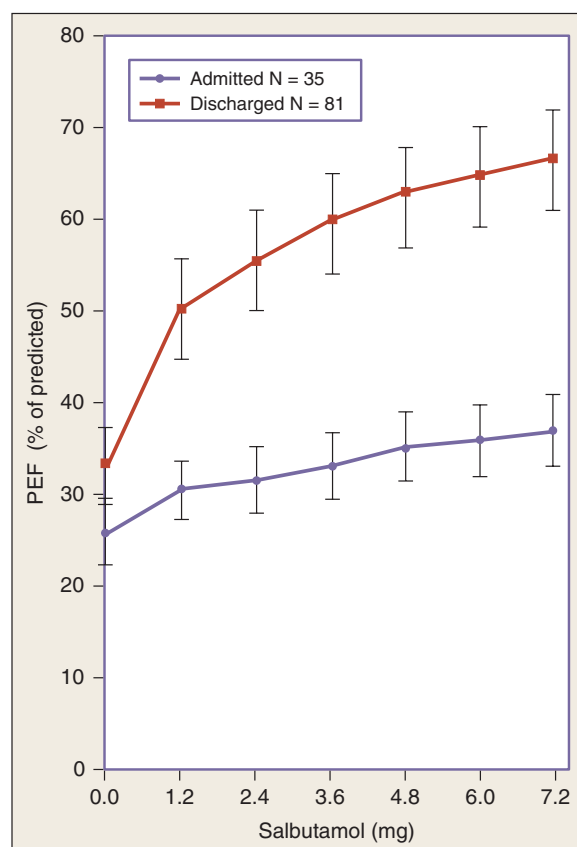


FIGURE 69-1 ■ Dose-response relationship to albuterol 4 puffs (400 μ g) every 10 minutes in 116 acute asthmatics, of whom 67% percent obtained discharge criteria after administration of 2.4 mg albuterol within 1 hour; half of the responders met discharge criteria after 12 puffs. Patients with a blunted cumulative dose-response relationship were hospitalized. (Reproduced with permission from Rodrigo C, Rodrigo G. Therapeutic response patterns to high and cumulative doses of salbutamol in acute severe asthma. *Chest* 1998;113:593.)

PHARMACOLOGIC MANAGEMENT

Selected drugs used in the treatment of acute asthma are listed in Table 69-3.

β_2 -Agonists

The bronchospastic component of acute asthma is treated with inhaled, short-acting β_2 -agonists (SABAs). They are delivered in a repetitive or continuous fashion depending on clinical response and side effects, which include tremor, tachycardia, and hypokalemia. A commonly recommended strategy is albuterol, 2.5 mg by nebulization, every 20 minutes during the first hour. In severe asthma exacerbations, continuous administration (same total dose) may be slightly superior to repetitive dosing, although there is little difference between the two strategies in most cases. Albuterol can be delivered effectively by metered dose inhaler (MDI); 4 to 8 puffs of albuterol by MDI with a spacer is equivalent to a 2.5-mg nebulizer treatment. MDIs with spacers are cheaper and faster; handheld nebulizers require less supervision and coordination. Treatment frequency after the first hour depends on the clinical response and side effects.

Although albuterol is the most widely used SABA, other SABAs are available, including levalbuterol. A recent meta-analysis demonstrated that levalbuterol was not superior to albuterol in acute asthma.¹⁰

There is no initial advantage to subcutaneous epinephrine or terbutaline in patients able to comply with inhaled therapy. In refractory

TABLE 69-3

Selected Drugs Used in the Treatment of Acute Asthma

| | |
|-------------------|---|
| Albuterol | 2.5 mg in 2.5 mL normal saline by nebulization every 15-20 min \times 3 in the first hour or 4-8 puffs by MDI with spacer every 10-20 min for 1 hour, then as required; for intubated patients, titrate to physiologic effect and side effects. |
| Levalbuterol | 1.25 mg by nebulization every 15-20 min \times 3 in the first hour, then as required |
| Epinephrine | 0.3 mL of a 1:1000 solution subcutaneously every 20 min \times 3. Terbutaline is favored in pregnancy when parenteral therapy is indicated. Use with caution in patients older than age 40 and in patients with coronary artery disease. |
| Corticosteroids | Methylprednisolone IV or prednisone PO 40-80 mg/d in 1 or 2 divided doses until PEFR reaches 70% of predicted or personal best |
| Anticholinergics | Ipratropium bromide 0.5 mg (with albuterol) by nebulization every 20 min, or 8 puffs by MDI with spacer (with albuterol) every 20 min |
| Magnesium sulfate | 2 g IV over 20 minutes, repeat once as required (total dose 4 g, unless hypomagnesemic) |

IV, intravenous; MDI, metered-dose inhaler; PEFR, peak expiratory flow rate; PO, per os (oral).

cases, however, subcutaneous treatment may be beneficial. Subcutaneous therapy is riskier and should be used with caution in older patients at risk for coronary artery disease. Long-acting β_2 -agonists (LABAs) are not commonly used in acute asthma, although formoterol (which has acute onset of action) is effective and safe in this setting.¹¹ LABA and inhaled corticosteroid (ICS) combination therapy can be initiated or continued in hospitalized patients receiving rescue therapy and may be required to achieve adequate outpatient control.

Ipratropium Bromide

The modest bronchodilator properties of ipratropium bromide preclude its use as a single agent in acute asthma, and the addition of ipratropium to albuterol is of limited benefit in patients with mild or moderate attacks. However, in patients with severe attacks, ipratropium added to albuterol is more effective than albuterol alone.¹² For nebulization in adults, 0.5 mg of ipratropium bromide is added to 2.5 mg of albuterol; by MDI, 4 to 8 puffs of ipratropium bromide are added to 4 to 8 puffs of albuterol. If a combination albuterol/ipratropium bromide inhaler is used, the recommended dose is 4 to 8 puffs every 20 minutes. The combined use of albuterol and ipratropium is indicated for the first 1 to 3 hours as guided by clinical response and toxicity, after which albuterol can be used as a single agent.

Corticosteroids

Systemic corticosteroids are recommended for all patients with acute severe asthma save the rare patient with an immediate and durable response to initial SABA therapy. Corticosteroids treat inflammation by promoting new protein synthesis, and their effects are typically delayed, underlining the importance of early initiation. Systemic steroids decrease hospitalization rates, speed the rate of recovery, and decrease the chance of relapse after discharge.

Oral steroids are as effective as parenteral steroids. Single-dose formulations of an intramuscular preparation are a reasonable choice in patients deemed unlikely to be compliant with oral steroids after discharge.

Various dosing regimens have been studied, and debate continues regarding the optimal dosing strategy. For hospitalized adults, the Expert Panel Report 3 recommends 40 to 80 mg/d of prednisone, methylprednisolone, or prednisolone in 1 or 2 divided doses until PEFR reaches 70% of predicted or the patient's personal best. For

outpatients, a common strategy is to use prednisone, 40 mg/d for 5 to 10 days, with early follow-up to judge clinical response and optimize the outpatient regimen.

There is no established role for high-dose ICSs in acute asthma. However, ICSs play a pivotal role in achieving outpatient asthma control, and patients discharged from the ED or hospital should be started on an ICS-based treatment program.

Other Therapies

Aminophylline does not confer additional bronchodilation in adults compared to standard care with β_2 -agonists. It increases the frequency of adverse effects such as tachyarrhythmias and should only be used in refractory cases.

The safety and efficacy of IV MgSO_4 in adults treated for acute asthma in the ED was the subject of a recent meta-analysis.¹³ The results demonstrate that a single infusion of 1.2 g or 2 g IV MgSO_4 over 15 to 30 minutes reduces hospital admissions and improves lung function in adults with acute asthma who have not responded adequately to supplemental oxygen, SABAs, and IV corticosteroids. There is no established role for inhaled MgSO_4 in acute asthma.¹⁴

There are insufficient data to recommend leukotriene modifiers in acute asthma. The most compelling data come from randomized trials of IV montelukast in adults, but the IV formulation is not available in the United States. There is no benefit to adding oral montelukast to conventional therapy.¹⁵

Methodologic differences, small patient numbers, and failure to control for upper airway obstruction have plagued studies of heliox. Taken in sum, the data do not support its routine use in acute asthma. However, heliox may be reasonable in more severe cases. In addition, data suggest that heliox as a driving gas for nebulized SABAs improves PEFRs and decreases hospital admissions in patients with severe attacks.¹⁶

NONINVASIVE VENTILATION

Despite the common and increasing use of noninvasive ventilation (NIV) in patients with acute asthma, limited data are available to inform its use in this setting. In one small, randomized trial, the addition of NIV to standard therapy accelerated improvement in lung function, decreased the inhaled bronchodilator requirements, and shortened the ICU and hospital lengths of stay.¹⁷ NIV decreases the work of breathing and may allow for more effective delivery of bronchodilators.

Noninvasive ventilation includes the use of low levels of nasal continuous positive airway pressure (CPAP) of 5 to 7.5 cm H_2O or, more commonly, bilevel positive airway pressure (BiPAP). One approach to BiPAP use is to start with 8 cm H_2O inspiratory pressure support and 3 cm H_2O of expiratory positive airway pressure. Pressures are adjusted as required to achieve common endpoints of respiratory rate (RR) below 25/min and tidal volume above 7 mL/kg.¹⁸ Noninvasive ventilation should be used only in alert, cooperative, and hemodynamically stable patients.

INTUBATION AND MECHANICAL VENTILATION

Respiratory arrest or impending arrest (e.g., extreme exhaustion, a quiet chest, progressive hypercapnia, and altered mental status) are indications for intubation. A common problem in the immediate postintubation period is hypotension, which stems from sedation and paralysis, hypovolemia, overzealous mechanical ventilation and possible tension pneumothorax.

Inappropriately fast respiratory rate during mechanical ventilation results in inadequate exhalation time and dangerous levels of dynamic hyperinflation. Clues to this condition include excessive efforts required to deliver manual breathes during Ambu bag ventilation, high airway pressures, hypotension, and tachycardia. When critical-dynamic

hyperinflation is suspected, a trial of hypopnea (2-3 breaths/min) or apnea in a well-oxygenated patient for 30 to 60 seconds is both diagnostic and therapeutic. This maneuver lowers lung volumes and airway pressures and increases cardiac preload to help regain cardiopulmonary stability. Close inspection of the chest radiograph is mandatory to rule out unilateral or bilateral pneumothorax.

Initial Ventilator Settings

Expiratory time (T_e), tidal volume (V_t), and the severity of airway obstruction determine the level of dynamic hyperinflation during mechanical ventilation.^{19,20} Expiratory time is determined by minute ventilation and the inspiratory flow rate. Lowering the respiratory rate prolongs T_e and allows for more complete exhalation (Fig. 69-2). The additional volume of gas emptied by this strategy may be small because of low expiratory flow rates, but even small changes in lung volume may be clinically relevant. Increasing the inspiratory flow rate may also prolong T_e . However, high inspiratory flow rates increase peak airway pressures and may worsen patient-machine synchrony. Furthermore, high inspiratory flow rates may increase the respiratory rate in spontaneously breathing patients and thereby actually decrease T_e . On the other hand, if the inspiratory flow is too low, T_e falls and lung volumes increase.

A reasonable choice for initial settings is an inspiratory flow rate of 60 LPM and an initial minute ventilation of 7 to 8 L/min in a 70-kg patient to avoid dangerous levels of dynamic hyperinflation.²¹ This goal can be achieved by choosing volume-controlled ventilation (VCV) with an RR between 12 and 14/min and a V_t between 7 and 8 mL/kg. In spontaneously breathing patients, a low level of set PEEP (e.g., 5 cm H_2O) decreases the inspiratory work of breathing by decreasing the pressure gradient required to overcome auto-PEEP, without aggravating lung inflation. Theoretically, pressure-controlled ventilation (PCV) may deliver more uniform distribution of ventilation than VCV, but the delivered V_t is more unstable with PCV and is affected by changes in the degree of bronchoconstriction.²² No data support AC

over SIMV with pressure support (PS) for major clinical outcomes in a broad range of patients,²³ but AC is more commonly used.³

Assessing Lung Inflation

The degree of dynamic hyperinflation is central to ventilator adjustments, but measuring lung volumes is challenging in clinical practice. The only validated method is to measure the volume gas at end inspiration, termed V_{ei} , by collecting expired gas from total lung capacity (TLC) to functional residual capacity (FRC) during 40 to 60 seconds of apnea. Although V_{ei} may underestimate air trapping in the presence of slowly emptying lung units, a V_{ei} greater than 20 mL/kg correlates with barotrauma.²¹ The utility of this measure is limited by the need for paralysis and expertise with expiratory gas collection. Alternate measures of lung inflation include the single-breath plateau pressure (Pplat) and auto-PEEP. Accurate measurements of Pplat and auto-PEEP require patient-ventilator synchrony and the absence of patient interference. Paralysis is generally not required. However, neither pressure has been validated as a predictor of outcome. Pplat (or lung distention pressure) is an estimate of average end-inspiratory alveolar pressure that is determined by briefly stopping flow at end inspiration (Fig. 69-3), but Pplat is also affected by properties of the chest wall and abdomen. Pplat is commonly limited to ≤ 30 cm H_2O .

Auto-PEEP is the lowest average alveolar pressure achieved during the respiratory cycle. It is obtained by measuring airway opening pressure during an end-expiratory hold maneuver (see Fig. 69-3). The persistence of expiratory gas flow at the beginning of inspiration (which can be detected by auscultation or flow tracings) also suggests auto-PEEP (see Fig. 69-2). Auto-PEEP may be underestimated when there is poor communication between alveoli and the airway opening.

Ventilator Adjustments

Although adjusting ventilator settings according to Pplat has not been validated in controlled trials, we recommend limiting Pplat as a general principle of management and suggest the following approach (Fig. 69-4). If initial ventilator settings result in Pplat above 30 cm H_2O , we lower the respiratory rate to decrease Pplat below 30 cm H_2O . While this maneuver may result in hypercapnia, this is generally well

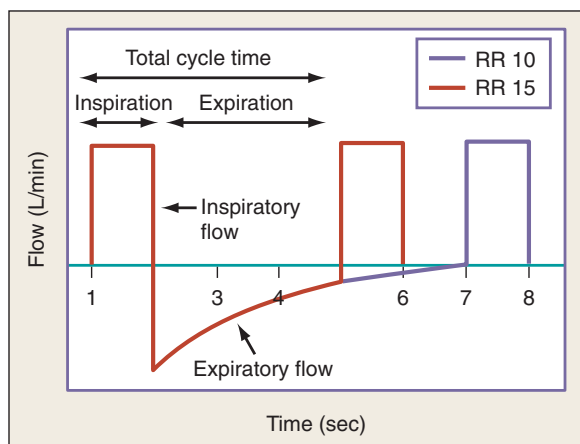


FIGURE 69-2 ■ Effects of changing respiratory rate (RR) on expiratory time (T_e) with a V_t of 1000 mL and a constant inspiratory flow rate of 60 LPM (1 LPS). Note that with RR of 15/min, total cycle time (amount of time allowed for one complete breath) is 4 seconds. Inspiratory time (T_i) is 1 second, and T_e is 3 seconds, resulting in an I:E of 1:3. Note that the expiratory flow persists at the time of the next delivered breath (as demonstrated by failure of the exhalation flow tracing to return to baseline or zero flow), suggesting the presence of auto-PEEP. By lowering RR to 10/min total cycle time increases to 6 seconds, and T_e is 5 seconds, resulting in an I:E of 1:5. Lower RR allows for greater exhalation of the delivered breath and lower end-expiratory plateau pressure (not shown), although effects are modest because of low end-expiratory flow rates.

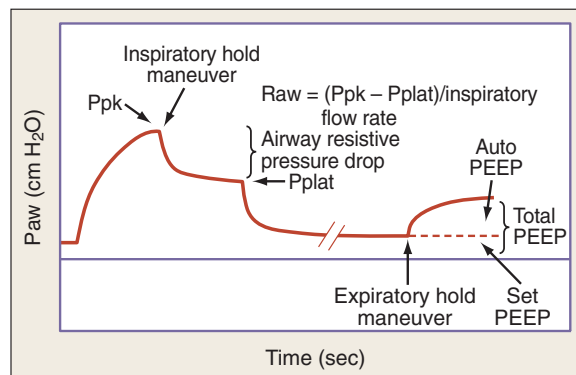


FIGURE 69-3 ■ Pressure-time tracing during mechanical ventilation demonstrating measurement of peak inspiratory pressure (Ppk), plateau pressure (Pplat), and auto-PEEP. While delivering a constant inspiratory flow (not shown), airway pressure (Paw) increases to Ppk, the sum of airway resistive pressure and Pplat. Airway resistive pressure and Pplat are determined by an inspiratory pause during which inspiratory flow is temporarily stopped to eliminate airway resistive pressure, allowing Paw to fall from Ppk to Pplat. If inspiratory flow is set at 60 L/min, the resistance pressure drop equals airway resistance (Raw) in units of cm H_2O /L/sec. An end-expiratory hold maneuver is performed to measure auto-PEEP. During this maneuver, Paw increases by the amount of auto-PEEP present. Note that end-inspiratory and end-expiratory hold maneuvers are performed on different breaths.

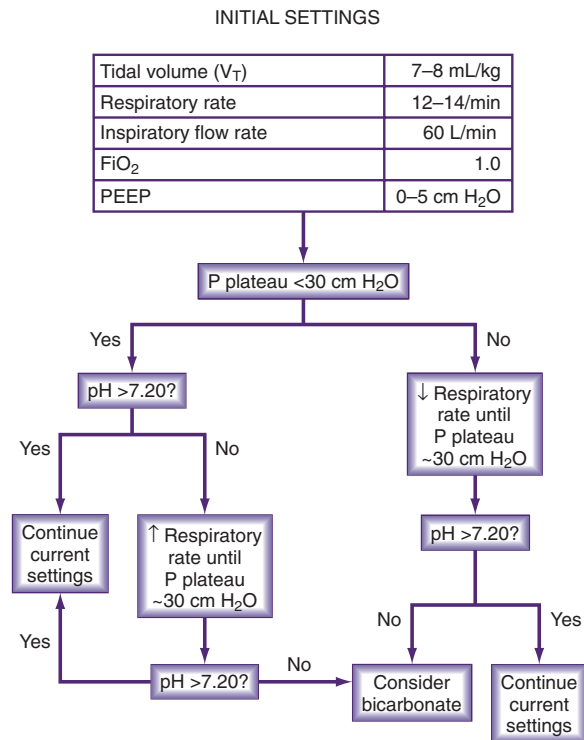


FIGURE 69-4 ■ Recommendations for initial ventilator settings and subsequent ventilator adjustments based on Pplat (end-inspiratory plateau pressure) and arterial pH in patients with severe asthma exacerbation.

tolerated. Anoxic encephalopathy and myocardial dysfunction are contraindications to permissive hypercapnia because of the potential for hypercapnia to dilate cerebral vessels, decrease myocardial contractility, and constrict the pulmonary vasculature. Lowering the respiratory rate may not increase $Paco_2$ as much as expected if it decreases hyperinflation and lowers dead space. If hypercapnia results in a blood pH of less than 7.20 and the respiratory rate cannot be increased because of the Pplat limit, we consider an infusion of sodium bicarbonate, although this has not been shown to improve outcome. If Pplat is less than 30 cm H_2O and pH is less than 7.20, the respiratory rate can be safely increased until Pplat reaches the 30-cm H_2O limit. Of note, strategies aimed at lowering Pplat are also expected to lower auto-PEEP.

Whether this strategy decreases the risk of barotrauma is unknown. One study of barotrauma in patients mechanically ventilated with limited V_t and airway pressures included 79 patients with asthma.²⁴ Five of these patients (6.3%) developed barotrauma. Tidal volumes and airway pressures did not differ between patients with and without barotrauma.

Sedation and Paralysis

Sedation improves patient comfort and safety and patient-ventilator synchrony. In patients who may be extubated within hours, propofol is recommended because it can achieve deep sedation while allowing for rapid reversal after discontinuation. Benzodiazepines are less expensive alternatives but are associated with a less predictable time to awakening and delirium. To provide amnesia, sedation, analgesia, and a suppressed respiratory drive, an opioid can be added to either propofol or a benzodiazepine. Daily interruption of sedatives and analgesics helps avoid undue accumulation.

Paralysis is indicated when safe and effective mechanical ventilation cannot be achieved by sedation and analgesia alone. The drug of choice is cisatracurium, which is essentially free of cardiovascular effects, does not release histamine, and does not rely on hepatic and

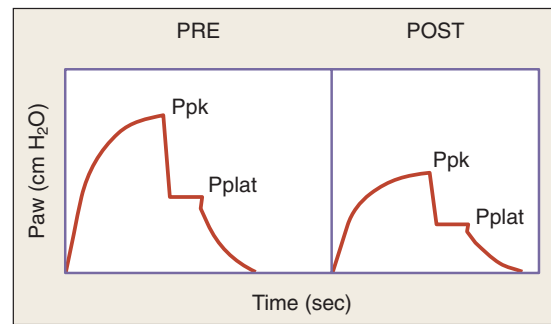


FIGURE 69-5 ■ Pressure-time tracings before and after successful administration of a bronchodilator. Note the drop in both airway resistive pressure and end-expiratory plateau pressure (Pplat), reflecting increased airway diameter and decreased lung inflation, respectively.

renal function for clearance. Paralytics have been associated with additional complications including myopathy, venous thromboembolism, and ventilator-associated pneumonia and should be discontinued as soon as possible.

Use of Bronchodilators During Mechanical Ventilation

Controlled trials are needed to inform the optimal use of bronchodilators in intubated patients and to provide evidence for or against current recommendations. Intubated patients generally require higher drug dosages to achieve a clinical effect. This may reflect the refractory nature of these patients or inadequate dose or delivery. Whether bronchodilators are administered by metered-dose inhaler (MDI) or nebulizer, patient-ventilator synchrony helps to optimize delivery. When MDIs are used during mechanical ventilation, a spacing device on the inspiratory limb of the ventilator is mandatory. When nebulizers are used, they should be placed close to the ventilator, and in-line humidifiers should be stopped during treatments. Dropping the inspiratory flow rate during nebulization helps minimize turbulence, but this strategy may worsen the extent of hyperinflation and should be time-limited.

Regardless of whether an MDI with spacer or nebulizer is used, higher drug dosages are required, and there should be a measurable fall in the peak-to-pause airway pressure gradient after bronchodilator delivery (Fig. 69-5). If no measurable drop in airway resistance occurs, then the patient may be refractory to bronchodilators, the delivery and/or dose of drug may be suboptimal, or there is another cause of fixed elevated airway resistance such as a kinked or plugged endotracheal tube.

Other Considerations

Rarely, the above management strategies fail to stabilize the patient. In these situations, general anesthetic bronchodilators may reduce peak pressures and $Paco_2$, but these agents are associated with hypotension and arrhythmias, and their benefits are short lived. Heliox delivered through the ventilator circuit may also decrease the peak pressure and $Paco_2$, but its use requires significant institutional expertise and planning. Limited evidence supports the use of mucolytic agents and even bronchoscopic lavage to help clear tenacious secretions. Importantly, a growing body of evidence demonstrates the successful use of extracorporeal life support in refractory cases with life-threatening DHI or respiratory acidosis despite optimal pharmacologic and ventilator management.

Extubation

Extubation criteria have not been validated for patients with acute asthma. One approach is to perform a spontaneous breathing trial

once Paco_2 normalizes without significant hyperinflation, airway resistance is $<20 \text{ cm H}_2\text{O/L/sec}$, mental status is acceptable, oxygen requirements are not excessive, PEEP is $\leq 5 \text{ cm H}_2\text{O}$, hemodynamics are stable, and secretions are not excessive. Patients with labile asthma may meet these criteria quickly after intubation; more commonly, 24 to 48 hours of treatment are required. After extubation, observation in an ICU is recommended for an additional 12 to 24 hours.

KEY POINTS

1. Failure to achieve control in the outpatient arena underlies many asthma exacerbations.
2. Severe exacerbations are characterized by diaphoresis, upright positioning, inability to speak in long sentences, use of accessory muscles, a widened pulsus paradoxus, and normo- or hypercapnia. Altered mental status, paradoxical breathing, bradycardia, and a quiet chest warn of imminent respiratory arrest.
3. Acutely ill asthmatics respond variably to inhaled β -agonists. Frequent (or continuous) administration of albuterol is required in refractory patients. Addition of ipratropium bromide to albuterol may confer additional benefit in patients with severe attacks.
4. Systemic steroids are indicated for severe asthma exacerbations.
5. Limited data support the use of noninvasive ventilation (NIV) to decrease inspiratory work of breathing in select patients.
6. Postintubation hypotension suggests inadequate expiratory time causing lung hyperinflation and decreased cardiac preload. A trial of apnea or hypopnea is both diagnostic and therapeutic in this setting. Tension pneumothorax is a concern in this clinical setting.
7. During mechanical ventilation, prolong the expiratory phase by setting low minute ventilation and an adequate inspiratory flow rate. Assess lung hyperinflation by measuring plateau pressure; if necessary, accept moderate hypercapnia to decrease lung hyperinflation.
8. Avoid prolonged paralysis and sedation during mechanical ventilation.
9. Establish a program to assess and achieve asthma control at the time of discharge to help prevent future exacerbations.

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■ References for this chapter can be found at expertconsult.com.

POSTEXACERBATION MANAGEMENT

The importance of education, adherence to controller agents, environmental control, and close follow-up cannot be overstated. Patients who have experienced severe asthma exacerbations are at risk for subsequent attacks and asthma-related death. In this regard, a tri-society task force report provides recommendations for antiinflammatory treatment after discharge and follow-up after acute asthma episodes.^{25,26}

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Chronic obstructive pulmonary disease (COPD) is a major cause of death and disability worldwide and is one of the most common reasons for intensive care unit (ICU) admission. Several monographs review this complex disorder in some detail.^{1,2} The intensivist's view of COPD is predominantly physiologic, focusing on the impact of the disrupted lung function on the individual's normal homeostatic mechanisms. Although many important insights that have shaped our understanding of COPD have come from ICU studies, other aspects of this disorder must be considered if a rational approach to COPD management is to be developed.

Access to ICU care for sick COPD patients remains relatively inequitable among different healthcare systems. In North America and parts of Western Europe, most patients are offered ICU care, but in other relatively developed healthcare systems (e.g., in the United Kingdom), this is not the case. Even physicians in the same healthcare system differ significantly in their selection of patients for ICU referral.³ These choices may be influenced by local resource availability, but they are also conditioned by the pessimistic view of the outcome achievable with this treatment intervention. However, poor response to treatment in the ICU is not universal, and extended periods of mechanical ventilation are not invariably required to manage patients with COPD⁴ successfully. Nevertheless, intensivists often take a particularly bleak view of the prognosis of COPD patients compared with others entering their units. In one prospective study, intensivists estimated the survival of the sickest COPD patients to be 10% at 180 days post admission, when in fact it was 40%.⁵ In a survivor population after mechanical ventilation, 96% were happy to have received ventilator support, despite their continuing physical problems.⁶ Survival appears to relate more to the severity of the acute illness, such as higher acute physiology scores, longer preceding hospital length of stay, the level of consciousness, and cardiac dysrhythmia, rather than premorbid factors such as age, forced expiratory volume (FEV₁), and functional capacity.⁷ Clearly, decisions about ventilator support should not be made in the emergency department without sufficient medical information or a proper discussion with the family, something that was seen in only a minority of cases in the 2014 England and Wales national audit hospitalizations due to COPD.⁸

DEFINITION AND NATURAL HISTORY

Although the most appropriate definition of COPD has been debated, it has less of an impact in the context of ICU care, where acute hospitalization is usual only in cases of severe and well-established disease. The currently favored definition, developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), is as follows:

*"Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles and gases. Exacerbations and comorbidities contribute to the overall severity in individual patients."*⁹

The emphasis here is on incompletely reversible airflow obstruction that is persistent and progressive though the importance of comorbidity and exacerbations is increasingly recognized; the latter being the

usual contact point for intensive care specialists. Symptoms and disability usually parallel these processes, although some individuals can apparently cope with a severe degree of airflow limitation without seeking medical assistance. Such patients finally present to the emergency room when they develop a severe exacerbation of COPD. In this situation, it is wisest to offer ventilatory support until the patient has at least had a chance to improve with conventional medical therapy. More common is a patient whose progressive illness is accompanied by repeated exacerbations, events that identify an accelerated decline in both lung function and health status.^{10,11} Such patients have often been hospitalized previously, and their response to treatment is usually clearly established.

The usual inhaled particles or gases that produce COPD are a complex mixture of hydrocarbons and particulates derived from tobacco smoke. These are the principal causes of COPD in the United States and Western Europe,¹² although other factors, such as poor lung function during childhood and childhood respiratory illness, bronchial hyperresponsiveness, self-reported asthma, and low birth weight, may also be important.¹³ The associated inflammatory changes, which persist when smoking stops,^{14,15} are thought to explain the airway and parenchymal destruction, as well as fibrosis within the lung.

The natural history of COPD explains why the number of patients presenting for ICU care has not diminished in the last three decades as might be expected, given the overall reduction in tobacco consumption in Western countries. This is illustrated by the classic study of Fletcher and Peto, which has now been confirmed by longitudinal data from the Framingham study^{16,17} (Fig. 70-1). Although the rate of decline of lung function is reduced in individuals who stop smoking, the lung function that is already lost can never be regained. Moreover, even if the rate of decline of lung function returns to normal, these patients are still more likely to experience disability as they age. Thus, in an aging population that contains many former smokers, a significant number will still develop complications of COPD that require ICU care. The important role of comorbidities in COPD has now been recognized.^{18,19} Most patients with significant symptoms due to COPD have at least one if not multiple comorbid diseases, especially cardiovascular problems.²⁰

PATHOLOGY

The pathologic features of COPD depend on the stage of the illness and the part of the lung examined.²¹ Central airways show mucous gland hypertrophy and goblet cell metaplasia, whereas more peripheral airways show variable combinations of smooth muscle hypertrophy, peribronchial fibrosis, luminal occlusion by mucus, and enlarged lymphoid follicles. Alveoli are often but not invariably enlarged by the loss of alveolar walls, with an attendant loss of support for the small non-cartilaginous airways in this region of the lung. There is evidence of persistent inflammation, with the presence of neutrophils in the airway lumen and macrophages in the airway wall. CD8⁺ T lymphocytes are more prominent in this response than in bronchial inflammation of an asthmatic type, although intermediate states appear to exist.²² Inflammatory cells are also present adjacent to breaks in the alveolar wall.²³ Overall, as the clinical and spirometric severity of the disease increases, so do the numbers of each cell population involved in the

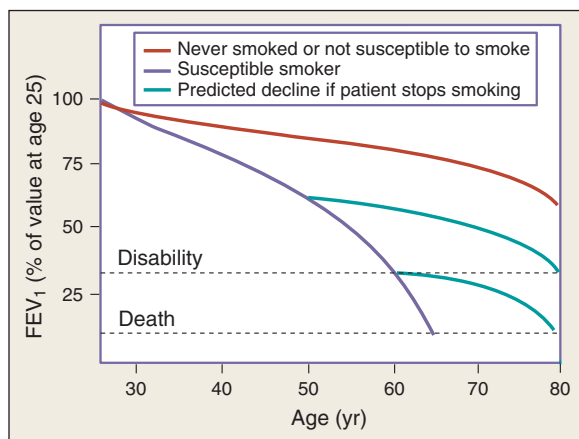


FIGURE 70-1 ■ Natural history of chronic obstructive pulmonary disease and the effect of smoking cessation. Compared with lung function standardised to age 25, smokers show an accelerated rate of decline in forced expiratory volume (FEV_1), which returns to more normal values when they stop smoking. However, they are operating at a lower FEV_1 than predicted for their age, and the physiologic decline continues. This explains why older ex-smokers can present to the ICU with severe disease despite years of abstinence. (Adapted from Fletcher C, Peto R. The natural history of chronic airway obstruction. *BMJ* 1977;1(6077):1645-8.)

inflammatory process.²⁴ In addition, extraluminal lymphoid follicles develop containing $CD4^+$ lymphocytes, possibly reflecting a response to repeated infective exacerbations.²⁴ Recent work has linked elements of this host immune response to the lung microbiome assessed using DNA sequencing.²⁵ Data obtained during exacerbations, though limited, support an increased role for neutrophils and, surprisingly, eosinophils,²⁶ with ongoing trials examining blood eosinophil count as a biomarker to determine use of corticosteroids during COPD exacerbations.²⁷

■ PHYSIOLOGY

The pathologic changes described above combine to produce the characteristic diagnostic finding of reduced FEV_1 at a given lung volume, which is usually assessed on a time basis as an FEV_1 /forced vital capacity (FVC) ratio of less than 0.7. Technically, this should be 70% of the age-adjusted normal value for this ratio, as lung elastic recoil declines with age, even in healthy individuals.

COPD affects all aspects of lung function, but its primary impact is a change in lung mechanics. This is traditionally analyzed regarding the static (no flow) and dynamic (flow) properties of the respiratory system.²⁸ Since chest wall mechanics are believed to be normal in COPD (although they are seldom measured directly), changes in the pressure-volume characteristics of the respiratory system are determined by alterations in lung compliance, often attributed to the loss of elastic recoil due to emphysema. How large a role this plays in changes in tissue compliance is not known. The resulting steeper slope, early onset inspiratory plateau, and increase in end-expiratory lung volume are typical of the pressure-volume relationships in patients with COPD. Changes in end-expiratory lung volume and increases in residual volume change the chest wall geometry and favor a lower, flatter diaphragm, as well as a more horizontal rib cage. These changes, in turn, impair the inspiratory muscles' ability to develop pressure and increase the overall work of breathing.²⁹ Expiratory muscle activation is common in more severe COPD^{30,31} even at rest and provides a useful clinical marker of respiratory distress. The dynamics of the respiratory system are influenced by static properties but also differ significantly

between inspiration and expiration. Maximum inspiratory flow is affected by inspiratory resistance, as well as by the inspiratory muscles' ability to develop pressure (and thus indirectly by chest wall geometry). Maximum expiratory flow is influenced by expiratory pressure generation and, more importantly, by the onset of volume-related airflow limitation, best described by the maximum expiratory flow-volume loop. As lung volume falls during expiration, airways close or become flow limited. Thus, the flow at a specific lung volume is reduced. Although an assessment of flow (FEV_1) relative to total volume change during expiration (FVC) is useful in defining COPD, an assessment of tidal flow limitation is more helpful in determining the degree of dyspnea experienced by the patient.³² More attention is now being paid to the determination of expiratory flow limitations under tidal conditions. In the past, detection was difficult, involving invasive measurements or a reliance on body plethysmography, which tended to overestimate the incidence of tidal expiratory flow limitation. The development of the negative expiratory pressure test and, more recently, within-breath variation in respiratory system reactance has changed this.³³ The within-breath method assesses more breaths, is less prone to observer error, and is likely to be automated in the future for ICU application.³⁴

In general, the lower the FEV_1 , the greater the likelihood that expiratory flow limitation is present. However, some COPD patients are not flow limited on every breath and regulate their end-expiratory lung volume to try to minimize this. When respiratory drive rises (e.g., during exercise), during disease exacerbations, or when minute ventilation increases to maintain gas exchange during ventilator weaning, this resting variation in expiratory lung volume is likely to decrease. If expiratory flow and hence tidal volume are to increase, end-expiratory lung volume must rise, further increasing the work of breathing and the sensation of respiratory distress. This process, described as *dynamic hyperinflation*, has been clearly demonstrated during exercise and can be lessened by bronchodilator treatment that aids lung emptying.³⁵

In the ICU, patients have a high respiratory drive during weaning and adopt a rapid, shallow breathing pattern. Total respiratory muscle work increases, in part because of the increased operating lung volumes but also due to the presence of intrinsic positive end-expiratory pressure (PEEPi). This represents the pressure that must be developed to overcome residual expiratory driving pressure before inspiratory flow can begin.³⁶ What is clear is that the overall impairment of mechanical function in COPD is substantial and that both static and dynamic properties interact. This concept is best captured by the time constant of the respiratory system, which is the product of the total respiratory system resistance in compliance. This is greatly lengthened in COPD and helps explain why lung emptying is delayed and dynamic hyperinflation occurs. There is substantial evidence of regional inhomogeneity in more severe COPD. Differences in the regional time constants explain why COPD patients are prone to barotrauma during mechanical ventilation, despite seemingly acceptable peak inspiratory pressures, as well as why gas exchange can be quite disordered in this population.

Gas Exchange

Arterial hypoxemia is common in COPD but becomes clinically significant only when the partial pressure of oxygen in arterial blood (P_{aO_2}) falls below 60 mm Hg, a problem largely confined to patients with an FEV_1 below 35% of their predicted value. It arises predominantly due to ventilation-perfusion mismatching, often worsens during exercise, and is readily corrected by a small increase in the inspired oxygen concentration, unless the situation is made worse by secretion retention or severe pneumonia.³⁷ Arterial hypercapnia is seen in some but not all hypoxemic patients who are clinically stable, but it is more frequent, at least temporarily, in hospitalized individuals.³⁸ A combination of ventilation-perfusion mismatching due to an increase in physiologic dead space and a degree of effective alveolar hypoventilation explains this phenomenon. Acute increases in the partial pressure of arterial carbon dioxide (P_{aCO_2}) precipitate respiratory acidosis, a more

reliable guide to prognosis and the need for ventilation than the PaCO_2 itself.^{39,40}

Control of Breathing

Despite years of study, there is no conclusive evidence that ventilatory control is abnormal in COPD patients. However, the response to sustained mechanical loading appears to be variable in healthy subjects⁴¹ and may explain why some individuals adopt the breathing patterns they do. Traditional techniques of studying respiratory control, which involve stimulation with exogenous CO_2 or nitrogen, suggest that respiratory drive is reduced. However, studies using mouth occlusion pressure techniques or recording the electrical activation of inspiratory muscles suggest that respiratory drive is elevated, even in those COPD patients who tolerate relatively high levels of CO_2 .^{42–44} Studies of breathing patterns have been more instructive. In general, the lower the tidal volume, the higher the PaCO_2 .⁴⁵ This is because the ratio of dead space (it is a fixed, predominantly anatomically determined volume) to tidal volume increases as the latter is reduced. Small tidal volumes are accompanied by an increased respiratory frequency to maintain the somewhat higher-than-normal level of minute ventilation. The resulting shortening of inspiratory time is also associated with hypercapnia.⁴⁵ The system appears to be regulated to minimize peak inspiratory pressure generation, even at the cost of impaired gas exchange. There are theoretical reasons for believing that this is both energy efficient and likely to minimize the occurrence of inspiratory muscle fatigue.⁴⁶ This also explains the usefulness of rapid, shallow breathing as an index of weaning failure when neuromechanical coupling in the respiratory system is under considerable stress.⁴⁷

Pulmonary Circulation

In the past, considerable attention was paid to the determination of pulmonary artery pressure in COPD patients, but this is now thought to be less important. Undoubtedly, pulmonary artery pressure increases by day and at night⁴⁸ in hypoxemic COPD patients, reflecting a combination of hypoxic vasoconstriction and pulmonary vascular remodeling. How important this is in the daily limitation of exercise reported by these patients is not clear, but it is known that treatment with domiciliary oxygen prevents disease progression⁴⁹ and may even reduce pulmonary artery pressure. More specific attempts at therapy, including treatment with vasodilators, phosphodiesterase enzyme type V (PDEV) inhibitors, and nitric oxide (studied inside and outside the ICU) have been unsuccessful, usually resulting in unacceptable worsening of ventilation-perfusion mismatching.⁵⁰ Further investigation and treatment is reserved for the small number of patients (<5%) who have severe pulmonary hypertension that is disproportionate to their COPD severity⁵¹ with an assessment of pulmonary hypertension now not part of a routine evaluation in COPD patients, but its occurrence is important to note when interpreting changes in central venous pressure in instrumented patients.

SYSTEMIC EFFECTS

There is good evidence that systemic (extrapulmonary) factors are important in COPD. Patients with a reduced body mass index die sooner than better-nourished individuals with a similar degree of pulmonary function impairment, although those who can gain weight fare better.⁵² There are data to show that peripheral muscle function is impaired,⁵³ fiber type is altered,⁵⁴ and exercise is associated with increased oxidative stress.⁵⁵ The earlier concept of a specific COPD myopathy has now largely been abandoned, as the major burden falls on the lower limb muscles, with preserved function in the upper limb muscle groups. This likely reflects inactivity, which is worse in those with exacerbated COPD.⁵⁶ Weakness of the quadriceps muscle is an independent guide to a poor prognosis.⁵⁷ In contrast, while the wealth of circulating biomarkers in COPD appear to relate to mortality, they have contributed little to practical management so far.⁵⁸

EXACERBATIONS

An *exacerbation* of COPD is currently defined as sustained worsening of the patient's condition from the stable state, beyond normal day-to-day variation, that is acute in onset and necessitates a change in regular medication.⁹ The key feature is the sustained change from usual daily symptoms. The operational requirement for a change in treatment is more arbitrary but is almost always present in patients referred to ICU care. Disease exacerbation is the principal cause of ICU admission with COPD, and patients commonly have or are at risk of developing significant *respiratory failure*, defined as a PaO_2 below 60 mm Hg with or without an increase in PaCO_2 .⁵⁹ The most common causes of an exacerbation are listed in Table 70-1. Viral and bacterial infections are both relevant,⁵⁴ with rhinoviruses commonly reported in most series; *Hemophilus influenzae* and *Streptococcus pneumoniae* are the principal microbial pathogens.^{60,61} Some patients, particularly those with a regular cough and green sputum production, develop persistent lower respiratory tract colonization, making the interpretation of qualitative microbiology difficult.⁶²

Not all exacerbations of COPD have an infectious precipitant, and changes in the degree of atmospheric pollution can precipitate events in some patients.⁶³ The frequency of exacerbation rises as spirometric impairment worsens⁶⁴ and evidence from a large, longitudinal study shows that for an individual, frequency of exacerbation is remarkably stable year on year.⁶⁵

The physiologic consequences of increased airflow obstruction secondary to increased inflammation within the bronchial tree are summarized in Fig. 70-2. Whatever the precipitant, the key event appears to be a change in lung mechanics. Previously, attention focused on alterations in respiratory system resistance, but more recent data emphasize that airway narrowing and closure may be more important, particularly by producing changes in operating lung volumes (see earlier discussion). Observations in patients recovering from hospitalized exacerbations have shown progressive improvements in respiratory system reactance (a measure of inspiratory resistance and flow limitation) together with reductions in end-expiratory lung volume that are most evident in patients reporting less dyspnoea.⁶⁶

Pneumonia is an important reason for hospitalization in COPD, is more frequently seen in these patients than in others, and is associated with more severe outcomes.⁶⁷ Pneumonia is diagnosed more frequently in patients taking the inhaled corticosteroid, fluticasone propionate,⁶⁸ especially older patients with worse airflow obstruction.⁶⁹ These pneumonias are not necessarily associated with poor outcome in terms of mortality or health status⁶⁸ and are not seen with all types of inhaled corticosteroids.^{70,71} At present, the benefit of inhaled corticosteroid treatment, especially combined with a long-acting inhaled bronchodilator, outweighs the apparent risk of increased pneumonia events.

TABLE 70-1

Causes of Chronic Obstructive Pulmonary Disease Exacerbation

NEW INFECTION:

Bacterial (*Hemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*)

Change in an existing strain (e.g., *H. influenzae*)

Viral (influenza, rhinovirus, respiratory syncytial virus)

ATMOSPHERIC POLLUTION:

Sulfur dioxide, oxides of nitrogen

TEMPERATURE CHANGE:

Often related to pollution episodes

INTERCURRENT ILLNESS*:

Pneumonia, pulmonary embolus, pneumothorax

POSTOPERATIVE:

Especially after upper abdominal surgery

*Clinical presentation is dominated by the primary illness, but respiratory failure can occur.

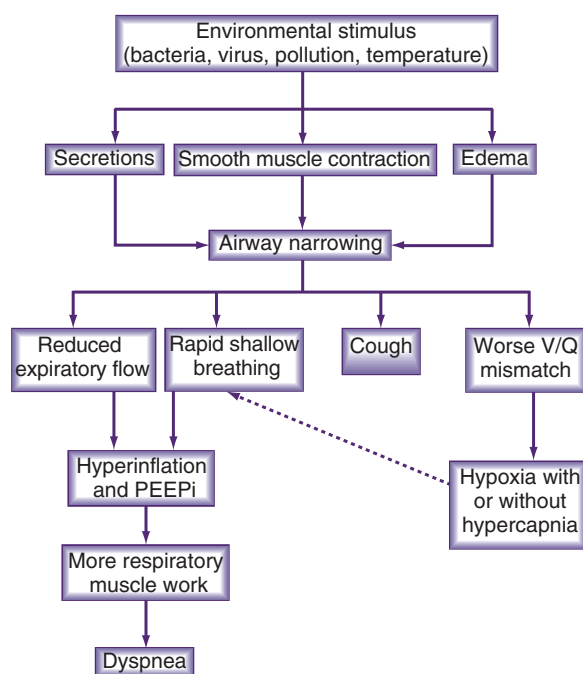


FIGURE 70-2 ■ Schematic of principal physiologic changes that accompany an exacerbation of chronic obstructive pulmonary disease. Note that deterioration in one area tends to produce worsening in other areas and leads to a downward spiral in functional abnormality. PEEPi, intrinsic positive end-expiratory pressure; V/Q, ventilation-perfusion.

TABLE 70-2

Indications for Invasive Mechanical Ventilation

| |
|---|
| Severe dyspnea, with use of accessory muscles and paradoxical abdominal motion |
| Respiratory frequency > 35 breaths/min |
| Life-threatening hypoxemia ($\text{PaO}_2 < 40$ mm Hg or $\text{PaO}_2/\text{FiO}_2 < 200$ mm Hg) |
| Severe acidosis ($\text{pH} < 7.25$) and hypercapnia ($\text{PaCO}_2 > 60$ mm Hg) |
| Respiratory arrest |
| Somnolence, impaired mental status |
| Cardiovascular complications (hypotension, shock, heart failure) |
| Other complications: metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion |
| Noninvasive positive pressure ventilation failure (or exclusion criteria) |
| FiO_2 , inspired oxygen fraction; PaCO_2 , partial pressure of carbon dioxide in arterial blood; PaO_2 , partial pressure of oxygen in arterial blood. |

■ INTENSIVE CARE UNIT REFERRAL

The need for ventilatory support is the primary reason for ICU referral among COPD patients. Although the various indications for mechanical ventilation (Table 70-2) vary in frequency from institution to institution, they represent the most common causes of ICU admission. Before referring a patient for ICU care, and especially for any form of ventilatory support, it is important to determine what degree of intervention is appropriate.

■ PRINCIPLES OF TREATMENT

Four general principles guide the management of COPD patients presenting acutely to the ICU, and each should contribute to shortening the duration of illness and stabilizing the patient physiologically until

either the natural course of the disease or the effects of therapy lead to its resolution.

Treat Precipitating Factors

Bacterial infection is the most common reason for ICU admission in COPD patients. There is now good evidence that antibiotics shorten the symptomatic period, even when patients are treated with corticosteroids⁷²; when given early, antibiotics are associated with lower mortality, fewer episodes of intubation, and shorter hospital stays.⁷³ Radiographic evidence of pneumonia likely requires a broadening of the antibiotic spectrum, but whether the infection is confined to the airways or involves the alveoli, antibiotic therapy should follow locally established guidelines designed to minimize the development of resistance within the ICU and to address known patterns of drug resistance in the community and the hospital. Broad-spectrum penicillins or, more commonly, cephalosporins are usually recommended, often with an intravenous macrolide. Colonization with methicillin-resistant *Staphylococcus aureus* is a frequent problem and requires particular vigilance in the selection of antibiotics. Likewise, excessive use of broad-spectrum agents can produce superinfection, such as *Clostridium difficile* diarrhea.

The 2009-10 H1N1 influenza A pandemic made the role of antiviral drugs clearer, and a meta-analysis showed that the early use of neuraminidase inhibitors (within 48 hours) was associated with a lower mortality rate, although this was not specific for acutely ill COPD patients.⁷⁴ In fact, the pandemic infection was not a particular problem for COPD patients, possibly reflecting prior partial immunity,⁷⁵ but if this virus is diagnosed, the use of antivirals such as oseltamivir is prudent. Similar considerations apply to other viral pneumonias.

Reduce Lung Volume and Increase Expiratory Flow

Agents that improve lung emptying, commonly by increasing airway caliber or preventing airway closure, interfere with the vicious circle of pulmonary hyperinflation. This has been demonstrated in stable patients using exercise as a model of hyperinflation,³⁵ but the data in spontaneously breathing COPD patients during exacerbations are much less satisfactory. Nonetheless, treatment with regular but high doses of short-acting nebulized β -agonists, such as albuterol or ipratropium (2.5-5 mg or 250-500 μg , respectively), is usually recommended. There is no clear evidence that one drug is better than the other,⁷⁶ and combination therapy is commonly used. Intravenous theophylline, or one of its derivatives, is often added to these regimens but is no more effective than a placebo infusion.^{77,78}

Reduce Pulmonary Inflammation

Several randomized, controlled trials have shown that oral corticosteroids shorten the duration of hospitalization and accelerate the improvement of postbronchodilator FEV_1 during an exacerbation of COPD.^{79,80} Patients randomized to treatment with oral corticosteroids were less likely to relapse during the subsequent month and showed a number of other benefits, although these did not always reach statistical significance.⁸¹ There is little detriment from giving a short (5-day) course of oral corticosteroids rather than a long (14-day) course and overall steroid dose is dramatically reduced.⁸² This has been confirmed in a meta-analysis.⁸³ In the ICU, corticosteroid treatment is often given peremptorily to patients on mechanical ventilation. Two recent studies have yielded conflicting results with one study using 10 days of tapering dose methylprednisolone showing a shorter period of ventilation and reduced noninvasive ventilation (NIV) failure,⁸⁴ while a larger study used up to 10 days of a higher dose prednisolone, showing no benefit but higher rates of hyperglycaemia.⁸⁵ A retrospective review of a dose of systemic corticosteroids used within the first 48 hours of admission to the ITU showed better lower ITU and hospital length of stay, shorter period of ventilation, less use of insulin,

and fewer fungal infections in COPD patients given less than 240 mg methylprednisolone per day.⁸⁶ Caution should be exercised because, in addition to the above effects, these individuals are often at risk for relatively acute-onset corticosteroid myopathy.⁸⁷ In the absence of a large randomized controlled trial and recognizing that 94% of patients in the retrospective review were prescribed systemic corticosteroids, it appears appropriate to use lower doses for shorter periods.

Manage Gas Exchange

It is relatively easy to improve oxygenation in an uncomplicated exacerbation of COPD.⁸⁸ Raising the inspired oxygen concentration to 28% to 35% is usually sufficient to achieve a P_{aO_2} greater than 90 mm Hg. However, this can be accompanied by an undesirable increase in P_{aCO_2} , with its accompanying respiratory acidosis. Such an increase in P_{aCO_2} impairs respiratory muscle function, at least during loaded breathing,⁸⁹ and often precedes more serious clinical deterioration, including impairment of consciousness. The reasons for this effect have been debated for many years, with some advocating a reduction in the respiratory drive from the carotid chemoreceptors and others citing a worsening ventilation-perfusion match as the cause.⁸⁸ Each view has evidence to support it, but the actual cause is likely a combination of both problems, with ventilation-perfusion mismatching being particularly important in severely ill patients and hypoventilation playing a larger role in those not yet sick enough to require intubation.⁹⁰

Although the phenomenon of oxygen-induced hypercapnia has been recognized for decades, it remains a real problem. In one large center in the United Kingdom, 34% of individuals exhibited evidence of oxygen-induced hypercapnia.⁴⁰ The use of high-flow oxygen in the emergency room is widespread, as is the false sense of security provided by a high oxygen saturation. Many intensivists have legitimate concerns about the failure to adequately oxygenate COPD patients with compromised circulation, along with the attendant risk of unanticipated mortality. However, the solution is to consider carefully the risks of excessive or insufficient oxygen in a given individual, rather than to adhere slavishly to one view or the other. Patients whose problems are predominantly due to COPD and who have a normal hemoglobin and preserved cardiac output can maintain adequate tissue oxygen delivery with an oxygen saturation as low as 85%, and they will do quite well if an arterial oxygen saturation (S_{aO_2}) of 90% to 93% is maintained. The modest increase in inspired oxygen needed to achieve this (often 24%-28%) is accompanied by less hypercapnia and may avoid the need for ventilatory support. However, if cardiac output is impaired (reduced blood pressure, poor peripheral circulation) or tissue metabolic demands are increased (e.g., in sepsis secondary to pneumonia), a higher S_{aO_2} will be required to ensure sufficient oxygen delivery. In this case, the consequences of any resultant hypercapnia, including the need for ventilatory support, must be accepted.

■ NONINVASIVE VENTILATION

This topic is reviewed in detail in Chapter 49, but some key issues relevant to COPD are worth emphasizing. Many of the data supporting the use of NIV were obtained in patients with hypercapnic respiratory failure due to COPD exacerbation, and several excellent reviews have analyzed these data.⁹¹⁻⁹³

NIV has a number of potentially beneficial effects in COPD. Intuitively, it seems reasonable to expect that it would increase tidal volume, improve CO_2 elimination, and hence reduce respiratory drive. Studies of gas exchange using a multiple inert gas elimination methodology confirmed that CO_2 elimination is increased, but overall ventilation-perfusion mismatch is not altered during NIV.⁹⁴ A more important effect is the unloading of the respiratory muscles, which are often close to fatigue conditions in severe episodes of respiratory failure. By assuming some of the additional work required to overcome intrinsic PEEP, NIV directly reduces the drive to breathe and the respiratory rate falls, which is a good prognostic feature.⁹⁵ Data from randomized, controlled trials suggest that there is a mean fall of 3.1 breaths per

TABLE 70-3

Efficacy of Noninvasive Ventilation Compared with Usual Care

| OUTCOME | NUMBER OF PATIENTS STUDIED | RELATIVE RISK (95% CONFIDENCE INTERVAL) | NNT |
|-------------------|----------------------------|---|-----|
| Treatment failure | 529 | 0.51 (0.38-0.67) | 5 |
| Death | 523 | 0.41 (0.26-0.64) | 8 |
| Intubation | 546 | 0.42 (0.31-0.59) | 5 |
| Complications | 143 | 0.32 (0.18-0.56) | 3 |

NNT, number needed to treat—the number of patients who must be treated to prevent this outcome in one individual.

minute (95% confidence interval: 4.3 to 1.9) with the institution of NIV in COPD patients.⁹³ This allows more effective emptying of the lungs and less dynamic hyperinflation. The resulting improvement in the intensity of breathlessness is usually a much earlier sign of successful NIV treatment in COPD than a change in blood gas tensions, which often lag behind evidence of clinical improvement.

Evidence-based reviews provide a reasonable series of recommendations based on the relative effectiveness of NIV. Key points, including the number of patients needed to be treated to prevent one significant event or complication, are shown in Table 70-3.⁹¹ NIV is associated with less treatment failure, lower mortality, fewer complications, and a lower intubation rate compared with conventional medical treatment. It reduces ICU or hospital stay by approximately three days and favorably influences gas exchange. With NIV, pH increases by a mean value of 0.03 (0.02-0.04), P_{aCO_2} falls by 3 mm Hg (5.9-0.23 mm Hg), and P_{aO_2} rises by 2 mm Hg (−2 to +6 mm Hg). The lower rate of nosocomial pneumonia associated with NIV is a particular advantage. No benefit was seen from the use of helium-oxygen mixture with NIV compared with oxygen alone.⁹⁶

Treatment failure, which occurs in 10% to 15% cases in many US hospitals,^{97,98} reflects an inability to adapt to NIV or progression of the underlying disease. Data suggest that patients likely to subsequently fail with NIV can be prospectively identified by a high blood sugar upon admission (irrespective of having diabetes), a raised respiratory rate, or a high APACHE 2 score. All of these variables are relatively effective predictors of risk, but combining them increases their discriminant power.⁹⁵ A more recent study confirmed the importance of acute physiology (APACHE 2 score) but also highlighted a higher failure rate and mortality if the individual had cancer.⁹⁷ In addition to its role in the acute phase of respiratory failure, NIV can be valuable as a “bridge” in helping patients wean from intermittent positive pressure ventilation. In an important multicenter prospective trial, Nava and colleagues randomized people who had failed a T-piece weaning trial to either NIV or further mechanical ventilation.⁹⁹ NIV was associated with fewer days of ventilatory support (10.2 versus 16.6, respectively), shorter ICU stay (15.1 versus 24 days), less nosocomial pneumonia, and better 60-day survival (92% versus 72%). These results were achieved in a unit with experience in NIV. The generic use of weaning by NIV has proven less successful, particularly if patients have a significant cardiac disease or established acute respiratory distress syndrome (ARDS).¹⁰⁰ However, further data from Spain have confirmed the value of this approach in hypercapnic patients limited primarily by COPD.^{101,102} When early extubation followed by NIV was compared with continued mechanical ventilation in a Cochrane review, the outcomes were superior in all areas.

Mechanical Ventilation

Mechanical ventilation should be considered when NIV is not appropriate or has failed. Patients with a pH below 7.25 are more likely to require this therapy, although most physicians now offer a trial of NIV

TABLE 70-4 Modes of Ventilation

| MODE | METHOD | COMMENT |
|--|--|---|
| Assist-control | Preset tidal volume, patient triggered with backup rate | Patient still performs substantial work of breathing; dynamic hyperinflation worsens this |
| Spontaneous intermittent mandatory ventilation | Preset number of breaths of a preset volume—patient does the rest | Patient still makes an effort during part of machine breath—involves more patient work, especially at low respiratory rates |
| Pressure support ventilation | Pressure set to augment each inspiration—tidal volume depends on patient effort, pulmonary mechanics, and pressure applied | Basis of noninvasive ventilation therapy; pressure titrated to a respiratory rate below 27 breaths/min; asynchrony with machine breaths a problem at high pressures |
| Proportional assist ventilation | Flow and volume generated proportional to patient effort | Experimental technique; requires accurate measurement of elastance and resistance + an intact drive to breathe; proven effective in COPD patients |

unless the patient is hemodynamically unstable or the treatment is contraindicated. Persistent significant hypoxemia despite treatment, hypotension, and impaired mental state are all predictors of imminent respiratory arrest and the need for intubation and institution of mechanical ventilation.

Ventilation Strategies

A wide range of ventilation strategies have been advocated for use in COPD, each with its proponents. However, none have shown a clear advantage over its competitors. Familiarity with the equipment in the context of COPD patients is probably more important than the relatively minor differences between ventilator modes. The most commonly used approaches, together with their proposed advantages, are summarized in [Table 70-4](#).

Assisted Ventilation and Weaning

As acidosis resolves and oxygen requirements fall, it is possible to reduce the degree of sedation and allow the patient to make some contribution to ventilation before weaning. Several modes of ventilatory support are available in these circumstances, and again, there is no specific advantage of one over another.^{103,104} There is an impression, however, that reliance on spontaneous intermittent mandatory ventilation prolongs subsequent weaning. Although not universally accepted, there are good data supporting the use of spontaneous breathing trials in clinically stable COPD patients to determine when they are ready to wean.¹⁰⁴⁻¹⁰⁶ The ability to sustain ventilation in the absence of increasing CO₂, worsening acidosis, or clinical distress (reflected by an increase in blood pressure, heart rate, or restlessness) is agreed to be a predictor of future weaning success. Although COPD patients are less likely to achieve these goals as early as other ICU patients, the reintubation rate in those who do meet these criteria is low.^{105,106} Unfortunately, breathing through the ventilator on a continuous positive airway pressure (CPAP) circuit may be associated with significant increases in inspiratory resistance,¹⁰⁷ and it is sensible to use pressure support to offset some of this additional respiratory work. This reflects the necessity of identifying patients who can be weaned using the ventilator

TABLE 70-5 Criteria for Weaning Failure

Increasing hypercapnia or worsening hypoxemia (<55 mm Hg)
pH < 7.32
Increased respiratory rate > 35 breaths/min
Increase in heart rate or blood pressure by 20% of baseline
Agitation, sweating, or impaired consciousness

alone and those who need more prolonged support. In the latter circumstance, weaning supported by NIV is particularly helpful.

A variety of predictors of weaning success have been developed to try to identify when successful weaning will occur. Unfortunately, none have proved entirely reliable and relatively few have been assessed prospectively. An empirical approach based on the criteria listed in [Table 70-5](#) is widely used. An aggressive policy toward weaning is justified in COPD patients because an inability to wean is invariably associated with a worse prognosis and prolonged ventilation.

NONVENTILATORY ISSUES

Therapy employed in spontaneously breathing patients is still required in those undergoing mechanical ventilation. High-dose nebulized bronchodilators are commonly used, alone and in combination,^{108,109} although it is important to pay attention to the details of drug delivery. If a metered dose inhaler is used instead, it should always be given with some form of spacer device for the same reason. Parenteral corticosteroids are commonly administered. This is not without hazard, particularly because of the real risk of myopathy, and this was reviewed earlier in the chapter.

Clearance of secretions is important in ventilated patients, and it is essential that the patient's hydration state be maintained. Whether specific mucolytic drugs such as *N*-acetylcysteine are helpful is unclear, and no good scientific studies to support or reject their use are available.

PROGNOSIS

The prognosis following an exacerbation of COPD is better than the gloomy outlook proposed by some physicians. Nonetheless, patients who experience exacerbations appear to have a more severe clinical course than those who do not, and they report a worse overall quality of life.¹¹⁰ Mortality after an ICU admission is significant, at least in recent North American series, 7.4% in patients treated with NIV and 16.1% in those treated with mechanical ventilation.⁹⁸ However, some groups have reported worse and individuals with COPD treated with long-term oxygen therapy who failed NIV and received mechanical ventilation had 23% in-hospital mortality and 45% 1-year mortality with 27% discharged to nursing care.¹¹¹ Patients with a low FEV₁, significant comorbidity, and a particularly poor performance status at home have the worst outlook.¹¹² These factors should be considered when decisions about the requirement for ventilatory support are made. However, as noted already, the physician's view of the very sick COPD patient can be unduly pessimistic. Exacerbations leave patients relatively immobile, and this has now been confirmed objectively.⁵⁶ The initial encouraging data concerning potential benefits from early rehabilitation have not been confirmed in a large RCT of patients hospitalized due to an acute COPD exacerbation but not ventilated. The intervention was robust and included aerobic and resistance training, neuromuscular electrical stimulation, a written self-management plan, and education. However, no reduction in readmission was seen in the following year.¹¹³

Changes in clinical practice continue to improve the outlook for COPD patients. The impact of NIV on their acute care has been enormous, as has closer adherence to evidence-based recommendations across the field of intensive care,¹¹⁴ something about which both practitioners and their patients can feel proud.

KEY POINTS

1. The prognosis of patients with chronic obstructive pulmonary disease (COPD) admitted to the ICU is better than commonly believed.
2. The burden of symptomatic COPD is likely to rise for several decades more, despite effective smoking cessation programs in many countries.
3. Small changes in forced expiratory flow are associated with significant impairment in lung mechanics, particularly airway closure and dynamic hyperinflation, and worse gas exchange.
4. Common upper respiratory tract pathogens and respiratory viruses precipitate most exacerbations of COPD. Treatment aimed at these agents is useful, but it is not as important as improving lung emptying and maintaining gas exchange until the acute insult resolves.
5. Oral and intravenous corticosteroids shorten the duration of an exacerbation and reduce the risk of relapse. However, high-dose treatment beyond 2 weeks provides no advantage and actually poses a risk, especially in ventilated patients.
6. Maintaining oxygenation is relatively easy, but there are risks of carbon dioxide retention and acidosis if high-flow oxygen is administered. An oxygen saturation between 91% and 93% ensures adequate tissue oxygen delivery if the cardiac output is stable.
7. Respiratory acidosis is a poor prognostic marker in COPD exacerbations and a strong indicator of the need for assisted ventilation.
8. Unless contraindicated, noninvasive ventilation (NIV) is the safest and most effective way of managing acute respiratory failure. More acidotic patients should be managed in an ICU with the option of endotracheal intubation and mechanical ventilation if NIV fails.
9. COPD patients meet conventional weaning criteria less frequently than other ICU patients do, but they are more likely to wean successfully when they do meet the criteria.
10. Seriously ill COPD patients should be encouraged to make advance directives, particularly after an ICU admission involving any form of ventilatory support.

■ References for this chapter can be found at expertconsult.com.

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Venous thromboembolism (VTE) comprises both deep venous thrombosis (DVT) and pulmonary embolism (PE). Intensive care unit (ICU) patients often have unique diagnostic and treatment issues related to VTE. Accurate risk stratification remains a critical component of the initial evaluation and treatment of patients who have acute PE. The primary treatment options for PE include anticoagulation and thrombolytic therapy, while catheter-based approaches, surgical therapy, and placement of an intravenous filter also play a role.¹⁻³

■ EPIDEMIOLOGY

VTE commonly complicates the course of hospitalized patients,⁴⁻⁶ especially those in the ICU⁷⁻⁸ and sometimes despite VTE prophylaxis.⁹ Acute PE remains an underdiagnosed condition, despite advances in diagnosis. In a study of trauma patients in an ICU, CT scans detected incidental PE in 24% of cases.⁷ A study of mechanically ventilated patients, undergoing chest CT unrelated to suspected PE, found PE in 18.7% of examined individuals.⁸

Studies of patients who received DVT prophylaxis in medical ICUs suggest that the existence of PE is detected in less than 2.5% of these populations.¹⁰⁻¹² Of note, a small proportion of patients will enter the ICU with undiagnosed proximal DVT.¹⁰ Studies of ICU patients who received DVT prophylaxis and underwent lower extremity venous compression ultrasound screening once to twice a week, and additional testing when clinically indicated, have a DVT incidence rate of 5.4% to 23.6%.^{9,10,13} In autopsy studies of critically ill patients, PE was found in 7% to 27%, and clinicians did not suspect PE in about one-third of these patients.¹⁴⁻¹⁸

PE causes approximately 100,000 to 180,000 deaths per year in the United States, and it ranks high among the causes of cardiovascular mortality.^{19,20} Most patients who die from PE remain undiagnosed during life,²¹ and many succumb suddenly or within a few hours of the acute event before therapy is initiated or takes effect.²² The mortality and morbidity of acute PE vary by clinical presentation, the presence of comorbid disease, and other underlying factors. Despite modern methods for diagnosis and treatment, PE continues to have a high mortality rate.²³⁻²⁵ During the first week after the diagnosis of PE, death and major bleeding occur more frequently than recurrent VTE.²³ Most deaths due to PE within the first 3 months of follow-up occur during the first week after diagnosis.²³ For example, in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), 10.5% of patients died during follow-up after diagnosis; 9 out of 10 (90%; 95%, 55.5%-99.7%) patients who died due to PE, died within 2 weeks of diagnosis.²⁶ In the Management and Prognosis in Pulmonary Embolism Trial (MAPPET), 9.6% of patients who had acute PE died during the hospital stay, and the majority (94.2%) of deaths were due to PE.²⁷ Overall, the majority of treated patients with PE survive and do not have a recurrent event or a major complication associated with therapy, although patients in the ICU typically have a more complicated course than others.^{12,28}

■ RISK FACTORS FOR PE

A method of classifying PE risk factors uses the categories of inherited, acquired, or unknown (idiopathic) (Box 71-1). Patients at risk for PE often have a combination of patient-related and setting-related

risk factors. Some risk factors are temporary or reversible, and others are permanent.^{29,30} The most common inherited risk factor for VTE includes gene polymorphisms (e.g., factor V Leiden and prothrombin gene G20210A), and less common abnormalities that lead to deficiencies of the natural anticoagulants protein C, protein S, and antithrombin.³¹⁻³³ The majority of patients with VTE do not require testing for such abnormalities, and most testing is not relevant in an ICU setting. Unprovoked (i.e., spontaneous or idiopathic) thrombosis, despite the absence of an inherited or acquired thrombophilia, predisposes patients to future thrombosis more than a history of provoked thrombosis due to a transient risk factor.²⁹ Acquired hypercoagulable states may arise secondary to malignancy, immobilization, infection, trauma, surgery, collagen vascular diseases, nephrotic syndrome, heparin-induced thrombocytopenia (HIT), disseminated intravascular coagulation (DIC), medications (e.g., estrogen), and pregnancy. Central intravenous catheters significantly increase the risk for DVT,³⁴⁻⁴¹ and femoral catheters especially increase the risk of DVT and associated PE.^{8,36,38} Hospitalized patients often have multiple risk factors for VTE, and most patients in the ICU have strong risk factors.^{8,13,29,34,42,43} The risk of VTE increases as the number of risk factors rises.^{32,44}

■ NATURAL HISTORY

Patients who do not receive treatment for acute PE may have a short-term mortality rate as high as 30%,⁴⁵ although a much lower rate is present in ambulatory patients.⁴⁶ Unselected patients with PE or VTE have a 30-day all-cause mortality rate of about 10%, based on registries and hospital discharge datasets.⁴⁷⁻⁵⁰ PE recurrence or progression may cause about half of the early deaths after the initial PE.⁵¹ While treated PE in normotensive patients who do not have evidence of right ventricular (RV) dysfunction has a short-term mortality rate of approximately 2%, the mortality rate increases as high as 30% in patients with shock and up to 65% in patients who present with cardiac arrest.^{4,12,50,52-55}

Patients have a reasonably low rate of VTE recurrence after treatment, especially while still in the ICU. Although the rate of recurrence is highest during the first few weeks after diagnosis, only about 2% of patients have recurrent VTE during that period.⁵⁶⁻⁵⁸ Patients with unprovoked VTE tend to have more recurrences than those who have an event provoked by a temporary risk factor.²⁹ In patients with acute PE and a subsequent recurrent VTE, the recurrent event typically occurs as PE instead of DVT.⁵⁹

Following an acute PE, about one-third of patients do not have complete resolution of thrombus within the first follow-up year, as determined by lung perfusion scintigraphy.⁶⁰⁻⁶² A small but significant proportion of patients with PE develop chronic thromboembolic pulmonary hypertension.⁶³

■ RISK FACTORS FOR DEATH AFTER PE

Older studies have associated hemodynamic decompensation after acute PE with an approximate three- to sevenfold increase in mortality.⁶⁴⁻⁶⁵ More recent large observational studies of PE have also described systolic arterial hypotension as the most significant prognostic indicator of poor outcome.^{23,27,50}

BOX 71-1**Common Risk Factors for PE in the ICU****CLINICAL RISK FACTORS**

Surgical and nonsurgical trauma, spinal cord injury
 Recent surgery
 Malignancy (risk varies based on malignancy)
 Nephrotic syndrome
 Heart failure
 Stroke; lower extremity paralysis
 Previous venous thromboembolism
 Age (>40 years, and increased risk with increased age)
 Obesity
 Pregnancy/postpartum
 Medications (e.g., estrogens, specific chemotherapeutic agents, erythropoietin-stimulating agents)
 Immobilization

ICU-ACQUIRED RISK FACTORS

Sepsis
 Central venous catheter
 Pharmacologic paralysis
 Respiratory failure
 Acute heart failure
 Mechanical ventilation
 Acute renal failure; dialysis
 Blood products (e.g., platelets, recombinant factor VIIa)
 Vasopressors

INHERITED OR ACQUIRED ABNORMALITIES

Factor V Leiden
 Prothrombin 20210A
 Protein C deficiency
 Protein S deficiency
 Antithrombin deficiency
 Antiphospholipid antibody syndrome
 Heparin-induced thrombocytopenia
 Myeloproliferative syndromes
 Dysfibrinogenemia

PATHOPHYSIOLOGY

An overall balance between thrombogenic stimuli and protective mechanisms is present under baseline physiologic conditions and prevents clinically meaningful thrombosis. The body's fibrinolytic system and natural anticoagulants typically prevent hypercoagulable states.⁶⁶ Categories of factors that predispose the development of venous thrombi include the activation of blood coagulation, vascular damage, and venous stasis (Virchow's triad). The protective mechanisms that counteract these thrombogenic stimuli include (1) the inactivation of activated coagulation factors by circulating inhibitors (e.g., antithrombin and activated protein C); (2) the clearance of activated coagulation factors and soluble fibrin/polymer complexes by the reticuloendothelial system and liver; and (3) dissolution of fibrin by fibrinolytic enzymes derived from plasma and endothelial cells and the digestion of fibrin by leukocytes. Impairment or deficiency within these systems may result in a hypercoagulable state and the formation of venous thrombi. The interaction between coagulation enzymes and cellular activity leads to thrombin generation and clot formation. Venous thrombi, composed predominantly of fibrin and red cells, have a variable and smaller component of platelets and leukocytes.⁶⁷

Thrombi may form in the veins, superficially (superficial vein thrombosis, SFVT) or deep (deep vein thrombosis, DVT). DVT may embolize to the lungs and lodge in the pulmonary arteries (i.e., PE). PE originates from thrombi in the deep veins of the lower extremities in at least 90% of patients.^{16,68,69} Most clinically important PE arise from thrombi in the popliteal or more proximal deep veins of the lower extremities, and usually, only part of the thrombus embolizes.⁷⁰ About half (i.e., 30% to 70%) of patients with PE detected by angiography also

have asymptomatic DVT of the lower extremities identified by a compression ultrasound.^{16,68,71-73} Asymptomatic PE occurs in at least 50% of patients with objectively documented symptomatic proximal lower extremity DVT.^{5,16} Other less common sources of PE include the deep pelvic veins, renal veins, inferior vena cava, right atrium and ventricle, and axillary veins. Air, fat, tumor, and foreign bodies may also embolize to the lungs.

Although many patients have asymptomatic PE, the acute clinical importance of PE depends on the embolic clot burden, the patient's cardiorespiratory reserve, and neurohumoral responses. PE may cause significant pulmonary and cardiovascular sequelae (Fig. 71-1).^{74,75} Pulmonary vascular obstruction may lead to increased pulmonary vascular resistance, and the elevation of the pulmonary artery pressure requires an occlusion of about 30%-50% of the total cross-sectional area of the pulmonary arterial bed.⁷⁶ Hypoxic vasoconstriction can also increase pulmonary vascular resistance. Shock commonly develops when PE occurs in the main pulmonary arteries or bifurcations. Inflammatory mediators (e.g., thromboxane A₂ and serotonin) play a role in vasoconstriction of the pulmonary vasculature, decreased perfusion, and increased vascular resistance.⁷⁷ Pulmonary arterial obstruction and vasoconstriction may produce hypoxemia via impaired alveolar gas exchange and increased lung dead space ventilation.⁷⁸ Ventilation-perfusion mismatch caused by capillary bed overflow in nonobstructed vessel zones will also contribute to hypoxemia. If present, a right to left shunt (e.g., patent foramen ovale) can also contribute to hypoxemia and might also predispose the patient to a paradoxical embolism. Hemodynamic disturbances also contribute to respiratory failure, as in the situation where low cardiac output results in the desaturation of mixed venous blood.

Patients typically compensate for PE-associated increased lung dead space ventilation⁷⁸ with increased ventilatory drive and minute ventilation, which leads to hypocapnia.^{74,75} However, patients with underlying lung disease or those receiving mechanical ventilation (i.e., sedated and not breathing above the set ventilator respiratory rate) may develop hypercapnia.⁷⁵ Normally, the end-tidal CO₂ approximates the PaCO₂. However, since end-tidal gas consists of a mixture of non-dead space and dead space gas, and since CO₂ does not transfer from the blood to the airway in nonperfused areas, the end-tidal CO₂ decreases in association with the increased dead space.⁷⁵

Abrupt increases in pulmonary vascular resistance associated with PE result in right ventricle (RV) dilation. Neurohumoral activation and subsequent inotropic and chronotropic stimulation improves flow through the partially obstructed pulmonary vascular bed.⁷⁸ However, prolonged elevations of RV pressure may cause a leftward bowing of the interventricular septum and decreased left ventricular (LV) filling during diastole.⁷⁹ If present, a right bundle branch blockage may contribute to the desynchronization of the ventricles. Decreased LV filling during early diastole can lead to decreased cardiac output and systemic hypotension.⁸⁰ Myocardial inflammation, increased right ventricular wall stress, and increased oxygen demand may cause RV ischemia and result in decreased RV contractility, RV cardiac output, LV preload, LV cardiac output, and systemic blood pressure.

RV microinfarction leads to the elevation of serum troponin levels.^{74,81-86} Cardiac myocyte injury triggers the release of the cardiac-specific markers cardiac troponin T (cTnT) and cardiac troponin I (cTnI). However, elevated cTnI levels may not occur with RV dysfunction. Cardiac wall stress associated with high ventricular filling pressures and myocardial hypoxia trigger the release of *B-type natriuretic peptides* (e.g., brain natriuretic peptide, BNP) and the N-terminal fragment of its prohormone, N-terminal pro-BNP (NT-proBNP), from coronary arteries and cardiac ventricular cells.^{74,81,87,88}

RISK FACTORS FOR RECURRENT VTE

Various studies have attempted to identify risk factors for recurrent VTE, including recurrent PEs that cause death in patients presenting initially with PE. Factors contributing to recurrent VTE in anticoagulated patients include the length of initial hospitalization, presence of

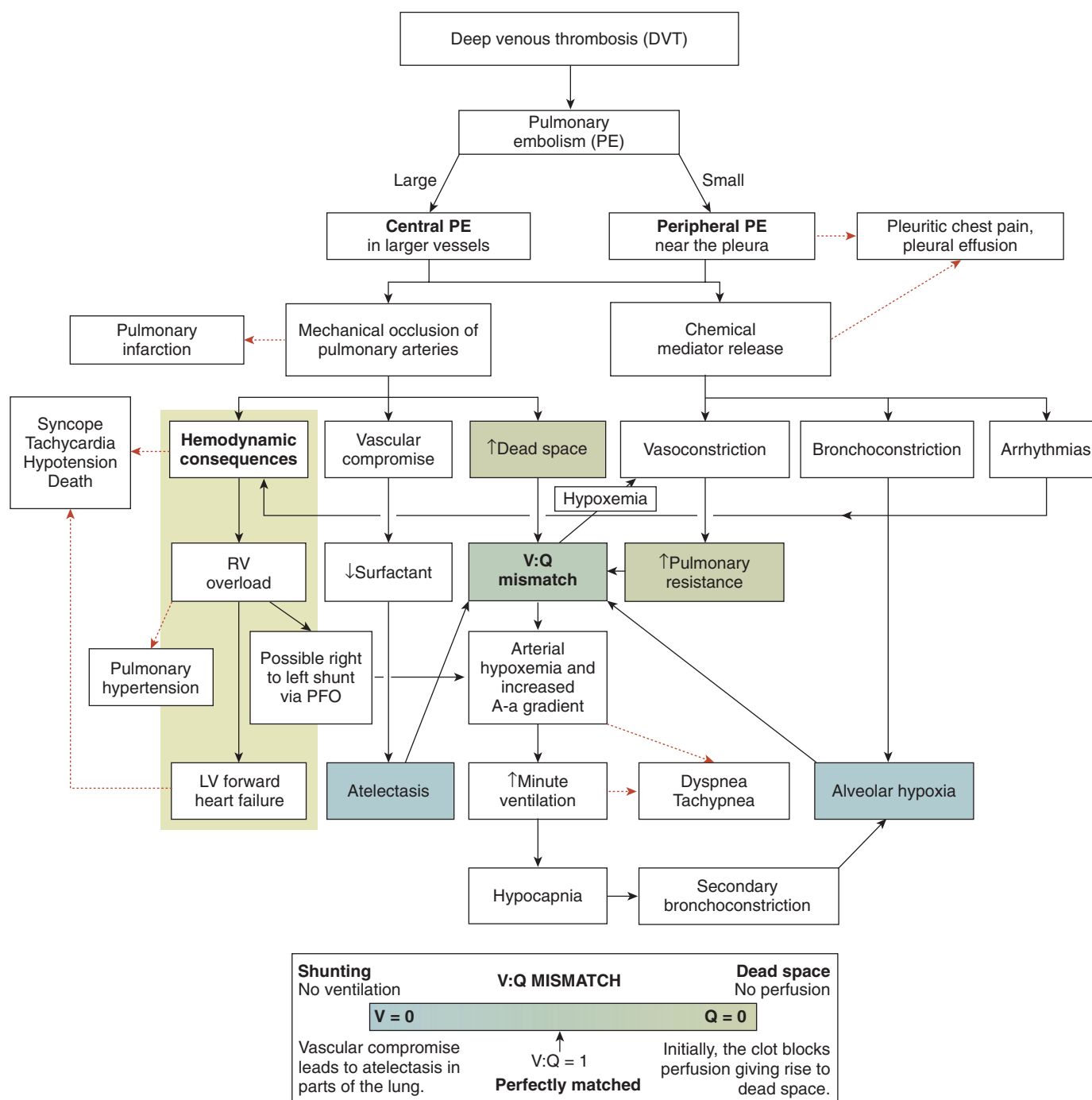


FIGURE 71-1 ■ PE pathophysiology. A-a, alveolar-arterial; DVT, deep vein thrombosis; PE, pulmonary embolism; PFO, patent foramen ovale; RV, right ventricle; VQ, ventilation-perfusion. (Adapted from Wong E, Chaudry S: Venous thromboembolism. McMaster Pathophysiology Review (www.pathophys.org), Hamilton, Ontario, Canada.)

cancer, older age, hospitalization for multiple injuries, and surgery within 3 months.^{89,90}

The location of DVT has an impact on the incidence of recurrence, and the presence of an iliofemoral DVT is associated with a higher rate of recurrent VTE compared with popliteal vein thrombosis.⁹¹ Additionally, the extensiveness of the DVT (e.g., venographic Marder Score) has a positive association with recurrent VTE events.⁹²

■ DIAGNOSIS (Fig. 71-2)

Clinical Features

The clinical presentation of PE depends on the size, number, and distribution of the emboli and on the patient's underlying cardiorespiratory reserve. Many cases of PE that occur in ICU patients go

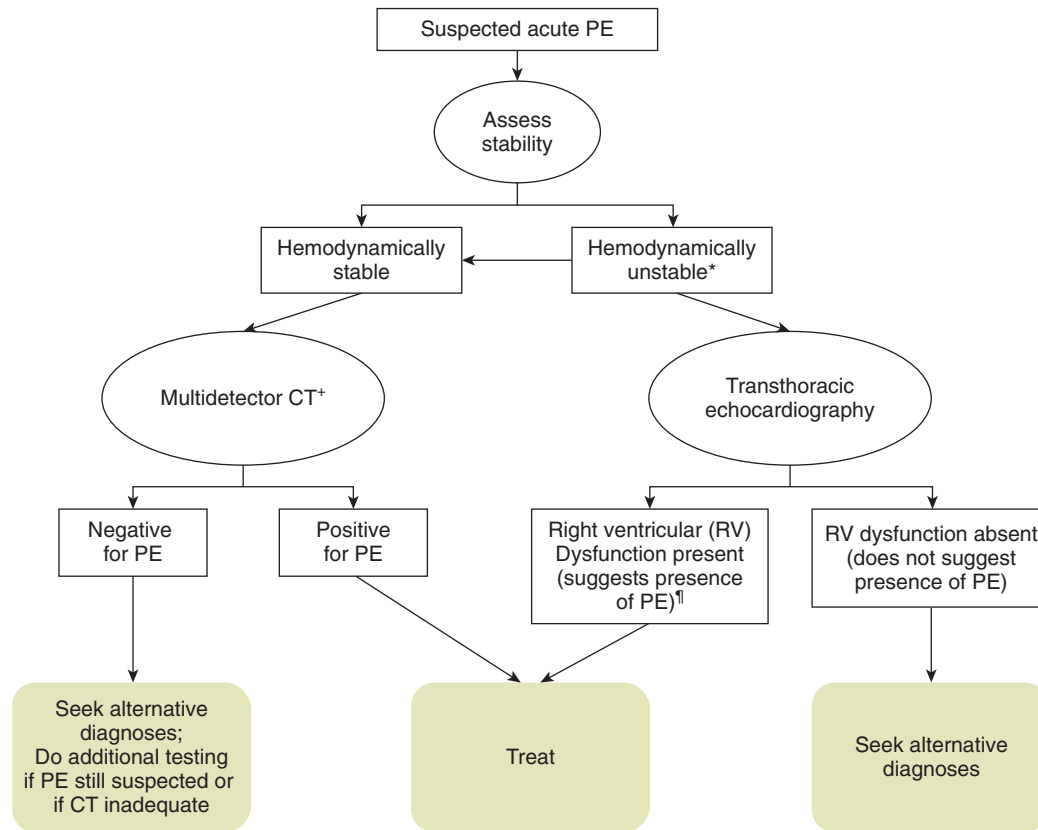


FIGURE 71-2 ■ Diagnostic evaluation for suspected acute pulmonary embolism (PE) in the intensive care unit (ICU). CT, computed tomography; ICU, intensive care unit; PE, pulmonary embolism. *Search for alternative and concomitant diagnoses. [†]If contraindication to intravenous (IV) contrast exists, consider ventilation-perfusion scintigraphy, lower extremity venous compression ultrasound, or MR angiography. [‡]Try to confirm the presence of PE with additional testing. Proximal lower extremity DVT serves as a surrogate to PE in the appropriate clinical setting.

unrecognized.^{93,94} Symptoms and signs of PE often overlap with other conditions in the ICU, and without objective testing, they alone should not be used to diagnose PE. The clinical manifestations of acute PE can generally be divided into several syndromes that overlap considerably: (1) dyspnea, sometimes with marked hypoxemia and tachypnea, with limited other associated clinical manifestations; (2) pulmonary infarction, often associated with pleuritic chest pain, cough, hemoptysis, pleural effusion, and pulmonary infiltrates on the chest radiograph or CT; (3) right ventricular failure or cardiovascular collapse, associated with tachycardia, hypotension, and possibly syncope; and (4) other nonspecific clinical features including fever, wheezing, anxiety, hypoxemia, and unexplained arrhythmia.^{95,96}

Differential Diagnosis

The differential diagnosis in patients with suspected PE includes cardiopulmonary disorders for each of the modes of presentation (see [Clinical Features](#)). For the presentation of dyspnea, tachypnea, and hypoxemia, the possible diagnoses include atelectasis, pneumonia, pneumothorax, pleural effusion, aspiration, pulmonary edema, bronchial obstruction, alveolar hemorrhage, and other pulmonary disorders. For pulmonary infarction exhibited by pleuritic chest pain or hemoptysis, possible diagnoses include pneumonia, pneumothorax, pericarditis, aortic dissection, pulmonary or bronchial neoplasm, pleurisy, costochondritis, muscle strain, and rib fracture. For the clinical presentation of right-sided heart failure or cardiovascular collapse, possible diagnoses include myocardial infarction, acute massive hem-

orrhage, sepsis, cardiac tamponade, heart failure, hypovolemia, and tension pneumothorax. Other considerations related to PE include sepsis, foreign body, fat, air, amniotic fluid, tumor emboli, and in situ thrombosis (e.g., sickle cell chest syndrome).¹ Though these conditions and venous thromboembolic PE may have similar supportive treatment, the requirement for unique disease-specific treatments requires a correct diagnosis.

Diagnostic Testing

DVT and PE are not separate and unrelated disorders but rather represent a continuous syndrome of VTE in which the initial clinical presentation may be symptoms of DVT, PE, or both. Therefore, strategies for the diagnosis of VTE include testing for PE and DVT.^{16,68,69} In the ICU, patients should undergo a rapid assessment for the potentially life-threatening disorders on the differential diagnosis list.

Assessment of Clinical Probability

Pretest probability plays a key role in the workup of patients with suspected PE, though most clinical prediction rules (e.g., Wells,⁹⁷ simplified Wells,⁹⁸ Geneva,⁹⁹ and simplified Geneva scores^{100,101}) have mainly undergone validation outside of the ICU setting.^{26,97,100-113} Combining pretest probability (e.g., Wells score) with diagnostic tests improves their diagnostic accuracy.¹¹⁴ Typical ICU evaluation for patients with suspected PE, including chest radiograph, electrocardiogram, and arterial blood gas, can assist in determining pretest probability and clinical severity, as well as information about other disorders,

even though they provide nonspecific information for PE diagnosis. If PE remains on the differential diagnosis list, then it warrants more specific testing.

Oxygen Assessment

Patients with PE most often do not have hypoxemia (i.e., low PaO₂ or SpO₂), though most have an abnormal alveolar-oxygen gradient.⁹⁶ Some studies suggest that up to 40% of patients with acute PE have a normal arterial oxygen saturation (SaO₂), and 20% have a normal alveolar-oxygen gradient.^{115,116}

Electrocardiography

Sinus tachycardia occurs in most patients with PE.⁹⁶ Classic findings on EKG of S1Q3T3 (S in V1, Q wave in V3, and T wave inversion in V3) and right bundle branch block do not occur in most patients with PE, and they have low positive predictive value when they do occur.¹¹⁷ Signs of RV strain that include right axis deviation and right ventricle hypertrophy may suggest the presence of PE.¹¹⁷⁻¹¹⁹

D-Dimer Assay

Plasma D-dimer levels become elevated in association with the activation of coagulation and fibrinolysis. Although D-dimer testing assists with directing a VTE workup in patients who have a low clinical probability of PE, it does not have a significant utility in the ICU. This is because most patients suspected of PE in the ICU have a high pretest probability of PE or a high likelihood of having a false-positive (i.e., low positive predictive value) D-dimer test.^{94,120} Therefore, patients in the ICU suspected of having VTE should undergo objective diagnostic imaging testing for PE without or despite any D-dimer test results.^{121,122}

Diagnostic Imaging for Suspected PE

In the ICU, the stability of the patient, the ability to lie flat and hold the breath, the findings on other imaging studies, the ability to receive an intravenous dye load, appropriate intravenous line access, and test availability play an important role in deciding which diagnostic test(s) to perform (see Fig. 71-2).

Chest Radiograph. The chest radiograph (CXR) usually reveals nonspecific findings in association with acute PE, but it may help to assess for other diagnoses promptly. Classic PE findings such as Westermark sign and Hampton's hump do not commonly occur.¹²³

Contrast-Enhanced Chest Computed Tomography (PE Protocol CT). Contrast-enhanced (multidetector) helical chest computed tomography (CT), also known as *CT angiography* (CTA), has become the most common and important diagnostic modality for assessing patients with suspected PE.¹²⁴⁻¹²⁷ CTA requires adequate IV access, ability to safely receive an intravenous iodinated dye load, ability to lie down and hold one's breath, ability to be safely transported to the imaging facility, appropriate body size/habitus to fit in the scanner, and willingness to receive radiation. Patients with a contraindication to CTA or inadequate CTA results should undergo other forms of testing.

The advantages of CTA over ventilation-perfusion scintigraphy (V/Q scan) include more diagnostic results (positive or negative) with fewer indeterminate or inadequate studies, and the detection of alternative or concomitant diagnoses (e.g., dissecting aortic aneurysm, pneumonia, and malignancy). CT may also assess for right ventricular dysfunction.^{128,129}

The PIOPED II study assessed the accuracy of multidetector CTA and combined CTA-CT venography (CTV).¹¹⁴ Among 824 patients with a reference diagnosis (based on a diagnostic algorithm) and a completed CT study (mainly 4-detector), CTA had poor image quality and inconclusive results in 6%. CTA had a sensitivity of 83% and a specificity of 96%. Positive results on CTA in combination with a high or intermediate probability of PE by Wells' criteria¹³⁰ had a positive predictive value (PPV) of 92% to 96%, while normal findings via CTA with a low clinical probability had a negative predictive value (NPV) of 96%. Thus, concordance of PE suspicion and CT results does not require further diagnostic testing. CT had poor diagnostic accuracy (about 60% PPV and NPV) when the clinical probability and the CT

results showed discordance, suggesting that PE suspicion/CT discordance should lead to further testing.¹¹⁴

The clinical significance of isolated subsegmental PE on CTA has raised debate, especially since it has a low PPV and poor interobserver reliability.^{131,132} In the presence of this type of PE, a venous compression ultrasound may assist with diagnostic and treatment decisions.^{1,2,133}

Incidental PE, clinically unsuspected but found on a CT, occurs in a small percentage of patients. Recommendations have recently moved for the treatment of small incidental PE (e.g., subsegmental or smaller),² although the guidelines recommend the treatment of larger (more proximal) incidental PE.^{1,2}

Radionuclide Lung Scanning. Despite the advances in chest CT diagnostic testing, lung ventilation/perfusion (V/Q) scintigraphy continues to play a role in the diagnosis of suspected PE.²⁶ VQ scans use an intravenous injection of technetium (Tc)-99m-labeled macroaggregated albumin particles to block a small fraction of the pulmonary capillaries and inhaled tracers (e.g., xenon-133 gas, Tc-99m-labeled aerosols, or Tc-99m-labeled carbon microparticles [Technegas]). VQ scans base their diagnosis on the expectation that hypoperfused segments of the lung (e.g., from PE) should exhibit normal ventilation and result in a V/Q mismatch as detected by gamma camera images.^{134,135}

V/Q scanning has an important role in patients with absolute or relative contraindications to CTA (e.g., IV contrast allergy, pregnancy, renal failure) or indeterminate CTA results.¹³⁶ For patients unable to be transported for a CT, they may undergo portable perfusion (Q) scanning (and possibly ventilation [V] scanning, if not mechanically ventilated) in the ICU. Additionally, since V/Q scans have significantly lower radiation exposure to the breast than CTA,¹³⁷ some consider it as the first-line imaging test for women of reproductive age.¹²⁵

V/Q scan results, earlier classified as normal, very low probability, low probability, intermediate probability, or high probability of PE,²⁶ are now more commonly classified as normal (and near normal), low probability, nondiagnostic (intermediate probability), and high probability.^{138,139} Some studies and guidelines propose a three-tier classification of normal (rules out PE), nondiagnostic (neither diagnostic for PE nor rules it out with a high likelihood), and high probability (diagnostic for PE in most patients).^{1,126,140,141} Similar to CT scan testing, VQ scan testing for PE has improved test characteristics when its results are combined with the objective grading of clinical suspicion. A normal or low-probability VQ scan in the setting of a low clinical suspicion adequately rules out PE, and a high-probability VQ scan in the setting of a high clinical suspicion adequately confirms PE with an acceptably small number of misclassified cases. However, these two scenarios of concordant test results and clinical suspicion only account for the minority of test results in hospitalized patients.^{26,142,143} In addition, V/Q scanning remains most useful in patients with a normal chest radiograph. Unfortunately, nondiagnostic V/Q scans commonly occur in the setting of an abnormal chest radiograph,²⁶ a common occurrence in the ICU. Approximately 70% of V/Q scans have inconclusive or nondiagnostic results, even when considered together with the pretest clinical probability.^{26,68,143} Nondiagnostic/indeterminate V/Q scan results or discordance between the clinical suspicion and the test results should lead to further testing because of concerns regarding diagnostic misclassification (false positives and negatives).¹ In this setting, objective testing for DVT with a venous compression ultrasound may provide added diagnostic value, and the ease of performance at the bedside often makes this test a good next step in the ICU.

Pulmonary Angiography. Pulmonary angiography uses intravenous iodinated contrast and selective catheterization of the pulmonary arteries. Diagnostic criteria for PE on angiography include two projections (views) of direct evidence of a thrombus seen as a filling defect or an amputation (cut-off) of a pulmonary arterial branch.²⁶ The procedure has a similar diagnostic accuracy to CT scanning.¹⁴⁴ Similar to CT, reader reliability significantly drops at the subsegmental level.^{145,146} Pulmonary angiography has a diagnostic role for the evaluation of suspected acute PE in the narrow setting of nondiagnostic noninvasive testing, high clinical suspicion, and available expertise. Pulmonary

angiography also plays a role in the percutaneous, catheter-directed treatment of acute PE. For patients who do undergo pulmonary angiography, hemodynamic measurements obtained during right heart catheterization may prove useful for management. Pulmonary angiography has a relatively low risk in patients who do not have pulmonary hypertension or cardiac failure.^{26,142} Pulmonary angiography has similar limitations and contraindications to CT scanning for ICU patients.

Cardiac Testing

Echocardiography. Echocardiography may detect a right heart thrombus¹⁴⁷⁻¹⁵⁰ or be used to visualize an embolism in transit. Findings on an echocardiogram that indirectly suggest the presence of PE include RV dilation and hypokinesis, an increase in the RV/LV diameter ratio; tricuspid regurgitation, paradoxical septal motion, interventricular septal shift toward the LV, McConnell's sign (i.e., hypokinesis of the free wall of the RV with normal motion of the apex), decreased tricuspid annulus plane systolic excursion (TAPSE),¹⁵¹ and pulmonary artery dilation. If echocardiography identifies pulmonary artery pressures or RV wall thickness beyond values consistent with acute RV pressure overload, this suggests an underlying or previously present RV dysfunction and the presence of some associated causal disorder. For hemodynamically stable patients with suspected acute PE, an abnormal echocardiogram with any of the findings noted above does not rule in PE (low PPV) unless a thrombus is seen.¹⁵²⁻¹⁵⁵ Echocardiography has a low NPV, so a lack of findings does not exclude PE in hemodynamically stable patients.¹⁵⁶⁻¹⁵⁸ Echocardiogram is not recommended as a routine part of a suspected PE evaluation in hemodynamically stable and normotensive patients.¹

In hypotensive patients, an echocardiogram that does not show signs of right heart dysfunction almost certainly excludes PE as the cause of the hemodynamic decompensation. An echocardiogram does assist with evaluating alternative etiologies for the hypotension (e.g., pericardial tamponade, valvular heart disease, left ventricular dysfunction, aortic dissection, and hypovolemia).

For patients diagnosed with PE by other means, echocardiography may assess cardiopulmonary reserves and evidence of end-organ damage (i.e., RV dysfunction). Echocardiography also provides a number of independent parameters related to pulmonary hemodynamics and can identify patients who have PE and a significantly increased risk of death.^{85,151,159-163} An echocardiogram may also provide clues to the cause of a cardiac arrest. Thus, echocardiography may assist with identification of potential candidates for thrombolysis or catheter fragmentation.¹⁶⁴⁻¹⁶⁷

Transesophageal ECHO (TEE) is not typically part of the diagnostic evaluation of patients with suspected or confirmed PE. However, TEE may identify central thrombus, especially in hemodynamically unstable patients.^{168,169}

Cardiac Blood Biomarkers. Cardiac biomarkers (e.g., troponin and BNP) have a low diagnostic accuracy for PE. These markers may have prognostic value (e.g., elevated values predict decompensation or death),^{83-85,163,170} although the literature lacks management studies that have validated their use in making treatment decisions in patients with acute PE. The NPV of these markers may be most useful for prognosis; those without elevated troponin and BNP have a lower risk of mortality from acute PE.¹

Venous Compression Ultrasonography. Venous compression ultrasonography uses the validated criterion of incomplete compressibility of a deep vein (assumed due to thrombus) for the diagnosis of DVT.^{72,171} A recent study of a lower extremity venous compression ultrasound performed by intensivists in the ICU had a sensitivity of 85% and a specificity of 96% for detecting DVT.¹⁷²

Most PE originates from lower extremity DVT.⁶⁸ Lower extremity venous compression ultrasonography shows DVT in 30%-50% of patients with acute PE.⁷⁰⁻⁷³ In studies of patients with suspected PE who had a positive D-dimer, the complete lower extremity venous ultrasound had a diagnostic yield almost twice that of testing limited to the proximal lower extremity, though distal DVT occurred without PE in about one-third of patients.^{173,174} However, the presence of

proximal lower extremity DVT has a high PPV for PE.¹⁰⁰ A venous compression ultrasound negative for DVT does not exclude the presence of PE.⁶⁸

Venous compression ultrasonography has a diagnostic role in patients with suspected PE, particularly those with inconclusive CT results,²⁶ nondiagnostic lung scan results,¹⁴³ or the inability to undergo imaging for PE, since detection of DVT (especially proximal DVT) confirms the presence of VTE. Detection of proximal DVT by objective testing provides an indication for standard treatment regardless of the presence or absence of PE, and it reduces the need for further diagnostic testing. For patients who have nondiagnostic CT or lung scan or CT results combined with negative lower extremity venous compression ultrasound results and adequate cardiopulmonary reserve, serial venous compression ultrasound testing and the withholding of anticoagulant therapy can be used as alternatives to pulmonary angiography.^{125,175,176}

DVT may occur in non-lower extremity sites in patients in the ICU.^{177,178} Patients with central venous access, especially those with cancer, have an increased risk of upper extremity DVT.^{177,179} Upper extremity DVT may cause PE. A recent large nested prospective cohort study did not find an association between clinically apparent non-lower extremity DVT and ICU mortality, although the study did not have adequate power for this assessment.¹⁷⁷ Upper extremity venous compression ultrasound has a lower sensitivity compared to lower extremity testing because of the higher difficulty for imaging the proximal veins.¹⁷¹

Integrated Strategies for Diagnosis of Pulmonary Embolism

Figures 71-2 and 71-3 summarize the approach to the diagnosis of suspected PE in the ICU. The specific approach used should depend on individual patient circumstances that dictate the urgency of the testing and treatment, what testing can be performed when the testing can occur, and what tests have already been completed. The approach should also rely on the local availability of technology, the expertise with the different diagnostic techniques, the timing of the tests, and the diagnostic test characteristics.

The diagnostic testing approach for patients in the ICU suspected of having PE depends on the presence or absence of shock and clinical instability. Without these conditions, patients may undergo transport for testing outside of the ICU. For unstable patients or those at high risk of complications during transport, patients should probably undergo bedside testing. Unstable patients should also undergo rapid testing to work through the differential diagnosis list of life-threatening illnesses and to allow for rapid intervention.

CLASSIFICATION

The PE classification schema uses the terms *acute* versus *chronic*, and acute PE has the most relevance to the ICU. Acute PE classification systems have often used the terms *massive*, *submassive*, and *other* over the past 50 years, and these categories relate to cardiovascular effects of the PE and patient prognosis.^{29,180} Massive PE has often been defined by acute right heart failure and associated hypotension (e.g., systolic blood pressure <90 mm Hg or a drop >40 mm Hg from baseline for at least 15 minutes) that remains present despite volume resuscitation and vasopressor therapy. Clinicians should treat related factors, such as arrhythmias and decreased cardiac output, and unrelated factors, such as hypovolemia, before defining the hypotension as refractory. Submassive PE has described patients who have PE-associated hemodynamic stability in the setting of right ventricular (RV) dysfunction. Patients who do not have symptoms and signs of massive or submassive PE have been grouped into the "other" category. Clinical characteristics define PE severity classification, although radiologic grading may also use these terms based on clot burden or the degree of arterial obstruction.

The recent European Society of Cardiology guidelines has moved away from the massive/submassive/other PE classification system

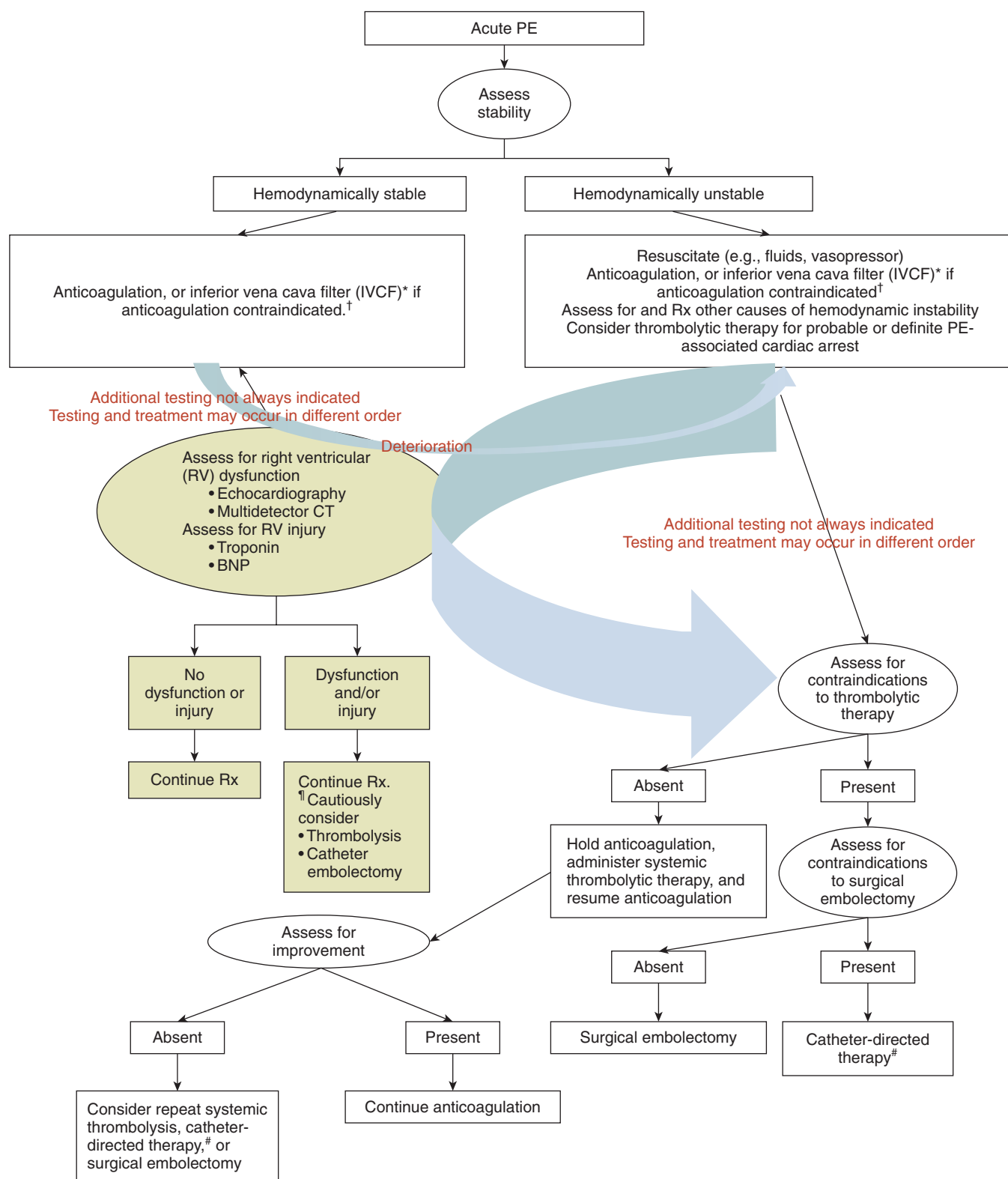


FIGURE 71-3 ■ Treatment of confirmed acute PE in the ICU. BNP, brain natriuretic peptide; CT, computed tomography; CUS, compression ultrasound; ICU, intensive care unit; IVCF, inferior vena cava filter; PE, pulmonary embolism; RV, right ventricle; Rx, treatment. *Temporary or permanent IVCF. †Anticoagulate after IVCF placement once contraindication to anticoagulation resolves. ‡If contraindications do not exist. †Catheter-directed therapy may include mechanical clot treatment and thrombolysis; the decision to use depends on availability and local expertise.

TABLE 71-1 Mortality Risk Classification of Patients Who Have Acute PE

| EARLY MORTALITY RISK | | RISK PARAMETERS AND SCORES | | | |
|----------------------|-------------------|----------------------------|--------------------------------------|--|--|
| | | SHOCK OR HYPOTENSION | PESI CLASS III-V OR sPESI $\geq 1^a$ | SIGNS OF RV DYSFUNCTION ON AN IMAGING TEST ^b | CARDIAC LABORATORY BIOMARKERS ^c |
| High | | + | (+) ^d | + | (+) ^d |
| Intermediate | Intermediate-high | — | + | Both positive | |
| | Intermediate-low | — | + | Either one (or none) positive ^e | |
| Low | | — | — | Assessment optional; if assessed, both negative ^e | |

LV, left ventricular; PE, pulmonary embolism; PESI, pulmonary embolism severity index; RV, right ventricular; sPESI, simplified pulmonary embolism severity index.

^aPESI Class III to V indicates moderate to very high 30-day mortality risk; sPESI ≥ 1 point(s) indicates high 30-day mortality risk.

^bEchocardiographic criteria of RV dysfunction include RV dilation and/or an increased end-diastolic RV-LV diameter ratio (in most studies, the reported threshold value was 0.9 or 1.0), hypokinesia of the free RV wall, or increased velocity of the tricuspid regurgitation jet. Computed tomographic (CT) angiography (four-chamber views of the heart) criterion for RV dysfunction consists of an increased end-diastolic RV/LV diameter ratio (≥ 0.9 or 1.0).

^cMarkers of myocardial injury (e.g., elevated cardiac troponin-I or -T concentrations in plasma) or heart failure as a result of right ventricular dysfunction (elevated natriuretic peptide concentrations in plasma).

^dClassify shock or hypotension as high risk, despite any PESI or sPESI score.

^eClassify low-risk PESI (class I-II) or sPESI patients (score of 0) who have associated elevated cardiac biomarkers or signs of RV dysfunction on imaging tests into the intermediate to low-risk category. Adapted from Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, Gibbs JS, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczyk P, Rasmussen LH, Schindler TH, Svitil P, Vonk Noordegraaf A, Zamorano JL, Zompatori M; Authors/Task Force Members. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC) Endorsed by the European Respiratory Society (ERS). Eur Heart J 2014;35:3033-3073 (Table 9).

toward an early mortality risk-based classification system that drives treatment decisions (Table 71-1).¹ The guideline uses four key risk assessment categories that assess for (1) hemodynamic instability (i.e., shock or hypotension present), (2) imaging-detected (echocardiogram or CT) signs of RV dysfunction, (3) elevated clinical risk score (by Pulmonary Embolism Severity Index [PESI] or simplified PESI, Table 71-2), and (4) abnormal cardiac laboratory biomarkers (i.e., troponin, BNP). High-risk PE patients have hemodynamic instability with imaging-detected signs of RV dysfunction, with or without an elevated clinical risk score and with or without abnormal cardiac laboratory biomarkers. Intermediate-risk PE patients do not have hemodynamic instability, but they have an elevated clinical risk score, and they may or may not have imaging-detected signs of RV dysfunction and or abnormal cardiac laboratory biomarkers. Low-risk PE patients do not have abnormalities in any of the four key risk assessments. The PE severity classification systems do not address all important clinical events such as hypoxemia, respiratory failure requiring mechanical ventilation, or worsening cardiovascular status that might occur within a specific risk class (e.g., greater tachycardia or a drop in blood pressure not meeting criteria for hypotension).

PROGNOSTIC ASSESSMENT AND SEVERITY INDICES

Indicators of a poor prognosis or adverse outcomes for patients who have PE include hemodynamic instability/hypotension, signs of RV dysfunction, elevated troponin, elevated BNP, coexisting DVT, thrombus burden, and right ventricular thrombus.^{23,25,70,81-85,92,151,157,159-161,163,170,181-189} Underlying risk factors include an age greater than 70 years, congestive heart failure, chronic obstructive pulmonary disease (COPD), and cancer.¹⁹⁰⁻¹⁹² Several prognostic scoring systems (e.g., the Pulmonary Embolism Severity Index [PESI],^{190,191} and the simplified PESI [sPESI],¹⁹² Geneva risk score,⁹⁹ simplified Geneva risk score,¹⁹³ Hestia criteria,¹⁹⁴ Shock Index,¹⁹⁵ Global Registry of Acute Coronary Events [GRACE] score,¹⁹⁶ PREP score,⁶² PROTECT multimarker index,¹⁸⁷ Bova score,¹⁸⁸ and RIETE score exist.¹⁹⁷ However, the clinical prediction tools have not been specifically developed for patients in the ICU. Of note, the prognostic markers often predict varying degrees of risk in different types of patients, such as those with hypotension and those without the condition.

TABLE 71-2

Original and Simplified Pulmonary Embolism Severity Index (PESI)

| VARIABLE | ORIGINAL PESI | SIMPLIFIED PESI |
|---|---------------|-------------------------------------|
| Age | Age, in years | 1 (if age > 80 years) |
| Male sex | +10 | — |
| History of cancer | +30 | 1 |
| History of heart failure | +10 | 1 for either or both of these items |
| History of chronic lung disease | +10 | — |
| Pulse > 110 beats/min | +20 | 1 |
| Systolic blood pressure < 100 mm Hg | +30 | 1 |
| Respiratory rate > 30 breaths/min | +20 | — |
| Temperature < 36°C | +20 | — |
| Altered mental status | +60 | — |
| Arterial oxyhemoglobin saturation (SaO ₂) < 90% | +20 | 1 |

30-DAY MORTALITY RISK STRATA (BASED ON THE SUM OF POINTS)

LOW-RISK PESI

Class I: <65 Points

(event rate 95% CI, 0-1.6%)

Class II: 66-85 Points

(event rate 95% CI, 1.7-3.5%)

HIGH-RISK PESI

Class III: 86-105 Points

(event rate 95% CI, 3.2-7.1%)

Class IV: 106-125 Points

(event rate 95% CI, 4.0-11.4%)

Class V: >125 Points

(event rate 95% CI, 10.0-24.5%)

LOW-RISK SPESI

0 Points

(event rate 95% CI, 0-2.1%)

HIGH-RISK SPESI

≥ 1 Point

(event rate 95% CI, 8.5-13.2%)

Assessment of RV Dysfunction

Studies have identified echocardiographic findings indicative of RV dysfunction as independent predictors of an adverse outcome in patients who have acute symptomatic PE.^{151,157,181,183,198} A meta-analysis found that RV dysfunction on the echocardiography had an odds ratio (OR) for short-term mortality of 2.5 (95% CI, 1.2 to 5.5).¹⁹⁹ Studies have also validated the use of CT angiography for assessing RV dilation.^{200,201} A recent systematic review showed that CT-assessed RV dysfunction had an association with increased risk of mortality in normotensive patients with PE (OR 1.8; 95% CI, 1.3 to 2.6), but the relatively small likelihood ratios and the small increase in the ability to classify risk with this approach suggest that the usefulness of basing therapeutic decision making solely on CT results does not appear warranted.¹⁸⁶ However, echocardiographic RV dysfunction has a weak independent association with short-term PE-related complications. Taken together, these findings suggest that RV dysfunction (assessed either by echocardiography or CT angiography) in itself should not significantly drive the decision to give thrombolytic therapy in normotensive patients with acute PE.²

Single markers of right ventricular (RV) dysfunction (e.g., on echocardiography, on spiral computed tomography [CT], elevated BNP) or myocardial injury (e.g., elevated cardiac troponin T or I testing) have an insufficient positive predictive value for PE-specific complications to drive decision making toward recanalization procedures, and studies have suggested that they only identify an intermediate- to low-risk group of patients with PE.^{25,85,186}

Assessment of Myocardial Injury

Studies of patients with acute PE have demonstrated an association between myocardial injury (assessed by elevated serum levels of troponin or heart-type fatty acid-binding protein [HFABP]) and short-term adverse in-hospital outcomes.^{83,86,202} Measurement of troponin and brain or B-type natriuretic peptides (BNP) may assist with estimating disease severity and prognosis in patients presenting with PE.^{85,159–163} A meta-analysis of studies of normotensive patients with acute PE showed a significant association between elevated troponin levels and increased mortality (OR 4.3; 95% CI, 2.1 to 8.5).⁸⁵ However, troponin alone did not appear to change the pretest clinical significance to a posttest probability of death. Moreover, the usefulness of basing therapeutic decision making solely on troponin levels does not appear to be warranted. While some observational studies have suggested that cardiac biomarkers may possess a prognostic value additive to that of echocardiography,^{81,82,182} the findings from the recently published Pulmonary Embolism Thrombolysis Trial (PEITHO) suggest that such a combination might not be strong enough to identify patients reliably at an increased risk for PE-related complications.²⁰³

Thrombus Burden

In patients who have VTE, thrombus burden has an association with death.^{70,92,204} In a prospective single-center cohort study of outpatients diagnosed with a first episode of acute symptomatic PE, investigators assessed the prognostic significance of concomitant DVT during the 3-month follow-up period after PE diagnosis.¹⁹² The DVT assessment by CCUS had a positive predictive value for a 90-day PE-related mortality of 6.6% (95% CI, 4.1% to 9.2%).

D-Dimer

Studies have correlated D-dimer levels with proximal location of PE, serious comorbidity, and mortality in patients with acute symptomatic PE.^{193,205–209} Recently, investigators used the international prospective Registro Informatizado de la Enfermedad TromboEmbolica Venosa (RIETE Registry) to assess the prognostic value of D-dimer levels obtained near the time of acute PE diagnosis for outcomes over the ensuing 15-days after diagnosis.²¹⁰ In a cohort of 1707 patients, the

all-cause mortality, increased as the D-dimer level increased, from 2.7% in the first quartile to 7.0% in the fourth quartile. Patients with D-dimer levels in the highest quartile also had an increased risk of fatal PE (OR 2.0; 95% CI, 1.0 to 3.8) and major bleeding (OR 3.2; 95% CI, 1.5 to 7.0). PE (either initial or recurrent) caused 45% of the deaths during the 15-day follow-up.

Combination of Prognostic Tests

Although they raised concern about PE severity, single markers of RV dysfunction and myocardial injury have an insufficient positive predictive value for PE-specific complications to drive decision making toward aggressive (e.g., thrombolytic) therapy.¹⁸² Observational studies have suggested an incremental prognostic value of the association of markers of RV dysfunction and injury over either alone^{81,82} or the combination of imaging testing and biomarkers to clinical prediction rules.¹⁸⁵

The PREP score includes the variables of cardiogenic shock, BNP, RV to left ventricle (LV) diameter ratio, underlying cardiac or respiratory disease, altered mental status, and cancer.⁶² The derivation study classified 247 of 570 PE patients (43%) in the highest risk category, and they had a risk of PE-related serious adverse events at 30 days of 22.9%.⁶²

The PROTECT study^{183,187} derived (n = 848) and validated (n = 529) a multimarker prognostication tool that consisted of BNP, cTnI, Simplified Pulmonary Embolism Severity Index [sPESI], and CCUS imaging (for concomitant DVT) for normotensive patients diagnosed with acute symptomatic PE in an emergency department (available at www.PEprognosis.com). The combination of abnormal test results for all PROTECT prognostic tests had a positive predictive value for the prediction of a complicated course (defined as death from any cause, hemodynamic collapse, and/or adjudicated recurrent PE) of 25.8% in the derivation cohort and 21.2% in the validation cohort.

A patient-level meta-analysis involving 2874 normotensive patients presenting to the hospital with acute PE found that significant predictors of PE-related complications included tachycardia, mild hypotension, cardiac dysfunction, and myocardial injury.¹⁸⁸ The Bova et al. model [Bova risk score] identified three stages (I, II, and III) with 30-day PE-related complication rates of 4.2%, 10.8%, and 29.2%, respectively. A recent study validated the Bova score for accurately assessing the risk for PE-related complications that occur within 30 days of PE diagnosis.¹⁸⁹

Observational studies have suggested that the combination of clinical variables (i.e., tachycardia and mild hypotension), myocardial injury, and RV dysfunction, particularly in those with concomitant DVT, identifies the more severe intermediate-risk patients with acute PE (i.e., “intermediate-high risk” according to European Society of Cardiology guideline)¹ who might benefit from intensive monitoring and even recanalization procedures. However, prognostic tools cannot predict a risk that is high enough to justify primary reperfusion in hemodynamically stable patients.^{2,211}

TREATMENT OF PE (see Fig. 71-3)

Objectives and Principles of Treatment

The objectives of PE treatment in ICU patients include (1) supportive care (e.g., treatment of hypotension and respiratory failure), (2) prevention of clinical deterioration or death associated with PE, (3) facilitating the resolution of PE, (4) prevention of recurrent VTE, and (5) avoidance of complications from therapy. Clinicians should make their treatment decisions for PE based on confidence in the diagnosis of PE, hemodynamic status of the patient, the degree of RV dysfunction/injury, bleeding risk, prognosis, patient preferences, and patient-specific factors that could affect treatment safety and efficacy.

In general, patients that have a nonhigh bleeding risk should undergo prompt initiation of empiric anticoagulation upon a high clinical suspicion of PE before the completion of diagnostic tests if the

testing cannot be completed rapidly. Patients diagnosed with PE should then rapidly achieve therapeutic anticoagulant levels. Anticoagulant therapy should undergo appropriate monitoring. Patients who have PE ruled out should have anticoagulation discontinued and prophylaxis for venous thromboembolism initiated.

Resuscitation

Regarding patients not already in an ICU, patients who have high-risk PE should be transferred to an ICU. Select patients who have intermediate-risk PE (submassive PE) could benefit from monitoring for deterioration in the ICU.

Patients who have PE and present with shock have a high risk of deterioration and death, especially in the hours following the development of shock. Hemodynamic instability associated with PE should lead to prompt resuscitation and consideration for thrombolytic therapy.

Volume Administration

Judicious volume infusion for resuscitation of RV dysfunction and decreased RV preload associated with PE may improve cardiac output.²¹² However, overdistention of the RV with volume resuscitation may impair subsequent left ventricular (LV) filling, LV output, and coronary perfusion.²¹³ Thus, patients who have hypotension associated with PE should receive appropriate amounts of intravenous fluids.²⁸

Vasopressors

Limited data exist regarding the use of vasopressors in humans with acute PE. A canine model demonstrated the superiority of norepinephrine over phenylephrine in increasing cardiac output and RV coronary blood flow, although both agents similarly improved the mean arterial blood pressure.²¹⁴ Although epinephrine and dobutamine may provide inotropic support, dobutamine has the disadvantage of causing or worsening systemic hypotension. Interestingly, raising the cardiac index may cause or worsen ventilation-perfusion mismatch through the redistribution of blood flow from partially obstructed pulmonary arteries to unobstructed vessels.²¹⁵ Thus patients who have hypotension associated with PE should undergo cautiously monitored vasoactive support.

Vasodilator Therapies

Interest has arisen in the use of pulmonary arterial vasodilators (e.g., inhaled nitric oxide and oral phosphodiesterase inhibitors) for the treatment of acute PE.^{216,217} Vasodilator drugs can affect hypoxic vasoconstriction, platelet activation, and the release of vasoactive mediators (e.g., endothelin, thromboxane). Theoretically, vasodilator treatment would lower the pulmonary artery pressure and unload the RV. However, clinical trials have not confirmed their efficacy and safety. Thus, the literature does not support the routine use of pulmonary arterial vasodilators in patients who have hypotension or marked hypoxemia associated with PE.

Supplemental Oxygen

Patients with PE often have an elevated alveolar-arterial gradient. In the patients who have PE associated with hypoxemia,^{74,75,96} supplemental oxygen will usually allow for the achievement of normoxemia.

Mechanical Ventilation and Sedation

Intubation and mechanical ventilation may assist with the treatment of rare episodes of respiratory failure associated with PE or may occur as part of resuscitation associated with PE (e.g., cardiac arrest). Some patients already receiving mechanical ventilation develop PE. For patients who have PE and undergo mechanical ventilation, ventilator-associated positive pressure ventilation may decrease the RV preload. In addition, sedative use associated with mechanical ventilation may cause systemic hypotension. Various approaches to mechanical ventilation (e.g., prone ventilation) can also decrease RV afterload.²¹⁸ Avoidance of excessive tidal volume and positive end-expiratory pressure, as

well as careful sedation management, should help to prevent the development or worsening of hypotension.²¹⁹

Mechanical Circulatory Support

Patients who have PE and associated circulatory collapse could potentially benefit from mechanical circulatory support.^{220,221} However, studies have not thoroughly investigated such therapies in this setting.

Initial Anticoagulation Considerations

Anticoagulation, the mainstay of treatment for acute PE, prevents new clot formation, extension and embolism of the source of the PE (e.g., DVT), and the recurrence of PE. Before making anticoagulant choices, clinicians should consider anticoagulant drug efficacy and safety regarding anticoagulant bioavailability and absorption issues, onset and time to peak, half-life, mechanism of clearance, drug interactions, ability to monitor anticoagulant effect, and reversibility. Clinicians should also consider issues related to upcoming or potential procedures or surgeries. Anticoagulant therapy for ICU patients typically should focus on short-term issues while long-term treatment plans can be determined after patients leave the ICU. Patients with PE and hypotension who receive anticoagulation should receive unfractionated heparin (UFH) instead of low-molecular-weight heparin (LMWH) or fondaparinux since the latter agents have not undergone rigorous testing under such conditions. In addition, for those patients who will or might receive thrombolytic therapy, the use of an anticoagulant with a short-half life might provide the greatest safety. Although ICU-specific studies of anticoagulant therapy for PE would provide the most relevant data, most treatment recommendations about standard anticoagulant treatment in the ICU are extrapolated from non-ICU data.

Bleeding Risk Assessment

All patients should undergo a bleeding risk assessment and evaluation for contraindications to anticoagulant therapy before the initiation of such treatment.² Absolute contraindications to anticoagulant treatment include intracranial bleeding, severe active bleeding, malignant hypertension, or recent brain, eye, or spinal cord surgery. Relative contraindications include recent major surgery, recent cerebrovascular accident, nonsevere active bleeding, severe hypertension, severe renal or hepatic failure, and severe thrombocytopenia (e.g., platelets <50,000/ μ L).²⁹ Since aspirin and other nonsteroidal antiinflammatory drugs significantly increase the risk of bleeding for patients who receive anticoagulants,²²² their use should be avoided or minimized. While studies have identified risk factors for anticoagulant-associated bleeding in patients who have VTE,^{223,224} those with a high bleeding risk often receive anticoagulation therapy because the benefits typically outweigh the risks.

Initial Anticoagulation

As described above, clinicians should consider using empiric initial parenteral anticoagulant therapy for suspected PE, especially for patients who do not have a high bleeding risk and for scenarios that include delayed diagnostic testing. After the confirmation of PE diagnosis, ICU patients deemed appropriate for anticoagulation should usually receive a parenteral agent.

Heparin Therapy

Unfractionated Heparin Therapy. Despite the frequent use of LMWH and newer nonvitamin K antagonist target-specific oral anticoagulants, unfractionated heparin (UFH) still has a major role in the initial treatment of VTE in ICU patients. Pertinent to patients in the ICU, UFH has the advantage of a relatively short half-life, a lack of significant dependence on renal clearance, and the reversibility of the anticoagulant effect of protamine sulfate.²²⁵

The anticoagulant activity of UFH depends on a unique pentasaccharide, present on about a third of heparin molecules, that binds to antithrombin (AT) and potentiates the inhibition of thrombin and

activated factor X (FXa).²²⁵⁻²²⁷ To a lesser degree, in a process independent of AT, heparin also catalyzes the inactivation of thrombin via plasma cofactor II.²²⁵ Heparin has a number of effects that include the release of tissue factor pathway inhibitor (TFPI), suppression of platelet function, increase in vascular permeability, and the binding to numerous plasma and platelet proteins, endothelial cells, and leukocytes.²²⁶

The anticoagulant response to a standard dose of UFH varies widely among patients. This varied response makes it necessary to monitor the anticoagulant effects of UFH, using either the activated partial thromboplastin time (aPTT) or heparin levels, and to titrate the dose to the individual patient.²²⁵

The efficacy of UFH therapy depends partly upon achieving a critical therapeutic level of UFH within the first 24 hours of treatment.²²⁸⁻²³⁰ Clinical trials have shown that failure to achieve a therapeutic aPTT threshold by 24 hours had a 23% subsequent recurrence VTE rate over 3 months of follow-up, compared with a rate of 4% to 6% for the patient group who had therapeutic levels at 24 hours.^{229,230} The minimum therapeutic threshold of UFH, as measured by the aPTT, is 1.5 times the mean of the control value or the upper limit of the normal aPTT range.²²⁸⁻²³⁰ The therapeutic range for UFH corresponds to a UFH blood level of 0.2 to 0.4 U/mL by the protamine sulfate titration assay and 0.35 to 0.70 by the anti-FXa assay. Each laboratory should establish the minimal therapeutic level of UFH, as measured by the aPTT, that will provide a UFH blood level of at least 0.35 U/mL by the anti-FXa assay for each batch of thromboplastin reagent being used, particularly if a new batch of reagent is provided by a different manufacturer.²²⁵

Numerous studies of UFH therapy have demonstrated the difficulties of successfully administering IV UFH. The previously popular clinical practice of using an ad hoc approach to UFH dose titration frequently resulted in inadequate therapy. Multiple studies have supported the use of a prescriptive approach or protocol for administering IV UFH for the treatment of patients with VTE.^{228,230} The protocols achieve therapeutic UFH levels in the vast majority of patients. A weight-based nomogram results in fewer episodes of recurrent VTE as compared to standard care.^{230,231} A commonly used nomogram uses an IV UFH bolus of 80 U/kg and an initial continuous IV drip rate of 18 U/kg/hour.²³⁰ The nomogram then determines the UFH adjustments based on the aPTT. Nomograms typically recommend checking the first aPTT about 6 hours after initiating UFH therapy. However, for ICU patients that have high-risk PE, and for some patients who have intermediate-risk PE, an aPTT obtained about 90 minutes after the UFH bolus should have a very high value (e.g., >150 sec). If the aPTT does not reach such a high value in this setting, then another UFH bolus is indicated.

The adjusted-dose and unadjusted dose of subcutaneous (SC) UFH has demonstrated efficacy in the initial treatment of VTE.²³²⁻²³⁵ Similar to IV UFH, achieving the therapeutic range by 24 hours improves the efficacy of SC UFH.²³⁶ However, because of concerns about absorption associated with body edema and hypotension, the IV route is preferred over the SC route in the ICU.²³⁷

Low-Molecular-Weight Heparin. Chemical or enzymatic depolymerization of UFH produces LMWHs that have different chemical structures and pharmacokinetics.^{238,239} Few studies have compared different LMWHs with respect to clinical outcomes, so the impact of these differences remains unclear.²³⁹ In comparison to UFH, LMWHs have increased bioavailability (>90% after subcutaneous injection), longer half-life, and more predictable clearance. These characteristics of LMWHs enable a weight-based once- or twice-daily subcutaneous injection that does not require laboratory monitoring.^{225,238-240} However, the renal clearance of LMWHs requires a dose or frequency reduction or complete avoidance (e.g., renal failure) in patients with significantly reduced renal function.

LMWHs have fewer serious complications, such as bleeding²³¹ and heparin-induced thrombocytopenia,²⁴¹⁻²⁴³ when compared with UFH. However, the subcutaneous use of anticoagulants in the ICU may lack efficacy. Among ICU patients receiving LMWH DVT prophylaxis,

those receiving vasopressors had lower anti-FXa activity than those not receiving vasopressors.^{244,245} Studies have shown variable results regarding anti-FXa activity in the setting of LMWH use in the setting of subcutaneous edema.^{237,246} The appropriate dosing of LMWH in morbidly obese patients remains unclear.²⁴⁷ Thus, in comparison to UFH, LMWH's lack of complete reversibility, its longer half-life, its renal clearance, and possible reduced efficacy in hypotensive and edematous patients may lead to the preferred use of UFH in the ICU.

Fondaparinux. Fondaparinux, a synthetic indirect inhibitor of factor Xa, has efficacy and safety similar to UFH²⁴⁸ for the initial treatment of PE or LMWH for the initial treatment of DVT.²⁴⁹ Fondaparinux has ICU issues similar to LMWHs, which may lead to the preferred use of UFH in this setting.

Oral Agents

Vitamin K Antagonists. Until recently, typical patients with PE might receive initial therapy of IV UFH, LMWH, or fondaparinux, overlapped with an oral vitamin K antagonist (VKA). However, those patients ill enough to receive ICU care often have reasons to forgo concomitant and long-term VKA therapy. The possibility of undergoing invasive procedures or surgery, high bleeding risk, the potential use of fibrinolytics, and other issues often weigh against the use of anticoagulants that have a long half-life (e.g., VKA). Long-term anticoagulation plans are best dealt with after the clinical problems requiring ICU care have been fully addressed.

Nonvitamin K Antagonist Target-Specific Oral Anticoagulants. Non-VKA oral anticoagulants have been classified into two target-specific categories, direct thrombin inhibitor (e.g., dabigatran) and direct Xa inhibitors (e.g., rivaroxaban, apixaban, and edoxaban). Since dabigatran²⁵⁰ and edoxaban²⁵¹ require 5 to 10 days of overlapping parenteral anticoagulant therapy for the treatment of VTE, these agents would not typically be used as initial therapy in the ICU. Compared to warfarin, the non-VKA oral agents have a more rapid onset, shorter half-life, wider therapeutic window, and more predictable pharmacokinetics. In general, these features allow the use of rivaroxaban²⁵² and apixaban²⁵³ for sole VTE oral therapy without the need for an overlapping parenteral agent, titration or dose adjustments in patients with normal renal function, and routine monitoring. Issues of concern that should limit the use of the non-VKA oral anticoagulants in the ICU include the need for oral intake and gastrointestinal absorption, the relatively long half-life in comparison to UFH, the lack of approved antidotes for the factor Xa inhibitors, drug level effects based on renal function, drug interactions, and the inability to monitor the anticoagulant effect fully.

Thrombolytic Therapy

Unlike the anticoagulants described above, thrombolytics lead to rapid clot lysis by converting plasminogen to plasmin. Fibrinolytic treatments now primarily consist of more fibrin-specific drugs (activators of plasmin where fibrin is already bound, such as in blood clots) that include alteplase, reteplase, and tenecteplase. Earlier fibrinolytic drugs consisted of less fibrin-specific agents (i.e., activators of plasmin in all body fluids) that included streptokinase and urokinase.²⁹ A number of tissues, including endothelial cells, produce the naturally occurring enzyme (serine protease) alteplase (recombinant tissue-type plasminogen activator, tPA; Activase). Alteplase has fibrin specificity, and fibrin-bound tPA has increased affinity for plasminogen; non-fibrin-bound tPA in the systemic circulation does not extensively activate plasminogen. The standard alteplase dose for PE is 100 mg IV over 2 hours. Recombinant technology has produced the tPA, reteplase (recombinant plasminogen activator, rPA; Retavase). Compared to alteplase, reteplase has less fibrin specificity and a longer half-life. For PE, reteplase is typically given as 10 U IV over 2 minutes, and 30 minutes later, another 10 U is given IV over 2 minutes. Genetic engineering has produced the multiple point mutant of recombinant tPA, tenecteplase (TNK-tPA; TNKase). Tenecteplase's longer plasma

half-life than reteplase and alteplase allows for its single intravenous bolus injection (e.g., 50 mg IV over 5 seconds). In comparison to the other fibrinolytic agents, it has high fibrin specificity and resistance to inhibition by plasminogen activator inhibitor 1 (PAI-1). Alteplase, streptokinase, and urokinase have U.S. Food and Drug Administration (FDA) approval for the treatment of PE, and most guidelines recommend the use of alteplase.

Thrombolytic therapy provides more rapid lysis of PE and more rapid restoration of pulmonary perfusion than anticoagulant treatment, with associated reduction in pulmonary artery pressure and resistance and an improvement in right ventricular function.^{28,52,167,254,255} Despite the belief that these drugs have life-saving effects, thrombolytic agents have not convincingly shown a mortality benefit in clinical trials.²¹¹ Although a recent meta-analysis suggested that thrombolytic therapy offers a survival benefit to patients with acute PE (OR 0.53), fibrinolytics also carry a significant risk of bleeding.²⁵⁶ Thrombolytic therapy has had mixed efficacy in normotensive patients who have acute PE associated with signs of right heart dysfunction (submassive PE or intermediate to high-risk PE) while being associated with an increase in major hemorrhage that includes intracranial bleeding.^{1,2,167,203,254-266} In addition, few head-to-head comparisons of thrombolytic drugs for acute PE have been conducted.²⁶⁷ Taking data from all published clinical trials and other studies into account,^{132,256,263,265,266,268} the guidelines recommended the use of thrombolytic therapy mainly in patients with acute PE and associated hemodynamic instability (i.e., high-risk or massive PE).^{1,2} Rescue thrombolytic therapy may benefit patients who develop cardiovascular collapse after the initial treatment with anticoagulant therapy alone.²

Fibrinolytic therapy appears to have the most benefit when initiated within 48 hours of PE symptom onset. However, thrombolysis may still have efficacy when used in patients who have had symptoms for up to 2 weeks.²⁶⁹

The primary risk of thrombolytic therapy is major bleeding, which may include intracranial hemorrhage, and bleeding associated with treatment with fibrinolytic agents may lead to death. A registry study showed a 22% risk of major bleeding and a 3% risk of intracranial bleeding in thrombolysis recipients who had acute massive (high-risk) PE.⁵² A recent meta-analysis suggests that fibrinolytics have a significant risk of major hemorrhage (9.2%) and intracranial hemorrhage (1.5%).²⁵⁶ In patients deemed appropriate for thrombolytic therapy, a higher adult age, and comorbidities are associated with an increased risk of bleeding.²⁷⁰ Before using thrombolytic therapy, it is crucial to ensure that no contraindications to its use exist (Box 71-2).

UFH may be discontinued or continued during thrombolytic therapy.¹ Guidelines typically recommend the discontinuation of treatment with any of the other anticoagulants,² although a recent study of tenecteplase did not stop the required LMWH therapy around the single dose lytic/placebo treatment.²⁶¹ If UFH is not continued during lytic therapy, it is reasonable to restart it when the aPTT drops back into the therapeutic range (from a supratherapeutic value). UFH should be continued after the completion of lytic therapy until it is deemed safe to use agents that have longer half-lives and decreased reversibility.

Imminent or Actual Cardiac Arrest

Placebo-controlled pilot studies have shown a higher rate of return of spontaneous circulation and perhaps survival after a bolus of either 50 mg of recombinant tissue plasminogen activator (rTPA; alteplase)²⁷¹ or 50 mg of tenecteplase.²⁷²

Complications of Anticoagulation and Thrombolytic Therapy

The most frequent severe adverse effects of anticoagulant and thrombolytic therapies consist of bleeding. UFH and LMWH also have the infrequent but concerning risk of heparin-induced thrombocytopenia.²⁷³⁻²⁷⁶

BOX 71-2 Contraindications* to Fibrinolytic Therapy

ABSOLUTE CONTRAINDICATIONS

Prior intracranial hemorrhage
Known structural cerebral vascular lesion
Known malignant intracranial neoplasm
Ischemic stroke within past 3 months (excluding stroke within past 3 hours)
Suspected aortic dissection
Serious active bleeding or major bleeding diathesis (excluding menses)
Significant closed-head trauma or facial trauma within past 3 months

RELATIVE CONTRAINDICATIONS

History of chronic, severe, poorly controlled hypertension
Severely uncontrolled hypertension on presentation (SBP > 180 mm Hg or DBP > 110 mm Hg)
History of ischemic stroke more than 3 months ago
Traumatic or prolonged (>10 minutes) CPR, or major surgery within past 3 weeks
Internal bleeding within past 4 weeks
Noncompressible vascular punctures
Recent invasive procedure
Prior exposure (more than 5 days ago) or prior allergic reaction to streptokinase
Pregnancy
Active peptic ulcer
Pericarditis or pericardial fluid
Current use of anticoagulant (e.g., warfarin sodium) with INR > 1.7 or PT > 15 seconds
Age > 75 years
Diabetic retinopathy

SBP, systolic blood pressure; DBP, diastolic blood pressure; CPR, cardiopulmonary resuscitation; INR, international normalized ratio; PT, prothrombin time.

*Severity of condition and judgment of clinician will determine the categorization of absolute versus relative contraindication; list not all inclusive.

Bleeding

Patients at particular risk of bleeding are those who have had recent surgery or trauma or who have other clinical factors that predispose individuals to bleeding on anticoagulants (Box 71-3).²⁹ Procedures, surgeries, and medications that affect the coagulation system or platelet function may also increase the risk of bleeding.

Management of bleeding will depend on the cause, location, and severity of bleeding, as well as concomitant factors that include medications, laboratory values, and patient preferences. Clinically relevant bleeding should lead to discontinuation of UFH or thrombolytic therapy temporarily or permanently, and supportive measures should be provided. If urgent reversal of heparin effect is required, protamine sulfate can be administered.²²⁵

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT), a well-recognized complication of UFH and LMWH therapy, usually occurs within 5 to 10 days after heparin treatment has started.²⁷³⁻²⁷⁶ Approximately 1% to 2% of patients receiving UFH will experience a decrease in platelet count to less than the normal range or a 50% fall in the platelet count within the normal range.²⁷³⁻²⁷⁶ In the majority of cases, this direct effect of heparin on platelets causes mild to moderate thrombocytopenia and has no adverse consequences. However, patients receiving UFH may develop an immune thrombocytopenia mediated by immunoglobulin G (IgG) antibodies directed against a complex of PF4 and heparin.²⁷³⁻²⁷⁶

LMWH has a lower incidence of HIT in comparison to UFH^{241,242,273-279}; however, the clinical manifestations of HIT associated with LMWH use may be as or more severe than those observed with UFH. Furthermore, UFH and LMWH have different kinetics for the nadir of platelet count, onset, and duration of thrombocytopenia.²⁴¹

HIT may have a rapid onset in patients who have had recent exposure to heparin.²⁷³⁻²⁷⁶ The onset of HIT may be delayed and occur

BOX 71-3

Risk Factors for Bleeding* with Initial Anticoagulant Therapy**RISK FACTORS**

| | |
|-------------------|---|
| Age > 65 years | Diabetes |
| Age > 75 years | Anemia |
| Previous bleeding | Antiplatelet therapy |
| Cancer | Poor anticoagulant control |
| Metastatic cancer | Comorbidity and reduced functional capacity |
| Renal failure | Recent surgery |
| Liver failure | Frequent falls |
| Thrombocytopenia | Alcohol abuse |
| Previous stroke | |

*List not all inclusive.

The increased bleeding risk associated with a risk factor will vary with (1) severity of the risk factor (e.g., location and extent of metastatic disease, platelet count), (2) temporal relationships (e.g., interval from surgery or a previous bleeding episode), and (3) previous effectiveness of correction of cause of bleeding (e.g., upper-GI bleeding).

Compared with low-risk patients (0 risk factors), moderate-risk patients (1 risk factor) have a twofold risk, and high-risk patients (≥ 2 risk factors) have an eightfold risk of major bleeding. Adapted from the American College of Chest Physicians, Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl.):e432 (Table 2).

as long as several weeks after the end of exposure to heparin, thus making this syndrome more difficult to diagnose. Furthermore, the incidence and severity of HIT vary among different patient populations. Patients having cardiac or orthopedic procedures have a higher incidence of HIT than medical patients.²⁷³⁻²⁷⁶

The development of HIT has an association with arterial and venous thromboses known as heparin-induced thrombocytopenia and thrombosis (HITT). These thrombotic events may lead to serious complications that include compartment syndrome, limb ischemia (requiring subsequent amputation), and death.²⁷³⁻²⁷⁶

Most centers use HIT-antibody testing with enzyme-linked immunosorbent assay (ELISA) for the PF4-heparin complex to diagnose HIT. Since the risk of false-positive tests with this very sensitive test, a potential diagnosis of HIT should undergo confirmation with a highly specific functional assay, such as a serotonin release assay (SRA).²⁷³⁻²⁷⁶

A high suspicion of HIT or a diagnosis of HIT should lead to the immediate discontinuation of heparin/LMWH anticoagulation and the discontinuation of overlap warfarin therapy.^{275,276,280} Patients with HIT should receive an alternative form of anticoagulation because of the high incidence of thrombosis associated with the discontinuation of the standard anticoagulants.^{275,276,280} The most commonly recommended alternative agents include the direct thrombin inhibitors argatroban^{275,280-282} or lepirudin.²⁸³⁻²⁸⁶ Both agents are administered by an IV infusion. Lepirudin undergoes renal excretion and may be used by patients who have hepatic insufficiency.^{275,280} Lepirudin has the disadvantage that with prolonged use, antibodies develop, and anaphylaxis may occur.²⁸⁷ Although not approved by the FDA for this indication, some medical centers use bivalirudin instead of lepirudin for the treatment of HIT. Argatroban has partial hepatic excretion, so it is the preferred agent in patients who have renal failure, though significant hepatic insufficiency contraindicates its use.^{275,280} Overlapping therapy with VKA should not be initiated until the platelet count has recovered. The alternative antithrombotic agent should be continued until the platelet count returns to $\geq 100 \times 10^9/L$ and an adequate duration of oral therapy has occurred (e.g., INR therapeutic for two consecutive days on VKA therapy).²⁷⁵ Argatroban by itself increases the INR beyond that observed with VKA therapy alone, and specific recommendations exist for INR monitoring in this setting.²⁸² Although it has been less studied, fondaparinux has been used as an alternative antithrombotic agent in HIT patients, and many clinicians prefer the use of the

subcutaneous, fixed doses of this agent^{288,289} over the adjusted-dose intravenous direct thrombin inhibitors. Limited data exist regarding use of the newer oral non-VKA anticoagulants in patients who have HIT/HITT.²⁹⁰

Nonpharmacologic Therapies

Inferior Vena Cava Filter

Insertion of an inferior vena cava (IVC) filter is indicated for patients who have an acute VTE and an absolute contraindication to anticoagulant therapy.^{1,2} If the contraindication resolves, the patient should receive a standard course of anticoagulation. IVC filters are also indicated for those rare patients who have an objectively documented recurrent VTE during adequate anticoagulant therapy.^{1,2}

IVC filters help prevent embolism of pelvic or lower extremity DVT. Studies have shown a decreased risk of PE, an increased risk of DVT, and no effect on overall mortality in patients with proximal DVT who had treatment with an IVC filter and anticoagulation, in comparison to sole treatment with anticoagulation.²⁹¹⁻²⁹³

If a transient contraindication to anticoagulation due to a temporary high risk of bleeding occurs, a patient with an acute VTE should have a retrievable IVC filter placed.²⁹⁴⁻²⁹⁶ Several types of removable/retrievable IVC filters exist and can provide a temporary physical barrier against emboli from the lower extremities; however, they likely increase the risk of DVT.²⁹¹ After the contraindication to anticoagulation resolves, the retrievable filter should be removed. Thus, filter removal requires a second procedure. Retrievable IVC filters should be removed within the manufacturer's recommended time window, and when they are no longer indicated to prevent long-term complications (e.g., recurrent DVT), some retrievable filters should not become permanent because of risks of filter-related complications (e.g., strut fracture with possible embolization, migration, penetration of the vein wall, tilting, and thrombosis).^{297,298}

A recent study showed that a retrievable IVC filter plus anticoagulation in hospitalized patients who have PE associated with DVT and at least one other severity risk factor did not reduce the risk of symptomatic recurrent PE over 3 months of follow-up in comparison to anticoagulation alone.²⁹⁹ Thus, retrievable IVC filters should not be part of routine VTE management.

Catheter-Directed Treatment

In patients who have RV failure and large, central embolic burden, the concept of mechanically reestablishing pulmonary blood flow has great appeal. However, catheter-based mechanical clot treatment, with (i.e., pharmacomechanical treatment) or without local thrombolytic therapy, lacks strong data supporting a greater efficacy/safety profile over pharmacologic therapy alone for treating submassive/intermediate-risk^{167,301-304} or massive/high-risk³⁰¹ PE.^{1,2} Catheter-based interventions that use lytic therapy have not been adequately compared to lytic therapy alone. Catheter-based interventions provide another potential treatment option for patients with massive /high-risk PE who have contraindications to anticoagulation and thrombolytic agents.^{1,2}

Surgical Embolectomy

Surgical embolectomy has a role in patients who have massive/high-risk PE and a contraindication to thrombolytic therapy or failed thrombolytic therapy.^{1,2} Depending on center expertise, catheter-based interventions should be considered as a potential alternative option to surgical embolectomy.^{1,2}

Surgical embolectomy for acute PE, often reserved for patients who fall within the most severe spectrum of those with massive/high-risk PE, has had high morbidity and mortality (25%) rates.³⁰⁵⁻³⁰⁷ However, surgical embolectomy on cardiopulmonary bypass with the heart in arrest for the rescue of patients remaining unstable despite IV thrombolytic therapy has had reasonable success.¹⁶⁴ In a series of patients with major PE in whom thrombolysis failed to improve clinical status, those who underwent surgical embolectomy had fewer recurrent PEs and a trend toward fewer deaths significantly compared to those who

received repeat IV thrombolysis.¹⁶⁵ Patients who have a right heart thrombus that straddles the interatrial septum via a patent foramen ovale/atrial septal defect should be considered for surgical embolectomy.³⁰⁸ Embolectomy for free-floating right heart thrombus remains controversial.³⁰⁹ Taken together, these studies suggest surgical embolectomy in expert centers has an important role in PE treatment in selected patients who fail or have a contraindication to aggressive medical therapy. Center-specific protocols for the management of such cases may improve outcomes.^{166,310}

MONITORING AND FOLLOW-UP

Patients in the ICU who undergo anticoagulation, thrombolytic therapy, catheter-based therapy, or surgery for acute PE should be closely monitored for nonimprovement or decompensation associated

with the PE or its treatment (e.g., bleeding, HIT/HITT). Monitoring of pulmonary, cardiovascular, renal/volume and hematologic status will assist with management. Regarding laboratory testing, patients who receive UFH, argatroban, or lepirudin should have close monitoring of the aPTT. Anticoagulated patients should initially undergo platelet count and hemoglobin monitoring. HIT-Ab testing may be warranted with the initial thromboembolic event, with a PLT count drop, or with a recurrent thrombotic event. Hypercoagulable testing is typically not indicated in the acute setting. The need for procedures and surgical interventions may lead to PE management changes. The need to temporarily discontinue or change anticoagulant therapy will require cautious timing of drug and dose changes. Hemodynamically stable patients who have acute PE should undergo additional testing if hemodynamic instability develops (see Fig. 71-3), and thrombolytic therapy should be considered for PE-associated deterioration.

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Pulmonary hypertension (PH) is defined as a pulmonary artery mean pressure (PAPm) of 25 mm Hg or greater and may be precapillary or postcapillary in etiology. Postcapillary causes include processes affecting the left side of the heart (e.g., left ventricular systolic or diastolic dysfunction, mitral stenosis or regurgitation, and aortic valvular disease) or, more rarely, the pulmonary veins (pulmonary veno-occlusive disease). Management of postcapillary PH typically involves treating the underlying left-sided cardiac process. Medications used to treat precapillary PH are often not only ineffective for postcapillary PH but may in fact be harmful, potentially leading to the development of pulmonary edema or systemic hypotension.

Precapillary PH, or pulmonary arterial hypertension (PAH), can be idiopathic (IPAH, previously known as *primary PH* [PPH]) or may occur in association with a variety of underlying disease processes, such as collagen vascular disease, portal hypertension, congenital systemic-to-pulmonary shunts, drug or toxin exposure, or human immunodeficiency virus (HIV) infection.¹ IPAH is principally a disease of young women, but it can affect all age groups and both sexes. A genetic predisposition may underlie a substantial proportion of these cases and is referred to as heritable pulmonary arterial hypertension (HPAH).²⁻⁸

Initial therapy may be directed at an underlying cause or contributing factors such as using continuous positive airway pressure (CPAP) and supplemental oxygen for PH associated with obstructive sleep apnea. Following the identification and treatment of underlying associated disorders and contributing factors, specific therapy for PAH should be considered. IPAH carried a very poor prognosis (median survival rate of approximately 2.8 years from the date of diagnosis) through the mid-1980s. Subsequently, a number of therapeutic options have been developed, and 12 have been approved by the U.S. Food and Drug Administration (FDA), falling into three classes of drugs: (1) prostacyclins, including intravenous epoprostenol, treprostinil (subcutaneously, intravenously, by inhalation, and orally), and inhaled iloprost; (2) endothelin receptor antagonists (bosentan, ambrisentan, and macitentan); and (3) drugs acting on the nitric oxide pathway, including the phosphodiesterase (PDE) type-5 inhibitors, sildenafil and tadalafil, and the guanylate cyclase activator, riociguat.

■ DIAGNOSIS

Symptoms, Signs, and Clinical History

As a result of the insidious onset of symptoms, PAH is often advanced at the time of diagnosis. Dyspnea upon exertion is the most common presenting symptom, but it is sometimes attributed to deconditioning or another cardiorespiratory ailment. Chest pain, mimicking angina pectoris, may also occur. Patients with advanced disease may present with syncope or signs and symptoms of right-sided heart failure, including lower extremity edema, jugular venous distention, and ascites.

The clinical history should focus initially on the exclusion of underlying causes of PH. Important clues to an underlying condition might include a previous history of a heart murmur, deep venous thrombosis (DVT) or pulmonary embolism, Raynaud's phenomenon, arthritis, arthralgias, rash, heavy alcohol consumption, hepatitis, heavy snoring, daytime hypersomnolence, morning headache, and morbid obesity. A careful family history should be obtained. Medication exposure, particularly to appetite suppressants and amphetamines, should be noted.

Cocaine is a powerful vasoconstrictor and may contribute to the development of PH. Intravenous drug abuse has been associated with the development of PAH.

Physical Examination

Signs of PAH may not become apparent until late in the disease. Findings, such as an accentuated second heart sound, a systolic murmur over the left sternal border, jugular venous distention, peripheral edema, and ascites might suggest the presence of PH and right ventricular dysfunction. Associated systemic diseases, such as collagen vascular disease or liver disease may also become apparent during routine examination.

Laboratory Evaluation

Laboratory evaluation can provide important information in detecting associated disorders and contributing factors. A collagen vascular screen including antinuclear antibodies, rheumatoid factor, and erythrocyte sedimentation rate is often helpful in detecting autoimmune disease, although some patients with IPAH will have a low-titer positive antinuclear antibody test.⁹ The scleroderma spectrum of disease, particularly limited scleroderma, or the CREST syndrome (e.g., calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias), has been associated with an increased risk of the development of PAH.^{10,11} Liver function tests (e.g., aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase) may be elevated in patients with right ventricular failure and passive hepatic congestion but may also be associated with underlying liver disease. Liver disease with portal hypertension has been associated with the development of PH. Thyroid disease may occur with increased frequency in patients with IPAH and should be excluded with thyroid function testing.¹² HIV testing and hepatitis serologic studies should be performed. Routine laboratory studies, such as complete blood cell count, complete metabolic panel, prothrombin time, and partial thromboplastin time are recommended during the initial evaluation and as indicated to monitor the patient's long-term clinical status.

Echocardiography

Doppler echocardiography is useful in assessing the severity of PH and detecting left-sided heart disease. Findings may include the enlargement of the right ventricle, flattening of the interventricular septum, and compression of the left ventricle. Bubble contrast echocardiography may detect a right-to-left shunt, but exclusion of a left-to-right intracardiac shunt may require cardiac catheterization with an oximetry series. Echocardiography may be useful as part of a long-term follow-up,^{13,14} although not all patients have suitable echocardiographic windows.

Radiographic Evaluation and Exclusion of Thromboembolic Disease

Chest radiography may reveal an enlargement of the central pulmonary vessels and evidence of right ventricular enlargement. Evidence of parenchymal lung disease may also be apparent. When parenchymal lung disease is suspected, pulmonary function testing and high-resolution computed tomography (CT) of the chest may be indicated.

Ventilation/perfusion (V/Q) lung scanning should be performed in an attempt to exclude chronic recurrent pulmonary thromboembolic disease, which is among the most preventable and treatable causes of PH. Diffuse mottled perfusion can be seen in IPAH, whereas larger segmental and subsegmental mismatched defects are suggestive of chronic recurrent pulmonary thromboembolic disease. Intermediate results on V/Q lung scanning may require pulmonary arteriography to obtain a definitive diagnosis. Although contrast medium-enhanced CT has been popularized recently for the diagnosis of acute pulmonary thromboembolic disease, there is limited experience with this technique for this particular condition. Accordingly, we recommend caution at present in using contrast-enhanced CT to exclude chronic recurrent thromboembolic disease.

Pulmonary Function Testing

Pulmonary function testing is indicated to detect underlying parenchymal lung disease. The diffusing capacity is often reduced in pulmonary vascular disease, consistent with impaired gas exchange.

Right-Sided Heart Catheterization and Vasoreactivity Testing

Right-sided heart catheterization remains an important part of the evaluation. Left-sided heart dysfunction and intracardiac shunts can be excluded, the degree of PH can be accurately quantified, and cardiac output can be measured. Pulmonary vascular resistance can then be calculated. Acute pulmonary vasoreactivity can be assessed using a short-acting agent, such as prostacyclin (epoprostenol), inhaled nitric oxide, or intravenous adenosine.¹ The consensus definition of a positive acute vasodilator response in a PAH patient is a fall of PAPm of at least 10 mm Hg to ≤ 40 mm Hg, with an increased or unchanged cardiac output. The primary objective of acute vasodilator testing in patients with PAH is to identify patients who might be effectively treated with oral calcium channel blockers. The acute response to a short-acting agent such as prostacyclin has been shown to be predictive of the response to a calcium channel blocker.¹⁴ Unstable patients or those in severe right-sided heart failure who would not be candidates for treatment with calcium channel blockers need not undergo vasodilator testing.

TREATMENT

General Care

Warfarin, Oxygen, Diuretics, Digoxin, and Vaccination

Improved survival has been reported with oral anticoagulation in IPAH.^{15,16} The target International Normalized Ratio (INR) in these patients is 1.5 to 2.5. Anticoagulation of patients with PAH due to other underlying processes, such as scleroderma or congenital heart disease, is controversial. Generally, patients with PAH treated with chronic intravenous epoprostenol are anticoagulated in the absence of contraindications, owing in part to the additional risk of catheter-associated thrombosis.

Hypoxemia is a pulmonary vasoconstrictor and can contribute to the development or progression of PAH. It is generally considered important to maintain oxygen saturations greater than 90% at all times. Supplemental oxygen use is more controversial in patients with Eisenmenger physiology but may decrease the need for phlebotomy and potentially reduce the occurrence of neurologic dysfunction and complications.

Diuretics are indicated in patients with evidence of right ventricular failure and volume overload (i.e., peripheral edema and ascites). Careful dietary restriction of sodium and fluid intake is important in the management of patients with PAH with right-sided heart failure. Rapid and excessive diuresis may produce systemic hypotension, renal

insufficiency, and syncope. Serum electrolytes and measures of renal function should be followed closely in patients receiving diuretic therapy.

Although not extensively studied in PAH, digitalis is sometimes utilized in refractory right ventricular failure or atrial dysrhythmias. Drug levels should be followed closely, particularly in patients with impaired renal function.

Because of the potentially devastating effects of respiratory infections in PAH, immunization against influenza and pneumococcal pneumonia is recommended.

Calcium Channel Blockers

Patients with IPAH who respond to vasodilators and calcium channel blockers¹⁵ generally have improved survival. Unfortunately, this tends to represent a relatively small proportion of patients, comprising fewer than 20% of IPAH patients and even fewer patients with other causes of PAH.

Prostanoids

Prostacyclin, a metabolite of arachidonic acid produced primarily in the vascular endothelium, is a potent systemic and pulmonary vasodilator that also has antiplatelet aggregatory effects. A relative deficiency of endogenous prostacyclin may contribute to the pathogenesis of PAH.¹⁷

Epoprostenol. Epoprostenol therapy is complicated by the need for continuous intravenous infusion. The drug is unstable at room temperature and is generally best kept cold before and during infusion. It has a very short half-life in the bloodstream (<6 minutes), is unstable in an acidic pH, and cannot be taken orally. Because of the short half-life, the risk of rebound worsening with abrupt or inadvertent interruption of the infusion and its effects on peripheral veins, it should be administered through an indwelling central venous catheter. Common side effects of epoprostenol therapy include headache, flushing, jaw pain with initial mastication, diarrhea, nausea, a blotchy erythematous rash, and musculoskeletal aches and pain (predominantly involving the legs and feet). These tend to be dose dependent and often respond to a cautious reduction in dose. Severe side effects can occur with an overdose of the drug. Acutely, overdosage can lead to systemic hypotension. Chronic overdosage can lead to the development of a hyperdynamic state and high-output cardiac failure.¹⁸ Abrupt or inadvertent interruption of the epoprostenol infusion should be avoided because this may lead to a rebound worsening of PH, with symptomatic deterioration and even death. Other complications of chronic intravenous therapy with epoprostenol include line-related infections (which can range from small exit-site reactions to tunnel infections and cellulitis), bacteremic infections with sepsis), catheter-associated venous thrombosis, systemic hypotension, thrombocytopenia, and ascites.

Treprostinil. Treprostinil, a prostacyclin analog with a half-life of 3 hours, is stable at room temperature. An international placebo-controlled, randomized trial demonstrated that treprostinil improved exercise tolerance, although the 16-meter median difference between treatment groups in 6-minute walking distance was relatively modest.¹⁹ Treprostinil also improved hemodynamic parameters. Common side effects included headache, diarrhea, nausea, rash, and jaw pain. Side effects related to the infusion site were common (85% of patients complained of infusion-site pain, and 83% had erythema or induration at the infusion site). Treprostinil is also approved for intravenous delivery based on bioequivalence with the subcutaneous route and is also approved as an inhaled preparation administered in doses of 6 to 54 μ g, 4 times daily.²⁰

Inhaled Iloprost. Iloprost is a chemically stable prostacyclin analog with a serum half-life of 20 to 25 minutes.²¹ In IPAH, acute inhalation of iloprost resulted in a more potent pulmonary vasodilator effect than acute nitric oxide inhalation.^{21,22} In uncontrolled and controlled studies of iloprost for various forms of PAH,^{23,24} inhaled iloprost at a total daily dose of 30 to 200 μ g divided in 6 to 12 inhalations improved functional class, exercise capacity, and pulmonary

hemodynamics for periods up to 1 year of follow-up. The treatment was generally well tolerated except for mild coughing, minor headache, and jaw pain in some patients. The most important drawback of inhaled iloprost is the relatively short duration of action, requiring the use of 6 to 9 inhalations per day.

Beraprost. Beraprost sodium is an orally active prostacyclin analog²⁵ that is absorbed rapidly under fasting conditions. It has been evaluated in peripheral vascular disorders, such as intermittent claudication,²⁶ Raynaud's phenomenon, and digital necrosis in systemic sclerosis,²⁷ with variable results. Although several small, open, uncontrolled studies reported beneficial hemodynamic effects with beraprost in patients with IPAH, two randomized double-blind, placebo-controlled trials have shown only modest improvement and suggest that beneficial effects of beraprost may diminish with time.^{28,29}

Endothelin Receptor Antagonists

Endothelin-1 is a vasoconstrictor and a smooth muscle mitogen that may contribute to the pathogenesis of PAH. Endothelin-1 expression, production, and concentration in plasma^{30,31} and lung tissue³² are elevated in patients with PAH, and these levels are correlated with disease severity.

Bosentan. Bosentan is a dual endothelin receptor blocker that has been shown to improve pulmonary hemodynamics and exercise tolerance and delay the time to clinical worsening in PAH patients falling into NYHA Classes III and IV.^{33,34} The most frequent and potentially serious side effect with bosentan is dose-dependent abnormal hepatic function (as indicated by elevated levels of alanine aminotransferase and aspartate aminotransferase). Because of the risk of potential hepatotoxicity, the FDA requires that liver function tests be performed at least monthly in patients receiving this drug. Bosentan may also be associated with the development of anemia, which is typically mild. Hemoglobin and hematocrit should also be checked regularly.

Ambrisentan. Ambrisentan is a selective endothelin-A receptor antagonist that has been shown to be effective in PAH.³⁵ The typical doses are 5 to 10 mg daily.

Macitentan. Macitentan is a dual endothelin receptor antagonist that has been shown to reduce disease progression in PAH and is associated with a low incidence of liver function abnormality and peripheral edema. The usual dose is 10 mg daily.

PDE Inhibitors

PDEs are enzymes that hydrolyze the cyclic nucleotides, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), as well as limit the intracellular signaling. Drugs that selectively inhibit cGMP-specific PDEs (or PDE type-5 inhibitors) augment the pulmonary vascular response to endogenous or inhaled nitric oxide in models of PH.³⁶⁻³⁷ PDE5 is strongly expressed in the lung, and PDE5 gene expression and activity are increased in chronic PH.³⁸

Sildenafil. Sildenafil is a potent specific PDE5 inhibitor that is approved for erectile dysfunction. Recent reports have shown that sildenafil blocks acute hypoxic pulmonary vasoconstriction in healthy adult volunteers and acutely reduces PAPm in patients with PAH.³⁹ In comparison with inhaled nitric oxide, sildenafil produces similar reductions in PAPm. However, unlike nitric oxide, sildenafil also had apparent systemic hemodynamic effects. When combined with inhaled nitric oxide, sildenafil appears to augment and prolong the effects of inhaled nitric oxide,⁴⁰ and it appears to prevent rebound pulmonary vasoconstriction after acute withdrawal of inhaled nitric oxide.⁴¹ Several randomized studies have demonstrated sildenafil's efficacy in PAH, both as monotherapy and in combination with epoprostenol.^{42,43} Sildenafil treatment in animal models with experimental lung injury reduced PAP, but gas exchange worsened owing to impaired V/Q mismatch.^{44,45} Accordingly, caution is advised when using sildenafil to treat PH in patients with severe lung disease.

Tadalafil. Tadalafil, another PDE5 inhibitor previously approved for erectile dysfunction, is approved for the treatment of PAH based on a randomized clinical trial.⁴⁶ Side effects appear to be similar to sildenafil. The recommended dosage is 40 mg daily.

Riociguat. Riociguat is a novel agent whose mechanism of action is the activation of soluble guanylate cyclase, thereby potentiating the vasodilatory action of cyclic GMP, the mediator through which nitric oxide exerts its vascular effects. Riociguat is approved for the treatment of both PAH and inoperable chronic thromboembolic PH (CTEPH) and is the only drug therapy that has regulatory approval for the latter condition.

Combination Therapy

The AMBITION trial demonstrated that treatment-naïve PAH patients treated with initial combination therapy of ambrisentan and tadalafil had a significant reduction in the relative risk of disease progression.^{46a} Additionally, greater reductions in N-terminal pro-brain natriuretic peptide (a biomarker of cardiac overload) and greater improvements in exercise capacity compared with patients who were treated with monotherapy using either agent alone were also observed. Based on these findings, many experienced clinicians have begun initiating PAH treatment with combination therapy.

Nitric Oxide

Nitric oxide contributes to the maintenance of normal vascular function and structure. It is particularly important in the normal adaptation of the lung circulation at birth, and impaired nitric oxide production may contribute to the development of neonatal PH. L-Arginine is the sole substrate for nitric oxide synthase and thus is essential for nitric oxide production.

Inhaled Nitric Oxide. Inhaled nitric oxide has been shown to have potent and selective pulmonary vasodilator effects during brief treatment of adults with IPAH.⁴⁷ It is a potent pulmonary vasodilator in newborns with PH (persistent PH of the newborn [PPHN]), children with congenital heart disease, and patients with postoperative PH, acute respiratory distress syndrome, or undergoing lung transplantation.⁴⁸ It is of substantial benefit in PPHN, decreasing the need for support with extracorporeal membrane oxygenation (ECMO).⁴⁹ Although inhaled nitric oxide has been used in diverse clinical settings, especially in intensive care medicine, FDA approval for this therapy is limited to newborns with hypoxemic respiratory failure at this time.

In chronic PAH, the use of inhaled nitric oxide has been primarily for acute testing of pulmonary vasoreactivity during cardiac catheterization¹ (see earlier) or for acute stabilization of patients during deterioration.

Lung Transplantation

Lung transplantation for PAH is generally reserved for patients whose condition is failing despite the best available medical therapy. Whereas lung transplantation is challenging in general, it is even more so in the group of patients with PAH.⁵⁰ Worldwide, overall survival is approximately 77% at 1 year and 44% at 5 years.⁵¹ Survival in PAH patients undergoing lung transplantation is 66% to 75% at 1 year (one center has reported 1- and 5-year actuarial survival of 75% and 57%, respectively).⁵² The higher early mortality in PAH patients may be related to higher anesthetic and operative risks, the need for cardiopulmonary bypass,⁵³ and the increased occurrence of postoperative reperfusion pulmonary edema in patients with PAH undergoing single lung transplantation. In this situation, reperfusion pulmonary edema may be aggravated by the increased blood flow to the newly engrafted lung. In addition, V/Q mismatching can be particularly severe.⁵⁴ Most centers therefore seem to prefer bilateral lung transplantation for patients with PAH.⁵⁵ The timing of transplantation in PAH is challenging. It is probably most useful for patients exhibiting clear evidence of deterioration, such as the decline in functional capacity and the development of right-sided heart failure despite maximal medical therapy.

Special Situations in the Intensive Care Unit

DVT Prophylaxis

Patients with PAH are likely at an increased risk for the occurrence of DVT and are certainly at increased risk for poor outcomes as a

consequence of the development of DVT. Patients with PAH are prone to a more sedentary lifestyle and to chronic venous congestion of the lower extremities owing to increased right-sided cardiac filling pressures. Hospitalization in the intensive care unit (ICU), often with discontinuation of anticoagulation in anticipation of invasive procedures, likely places these patients at even higher risk for DVT. For these reasons, meticulous attention must be paid to DVT prophylaxis.

Procedures and Surgery

Procedures and surgery in patients with PAH can be associated with substantially increased operative and perioperative risks. In addition, appropriate precautions should be undertaken to optimize outcomes. As always, careful consideration should be given to whether an invasive procedure is absolutely necessary.

Vasovagal Events

Patients with severe PAH are particularly prone to vasovagal events, which can lead to severe consequences including syncope, cardiopulmonary arrest, and death. Pain, nausea, vomiting, or even a bowel movement can lead to a vasovagal event in patients with severe PAH. Cardiac output may be particularly dependent on heart rate in this situation. Moreover, the bradycardia and systemic vasodilatation that accompany a vasovagal event can result in an abrupt decrease in systemic arterial pressure. Therefore, patients should be closely monitored for their heart rate during invasive procedures, with readily available atropine or a similar agent.

Avoidance of Hypoxemia and Hypercarbia

Hypoxemia and hypercarbia are both pulmonary vasoconstrictors and can contribute to the worsening of PH. Oversedation can lead to ventilatory insufficiency and precipitate clinical deterioration. Caution should be utilized in laparoscopic procedures in which carbon dioxide is used for abdominal insufflation, because absorption can lead to hypercarbia. The induction of anesthesia and intubation for surgical procedures can be a particularly high-risk period for patients with PAH. This is because they are at risk for vagal events, hypoxemia, hypercarbia, and shifts in intrathoracic pressure with associated changes in cardiac filling pressures.

Pregnancy

The hemodynamic changes in pregnancy are substantial and volume shifts occur immediately postpartum, with cardiac filling pressures increasing as a result of decompression of the vena cava and the return of uterine blood into the systemic circulation. The changes induced by pregnancy impose a significant hemodynamic stress in women with IPAH, leading to an estimated 30% to 50% mortality rate.^{56,57} A meta-analysis of the outcome of pulmonary vascular disease and pregnancy reported a maternal mortality rate of 36% in Eisenmenger's syndrome, 30% in IPAH, and 56% in secondary PH.⁵⁸ Because of high maternal and fetal morbidity and mortality rates, most experts recommend effective contraception and early fetal termination in the event of pregnancy.⁵⁹ There have been case reports of successful treatment of pregnant IPAH patients with chronic intravenous epoprostenol,⁶⁰⁻⁶² inhaled nitric oxide,⁶³⁻⁶⁵ and oral calcium channel blockers.⁶⁶ Endothelin receptor antagonists are classified as teratogenic and should be avoided in this setting. In general, management includes early hospitalization for monitoring, supportive therapy with cautious fluid management, supplemental oxygen, diuretics, and dobutamine, as needed. The use of a pulmonary artery catheter for close hemodynamic monitoring and titration of vasodilator and cardiotonic therapy also has been recommended. Recommendations regarding the mode of delivery remain controversial.

Portopulmonary Hypertension

Patients with chronic liver disease have an increased prevalence of pulmonary vascular disease.^{67,68} Two forms of pulmonary vascular disease can complicate chronic liver disease: (1) the hepatopulmonary syndrome and (2) portopulmonary hypertension. Both tend to occur

in patients with chronic, late-stage liver disease, and each may increase the risk associated with liver transplantation.

Hypoxemia and intrapulmonary shunting characterize hepatopulmonary syndrome. Shunting may be manifest echocardiographically by the late appearance (after three to five cardiac cycles) of bubble contrast in the left side of the heart. Treatment is generally supportive, with supplemental oxygen. The syndrome may improve in some patients after liver transplantation. Severe hepatopulmonary syndrome may increase the risk associated with undergoing liver transplantation.

Portopulmonary hypertension occurs in patients with chronic, late-stage liver disease and portal hypertension.⁶⁹ Portopulmonary hypertension often differs hemodynamically from IPAH, and these differences may affect the approach to therapy. Patients with portopulmonary hypertension have lower pulmonary arterial diastolic and mean pressures, higher cardiac outputs, and lower pulmonary and systemic resistances.⁷⁰ Later-stage patients may develop hemodynamic findings similar to those of patients with IPAH, and this group may have a poorer prognosis and be at higher risk with attempted liver transplantation. It is occasionally possible to make a borderline candidate for liver transplantation acceptable through aggressive treatment of the PAH. Supplemental oxygen should be used as needed to maintain saturations $\geq 91\%$ at times. Diuretic therapy should be utilized to control volume overload, edema, and ascites. Anticoagulant therapy has not been carefully studied in this population and should likely be avoided in patients with significant coagulopathy due to impaired hepatic synthetic capability and in patients at increased risk of bleeding due to gastroesophageal varices. There have been a number of case reports and small case series describing the use of intravenous epoprostenol for treatment of portopulmonary hypertension.⁷¹⁻⁷⁵ Interestingly, some patients may demonstrate improvement in their PH following liver transplantation.⁷⁶ Other patients may develop worsening of their PH well after transplantation. It may be possible to wean an occasional patient off epoprostenol after liver transplantation. This should probably be done very gradually under close observation. The development of increasing dyspnea, fluid retention, or fatigue should prompt the reevaluation and reinstitution of epoprostenol if necessary. Because of its potential for hepatotoxicity, caution is advised in using the oral endothelin antagonists in this population.

KEY POINTS

1. The evaluation of patients with pulmonary hypertension (PH) is directed at the detection of underlying contributing factors and associated conditions such as left-sided cardiac dysfunction, underlying congenital heart disease, pulmonary thromboembolic disease, collagen vascular disease, parenchymal lung disease, obstructive sleep apnea, liver disease, amphetamine or appetite suppressant use, intravenous drug abuse, or human immunodeficiency virus (HIV) infection.
2. Patients with severe PH are particularly prone to vasovagal events, and when these occur they can lead to severe consequences, including syncope, cardiopulmonary arrest, and death.
3. Hypoxemia and hypercarbia are both pulmonary vasoconstrictors and can contribute to the worsening of pulmonary hypertension.
4. The induction of anesthesia and intubation for surgical procedures can be a particularly high-risk time for patients with PAH, as they are at risk for vagal events, hypoxemia, hypercarbia, and shifts in intrathoracic pressure with associated changes in cardiac filling pressures.

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■ References for this chapter can be found at expertconsult.com.

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Pneumothorax is defined as air within the pleural space and typically results from injury to the visceral pleura or mediastinum. Pneumothorax is commonly seen in the intensive care unit (ICU) due to iatrogenic causes such as central line placement or barotrauma in mechanically ventilated patients. Tension pneumothorax can be seen in 4% to 15% of mechanically ventilated patients in the ICU.^{1,2} In addition, patients with chronic lung diseases, cardiothoracic surgery, or trauma have an increased risk of pneumothorax. A simple pneumothorax may rapidly progress to a fatal tension pneumothorax with resultant hypoxia and/or hypotension or cardiogenic shock. Therefore, it is imperative that healthcare workers in the ICU must be able to rapidly diagnose and treat a pneumothorax.

■ PATHOPHYSIOLOGY

Pneumothorax most commonly results from a tear in the visceral pleura, but may air may also enter the pleural space from the atmosphere (trauma/iatrogenic) or via gas-producing organisms in the setting of empyema.³ Spontaneous pneumothorax is considered “primary” when there is no obvious underlying lung disease and “secondary” when there is underlying lung disease such as emphysema or cystic lung disease. Primary spontaneous pneumothorax typically occurs in tall, thin males with an “ectomorph” body habitus, and is thought to be due to increasing pleural porosity or rupture of previously unseen subpleural blebs.⁴ As patients with secondary spontaneous pneumothorax have underlying lung disease with less cardiopulmonary reserves, they typically present more acutely than those with primary spontaneous pneumothorax, which requires more urgent drainage and hospitalization is recommended.⁵ Nonspontaneous pneumothorax occurs either due to penetrating or blunt trauma, as well as iatrogenic injury of the chest wall or visceral pleura. Traumatic pneumothorax is the second most common clinical finding after chest trauma, following broken ribs. Iatrogenic pneumothorax in the ICU most often occurs after central venous access, thoracentesis, transbronchial lung biopsy, and positive pressure ventilation.⁶

The progression from a simple pneumothorax to tension pneumothorax relies on the continued escape of gas into a closed pleural space. This leads to increasing transpleural pressure, the collapse of the lung, atelectasis, and hypoxemia. As the tension pneumothorax becomes more severe, venous return is limited resulting in a fall in cardiac output and shock.

Animal studies have investigated the pathophysiology of tension pneumothorax.^{7,8,9} Proposed mechanisms contributing to tension physiology include hypoxia due to shunting of blood through the atelectatic lung, hypoventilation due to increased transpleural pressure causing reduced diaphragmatic excursion, and decreased preload from increases in intrathoracic pressure. The traditionally taught mechanism of vena cava mechanical obstruction likely plays less of a role.¹⁰ Major clinical findings may differ depending on whether the patient is spontaneously breathing or on positive pressure ventilation. Hypoxia is usually the main finding in spontaneously breathing patients. Patients with the impaired respiratory drive (needed to decrease intrathoracic pressure and increase venous return) or hypovolemia, however, may have reductions in cardiac output.

Patients on mechanical ventilation pose the highest risk for hemodynamic instability. The rate of increase in volume in the pleura space

depends on the volume/pressure being delivered and degree of pleural injury. With an increasing volume of gas entering the pleural space, a critical point is reached resulting in decreased venous return and eventual equalization of pressure within the cardiac chambers leading to a decrease in cardiac output and, ultimately, cardiac arrest.¹¹

■ DIAGNOSIS AND EVALUATION

The diagnosis of pneumothorax in critically ill patients can sometimes be made with information from the history and physical examination, noting acute onset of dyspnea or chest pain, tachycardia, hypotension, decreased breath sounds, pulsus paradoxus, and contralateral tracheal deviation. Although clinical features can be used to diagnose the presence of a pneumothorax, it should be noted that many of these findings are nonspecific and have not been a reliable indicator of pneumothorax size especially in the case of spontaneous secondary pneumothorax where severe symptoms of dyspnea can be out of proportion to the size of the pneumothorax, and underlying emphysema can cause diminished breath sounds. Acute changes in ventilatory parameters, such as a reduction in tidal volume or increase in airway pressures resulting from reduced respiratory system compliance, may be associated with pneumothorax but can also be found in other disease states and, therefore, have the potential to be misinterpreted under different clinical scenarios. As a result, radiologic imaging remains the gold standard for the diagnosis of pneumothorax.¹²

While radiographic imaging is optimal to diagnose pneumothorax, equipment may not be readily available, and therapeutic treatment (i.e., needle decompression or chest tube) may be required in unstable patients on clinical grounds prior to radiographic confirmation¹³ (Fig. 73-1).

Portable chest radiographs traditionally have been the initial diagnostic test in the ICU to diagnose a pneumothorax. Most of these radiographs in the ICU have the patient in the supine or semirecumbent position rather than an erect position.¹⁴ However, caution should be exercised when interpreting supine radiographs as the most non-dominant part of the chest (where air will collect) is in the costophrenic recess, known as the “deep sulcus sign.”¹⁵ A skin fold on chest radiograph may resemble a pneumothorax by mimicking a sharp lung edge but, in fact, represents a normal finding.¹⁶ Skin folds may be seen in elderly or obese patients and can be confirmed by a repeat radiograph in a different position. Due to the limitations of chest radiography, it is important to treat the patient and not the radiograph. In the right clinical situation with concern for tension pneumothorax, clinicians should proceed with immediate pleural evacuation to avoid further clinical decompensation. If there is doubt in regards to the findings on a chest radiograph and the patient is stable, it is advised to seek the expert opinion of the radiologist and/or further imaging with ultrasound or chest computed tomography (CT).¹⁷

CT is the gold standard test for confirming the diagnosis and size of the pneumothorax. CT also allows for assessment of underlying lung parenchyma and pleural-based lesions and can differentiate bullous disease from pneumothorax, potentially avoiding inappropriate drainage and creation of a parenchymal-pleural fistula.¹⁸ With widespread use of CT scanning, the diagnosis of occult pneumothoraces has become more common. The occult pneumothorax is defined as a pneumothorax detected via CT that was not clinically suspected or

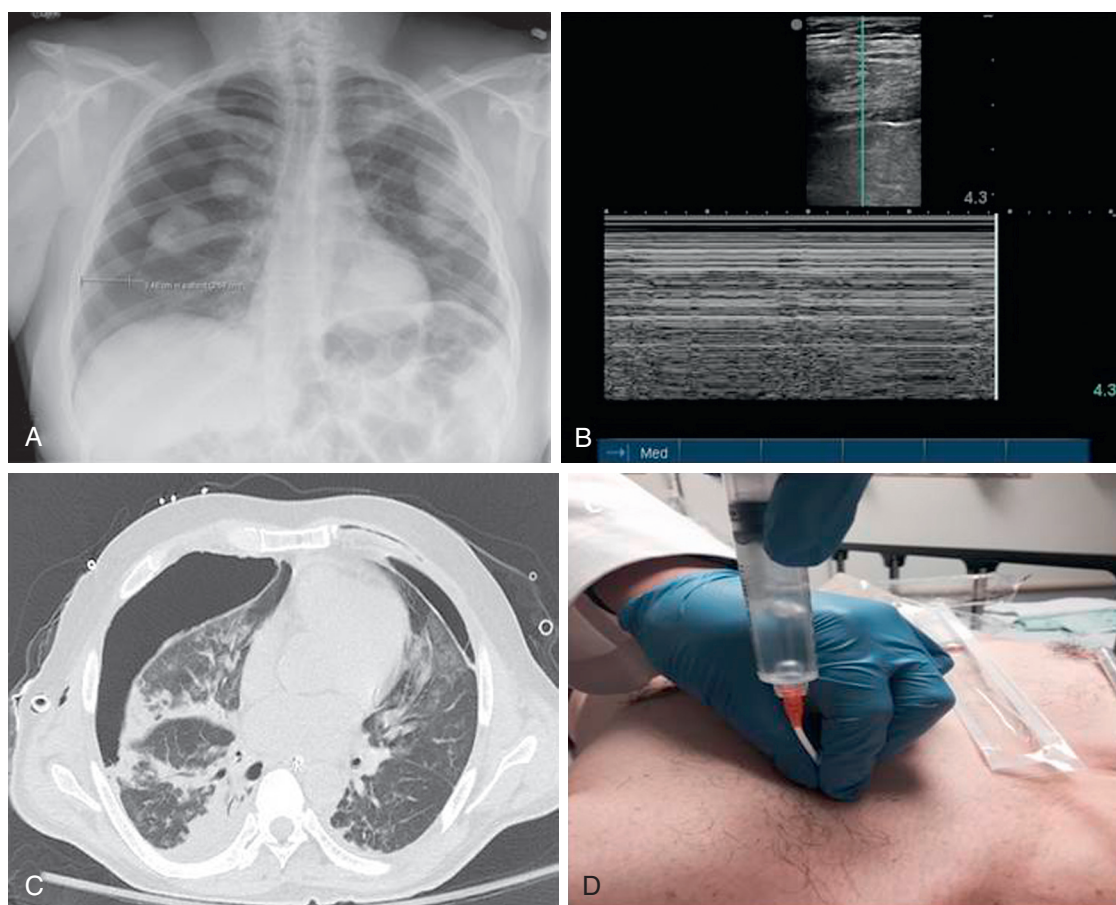


FIGURE 73-1 ■ Different modalities for diagnosing pneumothorax. **A**, Chest x-ray. **B**, US M-mode. **C**, CT scan. **D**, Needle Aspiration. CT, computed tomography; US, ultrasound.

recognized on standard chest radiography.¹⁹ This may be more common with the increased availability of CT scans. The overall incidence of trauma patients with an occult pneumothorax ranges from 2% to 15% and can be as high as 64% in multitrauma patients.²⁰ There is controversy on how to treat patients with an occult pneumothorax on mechanical ventilation due to the potential escalation to tension pneumothorax. A multicenter randomized study in a trauma population on mechanical ventilation did not show a difference in respiratory distress between observation vs. prophylactic chest tube insertion (relative risk: 0.71; 95% confidence interval: 0.40-1.27).²¹ Ultimately, 31% of the observed patients had subsequent chest tube placement nonurgently for worsening pneumothorax on imaging without an increase in morbidity. While this single study lends support for observation of occult pneumothoraces in mechanically ventilated patients in the trauma population, further studies are needed to guide management in different populations and situations. The expert consensus remains that clinical judgment is utilized to determine if drainage is needed.²²

Thoracic ultrasound has become an increasingly accessible tool in ICU for the diagnosis of pneumothorax. There are several advantages of ultrasound over chest radiograph and CT including availability at the bedside, absence of radiation, real-time imaging, and the ability to easily perform dynamic and repeat evaluations. A recent meta-analysis has shown that ultrasound is more sensitive and specific than a standard chest radiograph for detecting pneumothorax and can be used to assess lung re-expansion following tube thoracostomy.²³ The major pitfall in ultrasound is in acquiring the skills of image acquisition and interpretation for the nonradiologist.²⁴ Another limitation may be severe subcutaneous emphysema which will limit ultrasound waves penetrating into the thoracic cavity. A study comparing ultrasound to

CT/chest radiographs for the diagnosis of occult pneumothorax showed that the use of ultrasound detected 92% of occult pneumothoraces diagnosed with CT.²⁵ Ultrasound is extremely useful in ruling out pneumothorax after pleural procedures and central line placement, negating the need and time delay for a portable radiograph.^{26,27}

Normal movement of the underlying lung with respiration produces a “sliding” or “gliding” sign, and this dynamic movement identifies the visceral pleura and lung parenchyma. Examination of the lung with ultrasound commonly shows A-lines and B-lines. A-lines are horizontal, hyperechoic lines that represent reverberation artifacts of the visceral-parietal pleural interface. B-lines, also known as comet tail artifacts, are caused by echo reverberations of the air-filled lung and appear as narrow hyperechoic raylike opacities extending from the pleural line to the edge of the ultrasound screen without the fading that moves with lung sliding. As pleural air would block the visualization of the underlying lung, the presence of B-lines and lung sliding rules out a pneumothorax with a negative predictive value of 100% in the location of the chest probe.²⁸ It is important to examine several locations on the thorax, especially the superior anterior and lateral chest wall, where air would normally accumulate. One can also fail to see lung sliding when there is contralateral mainstem intubation, pleural-parenchymal adhesions, endobronchial obstruction, or diaphragmatic paralysis. Therefore, the main utility of ultrasound for assessment of pneumothorax lies in its ability to rule out a pneumothorax. Lung ultrasound, however, can also be used to rule in pneumothorax by identifying the point where the lung separates from the chest wall. This is seen as an area where normal lung sliding meets an area where no lung sliding is seen and has been termed the *lung point*. The lung point can be visualized with both B-mode and M-mode

ultrasound and, when seen, has 100% specificity for pneumothorax.²⁹ The sensitivity of the lung point for pneumothorax is inversely proportional to the size of the pneumothorax, as a large pneumothorax would prevent the parenchyma from opposing the chest wall. Ultrasound has recently been used to follow serially the lung point and determine if the pneumothorax is enlarging.

TREATMENT

The primary goal of the management of a pneumothorax is to restore normoxia and hemodynamic stability and evacuate air from the pleural space allowing visceral and parietal pleural apposition. Although many patients with a pneumothorax can be managed with supplemental oxygen and monitoring, the majority of patients in the ICU with a pneumothorax require evacuation of pleural space.³⁰ The etiology of the pneumothorax and clinical characteristics of the patient will dictate treatment. Pneumothorax secondary to barotrauma, tension pneumothorax, and concurrent sepsis has been significantly and independently associated with an increased risk of death in the ICU.³¹ The British Thoracic Society recommends intercostal drainage for all pneumothoraces in patients on a mechanical ventilator, as well as those exhibiting signs or suspicion of tension physiology, traumatic pneumo, or hemothorax and postsurgical pneumothoraces.³² The role of needle decompression has not been well elucidated for patients on mechanical ventilation, and there are data to suggest that the therapeutic effect of this intervention may be insufficient despite proper placement and positioning.^{33,34} If needle decompression is performed, standard tube thoracostomy is usually subsequently required for definitive management.

The standard treatment for a mechanically ventilated patient with a pneumothorax or tension pneumothorax is chest tube thoracostomy.^{35,36} Optimal chest tube size remains unclear due to the difficulty in assessing the degree of visceral pleural injury. The recent British Thoracic Society guidelines recommend a small-bore tube for the initial management of pneumothorax. These tubes are associated with less pain and likely have reduced complications in patients with thrombocytopenia or coagulopathy. The risk of serious complications associated with small-bore catheters is small with a frequency of organ injury of 0.2% and a malposition rate of 0.6%. The largest risk is drain blockage, with a rate of 8.1% and is easily preventable with scheduled sterile flushing to maintain patency.³⁷ The use of ultrasound has decreased the rate of complications and should be routinely used, especially in the nonemergent placement of chest tubes.¹³ If there is a high clinical suspicion of tension pneumothorax, chest tube insertion should not be

delayed while awaiting radiographic confirmation as the delay in care may become fatal; however, in this case, it may be prudent to perform open (surgical) thoracostomy as opposed to the modified Seldinger technique in order to avoid injury to the lung, heart, or other organs should pneumothorax not be present.¹⁷

PROLONGED AIR LEAK

Prolonged or persistent air leaks (>3-5 days) may represent a more complex problem requiring additional treatment beyond chest tube insertion. Factors such as poor nutrition, the size of the pleural injury, mechanical ventilation, and medications (i.e., steroids) may hinder resolution of a pneumothorax in the ICU. Current guidelines recommend early thoracic surgery consultation with video-assisted thoracoscopic surgery (VATS) over full or partial thoracotomy as the treatment of choice for prolonged pleural air leaks. While surgical intervention has been shown to be effective and safe for persistent air leakage, most studies do not include critically ill patients.^{38,39} For patients that are not good surgical candidates, bronchoscopic treatment implanting a unidirectional endobronchial valve to isolate and close the fistula has been described to be safe and effective and is approved for a humanitarian device exemption in the United States.⁴⁰ The valves are currently indicated for the treatment of prolonged air leaks or leaks that are likely to be prolonged (defined as >7 days) following lobectomy, segmentectomy, or surgical lung volume reduction. However, many valves in the United States are placed off-label in patients with secondary spontaneous pneumothorax. The procedure is performed by first identifying the “culprit” airway via sequential bronchoscopic balloon occlusion. When the airway leading to the alveolar-pleura fistula is occluded, the amount of air leak in the chest drainage system will stop or be significantly reduced. The valve is then sized and inserted through the working channel of the flexible bronchoscope.

KEY POINTS

1. Pneumothorax is common in the ICU and may have various clinical presentations.
2. Treatment of a highly suspected tension pneumothorax should not be delayed for radiographic confirmation.
3. Occult pneumothorax on mechanical ventilation should be closely monitored if chest tube insertion is readily available.

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Pneumonia is an infection of the gas-exchanging units of the lung and has a wide spectrum of clinical severity, ranging from mild outpatient illness to severe respiratory failure and sepsis. Together, pneumonia and influenza are the eighth leading cause of death in the United States and the number one cause of death from infectious diseases.^{1,2} Pneumonia in the community setting or within 48 hours following admission is termed *community-acquired pneumonia* (CAP). The “community” also includes patients with exposure to the health-care environment, and pneumonia in such patients is referred to as “health care-associated pneumonia” (HCAP). Some, but not all, patients with HCAP are at risk for infection by multidrug-resistant (MDR) pathogens and may require empiric broad-spectrum antibiotic therapy, but many can be managed with therapy directed against CAP pathogens.³ There has been increasing scrutiny by the Centers for Medicare and Medicaid Services on public reporting of outcomes and quality measures related to CAP.⁴ Pneumonia patients requiring mechanical ventilation (MV) or invasive vasopressor support are generally considered as having severe CAP (SCAP). However, there is no uniform definition for SCAP, and in the absence of these two factors, it is challenging to define severe pneumonia. Severity assessment scores may identify high-risk patients and help with site-of-care decisions, since a delay at the intensive care unit (ICU) level of care for patients with severe pneumonia is associated with worse outcomes. Biomarkers such as procalcitonin (PCT) are increasingly being used to identify patients with bacterial pneumonia and, along with severity assessment scores, may help identify high-risk patients and assist antimicrobial stewardship and de-escalation.⁵

INCIDENCE

The annual incidence of pneumonia ranges from 5 to 11 per 1000 population, and the majority of patients are treated out of the hospital.^{1,6} However, the major portion of the cost of treatment is focused on hospitalized patients, particularly those admitted to critical care units. In addition, those with comorbid illness and those of advanced age make up a large proportion of the hospitalized, critically ill CAP patients, and pneumonia in this population causes significant morbidity and mortality. Although CAP can vary from being a mild to a severe illness, very few hospitalized patients are severely ill enough to require ICU admission.^{7,8} Torres et al. specifically examined all ICU admissions over a 4-year period and noted that 10% were related to CAP; in this group, 42% were admitted directly to the ICU, 37% came to the ICU after admission to another ward, and 21% came after transfer from another hospital.⁷

The time to ICU admission may have an impact on subsequent prognosis. Woodhead et al. found that CAP accounted for 5.9% of all ICU admissions and that early admission (within 2 days of hospitalization) was associated with a lower mortality (46.3%) than late admission (>7 days in the hospital; 50.4% mortality).⁹ Recently, Restrepo and colleagues also noted a higher mortality among CAP patients admitted to the ICU after 48 hours as compared with direct admission or within 24 hours, even after adjustment for the severity of illness (47.4% vs. 23.2%, $P = 0.02$).¹⁰

The economic liability associated with CAP remains significant, at >\$17 billion annually in the United States.¹¹ Kaplan and colleagues evaluated the cost of care for 623,718 elderly patients with CAP in the United States and found that two-thirds of the population had one or

more underlying illnesses, with congestive heart failure, the most common comorbidity, present in 32%.⁸ The overall mortality rate was 10.6% but rose higher with advancing age, nursing home residence, and comorbid illness. The mean length of stay (LOS) was 7.6 days, and the costs generally paralleled the LOS but were disproportionately high for those needing MV. Kozma et al., in a study of around 1.5 million CAP admissions, showed a potential economic benefit of 2300 USD per one less day spent in the hospital per patient.¹² Other studies of CAP have reported that costs are higher for patients with comorbid illness than for those without, but in those without comorbid illness, the cost for those who died was less than for those who survived, while the opposite was true when the entire CAP population was considered.¹³

RISK FACTORS FOR DEVELOPING SCAP

In all studies of CAP, patients who were admitted to the hospital or ICU commonly had a number of coexisting illnesses, suggesting that individuals who are chronically ill have an increased risk of developing severe illness (Table 74-1).¹⁴ In studies of SCAP, serious coexisting illness was present in 46% to 66% of all patients.^{8,14,15} The common chronic illnesses in these patients are respiratory disease, cardiovascular disease, and diabetes mellitus.^{1,16,17} The most common respiratory illness in CAP patients is chronic obstructive pulmonary disease (COPD), a finding that applies to those with either the mild or severe forms of CAP.^{7,17}

Cigarette smoking has been identified as a risk factor for bacteremic pneumococcal infection, especially in younger patients with fewer comorbid conditions, and “current smoking” status is associated with a higher mortality in CAP patients than in nonsmokers or ex-smokers.^{7,18,19} Other common illnesses associated with CAP include malignancy, neurologic illness (including seizures), and acquired immune deficiency syndrome (AIDS).^{1,15} One study identified alcohol abuse as a risk factor, along with the failure to receive antibiotic therapy before hospital admission, which suggests that a delay in therapy may convert milder forms of pneumonia into a more severe illness.¹⁵ Genetic differences in the immune response may predispose certain individuals to more severe forms of infection and adverse outcomes.²⁰ Further, use of inhaled corticosteroids is related to an increased risk of developing serious pneumonia compared to placebo.²¹

PROGNOSTIC FACTORS

In recent years, there has been a trend toward increased hospitalizations in patients with a diagnosis of CAP, especially in the elderly and those with comorbid diseases, who may also have higher mortality.^{22,23} Various studies have pointed out a high inpatient mortality among CAP patients ranging from 12.1% to 24.4% and an even higher mortality in patients admitted to ICUs.^{17,24,25} Lately, investigators from the Community-Acquired Pneumonia Organization (CAPO) international cohort study reported mortality differences among patients hospitalized for CAP, with a higher frequency of deaths in Latin America (13.3%) compared with Europe (9.1%) and the United States (7.3%).²⁶

In a meta-analysis of 33,148 patients with CAP, the overall mortality rate (OR) was 13.7%, but those admitted to the ICU had a mortality rate of 36.5%. Factors associated with increased mortality in

TABLE 74-1

Risk Factors for Developing Severe Community-Acquired Pneumonia

Advanced age
 Comorbid illness (e.g., chronic respiratory illness, cardiovascular disease, diabetes mellitus, neurologic illness, renal insufficiency, malignancy)
 Cigarette smoking
 Alcohol abuse
 Absence of antibiotic therapy before hospitalization
 Failure to contain infection to its initial site of entry
 Immune suppression
 Genetic polymorphisms in the immune response

hospitalized CAP patients included male sex, pleuritic chest pain, hypothermia, systolic hypotension, tachypnea, diabetes mellitus, neoplastic disease, neurologic disease, bacteremia, leukopenia, and multilobar infiltrates.²⁵

Metersky et al. evaluated factors predicting in-hospital versus post-discharge mortality in 21,223 Medicare patients, 65 years old or older, admitted with a diagnosis of pneumonia.²⁴ The authors noted a mortality of 12.1% within 30 days of admission (52.4% of the deaths occurred during the hospital stay), and in-hospital mortality was higher in patients requiring MV on admission, and who had bacteremia, hypotension (blood pressure of less than 90 mm Hg systolic), respiratory rate of greater than 30 beats/min, pH of less than 7.35, and renal failure. Of note, the timing of death (early versus late) was unrelated to baseline patient demographic factors or comorbidities, but in-hospital mortality was related to the severity of illness.

In other studies, the clinical features that predicted a poor outcome (Table 74-2) included advanced age (>65 years), preexisting chronic illness of any type, the absence of fever on admission, respiratory rate greater than 30 breaths/min, diastolic or systolic hypotension, elevated blood urea nitrogen (BUN > 19.6 mg/dL), profound leukopenia or leukocytosis, inadequate antibiotic therapy, need for MV, hypoalbuminemia, and the presence of certain “high-risk” organisms (type III pneumococcus, *Staphylococcus aureus*, gram-negative bacilli, aspiration organisms, or postobstructive pneumonia).¹ One study of 3233 patients in Spain found that risk factors for all-cause mortality included a higher severity of illness on admission, the need for ICU care, and the presence of multilobar infiltrates. However, late mortality (after at least 3 days) was reduced if blood cultures were negative, antibiotic therapy was consistent with guidelines, and if an etiologic agent was identified.²⁷ In another prospective study of 1166 SCAP patients from 17 different countries, factors related to mortality at 28 days and at the 6-month follow-up were higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores, lower hematocrit, and the need for MV, and lower pH on arterial blood gas analysis predicted early mortality.¹⁷ Other studies have noted that an elevated red cell distribution width, alone or in combination with elevated BUN \geq 30 mg/dL, was related to increased 90-day mortality and a complicated hospital course in CAP patients, likely reflecting the inflammatory suppression of erythropoiesis in severe infection.^{28,29} In general, the severity of illness on admission affected early mortality the most, while therapy-related, modifiable risk factors affected late mortality.

Prina and colleagues noted a biphasic relationship between platelet count and mortality in hospitalized CAP patients, with increased mortality once the count was outside the range of 100,000 to 400,000/mm³.^{3,30} The authors noted more respiratory complications, such as empyema and pleural effusion in patients with thrombocytosis (platelet count $\geq 4 \times 10^5$ /mm³) than in those without thrombocytosis. On the other hand, those with thrombocytopenia (platelet count $\leq 10^5$ /mm³) had higher rates of severe sepsis, septic shock, invasive MV, and ICU admission than the rest of the population. In another study, Laserna and associates observed a biphasic relationship when relating CAP mortality to arterial partial pressure of carbon dioxide (PaCO₂)

TABLE 74-2

Risk Factors for a Poor Outcome from Community-Acquired Pneumonia**PATIENT-RELATED FACTORS**

Male sex
 Absence of pleuritic chest pain
 Nonclassic clinical presentation
 Neoplastic illness
 Neurologic illness
 Age >65 years
 Family history of severe pneumonia or death from sepsis

ABNORMAL PHYSICAL FINDINGS

Respiratory rate >30 breaths/min on admission
 Systolic (<90 mm Hg) or diastolic (<60 mm Hg) hypotension
 Tachycardia (>125 beats/min)
 High fever (>40°C) or afebrile
 Confusion

LABORATORY ABNORMALITIES

Blood urea nitrogen >19.6 mg/dL
 Leukocytosis or leukopenia (<4000/mm³)
 Multilobar radiographic abnormalities
 Rapidly progressive radiographic abnormalities during therapy
 Bacteremia
 Hyponatremia (<130 mmol/L)
 Multiple organ failure
 Respiratory failure
 Hypoalbuminemia
 Thrombocytopenia (<100,000/mm³) or thrombocytosis (>400,000/mm³)
 Arterial pH <7.35
 Pleural effusion

PATHOGEN-RELATED FACTORS

High-risk organisms
 Type III pneumococcus, *Staphylococcus aureus*, gram-negative bacilli (including *Pseudomonas aeruginosa*), aspiration organisms, severe acute respiratory syndrome
 Possibly high levels of penicillin resistance (minimal inhibitory concentration of at least 4 mg/L) in pneumococcus

THERAPY-RELATED FACTORS

Delay in initial antibiotic therapy (more than 4 hours)
 Initial therapy with inappropriate antibiotic therapy
 Failure to have a clinical response to empiric therapy within 72 hours

on admission, with both hypocapnia (PaCO₂ < 35 mm Hg) and hypercapnia (PaCO₂ > 45 mm Hg) being risk factors for high 30-day mortality and a higher need for ICU admission compared with patients with a normal PaCO₂, even after excluding patients with COPD.³¹

As with other acute severe infections, any delay in treatment or admission to the ICU in patients with SCAP can lead to higher rates of complications and increased mortality.¹⁰ Several studies have noted an increased mortality when CAP patients have a delay in the initiation of appropriate antibiotic therapy, with most studies using an average of 6 hours since being first evaluated in the emergency room as the cutoff value.^{1,7,15,32,33} Renaud et al., in a study of 453 CAP patients, noted that the 28-day mortality was 11.7% for those with an obvious need for ICU care who were directly admitted to the ICU, which was significantly lower than the 23.4% mortality rate of those without obvious need for ICU care and had delayed admission.³⁴ Hraiech and associates divided CAP patients into those requiring MV within 72 hours of the onset of CAP and those with progressive respiratory failure requiring invasive MV 4 or more days after the onset of CAP.³⁵ There was a significant difference in mortality between the early respiratory failure group compared with the late respiratory failure group (28% vs. 51%, $P = 0.03$), suggesting that a delay in the identification of respiratory failure, transfer to ICU, or the development of progressive symptoms have deleterious effects on patient outcome.

In a study evaluating early cardiac events, including myocardial infarction and cardiac arrest in 55,276 patients, Carr and colleagues noted that 8% of cardiac arrest cases occurred in pneumonia patients; in this population, 62% of cardiac arrests occurred in patients admitted to the ICU, and only about 50% were on vasopressors or required MV.³⁶ Cardiac arrest occurred earlier in the ICU than in the ward (at a median of 18.9 vs. 28.4 hours) and was generally not a shockable rhythm (asystole or pulseless electrical activity). These findings suggest that patients with CAP in the hospital, or even the ICU, commonly have cardiac ischemia and that the event may be abrupt and without warning, potentially causing cardiorespiratory arrest. In another study, a restrictive red blood cell transfusion strategy (target hemoglobin level –7 to 9 g/dL in all patients, except those with acute myocardial infarcts or unstable angina) was associated with better outcomes for CAP patients.³⁷

When these findings are viewed together, they suggest some general principles. Mortality is more likely in CAP patients who have severe physiologic derangements, serious underlying illnesses, a delay in the initiation of appropriate antimicrobial therapy or MV, and the presence of atypical clinical features. This last factor suggests that an unusual clinical presentation (low fever, nondistinct respiratory symptoms) is associated with mortality, which may be the result of its reflecting an inadequate inflammatory response to infection and because it can also lead to a delay in the recognition of pneumonia and the institution of appropriate therapy.

■ PATHOGENESIS

Pneumonia results when host defenses are overwhelmed by an infectious pathogen. This may occur because the patient has an inadequate immune response, often as the result of underlying comorbid illness, anatomic abnormalities, acute illness-associated immune dysfunction, or therapy-induced dysfunction of the immune system. Pneumonia can also occur in patients who have an adequate immune system if the host defense system is overwhelmed by a large inoculum of microorganisms or if the patient encounters a particularly virulent organism to which he or she has no preexisting immunity or to which the patient has an inability to form an adequate acute immune response.^{38,39}

Microaspiration of infected oropharyngeal secretions is the most common mechanism associated with pneumonia. Other routes of entry include inhalation, which applies primarily to viruses, *Legionella pneumophila*, *Mycobacterium tuberculosis*, hematogenous dissemination from extrapulmonary sites of infection (right-sided endocarditis), and direct extension from contiguous sites of infection (such as liver abscess). Thus, previously healthy individuals develop infection with virulent pathogens such as viruses, *L. pneumophila*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Streptococcus pneumoniae*. On the other hand, chronically ill patients can be infected by these organisms, as well as by organisms that commonly colonize patients but only cause infection when immune responses are inadequate. These organisms include enteric gram-negative bacteria (e.g., *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp.) and fungi.

Studies that have evaluated the normal lung immune response to infection have shown that in most patients with unilateral CAP, the inflammatory response is limited to the site of infection.³⁹ In patients with localized pneumonia, tumor necrosis factor alpha (TNF α), interleukin (IL)-6, and IL-8 levels were increased in the pneumonic lung and generally not increased in the uninvolved lung or in the serum.^{40,41} On the other hand, in patients with severe pneumonia, the immune response is characterized by a “spillover” of the immune response into the systemic circulation, reflected by increases in the serum levels of TNF α and IL-6.⁴² It remains uncertain why localization does not occur in all individuals and why some patients develop diffuse lung injury (e.g., acute respiratory distress syndrome [ARDS]) or systemic sepsis as a consequence of pneumonia. These complications may result from an inability to develop a brisk lung immune response as a consequence of specific bacterial virulence factors, inadequate or delayed therapy, or genetic polymorphisms that affect the immune response.⁴³

Pneumonia-associated inflammation may also impact the long-term mortality and cognitive decline in CAP patients.⁴⁴⁻⁴⁶

■ CLINICAL FEATURES

Symptoms and Physical Findings

Patients with CAP and an intact immune system have a normal pulmonary response to infection and generally have respiratory symptoms such as cough, sputum production, and dyspnea, along with fever and other complaints. Cough is the most common finding and is present in up to 80% of all patients but is less common in those who are elderly, those with serious comorbidities, or patients coming from nursing homes.⁴⁷ Pleuritic chest pain is also common in patients with CAP, and in one study, its absence was also identified as a poor prognostic finding.⁴⁸ The elderly generally have fewer respiratory symptoms than younger individuals, and as mentioned, the absence of clear-cut respiratory symptoms and an afebrile status are themselves predictors of an increased risk of death.^{1,49} In elderly patients, pneumonia can have a nonrespiratory presentation, with symptoms of confusion, falling, failure to thrive, altered functional capacity, or deterioration in a pre-existing medical illness, such as congestive heart failure.^{47,50,51}

Physical findings of pneumonia include tachypnea, crackles, rhonchi, and signs of consolidation (egophony, bronchial breath sounds, dullness to percussion). Patients should also be evaluated for signs of pleural effusion. In addition, extrapulmonary findings should be sought to rule out metastatic infection (arthritis, endocarditis, meningitis) or to add to the suspicion of an “atypical” pathogen, such as *M. pneumoniae* or *C. pneumoniae*, which can lead to complications such as bullous myringitis, rash, pericarditis, hepatitis, hemolytic anemia, or meningoencephalitis. In the elderly, an elevation of respiratory rate can be the initial presenting sign of pneumonia, preceding other clinical findings by as much as 1 to 2 days.⁵² In fact, in one study, tachypnea was the most common finding in elderly patients with pneumonia, being present in over 60% of all patients and occurring more often in the elderly than in younger patients with pneumonia.⁴⁷

Radiographic Features

For most patients, CAP is defined by a combination of clinical symptoms and the presence of a new radiographic infiltrate, but not all patients with this illness will have this finding when first evaluated. Even when the radiograph is negative, if the patient has appropriate symptoms and focal physical findings, pneumonia may still be present. Although some studies have suggested that febrile and dehydrated patients can have a normal chest radiograph when first admitted with pneumonia, the idea of hydrating pneumonia is in the realm of “conventional wisdom” and anecdotal reports. The presence of alveolar densities (lobar or bronchopneumonic) has been associated with a high likelihood of a bacterial etiology, but it is extremely difficult to distinguish among specific pathogens using patterns of radiographic abnormalities.⁵³ Chest radiographs may have prognostic value in patients with severe pneumonia, multilobar infiltrates, or rapid progression of infiltrates serving as poor prognostic signs, helping to identify patients who require intensive care.^{1,7} Computed tomography (CT) scan of the chest generally has a higher sensitivity in diagnosing occult pneumonia with an initially negative chest radiograph.⁵⁴ Chest CT can also have value in the critically ill patient in situations when a noninfectious process is being considered or when complications such as pneumothorax, empyema, or abscess are suspected. CT can suggest certain alternative noninfectious diagnoses such as granulomatous vasculitis, acute eosinophilic pneumonia, and bronchiolitis obliterans with organizing pneumonia.

Lung ultrasound (LUS) denotes a new technique that has increasingly been adopted for diagnosing pleural and pulmonary diseases. Various patterns with B and M mode ultrasound techniques including “tissue sign,” “shred or fractal sign,” and “dynamic air bronchograms” are seen with pulmonary consolidation; whereas the “sinusoidal sign”

and “quad sign” are seen with even small pleural effusion.⁵⁵ In a prospective, multicenter study including 362 patients with suspected CAP, LUS was found to have a sensitivity of 93.4% and specificity of 97.7% compared with chest x-ray and chest CT.⁵⁶ In that study, the combination of LUS and auscultation decreased the negative likelihood ratio to 0.04 (95% confidence interval [CI]: 0.02-0.09), but the technique is operator dependent, and about 8% of pneumonic lesions are not visualized by LUS. The noninvasive nature of the test and rapidity with which it can be performed make this test another tool in the armamentarium for critical care physicians, and a recent meta-analysis of 10 studies with 1172 patients supports the use of LUS by skilled practitioners.⁵⁷

Severity Scoring in CAP

Although there is no uniformly accepted definition for SCAP, this term generally refers to any patient who is admitted to the ICU because of CAP. Most of these patients have severe sepsis or “respiratory failure,” which is defined by the presence of hypoxemia or hypercarbia, and not all such patients require MV. Some patients with CAP are treated in the ICU because the pneumonia has led to clinical instability of an underlying disease, but the pneumonia itself may not be severe. Bacteremia does not always correlate with more severe illness, and its presence alone is not always a predictor of a poor outcome, with most episodes of bacteremia being due to pneumococcus. However, in the elderly with pneumococcal pneumonia, bacteremia is present in one-fourth of patients with CAP and is often associated with azotemia and multilobar involvement.⁵⁸ When an infection such as pneumonia is complicated by severe sepsis or septic shock (not just bacteremia), the outcome is adversely affected, with increases in mortality, LOS, and costs for survivors.

One approach to evaluating CAP patients is to use a scoring system to define prognosis and predict the risk of death. The most widely used prognostic scoring systems are the Pneumonia Severity Index (PSI) and a modification of the British Thoracic Society (BTS) scoring system, the CURB-65 score. Other prediction rules, such as the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) criteria for SCAP, the Australian SMART-COP, the Japanese A-DROP scoring system, CAP-PIRO, and the Spanish CURXO-80 have also been developed for risk prognostication and to help with appropriate resource utilization.^{1,59-61}

The investigators in the Pneumonia Outcomes Research Team (PORT) study developed a mortality prediction rule that classifies all patients into one of five groups (PSI classes I to V), each with a different level of risk for death.⁶² Patients in classes IV and V have predicted mortality risks of 8.2% to 9.3% and 27% to 31.1%, respectively, whereas those in classes I and II have predicted mortality risks of 0.1% to 0.4% and 0.6% to 0.7%, respectively. To use this scoring system, patients have points calculated based on factors such as age, sex, the presence of comorbid medical disease, certain physical findings, and laboratory data.⁶² While the PORT scoring system has been shown to be accurate for predicting mortality and prognosis, it does not directly measure the severity of illness, and a poor correlation has been found between mortality and the need for ICU admission.⁶³ In a study evaluating patients in PORT class V, only about 20% needed ICU admission, and they had an overall mortality of 37%, compared with the 20% mortality of the PSI V patients who did not need the ICU.⁶⁴ In general, the PSI V patients who needed the ICU tended to get more of their points from acute illness, whereas those not needing the ICU tended to score points because of chronic disease factors. In addition, in young patients without comorbid illness, the pneumonia must be particularly severe to place the patient in a high mortality risk group, and certain vital sign thresholds must be exceeded to accumulate points toward a poor prognosis.

For the critical care physician, underestimating the severity of illness is a more serious concern, and the use of the CURB-65 approach, modified from the BTS rule, is a simple and accurate way to address this issue. CURB-65, an acronym for the clinical features used to assess

pneumonia severity and prognosis, assigns 1 point, on a five-point scale, to confusion, blood urea greater than 7 mmol/L, respiratory rate greater than or equal to 30 breaths/min, blood pressure of <90 mm Hg systolic or ≤60 mm Hg diastolic, and age greater than or equal to 65 years. In one study, when the score was 0 to 1, the mortality rate was 0%, whereas the mortality was more than 20% for a score of 3 or higher, and those with a score of 2 had a mortality of 8.3%.⁶⁵ The use of the CURB-65 rules may be a problem in the elderly, reflecting the altered clinical presentations of pneumonia in this population. Interestingly, although the rule was not optimal in an elderly population and did not work as well as it did in other populations, it had a higher sensitivity for predicting mortality than the PSI, which is derived from the PORT study. Some studies have compared the PSI and CURB-65 and found them to be similar for identifying low-risk populations; however, the CURB-65 may be better at identifying poor prognosis in those with severe illness, compared with the PSI.⁶⁶ An amended version of the CURB-65 that does not use the laboratory measurement of BUN, known as the CRB-65, has also been found to be similarly accurate.⁶⁷ In another study comparing the performance of PSI and CURB-65 risk scores, the discriminatory power for 30-day mortality, using both PSI and CURB-65, was lower in HCAP than in CAP patients.⁶⁸

Other prognostic scoring systems have been developed to define the presence of severe pneumonia. Espana and associates estimated the need for ICU admission by the presence of one of two major criteria: arterial pH < 7.30 or systolic BP < 90 mm Hg.⁶¹ In the absence of these criteria, SCAP can also be identified by the presence of two of six minor criteria, including confusion, BUN > 30 mg/dL, respiratory rate > 30/min, PaO₂/FiO₂ ratio < 250, multilobar infiltrates, and an age of at least 80 years. When these criteria were met, the tool was 92% sensitive for identifying those with SCAP and was more accurate than the PSI or CURB-65 criteria, although not quite as specific as the CURB-65 rule.⁶¹ Using this approach, some criteria (acidosis and systolic hypotension) are weighted more heavily than others, which contrasts with some of the other approaches to define SCAP.

A different method than assessing risk for death is to use scoring systems to define the need for ICU interventions such as intensive respiratory and vasopressor support (IRVS). The SMART-COP tool was developed to predict the need for IRVS.⁶⁰ Using a multivariate model, there were eight clinical features associated with the need for IRVS: systolic blood pressure < 90 mm Hg, multilobar infiltrates, albumin < 3.5 g/dL, respiratory rate elevation (>25 breaths/min for those aged <50 years, and >30 breaths/min for those aged >50 years), tachycardia (>125 beats/min), confusion, low oxygen (<70 mm Hg if aged <50 years or <60 mm Hg if aged >50 years), and arterial pH < 7.35. Abnormalities in systolic blood pressure, oxygenation, and arterial pH each received 2 points, while the five other criteria received 1 point each, and with this system, the need for IRVS was predicted by a SMART-COP score of at least 3 points. Using this cutoff, the sensitivity for need for IRVS was 92.3% and the specificity was 62.3%, with positive and negative predictive values of 22% and 98.6%, respectively. The PSI and CURB-65 did not perform as well overall for predicting the need for IRVS.

The most recent ATS/IDSA guidelines for CAP suggested that ICU care be considered if the patient has one of two major criteria (need for MV or septic shock with the need for vasopressors) or three of nine minor criteria.¹ The minor criteria include respiratory rate > 30 breaths/min, PaO₂/FiO₂ ratio < 250, multilobar infiltrates, confusion/disorientation, uremia (BUN level > 20 mg/dL), leukopenia (white blood cell count < 4000 cells/mm³), thrombocytopenia (platelet count < 100,000 cells/mm³), hypothermia (core temperature < 36°C), and hypotension requiring aggressive fluid resuscitation. Other factors to consider in the decision-making process are hypoglycemia (in a non-diabetic patient), hyponatremia, acute alcohol intoxication, cirrhosis, asplenia, and unexplained metabolic acidosis. The use of these minor criteria alone requires validation, with one study showing that patients who met only minor criteria for ICU admission did not have an increase in mortality, while in another study, the use of four minor criteria instead of three improved the accuracy in defining the need for

ICU admission.^{69,70} Phua and colleagues showed that the ATS minor criteria had greater discriminatory power in the prediction of severity, ICU admission, and mortality than the PSI and CURB.⁷¹ Brown and associates noted that both the positive and negative predictive values of the minor criteria exceeded 80% if four criteria were used to define the need for ICU admission rather than just three criteria.⁷⁰ In a recent study, investigators simplified the ATS/IDSA criteria by excluding variables that occurred in <5% of cases, including leukopenia, thrombocytopenia, and hypothermia and noted similar predictive values for mortality and ICU admission as compared with those for the original ATS/IDSA criteria.⁷² In the same study, the addition of another variable, acidosis (pH < 7.35), improved the prediction for mortality and for ICU admission.

Rello and associates evaluated the “CAP-PIRO score” calculated within 24 hours of ICU admission.⁷³ In this study, 1 point was assigned for each variable: comorbidities (COPD, immunocompromised), age greater than 70 years, multilobar opacities on chest radiograph, shock, severe hypoxemia, acute renal failure, bacteremia, and ARDS. Patients were stratified into four levels of risk: (1) low, 0 to 2 points; (2) mild, 3 points; (3) high, 4 points; and (4) very high, 5 to 8 points. The PIRO score performed well as a 28-day mortality prediction tool in patients with CAP requiring ICU admission, with a better performance than APACHE II and the ATS/IDSA criteria.

The Risk of Early Admission to ICU (REA-ICU) index was derived from a dataset of nearly 5000 patients and is helpful as a tool on admission to identify patients who had no obvious indication for ICU management but subsequently required ICU care. It categorizes individuals into four risk groups based on 11 criteria independently associated with ICU admission: male gender, age younger than 80 years, comorbid conditions, respiratory rate of 30 breaths/min or higher, heart rate of 125 beats/min or higher, multilobar infiltrate or pleural effusion, white blood cell count less than 3 or 20,000/L or above, hypoxemia (oxygen saturation < 90% or arterial partial pressure of oxygen [PaO₂] < 60 mm Hg), BUN of 11 mmol/L or higher, pH less than 7.35, and sodium less than 130 mEq/L.⁷⁴ The mortality and likelihood of needing ICU care increased with each successive risk group, with the highest in class IV with a score ≥ 9. In a recent validation study including 850 CAP patients who had no obvious need for ICU care on admission, the REA-ICU index performed better than PSI but was similar to other tools (such as SMART-COP, CURXO-80, the 2007 ATS/IDSA minor severity criteria, and CURB-65) at defining the need for early ICU admission.⁷⁵ The need for sensitive criteria to define severe illness in CAP patients is important, since the benefit seems most certain if patients are admitted to the ICU early during the course of severe illness.

Role of Biomarkers in SCAP

The measurement of serum levels of biomarkers, such as C-reactive protein, midregional proadrenomedullin, midregional proatrial natriuretic peptide (MR-proANP), proarginine-vasopressin (Copeptin), proendothelin-1, or PCT, may be valuable in guiding the management of antibiotics for CAP. PCT is an acute phase reactant synthesized in the liver in response to bacterial, but not viral, infection. Studies on CAP have documented that serial measurement of the levels of PCT can guide the duration of antibiotic therapy, allowing cessation of therapy once levels fall and leading to a marked reduction in the duration of therapy compared with clinical judgment.^{5,76} In patients with SCAP, the measurement of initial and serial levels can help to identify those with a poor prognosis, and a low PCT value may distinguish which patients in PSI classes IV and V might be safely managed out of the ICU.⁷⁷ Kruger et al. reported that nonsurvivors had significantly higher median PCT levels on admission than survivors (0.88 vs. 0.13 ng/mL; $P = 0.0001$).⁷⁸ Low PCT accurately predicted patients at very low risk of death, even in those patients in a high prognostic scoring category by CURB-65 evaluation. Given its high negative predictive potential (98.9% with a PCT level of <0.228 ng/mL), patients with low initial PCT might be safely treated out of the ICU.⁷⁸ Huang

et al. found that 23.1% (126/546) of high-risk patients defined by PSI had low PCT levels on the first hospital day, and this subgroup had very low mortality, similar to low-risk patients.⁷⁹

In a prospective study of 685 CAP patients, Ramirez and associates evaluated the relationship between biomarkers and ICU admission.⁸⁰ Inflammatory biomarkers helped identify patients needing intensive care monitoring, including those requiring delayed ICU admission. No patient with ≥ 3 ATS minor severity criteria and PCT levels below the cutoff (0.35 ng/mL) needed ICU admission compared with 14 (23%) with levels above the cutoff ($P = 0.032$).⁸⁰ In another study, the authors compared the levels of three biomarkers—N-terminal pro-B-type natriuretic peptide (NT-proBNP), MR-proANP, and B-type natriuretic peptide (BNP)—with the PSI and CURB-65 scores for predicting short- and long-term mortality.⁸¹ The levels of NT-proBNP, MR-proANP, and BNP increased with the severity of pneumonia, and patients who died had higher levels of all three biomarkers. A combined assessment using categorical PSI score and NT-proBNP levels seemed beneficial over a single-marker approach for short- and long-term risk stratification. In a recent meta-analysis of seven studies including 1075 patients, using a PCT-based regimen in patients with severe sepsis or septic shock, the 28-day mortality was not different between the PCT-based regimen and standard treatment groups, but the PCT-guided group had a shorter duration of antimicrobial therapy.⁸² Using a PCT-based strategy led to more de-escalation and a shorter duration of antibiotic therapy, with no adverse effect on mortality.

Using biomarkers to adjudicate severity is best done in conjunction with clinical, microbiological, and pathologic data. A combined approach including severity scores and biomarkers can aid clinicians in assessing the severity of the illness and the need for the use of antibiotics, and serial measurements can be used to assess the treatment response. However, PCT or other biomarkers are not specific for pneumonia itself and can be elevated in other infectious or inflammatory conditions and, thus, should be interpreted with caution in patients with cardiac and renal failure.

ETIOLOGIC PATHOGENS

Even with extensive diagnostic testing, an etiologic agent is identified in only about half of all patients with CAP, pointing out the limited value of diagnostic testing and the possibility that we do not know all the organisms that can cause CAP.^{1,83} In the past 4 decades, a variety of new pathogens for this illness have been identified, including *L. pneumophila*, *C. pneumoniae*, Middle East respiratory syndrome coronavirus (MERS-CoV), avian-origin influenza A (H7N9), novel H1N1, H3N2 influenza, and hantavirus. In addition, antibiotic-resistant variants of common pathogens, such as *S. pneumoniae*, have become increasingly common. However, recent data show a decreased ICU mortality in pneumococcal CAP between 2000 and 2013, which likely reflects appropriate identification of SCAP, early antibiotic prescription, and increased use of combination therapy.⁸⁴

The likely pathogens for infection vary depending on patient risk factors for specific microorganisms and the presence of certain comorbid illnesses, but for all patient groups, including those with SCAP, pneumococcus is the most common pathogen.^{1,85} The incidence of antibiotic-resistant pneumococci has increased in recent years, and up to 40% of these organisms can have reduced sensitivity to penicillin or other antibiotics, although the clinical relevance of *in vitro* resistance is still uncertain.^{1,86,87} Although *S. pneumoniae* is the most common organism causing CAP, the frequency of pneumococcal pneumonia has declined, probably due to effective vaccination practices and a decreased incidence of smoking in adults.⁸⁸ Identified risk factors for drug-resistant *S. pneumoniae* (DRSP) include beta-lactam therapy in the past 3 months, alcoholism, age older than 65 years, immune suppression, multiple medical comorbidities, and contact with a child in daycare.^{1,89,90} Other common infecting organisms in those with SCAP include viruses (e.g., influenza, respiratory syncytial virus, and the coronavirus illness of severe acute respiratory syndrome [SARS]), *L.*

pneumophila, *M. pneumoniae*, *M. tuberculosis*, and *Haemophilus influenzae* (especially in smokers). In the setting of severe pneumonia, patients can be infected with *S. aureus* (including methicillin-resistant forms, or MRSA) or enteric gram-negatives and, rarely, anaerobes. In the elderly, including those with aspiration pneumonia, HCAP and, in those with underlying cardiopulmonary disease, enteric gram-negative organisms are often seen.

Although aspiration has often been considered a risk factor for anaerobic infection, studies of SCAP in elderly patients with aspiration risk factors have suggested that this population is very likely to have gram-negative infection.^{91,92} Risk factors for gram-negative organisms causing CAP are probable aspiration, previous hospital admission within 30 days of admission, previous antibiotic use within 30 days of admission, the presence of pulmonary comorbidity, smoking, and hyponatremia.^{93,94} Falguera and associates, in a study of 3272 episodes of CAP, found that 2% were caused by enteric gram-negatives (most commonly *P. aeruginosa*), and the risk factors for these organisms were COPD, current use of corticosteroids, prior antibiotic therapy, tachypnea > 30 breaths/min, and septic shock on admission.⁹⁵ Patients with these organisms needed ICU care more often and had a higher mortality and longer LOS than those without these pathogens present.

Primary pulmonary infection with atypical pathogens has been reported for patients with SCAP for many years. In fact, in one ICU in Spain, atypical pathogens were present in almost 25% of all patients, but the responsible organism varied over time. *Legionella* was the most common atypical pathogen leading to SCAP in 14% of patients during one time period, but in the same hospital a decade later, it was seen in only 2% of patients, having been replaced by *Mycoplasma* and *Chlamydia* infection, which were found in 17% of patients compared with only 6% a decade earlier.¹⁵ Several studies have shown that even if bacterial pathogens lead to CAP, they can be accompanied by atypical pathogens in the form of mixed infection.^{96,97} Atypical pathogens can include *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*, and some studies have shown that these infections are common in patients of all ages, not just young and healthy individuals; these organisms have even been reported among the elderly in nursing homes.^{1,96,98} When mixed infection is present, it may lead to a more complex course and a longer LOS than if a single pathogen is present, which may explain the increasing numbers of studies that show a reduction in CAP mortality, including those in the ICU, when initial therapy provides coverage for these organisms, compared with regimens that do not.^{99,100} Interestingly, multiple retrospective studies of pneumococcal bacteremia have shown a reduced mortality when dual therapy (usually involving a macrolide) rather than monotherapy is used, raising the possibility that even these patients have mixed infection with atypical pathogens.^{101,102} The frequency of atypical pathogens can be as high as 60%, with as many as 40% of all CAP patients having mixed infection.⁹⁷ These high incidence rates have been derived by serologic testing, which is of uncertain accuracy. Atypical organism pneumonia may not be a constant phenomenon, and the frequency of infection may vary over the course of time and with geography.

In the past, *S. aureus* was an uncommon cause of CAP, but it was capable of leading to severe pneumonia. In the past several years, a community-acquired strain of MRSA (CA-MRSA) has emerged as a cause of SCAP, particularly in patients without a history of previous hospitalization or chronic illness, often as a complication of influenza infection.^{1,103,104} The organism can lead to a severe, bilateral, necrotizing pneumonia, often related to toxin production by the organism. This organism is distinct from the nosocomial strain of MRSA and is clonal in origin, usually due to the USA 300 strain.

Risk Factors for Specific Pathogens

Table 74-3 summarizes the common pathogens causing CAP in hospitalized patients, including those admitted to the ICU. The classification is based on the presence of clinical risk factors for specific pathogens, referred to as “modifying factors.” The modifying factors for DRSP are age older than 65 years, beta-lactam therapy within the

TABLE 74-3

Common Pathogens Causing Community-Acquired Pneumonia

INPATIENT, WITH NO CARDIOPULMONARY DISEASE OR MODIFYING FACTORS

Streptococcus pneumoniae, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, mixed infection (bacteria plus atypical pathogen), viruses (including influenza), *Legionella* spp., and others (*Mycobacterium tuberculosis*, endemic fungi, *Pneumocystis jirovecii*)

INPATIENT, WITH CARDIOPULMONARY DISEASE AND/OR MODIFYING FACTORS

All of the above, but drug-resistant *S. pneumoniae* (DRSP) and enteric gram-negative organisms are more of a concern

SEVERE COMMUNITY-ACQUIRED PNEUMONIA, WITH NO RISKS FOR *PSEUDOMONAS AERUGINOSA*

S. pneumoniae (including DRSP), *Legionella* spp., *H. influenzae*, enteric gram-negative bacilli, *Staphylococcus aureus* (including methicillin-resistant *S. aureus*), *M. pneumoniae*, respiratory viruses (including influenza), others (*C. pneumoniae*, *M. tuberculosis*, endemic fungi)

SEVERE CAP, WITH RISKS FOR *P. AERUGINOSA*

All of the pathogens above plus *P. aeruginosa*

past 3 months, alcoholism, immune-suppressive illness (including therapy with corticosteroids), multiple medical comorbidities, and exposure to a child in daycare. For the patient with HCAP, infection by resistant gram-negatives and MRSA can occur, particularly if the patient has multiple risk factors, in addition to nursing home residence. These risk factors include severe illness, poor functional status, immune suppression, recent antibiotic therapy, and recent hospitalization in the past 3 months.¹⁰⁵ In predicting the likely etiologic pathogens for those admitted to the ICU, patients are divided into a population at risk for *Pseudomonas* infection and a population in whom this organism is unlikely to be present. The risk factors for *P. aeruginosa* infection are structural lung disease (bronchiectasis), corticosteroid therapy (>10 mg prednisone/day), broad-spectrum antibiotic therapy for more than 7 days in the past month, and malnutrition.¹ In a study of 935 patients admitted with CAP or HCAP, the authors evaluated risk factors for infection with MDR pathogens according to the ATS/IDSA 2005 HCAP guidelines.¹⁰⁶ Patients with at least one risk factor for MDR pathogens had more severe pneumonia on admission and a higher prevalence of severe sepsis compared with those without (45% vs. 29%, $P < 0.001$; 31% vs. 21%, $P = 0.001$), and of all the risk factors, hospitalization in the preceding 90 days (OR 4.87) and residence in a nursing home (OR 3.55) were independent predictors of infection with a resistant pathogen and mortality. Table 74-4 shows that certain clinical conditions are associated with specific pathogens, and these associations should be considered in all patients when obtaining a history.¹

Although a variety of radiographic patterns can be seen in pneumonia, specific findings generally cannot be used to predict the microbial etiology in CAP, but there are certain patterns to keep in mind. Focal consolidation can be seen in infections caused by pneumococcus, *Klebsiella* sp., aspiration (especially if in the lower lobes or other dependent segments), *S. aureus*, *H. influenzae*, *M. pneumoniae*, and *C. pneumoniae*. Interstitial infiltrates suggest viral pneumonia as well as infection due to *M. pneumoniae*, *C. pneumoniae*, *Chlamydia psittaci*, and *Pneumocystis jirovecii*. Lymphadenopathy with an interstitial pattern should raise concerns about anthrax, *Francisella tularensis*, and *C. psittaci*, whereas adenopathy can be seen with focal infiltrates in tuberculosis, fungal pneumonia, anthrax, and bacterial pneumonia. Cavitation can be the result of an aspiration lung abscess, infection with *S. aureus* or aerobic gram-negatives (including *P. aeruginosa*), tuberculosis, fungal infection (*Aspergillus*), nocardiosis, and actinomycosis.

TABLE 74-4 Clinical Associations with Specific Pathogens

| CONDITION | COMMONLY ENCOUNTERED PATHOGENS |
|--|--|
| Alcoholism | <i>Streptococcus pneumoniae</i> (including penicillin-resistant), anaerobes, gram-negative bacilli (possibly <i>Klebsiella pneumoniae</i>), tuberculosis |
| Chronic obstructive pulmonary disease/ current or former smoker | <i>S. pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> |
| Residence in nursing home | <i>S. pneumoniae</i> , gram-negative bacilli, <i>H. influenzae</i> , <i>Staphylococcus aureus</i> , <i>Chlamydia pneumoniae</i> ; consider <i>M. tuberculosis</i> . Consider anaerobes, but these are less common. |
| Poor dental hygiene | Anaerobes |
| Bat exposure | <i>Histoplasma capsulatum</i> |
| Bird exposure | <i>Chlamydia psittaci</i> , <i>Cryptococcus neoformans</i> , <i>H. capsulatum</i> |
| Rabbit exposure | <i>Francisella tularensis</i> |
| Travel to southwestern United States | <i>Coccidioidomycosis</i> ; hantavirus in selected areas |
| Exposure to farm animals or parturient cats | <i>Coxiella burnetii</i> (Q fever) |
| Post-influenza pneumonia | <i>S. pneumoniae</i> , <i>S. aureus</i> (including the community-acquired strain of methicillin-resistant <i>S. aureus</i>), <i>H. influenzae</i> |
| Structural disease of the lung (e.g., bronchiectasis, cystic fibrosis) | <i>Pseudomonas aeruginosa</i> , <i>Pseudomonas cepacia</i> , or <i>S. aureus</i> |
| Sickle cell disease, asplenia | Pneumococcus, <i>H. influenzae</i> |
| Suspected bioterrorism | Anthrax, tularemia, plague |
| Travel to Asia | Severe acute respiratory syndrome, tuberculosis, melioidosis |

Features of Specific Pathogens

Streptococcus pneumoniae

The most common pathogen for CAP, this organism is a gram-positive, lancet-shaped diplococcus, of which there are 84 different serotypes, each with a distinct antigenic polysaccharide capsule. Eighty-five percent of all infections are caused by one of 23 serotypes, which are included in a polysaccharide vaccine. Infection is most common in the winter and early spring, which may be related to the finding that up to 70% of patients have a preceding viral illness. The organism spreads from person to person and commonly colonizes the oropharynx before it leads to pneumonia. Pneumonia develops when the colonizing organisms are aspirated into a lung that is unable to contain the aspirated inoculum. Bacteremia is present in up to 20% of hospitalized patients, and extrapulmonary complications include meningitis, empyema, arthritis, endocarditis, and brain abscess. The burden of pneumococcal disease is often underestimated, since most studies report the incidence of bacteremic or invasive pneumococcal disease. Said and colleagues, in a systematic review and meta-analysis, estimated the proportion of CAP attributable to pneumococcus as 27.3% and, using urine antigen testing, helped diagnose an additional 11.4% of pneumococcal CAP beyond conventional techniques.¹⁰⁷ In that study, 24.8% of all cases were bacteremic, and it was more common among those with severe illness, no prior antibiotic use, and a positive human immunodeficiency virus (HIV) status. As mentioned elsewhere, there is also a trend toward improved survival with severe

pneumococcal CAP in the ICU due to improved antibiotic prescription practices and a decrease in smoking in recent years.⁸⁴

Since the mid-1990s, antibiotic resistance among pneumococci has become increasingly common, and penicillin resistance, along with resistance to other common antibiotics (macrolides, trimethoprim/sulfamethoxazole, selected cephalosporins), is present in over 40% of these organisms.^{1,86-90} Fortunately, most penicillin resistance is of the “intermediate” type (penicillin minimal inhibitory concentration [MIC] of 0.1 to 1.0 mg/L) and not of the high-level type (penicillin MIC of 2.0 or more). Although the clinical impact of *in vitro* resistance is uncertain, one large database has data showing that only organisms with a penicillin MIC of more than 4 mg/L can lead to an increased risk of death.⁸⁶ Recently, the definitions of resistance have been changed for non-meningeal infection, with sensitive being defined by a penicillin MIC ≤ 2 mg/L, intermediate as an MIC of 4 mg/L, and resistant as an MIC ≥ 8 mg/L.¹⁰⁸ While the clinical impact of resistance on outcomes such as mortality was hard to show using older definitions, with the new definitions of resistance, very few pathogens will be defined as resistant, but those that are may affect the outcome. In a recent study including 118 patients using the new definition for resistance, there was no difference in 30-day mortality between the penicillin-susceptible and -resistant groups.¹⁰⁹ The penicillin-resistant group had a higher frequency of having received antibiotics within the past 2 weeks, but interestingly, it was the susceptible group who had a higher frequency of worse initial presentation such as ICU admissions and bacteremia. In this cohort, both groups received equally broad spectrum antibiotics such as extended-spectrum cephalosporins, vancomycin, and a carbapenem.

The relationship between prior antibiotic use and subsequent pneumococcal resistance is well known, and prior therapy with macrolides, beta-lactams, and quinolones has been identified as a predisposing factor for subsequent resistance to the same class of antibiotic.^{89,110-112} The risk was no lower for therapy in the past 6 months compared with therapy in the past 1 month.¹¹² Other studies have shown that quinolone therapy can predispose to subsequent pneumococcal resistance to this class of antibiotics.^{110,111} In another study of patients with pneumococcal bacteremia, pneumococcal resistance to beta-lactams (penicillins and cephalosporins), macrolides, and quinolones was more likely if the patient had received the same agent in the past 3 months.¹¹⁰ Although some studies have shown that discordant therapy of drug-resistant pneumococcus can be a risk factor for mortality, in one study, discordant therapy was less likely if patients were treated with ceftriaxone or cefotaxime compared with other therapies.¹¹³ Thus, in clinical practice, resistance is not likely to affect the outcome, since current guidelines for SCAP recommend the use of these effective agents as empiric therapy. Macrolide-resistant pneumococci have also been described and can be either low- or high-level resistant, depending on whether the mechanism of resistance is efflux or ribosomal alteration, respectively. Although high-level resistance may be clinically relevant, this is generally not an issue in the management of ICU CAP, since all patients who receive macrolide therapy do so in combination with a highly active beta-lactam that is effective against pneumococcus, even if macrolide resistance is present.

Legionella pneumophila

This small, weakly staining, gram-negative bacillus was first characterized after an epidemic in 1976 and can occur either sporadically or in epidemic form. Although multiple serogroups of the species *L. pneumophila* have been described, and these account for 90% of all cases of legionnaires' disease, serogroup 1 is responsible for most cases. The other species that commonly causes human illness is *Legionella micdadei*, which is waterborne and can emanate from air-conditioning equipment, drinking water, lakes and river banks, water faucets, and shower heads.¹¹⁴ Infection is generally caused by inhalation of an infected aerosol generated by a contaminated water source. When a water system becomes infected in an institution, endemic outbreaks may occur. In its sporadic form, *Legionella* may account for 7% to 15% of all cases of CAP, being a particular concern in patients with

severe forms of illness.^{1,15,114} Recent studies show an increase in the reported cases of *Legionella*, especially in big cities like New York and a higher incidence in diabetes patients and those from poor neighborhoods.¹¹⁵

The classic *Legionella* syndrome is characterized by high fever, chills, headache, myalgias, and leukocytosis.¹¹⁴ The diagnosis is also suggested by the presence of pneumonia with preceding diarrhea, along with mental confusion, hyponatremia, relative bradycardia, and liver function abnormalities, but this syndrome is usually not present. Symptoms are rapidly progressive, and the patient may appear to be quite toxic. This classic syndrome is not always present, so this diagnosis should always be considered in patients admitted to the ICU with CAP and in those with rapidly progressive radiographic abnormalities. To establish this diagnosis serologically, it is necessary to collect both acute and convalescent titers. The urinary antigen test (UAT) is the single most accurate acute diagnostic test for *Legionella* but is specific only for serogroup 1 infection. However, it does not detect other types of *Legionella*, so a negative finding cannot rule out this infection. In recent years, most cases have been diagnosed with urinary antigen, and there has been less reliance on serology and culture.¹¹⁶ With this increased reliance on UAT, the case fatality rate of *Legionella* has fallen, possibly reflecting diagnosis of less severe illness than in the past.¹¹⁶

Staphylococcus aureus

Staphylococcus aureus can lead to severe forms of CAP, which can be necrotizing, develop cavitory pneumonia, and have hematogenous dissemination to multiple sites in the body. The organism can also seed the lung hematogenously from valvular vegetations in patients with right-sided endocarditis or from septic venous thrombophlebitis (from central venous catheter or jugular vein infection). When a patient develops postinfluenza pneumonia, *S. aureus* can lead to secondary bacterial infection and, in the United States, CA-MRSA have emerged, primarily in skin and soft tissue infections, but also as a cause of SCAP. CA-MRSA is a clonal disease, emanating from the USA 300 clone of *S. aureus*, and is clinically and bacteriologically different from the strains of MRSA that cause nosocomial pneumonia.¹⁰³ In addition, it can infect previously healthy individuals, and the classic clinical presentation of this pathogen causing CAP is as a complication of a preceding viral or influenza infection.

This illness is characterized by a severe, bilateral, necrotizing pneumonia, which may be related to staphylococcal virulence factors such as Panton-Valentine leukocidin (PVL). In a prospective study of 627 patients from 12 emergency departments across the United States during two influenza seasons, the authors isolated CA-MRSA from 2.4% of all patients and 5% of patients admitted to the ICU; the mortality rate was 14%, and all isolates were of the USA 300 strain.¹¹⁷ CA-MRSA patients had severe infection with multiple infiltrates or cavities on chest imaging, were intubated or required vasopressors, and, compared with other patients, were more likely to develop illness after nursing home admission in the previous year or after close contact in the previous month with someone with a skin infection. Since the pathogenesis of pneumonia due to this organism may be related to toxin production by the bacteria, therapy may need to involve both an antibacterial agent and an antitoxin-producing agent.¹⁰⁴ Sicot and associates, in a study of 133 patients with PVL-positive CAP, found similar mortality rates between patients who had MRSA and methicillin-susceptible *S. aureus*. However, treatment with antibiotics with antitoxin effects (clindamycin, rifampin, and linezolid) was associated with a reduced mortality compared with those who did not receive antitoxin therapy (6.1% vs. 52.3%, $P < 0.001$), although only about one-third of patients received this therapy.¹¹⁸ The frequency of this illness is still relatively low, but it does occur sporadically, with certain geographic areas having a high frequency, especially during influenza season.

Other Organisms

The incidence of viral pneumonia is difficult to define, but one careful study of over 300 nonimmunocompromised CAP patients

looked for viral pneumonia by paired serologies and found that 18% had viral pneumonia, with about half being pure viral infection and the others being mixed with bacterial pneumonia.¹¹⁹ Influenza (A more than B), parainfluenza, and adenovirus were the most commonly identified viral agents. Viral illnesses that can lead to respiratory failure, in addition to influenza, include respiratory syncytial virus (which can affect the elderly), varicella (a particular concern in pregnant females with chickenpox), and hantavirus (endemic in the Four Corners area of New Mexico).¹²⁰ In a recent study in patients with severe pneumonia using polymerase chain reaction (PCR) techniques, the authors found viral infection to be common: 36.4% ($n = 72$) had positive viral markers, and 9.1% ($n = 18$) had bacterial and viral co-infections.¹²¹

It is important to always consider the diagnosis of tuberculosis in patients with SCAP and fungal infections with coccidioidomycosis and histoplasmosis in endemic areas, especially in HIV-infected persons. Several rickettsiae can also cause CAP, including Q fever (*Coxiella burnetii*), which occurs worldwide, Rocky Mountain spotted fever (RMSF), and scrub typhus (*Rickettsia tsutsugamushi*) in Asia and Australia. Transmission typically involves an intermediate vector, often ticks (Q fever, RMSF) or mites (scrub typhus), but also sheep, cows, and contaminated milk (Q fever). These infections have a variable incubation period, ranging from days to a few weeks, and are characterized by a febrile syndrome that may have a pneumonic component and a maculopapular rash (Q fever and RMSF).

Influenza. Influenza should always be considered during epidemic times and can lead to primary viral pneumonia or to secondary bacterial infection with pneumococcus, *S. aureus*, or *H. influenzae*. In April 2009, an outbreak of H1N1 influenza infected approximately 61 million people worldwide, with as many as 13,000 deaths. H1N1 influenza, in contrast to seasonal flu, affected younger people more than the elderly, and high-risk populations included pregnant women and those with obesity.¹²² In one series, 12% of all hospitalized patients with H1N1 infection were administered MV, and 6% of hospitalized patients died.¹²³ Antiviral therapy with zanamivir and oseltamivir may reduce the severity of illness, particularly if given early, and the role of corticosteroids for patients with severe illness is controversial.^{122,124} The frequency of documented bacterial pneumonia complicating this illness varies from <5% to >25% of patients with radiographic pneumonia. Muscedere and associates evaluated the risk of coexistent or secondarily acquired bacterial respiratory tract or bloodstream-positive cultures in 681 patients with 2009 influenza A (H1N1) infection.¹²⁵ In that study, 38% of patients had at least a positive blood or respiratory culture during their ICU stay, although almost all the patients received antibiotics; patients with any positive cultures had higher morbidity, with more days on the ventilator, longer ICU and hospital LOS, and higher hospital mortality compared with those with negative cultures. Recently, during the spring of 2013, infection with novel avian-origin influenza A (H7N9) emerged in China and was related to exposure to live animals, including chickens (82%).¹²⁶ It was linked with a high incidence of respiratory failure and ICU admission, especially in those with comorbid conditions, and mortality ranged from 27% to 34% among ICU patients.^{126,127}

Severe Acute Respiratory Syndrome. In late 2003, a respiratory viral infection, caused by a coronavirus, emerged in parts of Asia and was termed SARS. The illness affected people from a variety of endemic areas in Asia but was seen in North America when an outbreak occurred in Toronto, Canada. Importantly, worldwide, as many as 20% of affected patients were health care workers, particularly those caring for patients admitted to the ICU. Transmission risk was greatest during emergent intubation, and was also possible during noninvasive ventilation, making this latter modality of therapy contraindicated if SARS is suspected.¹²⁸ Infection control may be quite effective in preventing the spread of SARS to health care workers and includes the careful handling of respiratory secretions, ventilator circuits, the use of N-95 respirator masks, and careful gowning and gloving.¹²⁹ Even more elaborate infection control measures, including personal air exchange units, are needed for health care workers involved in high-risk procedures such

as intubation. The mortality rate for ICU-admitted SARS patients was over 30%, and when patients died, it was generally from multiple system organ failure and sepsis. There is no specific therapy, but anecdotal reports have suggested a benefit of the use of pulse doses of corticosteroids and ribavirin.

Middle East Respiratory Syndrome Coronavirus. A new coronavirus outbreak, subsequently named *MERS-CoV*, started in September 2012 in the Arabian Peninsula.¹³⁰ Patients presented with severe acute pneumonia, with hypoxemic respiratory and renal failure. It can occur sporadically in the community, as well as from health-care-associated human-to-human transmission.¹³¹ The infection was associated with a very high fatality rate of up to 60%, especially in patients with medical comorbidities, and the majority of patients required invasive respiratory support and had extrapulmonary manifestations, mainly kidney failure.¹³² The roles of steroids, oseltamivir, ribavirin, and interferon for treatment are uncertain.

Bioterrorism Considerations

Certain airborne pathogens can cause pneumonia as the result of deliberate dissemination by the aerosol route, in the form of a biologic weapon, and present a clinical syndrome of CAP. The pathogens that are most likely to be used in this fashion and that can lead to severe pulmonary infection are *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), and *F. tularensis* (tularemia).¹³³⁻¹³⁷ The Centers for Disease Control and Prevention has classified these agents as category A pathogens because of their high mortality rate and their potential impact on public health.¹³³ Other pneumonic pathogens could also serve as agents of biologic warfare but are potentially less serious and are classed in category B and include *C. burnetii* and *Brucella* sp. Certain emerging pathogens are category C agents and are not widely available as weapons but have the potential for high morbidity and mortality, including hantavirus and MDR tuberculosis. Some agents of bioterrorism can be spread via the aerosol route but do not generally present as pneumonia and include smallpox and viral hemorrhagic fevers (Ebola, Marburg).

DIAGNOSTIC EVALUATION

As discussed, the diagnosis of CAP is suggested by the patient's history and physical examination and confirmed by chest radiograph. The history may suggest certain pathogens on the basis of epidemiologic considerations (Table 74-4), but the clinical features and chest radiograph cannot give an exact etiologic diagnosis. In patients with SCAP, diagnostic testing is performed to define the presence of pneumonia, the severity of illness and its complications, and the etiologic pathogen. Although defining a specific etiologic diagnosis of CAP allows for focused antibiotic therapy, most patients do not have a specific pathogen identified, and many who do have this diagnosis made days or weeks later, as the results of cultures or serologic testing become available. An etiologic diagnosis is best established if blood or pleural fluid cultures identify a pathogen, if bronchoscopic techniques demonstrate an organism in high concentrations, or if serologic testing confirms a fourfold rise in titers to specific pathogens (comparing acute and convalescent samples collected weeks apart).

For ICU-admitted patients, after a chest radiograph defines the presence of pneumonia, testing should include an assessment of oxygenation (pulse oximetry or blood gas, the latter if retention of carbon dioxide is suspected), routine admission blood work, and two sets of blood cultures¹ (Table 74-5). Although blood cultures are positive in only 10% to 20% of CAP patients, they can be used to define a specific diagnosis and to define the presence of drug-resistant pneumococci.^{1,86} Blood cultures are not routine for all admitted patients but should be performed in those with severe illness, especially if the patient has not received antibiotics prior to admission, since the incidence of a true-positive result is high in this population.¹³⁸ If the patient has a pleural effusion, this should be tapped and the fluid sent for culture and biochemical analysis.

Sputum culture can help to identify the presence of a drug-resistant or unusual pathogen and should be obtained from all critically ill patients who are intubated.¹ UAT for pneumococcus or *Legionella* has some potential value for providing a rapid diagnosis. *Legionella* urinary

TABLE 74-5 Diagnostic Testing for Community-Acquired Pneumonia

| TEST | SENSITIVITY | SPECIFICITY | COMMENT |
|---|--------------------------------|------------------------------|---|
| Chest radiograph | 65%-85% | 85%-95% | Computed tomography is more sensitive to infiltrates. Recommended for all patients. |
| Computed tomography | Gold standard | Not infection specific | Should not be performed routinely but helpful to identify cavitation and loculated pleural fluid. Recommended in the evaluation of nonresponding patients. |
| Blood cultures | 10%-20% | High when positive | Usually shows pneumococcus (in 50%-80% of positive samples) and defines antibiotic susceptibility. Recommended in patients with severe CAP, particularly if not on antibiotic therapy at the time of testing. |
| Sputum Gram stain | 40%-100% depending on criteria | 0-100% depending on criteria | Can correlate with sputum culture to define predominant organism and can be used to identify unsuspected pathogens. Recommended if sputum culture is obtained. May not be able to narrow empiric therapy choices. |
| Sputum culture | | | Use if suspect drug-resistant or unusual pathogen, but a positive result cannot differentiate colonization from infection. Obtain via tracheal aspirate in all intubated patients. |
| Oximetry or arterial blood gas | | | Define both severity of infection and need for oxygen; if hypercarbia is suspected, a blood gas sample is needed. Recommended in severe community-acquired pneumonia. |
| Serologic testing for <i>Legionella</i> , <i>Chlamydia pneumoniae</i> , <i>Mycobacterium pneumoniae</i> , viruses | | | Accurate, but usually requires acute and convalescent titers collected 4 to 6 weeks apart. Not routinely recommended. |
| <i>Legionella</i> urinary antigen | 50%-80% | | Specific to serogroup 1, but the best acute diagnostic test for <i>Legionella</i> . |
| Pneumococcal urinary antigen | 70%-100% | 80% | False positives if recent pneumococcal infection. Can increase sensitivity with concentrated urine. |
| Serum procalcitonin | | | Not a routine test, but if performed, should be measured with the highly sensitive Kryptor assay. May help guide duration of therapy and need for ICU admission. |

antigen is specific to serogroup 1 infection and is positive in a little more than half of all infected patients; however, it is the test that is most likely to be positive in the setting of acute illness.¹³⁹ UAT is also available for detecting the capsular polysaccharide of *S. pneumoniae* and has 77% to 88% sensitivity in patients with bacteremic pneumococcal pneumonia but only 64% sensitivity in those with nonbacteremic pneumonia.^{88,140} The sensitivity of pneumococcal UAT increases if concentrated urine is examined, and it can be positive even in the presence of antibiotic therapy; however, false-positive tests can occur in patients who have had recent pneumococcal infection.¹⁴¹ The role of Gram's stain of sputum to guide initial antibiotic therapy is controversial, but this test has its greatest value in guiding the interpretation of sputum culture and can be used to define the predominant organism present in the sample. Gram's stain can be used to broaden initial empiric therapy by enhancing the suspicion for organisms that are not covered in routine empiric therapy (such as *S. aureus* being suggested by the presence of clusters of gram-positive cocci, especially during a time of epidemic influenza).¹

Routine serologic testing is not recommended.¹ Nucleic acid amplification tests and PCR assays provide rapid test results in CAP for atypical agents such as viruses, *Mycoplasma*, *Chlamydia*, and *Legionella*. The usefulness of PCR assays in managing CAP has not been proven, and the concern with this method is that it is so sensitive that, if a respiratory sample is positive, it cannot distinguish colonization from infection. However, the test may be valuable if negative, because the absence of a suspected pathogen by PCR may permit a more focused antibiotic therapy approach. Biomarkers, as mentioned earlier, are helpful in antibiotic stewardship, and a low serum PCT concentration (<0.1 µg/L) may be helpful to support a decision to withhold or discontinue antibiotics.⁷⁶

Bronchoscopy is not indicated as a routine diagnostic test and should be restricted to immunocompromised patients and selected individuals with SCAP. Several studies^{142,143} have not shown any improvement in outcome when a specific etiologic diagnosis is made for patients with SCAP. Rather, the outcome is improved if the initial empiric therapy is accurate and the patient has prompt clinical improvement.¹⁴³ However, patients who have rapidly progressive lung infection despite therapy may benefit from invasive diagnostic testing, but again, a favorable impact of this testing on patient outcome has not been demonstrated. One population that should be considered for invasive testing is corticosteroid-treated COPD patients who have slowly responding or nonresponding pneumonia, because these individuals are at risk for infection with *Aspergillus* and this organism can be recovered from bronchoscopic samples. In addition, bronchoscopy may have value for the nonresponding patient or other immunosuppressed individuals.¹⁴⁴

In patients with SCAP, diagnostic testing may be valuable for guiding modifications of antibiotic therapy, rather than affecting the choice of initial therapy.¹⁴⁵ In one study, nearly 40% of patients had no pathogens identified, and pathogen-directed therapy had no overall impact on mortality or LOS, but led to fewer adverse events than empiric therapy and was also accompanied by a lower mortality for patients admitted to the ICU.¹⁴⁶ In addition, studies have emphasized the mortality benefit of prompt administration of effective antibiotic therapy.¹⁴⁷ Thus, therapy should never be delayed for the purpose of diagnostic testing, and the diagnostic workup should be streamlined, with all patients receiving empiric therapy based on algorithms as soon as possible.

TREATMENT

Initial antibiotic therapy for SCAP is necessarily empiric, with the goal of targeting the likely etiologic pathogens, based on the considerations in Tables 74-3 and 74-4, which categorize patients on the basis of the severity of illness and risk factors for specific pathogens. The likelihood of infection by organisms such as DRSP, enteric gram-negative organisms, and *P. aeruginosa* is determined by the presence of

TABLE 74-6

Empiric Therapy Regimens for Severe Community-Acquired Pneumonia

NO PSEUDOMONAL RISK FACTORS

Selected beta-lactam (cefotaxime, ceftriaxone)

plus

Intravenously administered macrolide or quinolone (moxifloxacin or levofloxacin*)

PSEUDOMONAL RISK FACTORS PRESENT

Selected antipseudomonal beta-lactam (cefepime, piperacillin/tazobactam, imipenem, meropenem)

plus

Ciprofloxacin

or

Selected antipseudomonal beta-lactam

plus

Aminoglycoside

plus

Intravenously administered macrolide or antipseudomonal quinolone (moxifloxacin or levofloxacin*)

NOTE: Although routine methicillin-resistant *Staphylococcus aureus* (MRSA) coverage is NOT recommended for all severe community-acquired pneumonia, consider community-acquired MRSA, especially after influenza and with bilateral necrotizing pneumonia, and if suspected, treat by adding either linezolid or the combination of vancomycin and clindamycin.

*For patients with normal renal function, the recommended dose of levofloxacin is 750 mg daily.

cardiopulmonary disease or “modifying factors.”¹ Although a set of likely pathogens can be predicted for each patient (Table 74-3), and this information can be used to guide initial empiric therapy, if diagnostic testing shows the presence of a specific pathogen, then therapy can be focused.

In choosing empiric therapy of CAP, certain principles and therapeutic approaches should be followed (Table 74-6).^{1,148} All individuals should be treated for DRSP and atypical pathogens, but only those with appropriate risk factors (see earlier) should have coverage for *P. aeruginosa*, and patients with bilateral necrotizing pneumonia after influenza need coverage for CA-MRSA.¹ All patients admitted to the ICU require combination therapy using a beta-lactam with either a macrolide or quinolone, plus the addition of other agents, depending on the clinical setting.^{1,149} The recommendation to avoid monotherapy is based on the fact that the efficacy (especially for meningitis complicating pneumonia), effective dosing, and safety of any single agent, including quinolone monotherapy, has not been established for ICU-admitted CAP patients. From the available data, it appears that adding either a macrolide or quinolone leads to similar results, although some data in patients with bacteremic CAP, especially with pneumococcus, suggest that a macrolide may have particular advantages, possibly because of its antiinflammatory effects.^{101,102,150,151}

In one study of 529 patients with ICU-admitted CAP, combination therapy with a beta-lactam plus either a macrolide or quinolone led to improved survival for the population with shock needing pressors (279 patients), compared with the use of monotherapy.¹⁵² Another study in SCAP patients (not all pneumococcal) also confirmed the benefit of adding a macrolide as part of the initial empiric therapy, but not a quinolone, for reducing mortality.¹⁵³ In a recent study comparing the impact of dual (β-lactam plus macrolide or fluoroquinolone [n = 394]) versus monotherapy (β-lactam alone [n = 471]) in immunocompetent SCAP, there was no difference in the 60-day mortality between the two groups.¹⁵⁴ However, there was a survival advantage for patients who had initial adequate antibiotic therapy, and those who received dual therapy had a higher frequency of initial adequate antibiotics. In one study comparing high-dose levofloxacin to a beta-lactam/quinolone combination, the single-agent regimen was effective overall. However, patients in septic shock were excluded, and there was a trend to a worse outcome with monotherapy for individuals receiving MV.¹⁴⁹ In a meta-analysis of SCAP, the addition of a macrolide to a beta-lactam was associated with

reduced mortality compared with other regimens.¹⁵⁵ If *Legionella* is suspected, then the use of a quinolone may be preferable, since these agents have been highly successful in treating pneumonia caused by this organism and may possibly be more effective than macrolides.¹⁵⁶

For patients with pseudomonal risk factors, therapy can be with a two-drug regimen, using an antipseudomonal beta-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) plus ciprofloxacin (the most active antipseudomonal quinolone) or levofloxacin. Alternatively, a three-drug regimen can be used, combining an antipseudomonal beta-lactam plus an aminoglycoside plus either an intravenous antipneumococcal quinolone (moxifloxacin or levofloxacin) or a macrolide.¹ If CA-MRSA is suspected, therapy can be with either vancomycin or linezolid, although other agents might be effective, since this pathogen is not as antibiotic resistant as nosocomial MRSA. However, since CA-MRSA is in part a toxin-mediated illness, the use of an agent that inhibits toxin production, along with an antibacterial effect, is recommended by some.¹⁰⁴ To do this, linezolid can be used alone (since it acts to inhibit protein synthesis), or clindamycin can be added to vancomycin.

HCAP patients can be treated in the same manner as other SCAP patients, but some will need coverage for nosocomial pneumonia pathogens, including MDR gram-negatives and nosocomial MRSA.¹⁰⁵ The benefit of a macrolide in reducing mortality may not be as dramatic in HCAP patients as in CAP patients.¹⁵⁷ Those who need coverage for MDR organisms are individuals with severe HCAP who have an additional risk factor (besides just residence in a nursing home), while those without such risk factors can receive the SCAP regimens. The risk factors for MDR pathogen infection include poor functional status, immune suppression, recent antibiotic therapy, or recent hospitalization.¹⁰⁵ Those at risk for MDR pathogens should receive dual antipseudomonal therapy (beta-lactam plus an aminoglycoside) plus MRSA coverage (linezolid or vancomycin). Maruyama and colleagues prospectively applied an algorithm based on the presence of MDR risk factors (immunosuppression, hospitalization within the past 90 days, poor functional status: Barthel Index score < 50, and antibiotic therapy within the past 6 months) and severity of illness (requiring ICU admission or MV) to determine outcomes on CAP and HCAP patients.¹⁵⁸ Using the algorithm, the investigators used CAP therapy for HCAP patients with 0-1 risk factors and the hospital acquired pneumonia (HAP) regimen for more than two risk factors, but the majority (92.9%) received appropriate therapy for the identified pathogens, and thus, broader spectrum antibiotics can be potentially limited even in patients with HCAP.

Although they should not be used as monotherapy for ICU-admitted CAP patients, antipneumococcal quinolones have assumed great importance because they can cover pneumococcus (including DRSP), nonpseudomonal gram-negative organisms, and atypical pathogens.¹ Quinolones penetrate well into respiratory secretions and are highly bioavailable, achieving the same serum levels with oral or intravenous therapy, and thereby allowing a rapid switch to oral therapy in responding patients. The available intravenous agents that are active against pneumococcus are moxifloxacin and levofloxacin.¹⁵⁹ Based on *in vitro* activity, the recommended doses for moxifloxacin and levofloxacin are 400 mg daily and 750 mg daily, respectively, with the need to adjust dosing of levofloxacin (but not moxifloxacin) in patients with renal insufficiency.

Timeliness of Initial Therapy

For inpatients with CAP, timely and accurate therapy is essential to reduce mortality. In patients with SCAP, improved survival has been shown to occur if initial empiric therapy is accurate and if it leads to a rapid clinical response.^{99,143,147} In one study, if initial therapy led to a clinical response within 72 hours, mortality of SCAP was approximately 10%, compared with a mortality rate of 60% in patients who had initially ineffective therapy.¹⁴³ For CAP in general, early therapy is associated with reduced mortality compared with therapy given later; if the patient has pneumonia with sepsis and hypotension, mortality rises by nearly 8% for every hour of delay in starting therapy.¹⁶⁰

Duration of Therapy

There is little information on the proper duration of therapy in patients with CAP, especially those with severe illness. Even in the presence of pneumococcal bacteremia, short durations of therapy may be possible, with a rapid switch from intravenous to oral therapy in responding patients.¹⁶¹ Generally, *S. pneumoniae* can be treated for 5 to 7 days if the patient is responding rapidly and has received the correct dose of an accurate therapy. The presence of extrapulmonary infection (e.g., meningitis) and the identification of certain pathogens (such as bacteremic *S. aureus* and *P. aeruginosa*) may require a longer duration of therapy. Identification of *L. pneumophila* pneumonia may require at least 14 days of therapy, depending on the severity of illness and host defense impairments, but shorter durations with quinolone therapy have been shown to be effective. Most therapy in the ICU will be given intravenously; however, recent studies, using a variety of antibiotics, have suggested that oral therapy may be instituted after as early as 2 to 3 days of parenteral therapy, assuming that the patient's condition has stabilized and the patient is afebrile.¹ The switch to oral therapy, even in severely ill patients, may be facilitated by the use of quinolones that are highly bioavailable and achieve the same serum levels with oral therapy as with intravenous therapy.

The initial PCT level may accurately predict a positive blood culture in pneumonia patients, and serial measurements help with antibiotic de-escalation and withdrawal in CAP patients.^{162,163} In a randomized trial of antibiotic therapy in the ICU, PCT guidance led to a reduction in the duration of therapy compared with standard care in all patients, including those with SCAP.¹⁶⁴ A recent meta-analysis of 14 randomized trials favored a PCT-based treatment algorithm for antibiotic de-escalation without an increase in either mortality or treatment failure.¹⁶⁵

Adjunctive Therapy Measures

In addition to antibiotic therapy, patients with SCAP may require chest physiotherapy, especially if they have either an excessive volume of purulent sputum (>30 mL/day) or severe respiratory muscle weakness resulting in ineffective cough.¹⁶⁶ Aerosolized humidification has been used to reduce sputum viscosity, thereby enhancing clearance in patients who have generally ineffective cough. However, it is likely that much of the generated water vapor is deposited in the upper airway, where it is likely to stimulate cough but unlikely to influence the rheologic properties of the sputum. Bronchodilator therapy, which also enhances mucociliary clearance and ciliary beat frequency, is most likely to be of benefit in patients with pneumonia complicating COPD. A recent Cochrane review did not find convincing evidence supporting the role of chest physiotherapy in pneumonia patients.¹⁶⁷

Previous studies looking into the use of adjunctive corticosteroids in patients with SCAP have shown mixed results.^{168,169} Although the role of corticosteroids in the routine therapy of CAP is not established, steroids may be beneficial in patients with sepsis and relative adrenal insufficiency, which occurs in a high proportion of patients with SCAP.¹⁷⁰ A recent meta-analysis of nine trials involving 1001 patients did not support the routine use of corticosteroids in CAP patients, but showed that it may improve mortality in a subset with SCAP.¹⁷¹ Another setting in which corticosteroids may have benefit is in pneumococcal pneumonia that is complicated by meningitis, where pretreatment with corticosteroids prior to antibiotic therapy may lead to more favorable neurologic outcomes.¹⁷² Recently, Torres and associates, in a randomized, prospective study, found that in patients with SCAP and elevated C-reactive protein > 150 mg/L at admission, administration of intravenous methylprednisolone (bolus of 0.5 mg/kg per 12 hours) led to less treatment failure compared with placebo.¹⁷³ In that study, there was no significant difference in hospital mortality between the two groups. Adjunctive immune therapy with granulocyte colony-stimulating factor has also been used in SCAP, with no benefit in mortality or in the course of illness resolution.¹⁷⁴

Evaluation of Response to Therapy

The majority of patients will respond rapidly to accurate empiric therapy within 24 to 72 hours. Clinical response is defined as improvement in the symptoms of cough, sputum production, and dyspnea, along with the ability to take medications orally, declining white blood cell count, and an afebrile status on at least two occasions 8 hours apart.¹ In the critically ill patient, improvement in oxygenation may be one of the earliest signs of response to therapy, although few studies have examined MV patients.¹ Radiographic improvement lags behind clinical improvement and, in general, 50% of patients with pneumococcal pneumonia have radiographic clearing at 5 weeks, whereas the majority clears in 2 to 3 months. With bacteremic disease, 50% of patients have a clear chest radiograph at 9 weeks, and most are clear by 18 weeks.¹⁷⁵ Radiographic resolution is most influenced by the number of lobes involved and the age of the patient. Radiographic clearance of CAP decreases by 20% per decade after the age of 20 years, and patients with multilobar infiltrates take longer to clear than those with unilobar disease.¹⁷⁵

If the patient fails to respond to appropriate therapy during the expected time interval, then it is necessary to consider infection with a drug-resistant or unusual pathogen (tuberculosis, *C. burnetii*, *Burkholderia pseudomallei*, *C. psittaci*, endemic fungi, or hantavirus), a pneumonic complication (lung abscess, endocarditis, empyema), or a noninfectious process that mimics pneumonia (bronchiolitis obliterans with organizing pneumonia, hypersensitivity pneumonitis, pulmonary vasculitis, bronchoalveolar cell carcinoma, lymphoma, pulmonary embolus).¹ The evaluation of the nonresponding patient should be individualized but may include CT of the chest, pulmonary angiography, bronchoscopy, and, occasionally, open lung biopsy.

PREVENTION

Prevention of CAP is important for all population groups but especially the elderly patient, who is at risk for both a higher frequency of infection and a more severe course of illness. Appropriate patients should be vaccinated with both pneumococcal and influenza vaccines, and cigarette smoking should be stopped in all at-risk patients. Even for the patient who is recovering from CAP, immunization while in the hospital is appropriate to prevent future episodes of infection, and the evaluation of all patients for vaccination need and the provision of information about smoking cessation have been performance standards used to evaluate the hospital care of CAP patients.¹

Pneumococcal Vaccine

Pneumococcal capsular polysaccharide vaccine can prevent pneumonia in otherwise healthy populations, as was initially demonstrated in South African gold miners and American military recruits.^{1,176} The benefits in individuals of advanced age or with underlying conditions in nonepidemic environments are less clearly defined. The polysaccharide vaccine efficacy has ranged from 65% to 84% in patients with diabetes mellitus, coronary artery disease, congestive heart failure, chronic pulmonary disease, and anatomic asplenia.¹⁷⁶ In immunocompetent patients over the age of 65 years, effectiveness has been documented to be 75%. In the immunocompromised patient, effectiveness has not been proven, and this includes patients with sickle cell disease, chronic renal failure, immunoglobulin deficiency, Hodgkin's disease, lymphoma, leukemia, and multiple myeloma. A single revaccination is indicated in a person who is older than 65 years of age who initially received the vaccine more than 5 years earlier and was younger than 65 years of age at the first vaccination.^{1,90} If the initial vaccination was given at the age of 65 years or older, a repeat vaccination is not indicated unless the patient has anatomic or functional asplenia or has one of the immunocompromising conditions listed earlier. In these patients, revaccination is indicated, and the second dose is given at least 5 years after the original dose.

The available polysaccharide pneumococcal vaccine is widely underutilized, especially as the 23-valent pneumococcal vaccine contains 23 pneumococcal serotypes that cause 85% of all infections due to pneumococcus. Two protein-conjugated pneumococcal vaccines have been licensed, and are more immunogenic than the older vaccine, but contain only 7 and 13 serotypes.¹ However, the conjugate vaccine has had benefit for adults, even when given to only children, demonstrating a "herd immunity" effect.¹⁷⁷ The 13-valent pneumococcal conjugate vaccine (PCV13) was approved by the Food and Drug Administration in late 2011 for use among adults aged ≥ 50 years.¹⁷⁸ Based on the recent report from the randomized, placebo-controlled trial evaluating the efficacy of PCV13 for preventing CAP among adults aged ≥ 65 years (CAPITA: Community-Acquired Pneumonia Immunization Trial in Adults), the Advisory Committee on Immunization Practices recommended routine use of PCV13 among adults aged ≥ 65 years from August 2014.¹⁷⁸ PCV13 should be administered in series with the 23-valent pneumococcal polysaccharide vaccine, giving PCV13 first, if possible. PCV13 and 23-valent pneumococcal polysaccharide vaccine vaccination are also recommended in patients with chronic pulmonary diseases on steroids or receiving immunomodulating therapy or who have concurrent sickle cell disease or other hemoglobinopathies, primary immunodeficiency disorders, HIV infection/AIDS, nephrotic syndrome, and hematologic or solid malignancies.¹⁷⁹

Hospital-based immunization could be highly effective, because over 60% of all patients with CAP have been admitted to the hospital, for some indication, in the preceding 4 years, and hospitalization could be defined as an appropriate time for vaccination. Pneumococcal vaccine can be given simultaneously with other vaccines, such as influenza vaccine, but each should be given at a separate site, and the vaccine can, and often should, be given before discharge in the patient admitted for CAP.

Influenza Vaccination

Influenza epidemics contribute to both morbidity and mortality by causing direct infection and by leading to postinfluenza complications. The influenza vaccine preparations are revised annually to account for changes in the antigenic nature of the virus (antigenic drift) that occurs each season. Three strains are represented in each vaccine preparation: two influenza A strains (H3N2 and H1N1) and one influenza B strain. Vaccination should be given to all patients older than the age of 65 years and to those with chronic medical illness (including nursing home residents) and to those who provide health care to patients at risk for complicated influenza.¹ It is given yearly, usually between September and mid-November. While the traditional influenza vaccine contains an inactivated virus, there is now an intranasal vaccine containing a live attenuated influenza virus. It is currently approved for individuals aged 5 to 49 years who are not immune suppressed or chronically ill and who do not have asthma. When the vaccine matches the circulating strain, it can prevent illness in 70% to 90% of healthy persons younger than the age of 65 years.^{1,180} For older persons with chronic illness, the efficacy is lower, but the vaccine can still attenuate the influenza infection, lead to fewer lower respiratory tract infections, and reduce the associated morbidity and mortality that follow influenza. In many studies, the vaccine has been shown to be cost-effective and able to prevent severe illness and death and to reduce the occurrence of secondary pneumonia and hospitalization.¹⁸⁰ For those above 65 years of age, a higher dose influenza vaccine (60 μ g of hemagglutinin per strain) has been shown to provide better protection.^{181,182} In a randomized study including 31,989 participants, the high-dose vaccine induced significantly higher antibody responses and provided better protection against laboratory-confirmed influenza illness than the standard vaccine.¹⁸¹ In another study, Izurieta and colleagues, from a large Medicare database of participants aged ≥ 65 years, found that those who had received high-dose inactivated influenza vaccine during the 2012-2013 influenza seasons were less likely to have influenza-related medical encounters and hospitalization than those who had received the standard-dose vaccine.¹⁸³

KEY POINTS

1. Community-acquired pneumonia (CAP) is a common illness, but only about 20% of all affected patients are admitted to the hospital, and only 10% to 20% of admitted patients require ICU care.
2. Risk factors for severe CAP include smoking, alcohol abuse, serious comorbid medical illnesses, and advanced age.
3. Risk factors for CAP mortality include severe physiologic abnormalities, delays in the initiation of appropriate antibiotic therapy, advanced age, genetic abnormalities in the immune response, rapid radiographic progression, the development of respiratory failure, and the presence of certain high-risk pathogens.
4. Prognostic scoring systems are useful for predicting CAP mortality but are less accurate for identifying patients who require ICU care. ICU care is needed for patients with respiratory failure, multilobar infiltrates, severe hypoxemia ($\text{PaO}_2/\text{FiO}_2$ ratio < 250), and systolic blood pressure lower than 90 mm Hg. Early recognition of severe CAP may allow the ICU to be used in a fashion that can reduce the mortality of this illness.
5. The failure to localize infection to a single site in the lung, with excessive systemic and pulmonary inflammation, is a common feature in patients with severe forms of CAP.
6. The clinical features of pneumonia cannot help to predict the microbial etiology, especially in older patients with impaired immune response who commonly have less dramatic clinical findings than younger patients with a similar severity of illness.
7. The most common pathogens causing severe CAP include pneumococcus, atypical pathogens (*Legionella* spp., *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*), enteric gram-negatives (including *Pseudomonas aeruginosa*), *Staphylococcus aureus* (including community-acquired methicillin-resistant strains), and *Haemophilus influenzae*, but infection can also be the result of viral illness (influenza, severe acute respiratory syndrome), bioterrorism (anthrax), and other miscellaneous organisms.
8. Antibiotic-resistant pneumococci are increasingly common and must be considered in the choice of initial antibiotic therapy for severe CAP, but the impact of resistance on the outcomes of patients is uncertain.
9. It may be difficult to establish an exact etiologic diagnosis in patients with severe CAP, but diagnostic testing should always include a chest radiograph, oxygenation assessment, blood cultures, and, in selected patients, sputum Gram's stain and culture, bronchoscopic culture, and urinary antigen testing for *Legionella* and pneumococcus.
10. Therapy for severe CAP must be administered promptly and empirically, using multiple antibiotics directed against pneumococcus, atypical pathogens, enteric gram-negative organisms, and, in some patients, *P. aeruginosa* and community-acquired methicillin-resistant *S. aureus*. This usually requires the combination of a specific beta-lactam with either a macrolide or a quinolone and sometimes the addition of other agents. Quinolone monotherapy is not recommended for the empiric management of severe CAP. In patients with severe CAP after influenza, community-acquired methicillin-resistant *S. aureus* should be considered.
11. Biomarkers such as procalcitonin may help identify bacterial infection, and serial measurements will help with antibiotic stewardship.
12. Nonresponse in severe CAP can be recognized as early on as 24 to 48 hours and requires consideration of unusual or drug-resistant pathogens, noninfectious diseases that mimic pneumonia, and pneumonia complications.
13. Prevention of pneumonia can be accomplished by focusing on smoking cessation and immunization for pneumococcus and influenza, with consideration of a hospital-based immunization program. The 13-valent pneumococcal conjugate vaccine (PCV13) was approved by the Food and Drug Administration in late 2011 for use among adults aged ≥ 50 years, and recent evidence suggests using PCV13 in series with the 23-valent pneumococcal polysaccharide vaccine among patients ≥ 65 years of age.

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DEFINITIONS

Nosocomial pneumonia is an infection of the pulmonary parenchyma caused by pathogens present in hospital settings.¹ Nosocomial pneumonia develops in patients admitted to the hospital for more than 48 hours, and the incubation period is usually no longer than 2 days. Among nosocomial pneumonias, ventilator-associated pneumonia (VAP), which will be the main focus of this chapter, develops in intensive care unit (ICU) patients who have been mechanically ventilated for at least 48 hours. In contrast, ventilator-associated tracheobronchitis (VAT) is characterized by signs of respiratory infection, without new radiologic infiltrates.² Healthcare-associated pneumonia (HCAP) develops in patients who are not hospitalized,¹ but have risks for being colonized by nosocomial multidrug-resistant (MDR) pathogens. Risk factors for developing HCAP are hospitalization for 2 days or more within the preceding 90 days, residence in a nursing home or extended care facility, home infusion therapy, chronic dialysis, home wound care, and contact with subjects colonized by MDR pathogens. Several North American studies³ have reported that MDR microorganisms primarily cause HCAP; conversely, European data⁴ show greater similarity in microbiology with community-acquired pneumonia.

Nosocomial pneumonia is classified based on the presence of microorganisms isolated from respiratory surveillance cultures and includes the following categories⁵:

1. Primary endogenous pneumonia: causative microorganisms are isolated in surveillance cultures on admission.
2. Secondary endogenous pneumonia: causative microorganisms are nosocomial pathogens not present on admission but have colonized the patient during a hospital stay.
3. Exogenous pneumonia: caused by microorganisms not originally isolated from surveillance cultures; hence the patient is not a previous carrier.

The time of onset for nosocomial pneumonia reflects possible etiologies, empirical antimicrobial treatment, and outcomes. Previously, VAP has been categorized as either early or late onset.⁶ In an interesting trial by Trouillet et al.,⁷ three variables were significant for predicting infection with MDR: duration of mechanical ventilation (MV) ≥ 7 days (odds ratio [OR] = 6.0), prior antibiotic use (OR = 13.5), and prior use of broad-spectrum antimicrobial agents (OR = 4.1). More recent reports⁸⁻¹¹ challenge this classification. Indeed, investigators recently have found comparable microbial etiologies between patients with early or late-onset VAP. This may be related to the worldwide rise in MDR and emphasizes that the local ICU ecology is the most important risk factor for acquiring MDR pathogens, irrespective of the length of intubation.

EPIDEMIOLOGY

Incidence and Associated Burden

Nosocomial pneumonia is the second most common nosocomial infection and the leading cause of death from nosocomial infections among critically ill patients. Incidence ranges from 5 to more than 20 cases per 1000 hospital admissions,¹ with the highest rates in immunocompromised, surgical, and elderly patients. Approximately

one-third of nosocomial pneumonias are acquired in the ICU, with VAP being the majority of these ICU-acquired pneumonias. Epidemiology studies from United States report a VAP incidence density between 2 and 16 episodes per 1000 ventilator-days.¹² In comparison with previous reports, the incidence of VAP is decreasing,¹³ likely due to better implementation of prophylactic strategies. Cook et al.¹⁴ estimated that the risk of VAP is 3% during the first 5 days on MV, 2% from the 5th to the 10th days, and 1% for subsequent days. Nosocomial pneumonia, and particularly VAP, increases the duration of hospitalization and healthcare costs. Worsened clinical outcomes associated with VAP have been consistently reported throughout the years.^{15,16} As a result, mean hospital charges per VAP patient have been estimated to increase by approximately US\$40,000.^{15,16}

Mortality

The crude mortality from nosocomial pneumonia may be as high as 30% to 70%.¹ Several reports have estimated that one-third to one-half of all VAP-related deaths are the direct result of the infection, with a higher mortality rate in cases caused by *Pseudomonas aeruginosa*¹⁷ and *Acinetobacter* spp.¹⁸ Attributable VAP mortality has been defined as the percentage of deaths that would not have occurred in the absence of the infection. Recent studies have reappraised the impact of VAP on mortality.¹⁹⁻²¹ In particular, as mentioned earlier, the risk of VAP is time-dependent, possibly causing a significant time-dependent bias, because mortality and ICU discharge act as competing endpoints. Thus, the most recent studies reported an attributable mortality associated with VAP of 10%,^{21,22} with surgical patients and patients with mid-range severity of illness at the highest associated risk.

PATHOGENESIS

Extensive laboratory and clinical work have determined the key pathogenic mechanisms of VAP. Pathogens must first gain access to the airways to cause pneumonia, and intubated patients are at high risk for aspiration of colonized oropharyngeal secretions. In healthy, nonintubated patients, when bacteria gain access to the respiratory tract, colonization is prevented through defense mechanisms, such as a cough, mucus clearance, and cellular and humoral immune responses. Critically ill and intubated patients are already at a high risk for infection because of underlying illness, comorbidities, malnutrition, and invasive devices or procedures. However, tracheal intubation is the *conditio sine qua non* for the development of VAP, because it facilitates aspiration of pathogens and hinders intrinsic respiratory defenses.

Role of the Endotracheal Tube in the Pathogenesis of VAP

Pulmonary aspiration of the colonized oropharyngeal secretions across the endotracheal tube (ETT) cuff is the main pathogenic mechanism for the development of VAP. The most commonly used ETT for long-term mechanically ventilated patients comprises a high-volume, low-pressure (HVLP) cuff. HVLP cuffs were originally designed to prevent tracheal injury.²³ However, the diameter of the HVLP cuff is two to three times larger than the tracheal diameter, so when the ETT cuff is

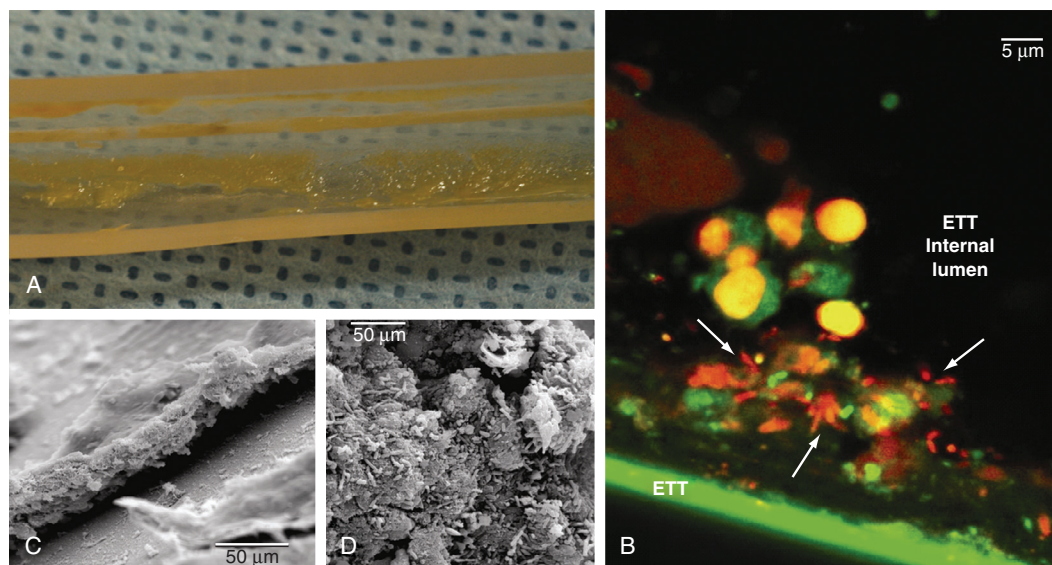


FIGURE 75-1 ■ Laboratory studies to assess biofilm formation on the internal surface of the tracheal tube, following oropharyngeal challenge in pigs of *Pseudomonas aeruginosa* (strain PAO1) and 72 hours of mechanical ventilation. **A**, Internal surface of the tracheal tube at extubation, largely covered by respiratory secretions. **B**, Cross-section of tracheal tube stained with LIVE/DEAD BacLight bacterial viability kit and imaged with confocal scanning laser microscopy. Bacterial biofilm adheres to internal ETT surface. White arrows indicate bacteria embedded into biofilm matrix. **C**, Scanning electron microscopy of tracheal tube lumen. Note the presence of amorphous deposits on most of the surface. **D**, Higher magnification of tracheal tube lumen through scanning electron microscopy. *P. aeruginosa* sessile cells are clearly visible within biofilm extracellular polymeric substance. ETT, endotracheal tube.

inflated within the trachea, folds invariably form along the cuff surface, causing consistent aspiration of oropharyngeal secretions.²⁴

Pathogens may also grow on the internal surface of the ETT and ultimately translocate into the lungs. Bacteria easily adhere to the ETT internal surface to form a structure called a *biofilm*²⁵ (Fig. 75-1). Biofilm is composed of sessile bacteria embedded within a self-produced exopolysaccharide matrix.²⁶ Biofilm on the internal surface of an ETT can be identified early following tracheal intubation.²⁷⁻²⁹ Sessile bacteria undergo phenotypic differentiation from their planktonic counterparts to improve survival. Indeed, sessile bacteria are difficult to eradicate by the host's immune response or antibiotics.³⁰ During MV, biofilm particles may dislodge into the airways as a result of the inspiratory airflow²⁵ and invasive medical interventions, such as tracheal aspiration.³¹ Several studies^{27-29,32} have confirmed that the ETT biofilm constitutes a persistent source of colonization.

Sources of Colonization

Patients are colonized exogenously by contaminated respiratory equipment, the ICU environment, and the hands of the ICU staff. Several reports have described ICU outbreaks due to colonized bronchoscopes,^{33,34} water supply,³⁵ respiratory equipment,³⁶ humidifiers,³⁷ ventilator temperature sensors,³⁸ respiratory nebulizers,³⁹ and the contaminated ICU environment.⁴⁰

Endogenous colonization is the primary pathogenic mechanism for VAP development. In the critically ill patient, the oral flora shifts early to a predominance of aerobic gram-negative pathogens,⁴¹ *P. aeruginosa*, and methicillin-resistant *Staphylococcus aureus* (MRSA). Pulmonary aspiration of oropharyngeal contents increases the risk for airway colonization and infection. Following aspiration and colonization of the airways, the occurrence of VAP primarily depends on the size of the inoculum, functional status of the patient, and the competency of host defenses. There remains controversy regarding the exact

sequence of colonization and source of infection in the pathogenesis of VAP. Early studies by Feldman et al.⁴² found that in patients undergoing MV; the oropharynx is the first site to be colonized by pathogens (36 hours), followed by the stomach (36-60 hours), the lower respiratory tract (60-84 hours), and the ETT thereafter (60-96 hours).

Oropharyngeal Colonization

In ICU patients, several oropharyngeal defense mechanisms are dramatically altered. First, comorbidities and inherent patient characteristics, such as alcohol abuse,⁴³⁻⁴⁵ diabetes,^{46,47} and chronic obstructive pulmonary disease (COPD),⁴⁸ are well-known risk factors for Gram-negative oropharyngeal colonization. Elderly patients,⁴⁹⁻⁵² patients with disabilities,⁵³ and patients tracheally intubated for extended periods are at increased risk for overgrowth of oropharyngeal pathogens, because of their inability to carry out effective oral care. Additionally, the extensive use of antibiotics in critical care settings promotes overgrowth of oropharyngeal pathogens.^{54,55} Second, during critical illness, the antimicrobial effectiveness of saliva is highly impaired due to a dramatic reduction in the salivary flow,⁵⁶ decreased pH,⁵⁷ and increased amount of proteases released by host immune cells and periodontal bacteria.⁵⁸⁻⁶⁰ Bacteria that colonize the oropharynx also produce a large variety of hydrolases that lead to increased expression of key receptors for bacterial adhesion.⁶¹⁻⁶³

Fourrier and collaborators⁶⁴ found that prolonged ICU stay increased the risk for oropharyngeal colonization, which ultimately led to nosocomial pulmonary infection. Azarpazhooh et al.⁶⁵ found evidence of an association of pneumonia with oral health (OR = 1.2 to 9.6, depending on oral health indicators); improved oral hygiene reduced the occurrence of respiratory infection among high-risk elderly adults. Interestingly, in a study by Heo,⁶⁶ oral respiratory pathogens were often genetically identical to pathogens recovered from the lower airways, and rapid changes of bacterial species in both oral and pulmonary sites occurred.

Sinuses

The association between sinusitis and VAP has long been debated.⁶⁷ Several studies have confirmed that orotracheal as compared to nasotracheal intubation is associated with a decreased incidence of sinusitis⁶⁸⁻⁷⁰ and that the incidence of VAP is lower in patients who do not develop sinusitis.⁷¹ A study by Holzapfel et al.⁷² evaluated the incidence of nosocomial maxillary sinusitis and pneumonia in patients who underwent either nasotracheal or orotracheal intubation. The authors found that sinusitis increased the risk of nosocomial pneumonia by a factor of 3.8.

Stomach

According to the gastropulmonary hypothesis of colonization, the stomach of ICU patients is colonized by pathogens due to gastric alkalization associated with enteral nutrition and drugs for prevention of gastrointestinal bleeding.⁷³ Continuous gastroesophageal reflux facilitates translocation of microbes into the oropharynx, which is then aspirated across the ETT cuff. Early studies have shown that in tracheally intubated patients, gastric pH higher than 4 was consistently associated with gastric colonization.^{74,75} However, the association between gastric colonization and VAP found in early studies⁷⁶⁻⁷⁸ has been challenged.^{79,80} Overall, this area remains highly controversial, and several studies^{42,79,81-84} have not found a relationship with bacteria causing VAP as first originating in the stomach.

Impairment of Respiratory Defense During Critical Illness and Tracheal Intubation

In healthy subjects, the anatomic laryngeal barrier prevents aspiration of pathogen-laden oropharyngeal contents. Following intubation, the ETT completely bypasses these anatomic barriers. A cough is one of the most efficient mechanisms to prevent further translocation of pathogens that may have gained access to airways. Tracheal intubation prevents the closure of the glottis. Hence, it hinders cough⁸⁵; moreover, intubated patients are often sedated and unable to generate high expiratory flows.

Mucociliary clearance is the primary innate airway defense mechanism to clear pathogens. In young, healthy nonsmokers, the mucociliary velocity ranges between 10 and 20 mm/min. Studies in animals have shown that inflation of the ETT cuff lowers mucociliary velocity by 50% after only 2 hours.⁸⁶ Clinical studies⁸⁷ in critically ill patients have found similar reduced mucociliary velocity (0.8-1.4 mm/min) and higher risks for pulmonary complications.

As previously mentioned, the daily hazard rate for developing VAP is higher during the first days of MV.¹⁴ Investigators have found that a temporary immunoparalysis can be found early in the course of the critical illness and admission to the ICU.⁸⁸ In particular, researchers have assessed human leukocyte antigen-DR (HLA-DR) expression on peripheral monocytes as a marker of immune function.⁸⁹ Low levels of HLA-DR expression have been found in patients who subsequently developed nosocomial pneumonia.⁹⁰

Etiologic Agents for Nosocomial Pneumonia

Nosocomial pneumonia may be caused by a variety of pathogens; also, in many patients, more than one pathogen may be isolated. Microorganisms responsible for nosocomial pneumonia differ according to the ICU population, the duration of hospital and ICU stays, and the specific diagnostic method(s) used. VAP is commonly caused by aerobic pathogens, often MDR, including *P. aeruginosa*, *Acinetobacter* species, carbapenemase-containing *Klebsiella pneumoniae*, and MRSA.¹ Data from 7087 infected patients (63.5% with respiratory tract infection) from the Extended Prevalence of Infection in Intensive Care (EPIC II) study⁹¹ have confirmed that *Pseudomonas* spp. and *S. aureus* are the most common isolated pathogens in ICUs.

Esperatti et al.⁹² prospectively evaluated 315 ICU patients with HAP admitted to an ICU; among those, 52% were invasively ventilated,

whereas 48% were either on spontaneous or noninvasive ventilation (NIV). Interestingly, the proportion of causative pathogens was similar between groups, except for a higher proportion of *Streptococcus pneumoniae* in patients not invasively ventilated. Thus, it seems that in ICU-acquired pneumonia, the overall frequency of MDR pathogens and MRSA is sufficiently high to warrant the use of broad empirical therapy.

The high rate of polymicrobial infection in VAP has been shown repeatedly. Combes and colleagues⁹³ studied 124 ICU patients, of whom 52% had monomicrobial VAP and 48% polymicrobial VAP. In most patients, two different bacterial species were isolated (34%); however, up to four different bacterial species coexisted in 7 patients (6%). Interestingly, no differences were detected in mortality rate at 30 days among patients with polymicrobial or monomicrobial infection. A study by Teixeira et al.⁹⁴ investigated risk factors for inadequate empirical antimicrobial therapy in 151 ICU patients and found that inadequate antimicrobial treatment was associated with polymicrobial VAP (OR = 3.67; 95% confidence interval [CI] = 1.21-11.12; *P* = 0.02), and higher mortality.

Underlying diseases may predispose patients to infection with specific organisms. Patients with COPD are at increased risk for *Haemophilus influenzae*, *Moraxella catarrhalis*, *P. aeruginosa*, or *S. pneumoniae* infections.^{95,96} Patients with acute respiratory distress syndrome (ARDS) are at higher risk for developing VAP caused by *S. aureus*, *P. aeruginosa*, and *Acinetobacter baumannii*, and often in these patients, VAP is caused by multiple pathogens.^{97,98} Finally, trauma and neurologic patients are at increased risk for *S. aureus*, *Haemophilus*, and *S. pneumoniae* infections.⁹⁹⁻¹⁰¹

Causative pathogens of VAP that are potentially multiresistant are *P. aeruginosa*, MRSA, *Acinetobacter* spp., *S. maltophilia*, *Burkholderia cepacia*, and *K. pneumoniae*.⁸ Conversely, *S. pneumoniae*, *H. influenzae*, methicillin-sensitive *S. aureus* (MSSA), and antibiotic-sensitive Enterobacteriaceae are not considered MDR pathogens. In the majority of the cases, resistance to third- and fourth-generation cephalosporins in carbapenem-susceptible strains of *Escherichia coli* and *K. pneumoniae* is caused by the acquisition of plasmidic Ambler class A extended-spectrum β -lactamases or AmpC-like cephalosporinases.¹⁰² Resistance to carbapenems in Enterobacteriaceae is caused by the acquisition of plasmidic carbapenemases, either of Ambler class A (mainly *K. pneumoniae* carbapenemase), B, or D.¹⁰² Importantly, plasmids harboring extended-spectrum β -lactamase (ESBL)-encoding and/or carbapenemase-encoding genes often carry other resistance genes, which ultimately confer pan-drug resistance. Conversely, carbapenem resistance in *P. aeruginosa* and *A. baumannii* may be caused by loss of outer membrane porins, hyperexpression of efflux pump systems, and carbapenemase production. In 2010, linezolid-resistant MRSA was reported,¹⁰³ due to a plasmid harboring the chloramphenicol-florfenicol resistance gene.¹⁰⁴⁻¹⁰⁶

Patients at risk of being colonized by MDR pathogens are extremely heterogeneous, often present several comorbidities, and many receive antibiotics during their hospitalization. The incidence of MDR pathogens is also closely linked to local factors and varies widely from one institution to another.¹⁰⁷ Therefore, clinicians must be aware of their ICU local ecology and antibiotic susceptibility to avoid the administration of inadequate initial antimicrobial therapy.

Legionella pneumophila as the cause of nosocomial pneumonia should be considered, particularly in immunocompromised patients.¹⁰⁸ Often, the source of legionellosis outbreaks within the hospital is a water system that has become colonized by the microorganism.¹⁰⁹

A primary mechanism for VAP development is through aspiration of oropharyngeal contents, and the oropharynx is highly colonized by anaerobes. Robert et al.¹¹⁰ studied 26 mechanically ventilated patients and found that 15 patients became colonized with 28 different anaerobic strains. Similarly, Dore et al.¹¹¹ found anaerobic bacteria in 30 (23%) of 130 patients diagnosed with VAP but always in association with aerobic pathogens. Importantly, empirical antibiotic therapy active against anaerobic bacteria appears to improve short-term outcomes in patients with VAP. Nevertheless, the role of anaerobes in VAP

is still considered to be controversial. In particular, Marik et al.¹¹² studied microbiology of 185 episodes of suspected VAP through blind protected specimen brush (PSB) sampling and mini-BAL and were unable to identify anaerobes as the causative pathogens of VAP.

Rarely, VAP is caused by fungi. *Candida* spp. and *Aspergillus fumigatus*¹¹³ are the most commonly isolated fungi, predominantly in immunocompromised patients. *Candida* promotes the development of pneumonia by creating biofilms that facilitate bacterial colonization.¹¹⁴ Moreover, *Candida* seems to reduce host immune response.¹¹⁵ Thus, clinical studies have shown that *Candida* colonization increases the risk of VAP by *P. aeruginosa*.¹¹⁶ Yet, in a postmortem study of patients with evidence of pneumonia at autopsy and isolation of *Candida* from respiratory samples, no case of *Candida* pneumonia was found.¹¹⁷ Interestingly, colonization by *Candida* has also been associated with longer MV, ICU and hospital stays, and in-hospital mortality.¹¹⁸⁻¹²⁰ Some investigators argue that the presence of *Candida* is merely a marker of severity rather than a true etiologic factor for VAP.¹²¹

Viruses may also cause VAP. Herpes simplex virus type-1 (HSV-1) nosocomial pneumonia is more frequently reported in immunocompromised patients and patients with ARDS,¹²² major surgery,^{123,124} or extensive burns.¹²⁵ Luyt et al. demonstrated in 201 patients with clinical suspicion of VAP that 21% had HSV-1 pneumonia.¹²⁶ Several studies¹²⁷⁻¹³⁰ have reported a high incidence of active CMV infection in mechanically ventilated patients. Chiche et al.¹³⁰ studied 242 immunocompetent ICU patients and found active CMV infection in 39 (16%) individuals. At 28 days, only 15% of the patients with active CMV infection were weaned and alive, in comparison to 52% of patients free of CMV infection ($P < 0.001$).

PREVENTION

Nosocomial pneumonia is associated with high morbidity and mortality and constitutes an important burden for the healthcare system. Therefore, preventive strategies should be implemented to reduce the overall incidence of the disease (Box 75-1). The Institute for Healthcare Improvement recommends that approaches with proven efficacy in infection control should be implemented together as a bundle because combined, they are expected to result in a better outcome than when implemented individually. Designing a preventive bundle is just the first step and must be followed by a continuous assessment of

healthcare personnel compliance and improvements to implement interventions. Several reports¹³¹⁻¹³³ have found consistent reductions in the incidence of VAP following the implementation of VAP preventive bundles.

General Prophylactic Measures

Maintaining high levels of education among ICU personnel relating to VAP pathophysiology and preventive strategies can be effective in reducing its incidence.¹³¹ Needleman et al.¹³⁴ studied administrative data from 799 hospitals in 11 states (covering 5,075,969 discharges of medical patients and 1,104,659 discharges of surgical patients) and found that a higher proportion of hours of care per day provided by registered nurses, compared to licensed practical nurses and nurses' aides, was associated with lower incidence of pneumonia.

Adherence to simple infection-control measures, such as alcohol-based hand disinfection,^{135,136} effectively reduces cross-transmission of pathogens and incidence of VAP. The World Health Organization has endorsed hand hygiene as the single most important element of strategies to prevent healthcare-associated infections.¹³⁷ Overall, most studies conducted in ICUs have shown consistent results and a temporal association between implementation of alcohol-based hand hygiene and reduction of nosocomial infections.^{135,138}

Investigators demonstrated that patient transport outside the ICU was associated with increased risk for VAP.^{139,140} Clinicians and nursing staff should carefully check the internal pressure of the ETT cuff prior to and during patient transport. Also, ventilator circuits should be carefully manipulated to prevent the aspiration of colonized fluids from within the circuit.

Daily interruption or lightening of sedation¹⁴¹⁻¹⁴³ and early mobilization,¹⁴⁴ as well as avoidance of paralytic agents, is highly recommended to avoid impairment of respiratory defenses, prolonged tracheal intubation, and VAP.

There is evidence of shorter length of MV, reduced rate of failed extubation, and decreased incidence of VAP when protocol-driven weaning from the ventilator is implemented.¹⁴⁵⁻¹⁴⁸ Marelich et al.¹⁴⁶ randomized 385 patients to receive either a protocol-driven weaning procedure or standard care and found that duration of MV was decreased from a median of 124 hours for the control group to 68 hours in the protocol-driven weaning group ($P = 0.0001$). Moreover, a trend toward less VAP was found in the treatment group ($P = 0.061$).

NIV

Tracheal intubation and MV account for the main risk for nosocomial pneumonia and should therefore be avoided whenever possible. NIV is an attractive alternative for patients with acute exacerbations of COPD or acute hypoxemic respiratory failure and for some immunocompromised patients with pulmonary infiltrates and respiratory failure.¹⁴⁹⁻¹⁵³ NIV can also be safely used to facilitate early extubation and avoid continued invasive weaning. A meta-analysis¹⁵⁴ confirmed that noninvasive weaning is associated with reduced mortality, VAP, and length of stay in the ICU and hospital. Other reports^{155,156} have emphasized the role of NIV in preventing re-intubation in recently extubated patients at risk for relapse and respiratory failure. Kohlenberg et al.¹⁵⁷ pooled data of 400 ICUs in Germany and found a mean pneumonia incidence of 1.58 and 5.44 cases per 1000 ventilator days for NIV and invasive MV, respectively. Therefore, when indicated, NIV should be attempted to avoid tracheal intubation and reduce the overall duration of tracheal intubation.

Tracheal Tube Cuff

Currently, in critical care settings, patients are intubated with ETT comprising high-volume low-pressure cuffs. Upon inflation, folds form along the cuff surface, and colonized oropharyngeal secretions may leak through these folds. Novel ETT cuffs made of polyurethane,¹⁵⁸ silicone,¹⁵⁹ and latex¹⁶⁰ have been developed and tested in the

BOX 75-1

Preventive Strategies for Nosocomial Pneumonia

- Implementation, as a bundle, of nosocomial pneumonia preventive strategies that have proven efficacy in reducing morbidity and mortality
- Implementation of educational programs for caregivers and frequent performance feedbacks and compliance assessment
- Strict alcohol-based hand hygiene
- Avoidance of tracheal intubation and use of NIV when indicated
- Daily sedation vacation and implementation of weaning protocols
- No ventilatory circuit tube changes unless the circuit is soiled or damaged
- Use of tracheal tube with cuff made of novel materials and shapes
- Use of silver-coated tracheal tube
- Application of low-level PEEP during tracheal intubation
- Aspiration of subglottic secretions
- Internal cuff pressure maintained within the recommended range and carefully controlled during transport of patients outside ICU
- Oral care with chlorhexidine
- Avoid stress ulcer prophylaxis in very low-risk patients for gastrointestinal bleed, and consider use of sucralfate when indicated.
- Semirecumbent patient positioning
- Continuous lateral rotation therapy
- Postpyloric feeding in patients who have impaired gastric emptying
- SDD for patients requiring >48 hours of mechanical ventilation

ICU, intensive care unit; NIV, noninvasive ventilation; PEEP, positive end-expiratory pressure; SDD, selective digestive decontamination.

laboratory and clinical trials. In particular, the polyurethane cuff has a thickness of 5 to 10 μm , in comparison to 50 μm for PVC cuffs. Hence, upon inflation, smaller folds form with polyurethane cuffs, and aspiration of secretions above the cuff can be prevented or reduced. Some investigators have attempted to prevent aspiration by modifying the shape of the cuff.¹⁶¹ In comparison to standard cuffs with cylindrical shapes, cuffs designed with a smooth, tapering shape allow elimination of folds for a full circumference of the trachea or cuff contact zone, irrespective of the cuff material.

A few studies in medical ICU patients have shown that polyurethane cuffs reduce risks of developing VAP.^{162,163} The polyurethane-cuffed ETT has also shown benefits in reducing early postoperative pneumonia in cardiac surgical patients.^{164,165} Interestingly, in a recent multicenter study,¹⁶⁶ cuffs composed of cylindrical polyvinyl chloride, cylindrical polyurethane, conical polyvinyl chloride, or conical polyurethane were compared in the prevention of VAP, and no benefits were found with the use of polyurethane or conical cuffs. Silicone¹⁵⁹ and latex¹⁶⁰ cuffs are low volume and low pressure and are potential alternatives to PVC cuffs since folds are never formed upon inflation within the trachea. In a clinical trial on patients undergoing anesthesia or admitted to the ICU, Young et al.¹⁵⁹ demonstrated high effectiveness of a silicone cuff in reducing pulmonary aspiration. In our opinion, due to the lack of clear evidence on the benefits of these new cuffs, their use should be only limited to patients at very high risk of developing VAP.

It is important to maintain the internal ETT cuff pressure between 25 and 30 cm H₂O to prevent aspiration of contaminated secretions into the lower airways and tracheal injury. Several studies¹⁶⁷⁻¹⁶⁹ have demonstrated that frequently the ETT cuff was underinflated or hyperinflated using standard management. Continuous control of internal cuff pressure reduces risks of significant deflation and pulmonary aspiration.

Ventilatory settings may play a role in the pathogenesis of VAP. In particular, PEEP may decrease the incidence of VAP by counteracting hydrostatic pressure exerted by oropharyngeal secretions above the ETT cuff, hence reducing pulmonary aspiration.^{170,171} Lucangelo et al.¹⁷² assessed the effects of 5 to 8 cm H₂O PEEP in normoxemic ventilated patients and showed a reduction in the rate of VAP. Thus, in the absence of major contraindications, a low level of PEEP should be maintained to avoid pulmonary aspiration.

Tracheal Tubes Coated with Antimicrobial Agents

Coating the ETT with antimicrobial agents, such as silver, is a promising strategy to prevent biofilm formation on its internal surface and VAP.¹⁷³ Olson et al.¹⁷⁴ tested a silver-coated ETT in dogs challenged with *P. aeruginosa* into the oropharynx. Using the new tube, the investigators were able to postpone colonization of the ETT inner surface and reduce pulmonary bacterial burden. Similarly, Berra et al.¹⁷⁵ studied a silver sulfadiazine/chlorhexidine-coated ETT in sheep. After 24 hours of MV, standard ETTs and ventilatory circuits were heavily colonized, whereas the novel coated ETT fully avoided colonization. Interestingly, the efficacy of silver-based coatings seems to decrease over time. Indeed, animal studies reported heavy colonization of silver-coated ETTs after 72 hours of MV. To date, only one laboratory study¹⁷⁶ has shown the absence of ETT biofilm formation up to 168 hours of MV, when silver sulfadiazine ETTs were regularly cleaned with the Mucus Shaver.¹⁷⁷ The North American Silver-Coated Endotracheal Tube (NASCENT) randomized trial¹⁷⁸ compared the preventive effects of a silver-coated vs. conventional ETT. The silver-coated ETT was associated with a lower incidence of microbiologically confirmed VAP (4.8% vs. 7.5%; $P = 0.03$), for a relative risk reduction of 35.9%. A retrospective cohort analysis by Afessa et al.¹⁷⁹ showed that the silver-coated ETT was associated with reduced mortality in patients with VAP (14% vs. 36% in silver and control ETT, respectively, $P = 0.03$). Mortality was higher in those without VAP. In conclusion, ETT coated with antimicrobial agents could reduce the incidence of VAP, but the

evidence supporting its use comes only from one study, with significant limitations.¹⁸⁰ Thus, clinicians should carefully consider benefits and limitations of these ETTs and properly direct the use of silver-coated tubes to patients expected to be ventilated for longer periods of time and with higher risks for nosocomial pneumonia. Shorr et al.¹⁸¹ analyzed the cost-effectiveness of the silver-coated ETT and found that per each prevented VAP, US\$12,840 was saved.

Aspiration of Subglottic Secretions

Aspiration of colonized subglottic secretions through dedicated ETTs reduces hydrostatic pressure exerted above the cuff and potentially prevents leakage across the cuff. A meta-analysis¹⁸² has shown that drainage of subglottic secretions reduced the overall risk ratio (RR) for VAP by half (RR, 0.55; 95% CI, 0.46-0.66; $P < 0.01$). In a multicenter trial by Lacherade et al.,¹⁸³ 333 patients were randomized to be intubated with either an ETT that allowed drainage of subglottic secretions or a standard ETT. Microbiologically confirmed VAP occurred in 14.8% of the patients in the treatment group, compared to 25.6% of the patients intubated with a standard tube ($P = 0.02$). Interestingly, subglottic secretion drainage has been consistently associated with tracheal injury in clinical¹⁸⁴ and laboratory studies.^{24,185}

Tracheostomy

Tracheostomized patients present the same risks for aspiration of pathogen-laden secretions pooled above the cuff as orotracheally intubated patients. In the most recent meta-analysis¹⁸⁶ that assessed outcomes of early versus late tracheostomy, early tracheostomy did not reduce the incidence of VAP. Early tracheostomy may improve patient comfort, ability to communicate, capability for oral feeding, reduce the need for sedation and analgesia, and reduce airway resistance in comparison to standard ETTs. These factors are of paramount importance during the weaning period to shorten the duration of tracheal intubation.

Ventilator Circuit Management

Clinical trials in adults¹⁸⁷⁻¹⁹² and meta-analyses¹⁹³ have demonstrated that a routine change of the ventilator circuit does not decrease risks for VAP or costs. Therefore, circuits should not be changed unless the circuit is soiled or damaged. Importantly, inadvertent flushing of the contaminated condensate into the lower airways or nebulizers should always be avoided by careful emptying of ventilator circuits and water traps.^{194,195}

The latest meta-analysis¹⁹⁶ that assessed the effects of heated humidifiers (HH) and heat and moisture exchangers (HME) on prevention of nosocomial pneumonia showed no effect on pneumonia prevention. To date, neither humidification strategy can be recommended as a pneumonia prevention tool. However, it is rational to deliver inspiratory gases at body temperature or slightly below and at the highest relative humidity to prevent loss of heat and moisture from the airways, change in rheologic properties of secretions, and impairment of mucociliary clearance. Therefore, the use of HH is particularly indicated in patients with hypothermia, prolonged MV, thick secretions, and chronic respiratory disorders. Finally, studies¹⁹⁷⁻²⁰¹ testing less frequent changes of HMEs have not found increased risks for VAP. HMEs should be changed periodically (i.e., every 72 hours), to ensure good performance.

Closed tracheal suctioning systems have been introduced in clinical settings to avoid adverse events associated with ventilator disconnection during open tracheal suctioning and exogenous contamination of suction catheters entering the ETT. Three meta-analyses²⁰²⁻²⁰⁴ have compared the closed to the open tracheal suction system in mechanically ventilated patients and found no benefits of VAP prevention.

The use of a saline solution instilled into the ETT before tracheal suctioning remains controversial. A systematic review²⁰⁵ consistently

found a decrease in patient oxygenation in most studies. Only one study²⁰⁶ found a lower incidence of microbiologically proven VAP (saline instillation versus no treatment: 23.5% vs. 10.8%; $P = 0.008$). Importantly, in sedated patients in the semirecumbent position and with the ETT internal surface highly colonized, saline instillation may increase risks for translocation of pathogens into the airways.

Body Position

Early studies demonstrated that intubated patients are at higher risk for gastropulmonary aspiration when placed in the supine position (0 degrees) as compared with a semirecumbent position (45 degrees).^{73,207,208} One randomized trial²⁰⁹ demonstrated a reduction in the incidence of VAP in patients positioned in the semirecumbent position compared with patients completely supine, particularly during enteral feeding. A later randomized trial²¹⁰ found limited feasibility of the intervention and no differences in VAP incidence. Thus, as strongly suggested by the American¹ and European guidelines,²¹¹ intubated patients should be preferentially kept in the semirecumbent position (30-45 degrees) rather than supine (0 degrees), especially when receiving enteral feeding.

Laboratory reports^{212,213} have challenged the preventive benefits of the semirecumbent position. Theoretically, in tracheally intubated patients a tracheal orientation above horizontal might facilitate aspiration across the ETT cuff. Conversely, laboratory studies^{213,214} consistently found that the lateral-Trendelenburg position enhances mucous drainage and decreases risks for VAP. Currently, a multicenter clinical trial is testing in critically ill patients the efficacy, safety, and feasibility of the lateral-Trendelenburg position in the prevention of VAP (available from ClinicalTrials.gov; NLM Identifier: NCT01138540).

Rotating Bed

Several ICU beds permit the rotation of patients in the longitudinal axis from one lateral position to the other and reduce extravascular lung water, improve the ventilation-perfusion ratio, and enhance mobilization of airway secretions.²¹⁵ Meta-analyses²¹⁶⁻²¹⁸ have shown a significant reduction in the incidence of VAP in patients undergoing rotation therapy. Staudinger et al.²¹⁹ studied the effects of continuous lateral rotation therapy and found a VAP incidence of 11% in the rotation group and 23% in the control group ($P = 0.048$). The authors also found that the duration of ventilation (8 ± 5 vs. 14 ± 23 days; $P = 0.02$) and length of stay (25 ± 22 days vs. 39 ± 45 days; $P = 0.01$) were significantly shorter in the rotational group. In conclusion, in patients at a higher risk for prolonged immobilization and respiratory infection, continuous lateral rotation therapy should be considered for exerting additive effects to other preventive measures for VAP.

Stress Ulcer Prophylaxis and Enteral Feeding

Sucralfate, histamine type 2 blockers (H_2 blockers), or proton pump inhibitors (PPIs) are the most common medication for stress ulcer prophylaxis. Sucralfate is the only treatment that does not cause gastric alkalization. Early studies found a higher incidence of pneumonia in patients with alkalized gastric contents,⁷⁶⁻⁷⁸ whereas others have not.^{80,220} Cook et al.²²⁰ found a higher risk of GI bleeding using sucralfate and no significant difference in VAP incidence: 19.1% and 16.2% in patients treated with H_2 blockers or sucralfate, respectively. Likewise, in a recent meta-analysis,²²¹ PPIs were more effective than H_2 blockers at reducing upper gastrointestinal bleeding, without differences in VAP (relative risk = 1.06; 95% CI = 0.73-1.52; $P = 0.76$). In conclusion, GI bleeding is a serious complication in critically ill patients. The actual risk for VAP is unknown when accurate methods of enteral feeding (i.e., avoiding large gastric residual volumes) or other preventive measures are used in combination with stress ulcer prophylaxis. Therefore, clinicians must weigh the potential benefit of sucralfate (with potentially less VAP and more GI bleeding) versus H_2 blockers/PPI (with potentially more VAP and less GI

bleeding) and probably limit stress ulcer prophylaxis to high-risk patients.

Enteral nutrition has been considered a risk factor for the development of VAP, because of increased risks for gastric alkalization, gastroesophageal reflux, and gastropulmonary aspiration. However, its alternative, parenteral nutrition, is associated with higher risks for catheter-related infections, complications of line insertions, higher costs, and loss of intestinal villous architecture, which may facilitate enteral microbial translocation. A large meta-analysis²²² of 11 studies comprising more than 500 critically ill patients found that the use of parenteral nutrition was associated with more infectious complications, compared to early enteral nutrition (OR = 1.47; 95% CI = 0.90-2.38; $P = 0.12$). Conversely, studies in medical ICU patients have demonstrated a higher risk for VAP with early enteral feeding.^{223,224} Therefore, in medical ICU patients, the benefits of early nutrition should be balanced with associated increased risks for VAP.

Many ICU patients present impaired gastric emptying; hence, the placement of the feeding tube beyond the pylorus has the potential to achieve nutrition goals without increased risks for gastropulmonary aspiration. The most recent meta-analysis by Jiyong et al.²²⁵ found that small bowel feedings were associated with a lower incidence of pneumonia (RR = 0.63; 95% CI = 0.48-0.83; $P = 0.001$). In an interesting report by Davies and collaborators,²²⁶ in mechanically ventilated patients with mildly elevated gastric residual volumes and already receiving nasogastric nutrition, early postpyloric nutrition did not increase energy delivery or reduce the frequency of pneumonia. Therefore, postpyloric feeding should be preferred only when impaired gastric emptying is present. Finally, a recent study²²⁷ challenged the utility of routine monitoring of residual gastric volume in 449 patients receiving invasive MV and early enteral nutrition. VAP occurred in 16.7% of the patients without routine monitoring, in comparison with 15.8% in the control group.

Modulation of Oropharyngeal and Gastrointestinal Colonization

Given the pivotal role of oropharyngeal colonization in the development of VAP,⁴¹ many decontamination strategies have been developed, which include hand washing, oral hygiene and tooth brushing,²²⁸ selective oral decontamination with topical nonabsorbable antibiotics,²²⁹ and oropharyngeal rinsing with antiseptics.²³⁰ Chlorhexidine is a cationic chlorophenyl bis-biguanide antiseptic that has long been used as an inhibitor of dental plaque formation and gingivitis. A meta-analysis²³⁰ of studies assessing the benefits of chlorhexidine on the reduction of VAP reported fewer lower respiratory tract infections in cardiac surgery patients (RR = 0.56; 95% CI = 0.41-0.77) without a significant mortality difference (RR = 0.88; 95% CI = 0.25-2.14). Results in noncardiac ICU populations are inconsistent. Most of the studies described earlier used chlorhexidine concentrations up to 0.2%. This concentration may not be effective in most ICU patients with high levels of oropharyngeal colonization. Studies^{231,232} have demonstrated significant reductions in VAP rates when chlorhexidine concentration was increased to 2%. Therefore, oral decontamination with chlorhexidine should be routinely used, specifically in cardiothoracic patients. In other ICU populations, the use of higher chlorhexidine concentrations could be a promising option. Alternatively, some investigators recently tested once-daily bathing of all patients with disposable cloths impregnated with 2% chlorhexidine as a preemptive strategy for nosocomial infections, but they did not find any significant benefit with this approach.²³³

Selective digestive decontamination (SDD) comprises a combination of nonabsorbable antibiotics against gram-negative pathogens (i.e., tobramycin and polymyxin E), plus either amphotericin B or nystatin. These agents are administered into the GI tract to prevent oropharyngeal and gastric colonization with aerobic Gram-negative bacilli and *Candida* spp. while preserving the anaerobic flora. Some regimens include a short course of systemic antibiotics (i.e., cefotaxime). SDD was originally applied to oncologic and hematologic

patients with severe immunosuppression.^{234,235} In the early 1980s, Stoutenbeek introduced this practice into critical care medicine.²³⁶ Since then, a remarkable number of clinical trials and meta-analyses confirmed the benefits associated with the use of SDD, which was associated with a reduction in the incidence of VAP, bacterial bloodstream infections, and mortality.²³⁷ Currently, SDD is primarily applied in European centers with low levels of MDR.²³⁸

Randomized clinical trials^{229,239,240} and meta-analyses²³⁷ confirmed that SDD confers protection against nosocomial pneumonia. Several factors should be taken into account before extending its use worldwide. First, the most recent investigations on the intestinal microbiota highlight the variability, interactions, and complexity of gastrointestinal bacterial colonies, and systemic consequences of changes in gut colonization.²⁴¹⁻²⁴⁷ Indeed, it is known that more than 10^{11} bacteria per gram of feces, comprising more than 1000 different species, are present in our intestinal system.²⁴⁸ Large interindividual variations in bacterial patterns are evident even among humans living in the same geographic region.²⁴⁹ With the advent of individualized medicine, the use of a unit-wide single SDD regimen for all ICU population subtypes²⁵⁰ seems farfetched. In addition, even the selectivity of SDD against aerobic Gram-negative bacteria has been challenged.²⁵¹ Thus, the impact of SDD on the intestinal microbiota and the resulting alterations of bacterial diversity need further evaluation. Second, one of the most recurrent arguments for not using SDD is that microorganisms not addressed by the regimen may be selected (i.e., MRSA and *Enterococcus* spp.) or MDR for the applied antibiotics may increase. A recent study²⁵² demonstrated an increase in anaerobic flora antibiotic resistance genes during SDD, particularly highly transferable genes conferring resistance to aminoglycosides. In line with these results, Oostdijk and collaborators²³⁹ found increases in aminoglycoside-resistant Gram-negative bacteria during SDD use. Finally, in one older study²⁵³ by the same group that explored recolonization following SDD, increased intestinal colonization with Gram-negative bacteria resistant to ceftazidime, tobramycin, or ciprofloxacin was found. Likewise, resistance to ceftazidime increased gradually in the respiratory tract during SDD and even further post intervention, for all three antibiotics. This suggests that there are still several unknown effects of SDD that need to be addressed. An ongoing European trial is addressing these questions. The R-GNOSIS (Resistance in Gram-Negative Organisms: Studying Intervention Strategies) is evaluating the most effective measures to reduce infections caused by MDR pathogens and to understand the ecologic effects of decolonization strategies in patients admitted to the ICU (available from <https://www.clinicaltrials.gov/ct2/show/NCT02208154?term=bonten&rank=2>).

Only one study²⁵⁴ has demonstrated that a short course of cefuroxime in patients with structural coma or severe burns was an effective prophylactic strategy to decrease the VAP rate. However, routine use of parenteral antibiotics is not recommended until more data become available.

Several clinical trials have attempted to modify GI and oropharyngeal growth of pathogens through the use of probiotics. Probiotics are microorganisms that can be administered either as individual strains or in various combinations. These microorganisms are often administered with nondigestible food ingredients that facilitate bacterial growth and activity (prebiotics). Products containing both probiotics and prebiotics are called *synbiotics*. The latest meta-analysis²⁵⁵ on the effects of probiotics suggests that probiotics may reduce the incidence of VAP. The quality of the evidence is low and is lacking to draw firm conclusions on this subject.

DIAGNOSIS

The diagnosis of VAP is a controversial issue.²⁵⁶⁻²⁵⁸ Clinical signs suggestive of pneumonia, such as fever, tachycardia, and leukocytosis, are nonspecific in critically ill patients.^{259,260} Moreover, particularly in ventilated patients with bronchiectasis and/or COPD, the chest radiograph is difficult to interpret, and it may not reveal subtle lung infiltrates, which are only detected by computed tomography (CT) scans.²⁶¹

TABLE 75-1 The Clinical Pulmonary Infection Score (CPIS)

| CRITERION | 0 | 1 | 2 |
|------------------------------------|-------------------|------------------|--|
| Tracheal secretions | Absent | Not purulent | Abundant and purulent |
| Chest x-ray infiltrates | No | Diffuse | Localized |
| Temperature, °C | ≥36.5 and ≤38.4 | ≥38.5 or ≤38.9 | ≥39 or ≤36 |
| Leukocytes | ≥4000 and ≤11,000 | <4000 or >11,000 | <4000 or >11,000 + immature neutrophils >50% or >500 |
| PaO ₂ /FiO ₂ | >240 or ARDS | | ≤240, no ARDS |
| Microbiology | Negative | | Positive |

Data from Pugin J, Auckenthaler R, Mili N, et al. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and non-bronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis* 1991;143:1121-9.

CPIS is considered positive with a score ≥6.

ARDS, acute respiratory distress syndrome.

When infiltrates are evident, the differential diagnosis is challenging (i.e., cardiogenic and noncardiogenic pulmonary edema, pulmonary contusion, and atelectasis).

Few studies have examined the accuracy of portable chest radiographs in the diagnosis of VAP.²⁶²⁻²⁶⁵ In mechanically ventilated patients with autopsy-proven VAP, no single radiographic sign had a diagnostic accuracy greater than 68%.²⁶⁵ In patients with ARDS, marked heterogeneity of radiographic abnormalities has been reported.²⁶⁶ A clinical study showed the presence of lung infection in only 42% of the patients with clinically suspected VAP.²⁶⁷ The presence of air bronchograms may increase the specificity of chest radiographs in ARDS patients.

The Clinical Pulmonary Infection Score (CPIS) is based on six clinical assessments (Table 75-1).²⁶⁸ The CPIS showed a good correlation ($r = 0.84$; $P < 0.0001$) with quantitative bacteriology of BAL samples. Moreover, a value ≥6 was the threshold to accurately identify patients with pneumonia. The value of CPIS remains to be validated in a large prospective study, especially in patients with bilateral pulmonary infiltrates.

The presence of bacteria in the lower airways of intubated patients is not sufficient to diagnose VAP, because it could be only nonpathogenic colonization or VAT.^{41,269} Cultures of endotracheal aspirate from patients with respiratory failure and histologically documented pneumonia, simultaneously obtained from the trachea and lung tissue, agreed in only 40% of cases, with a 82% sensitivity and 27% specificity.²⁷⁰ Similarly, in another study, only 23% of colonized patients subsequently developed VAP.⁴¹

Many sampling procedures of respiratory secretions, such as sputum collection, endotracheal aspirates, BAL, and PSB, are available. In addition, there are several microbiological techniques, including Gram staining and intracellular organism count, for specimens obtained via BAL. Each diagnostic technique has advantages as well as limitations and provides different diagnostic specificity and sensitivity.

Qualitative cultures of endotracheal aspirates have a high percentage of false-positive results. Conversely, quantitative culture techniques are more reliable if appropriate cutoff criteria are applied. When patients develop pneumonia, pathogens are present in the lower respiratory tract secretions at concentrations of at least 10^5 to 10^6 CFU/mL.²⁷¹⁻²⁷⁴ The current diagnostic threshold proposed for tracheal aspirates is 10^6 CFU/mL. Similarly, PSB collects between 0.001 and 0.01 mL of secretions. Therefore, the presence of more than 10^3 bacteria in the originally diluted sample (1 mL) represents 10^5 to 10^6 CFU/mL in

pulmonary secretions. Finally, 10^4 CFU/mL is considered the cutoff for BAL, which collects 1 mL of secretions in 10 to 100 mL of effluent.

In one study,²⁷⁴ only 40% of the microorganisms cultured in endotracheal aspirate samples coincided with those obtained from PSB specimens. Also, when quantitative cultures of different lower respiratory tract specimens were compared with postmortem quantitative lung biopsy cultures, all techniques for detecting VAP were of limited value.²⁷⁵

A major problem in the management of patients with suspicion of VAP is the use of antibiotics. The indiscriminate administration of antimicrobial agents for patients in the ICU may contribute to the emergence of MDR pathogens and increase the risk of superinfections with increased morbidity and mortality, as well as expose the patient to antibiotic-related adverse effects and higher costs.²⁷⁶ On the other hand, correct and prompt treatment of pneumonia results in better patient survival.²⁷⁷⁻²⁸⁰ Inadequate empirical antibiotic treatment, initiated before obtaining the results of cultures from respiratory secretions was associated with greater hospital mortality compared with antibiotic regimens that provided adequate antimicrobial coverage based on microbiological culture results.²⁸¹⁻²⁸⁵ However, the choice of initial antibiotic treatment is often difficult due to previous antibiotic treatment,²⁸⁶ prevalence of MDR pathogens,⁷ and colonizing pathogens.²⁸⁷⁻²⁸⁹

Recently, several alternative techniques to perform microbial cultures have been developed that achieve a more rapid and accurate diagnosis of nosocomial pneumonia (i.e., high multiplexing real-time polymerase chain reaction arrays²⁹⁰ and fluorescent in situ hybridization of bacteria).²⁹¹ These methods proved to be feasible for rapidly detecting causative pathogens. Additionally, efforts have been made to detect rapidly the most important MDR genes, such as *mecA*, *blaKPC*, *blaIMP*, *blaVIM*, and *blaOXA*.²⁹² Finally, a Spanish study tested a rapid E-test antibiogram for six antibiotic agents that could provide antibiotic susceptibility within 24 hours and found that the use of this technique resulted in more appropriate and reduced use of antibiotics in VAP patients.²⁹³

Ventilator-Associated Events Surveillance Algorithm

The Centers for Disease Control introduced the ventilator-associated events (VAE) surveillance definition algorithm²⁹⁴ to monitor complications in mechanically ventilated patients (Fig. 75-2). This new algorithm was developed to monitor objectively pulmonary complications associated with worse outcomes in mechanically ventilated patients. Importantly, reports demonstrated poor concordance between infection-related ventilator-associated condition (IVAC), possible and probable VAP, and VAP diagnosed with standard criteria.^{295,296} In a study by Boudma and collaborators,²⁹⁷ sensitivity and specificity of diagnosing VAP were 0.92 and 0.28 for the ventilator-associated condition, and 0.67 and 0.75 for infection-related ventilator-associated complication, respectively. Boyer et al.²⁹⁸ studied 1209 patients ventilated for ≥ 2 calendar days with 5.5% VAE. The most common causes of VACs included IVACs (50.7%), ARDS (16.4%), pulmonary edema (14.9%), and atelectasis (9.0%). The sensitivity of the VAE algorithm for the detection of VAP was only 25.9% (95% CI = 16.7%-34.5%). Thus, the VAE algorithm should be considered as a powerful benchmarking tool but with marginal value for the diagnosis of VAP.

Diagnostic Strategies for Hospital-Acquired Pneumonia

An ideal diagnostic strategy for patients with clinical suspicion of hospital-acquired pneumonia should reach the following objectives:

1. Accurately identify patients with true pulmonary infection and isolate the causative microorganisms to initiate promptly appropriate antimicrobial treatment and subsequently to optimize therapy based on the susceptibility of the pathogens.
2. Identify patients with extrapulmonary sites of infection.
3. Withhold and/or withdraw antibiotics in patients without infection.

The diagnosis of nosocomial pneumonia begins with clinical suspicion. The presence of a new or progressive radiographic infiltrates plus at least two of three clinical criteria (fever/hypothermia, leukocytosis/leukopenia, and purulent secretions) represents the starting point to begin diagnostic procedures.

Two diagnostic algorithms can be used when there is clinical suspicion of nosocomial pneumonia. The clinical approach recommends treating every patient with suspicion of having a pulmonary infection with new antibiotics even when the likelihood of infection is low (Fig. 75-3). However, samples of respiratory secretions (e.g., endotracheal aspirate or sputum) should be obtained before the initiation of antibiotic treatment. In this strategy, the selection of an appropriate empirical therapy is based on risk factors and local resistance patterns. The etiology of pneumonia is defined by semiquantitative cultures of endotracheal aspirates or sputum, with an initial microscopic examination of the Gram stain. Antimicrobial therapy is adjusted according to culture results or the clinical response. The semiquantitative culture of tracheal aspirates has the advantage that no specialized microbiological techniques are required and the sensitivity is high. This clinical strategy provides antimicrobial treatment to the majority of the patients with suspicion of HAP and yields a low rate of false negatives. If the tracheal aspirate culture does not demonstrate pathogens and the patient has not received new antibiotics within the previous 72 hours, the diagnosis of pneumonia is unlikely.²⁸⁵ This strategy is useful in centers where bronchoscopic methods are not always available. The main drawback of this strategy is that the high sensitivity of semiquantitative cultures of tracheal aspirates leads to an overestimation of the incidence of HAP and overuse of antibiotics.

The bacteriologic strategy is based on the results of quantitative cultures of lower respiratory secretions (Fig. 75-4). The procedure used to collect the samples (endotracheal aspirate, BAL, or PSB) may be invasive (bronchoscopic) or noninvasive (blind procedures). The bacteriologic strategy attempts to identify accurately patients with true HAP so that only infected patients are treated and clinical outcomes are improved.^{283,289} Such a strategy reduces the risks for overuse of antibiotics, since quantitative cultures yield fewer microorganisms above the threshold, in comparison to semiquantitative cultures. Among the disadvantages of the bacteriologic strategy is the possibility of obtaining false-negative results that lead to delayed antibiotic treatment in a patient with pneumonia. Moreover, results using the bacteriologic strategy may lack reproducibility, and often no microbiological information is available at the time of initiation of empirical antibiotic therapy.

Four randomized controlled trials (RCTs)^{283,299-301} have assessed the impact of diagnostic strategies on antibiotic use and outcome in patients with clinically suspected VAP. In three small studies,^{283,299,300} invasive diagnostic techniques resulted in a greater number of antibiotic changes than noninvasive techniques; however, no differences in mortality and morbidity were found when either invasive (PSB and/or BAL) or noninvasive (quantitative endotracheal aspirate cultures) techniques were used. By contrast, a larger trial³⁰¹ showed a reduction in mortality, reduced use of antibiotics, and increased number of antibiotic-free days using invasive diagnostic techniques. This study was limited, however, by the use of qualitative cultures of tracheal aspirates, thereby limiting comparison with other clinical trials. Irrespective of the methods used to obtain respiratory samples, it is strongly recommended that samples be obtained before starting new antibiotics, or a lower threshold should be used in patients with recent antibiotic changes.^{302,303}

A clinical trial³⁰⁴ compared the quantitative culture of BAL fluid and culture of endotracheal aspirate in critically ill patients with suspected VAP. This study was part of a larger 2-by-2 factorial design also comparing empirical antimicrobial monotherapy (a carbapenem) and combination therapy (a carbapenem plus a fluoroquinolone). A total of 740 patients in 28 ICUs throughout Canada and the United States were enrolled, and the authors found no difference in the 28-day mortality rate between the BAL group and the endotracheal aspiration group (18.9% and 18.4%, respectively; $P = 0.94$). The BAL group and

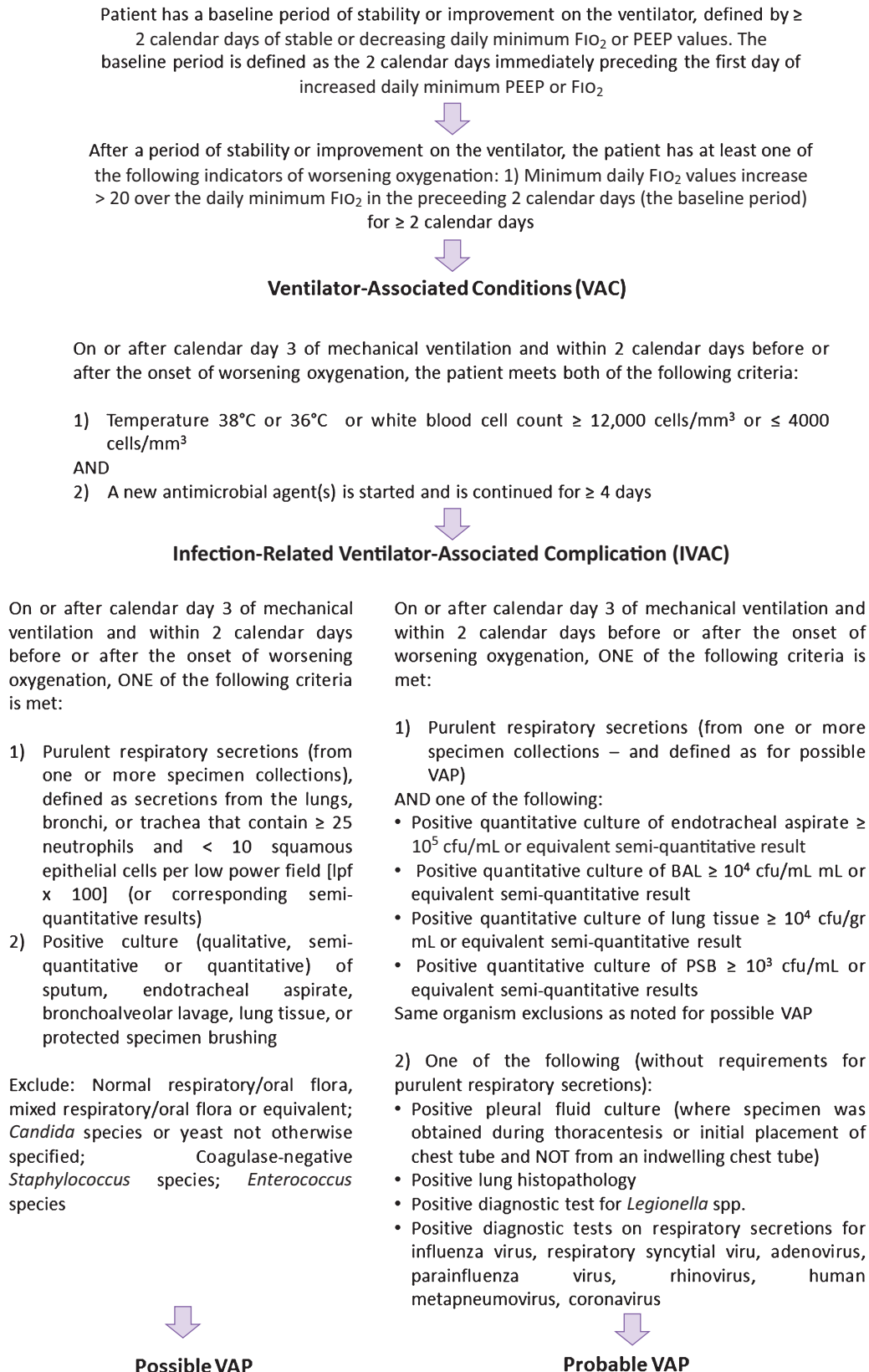


FIGURE 75-2 ■ Ventilator-associated events surveillance protocol. CFU, colony forming units; FiO_2 , fraction of inspired oxygen; PEEP, positive end-expiratory pressure; VAP, ventilator-associated pneumonia. (Full surveillance protocol available at: <http://www.cdc.gov/nhsn/acute-care-hospital/vae/index.html> for eligible antimicrobials.)

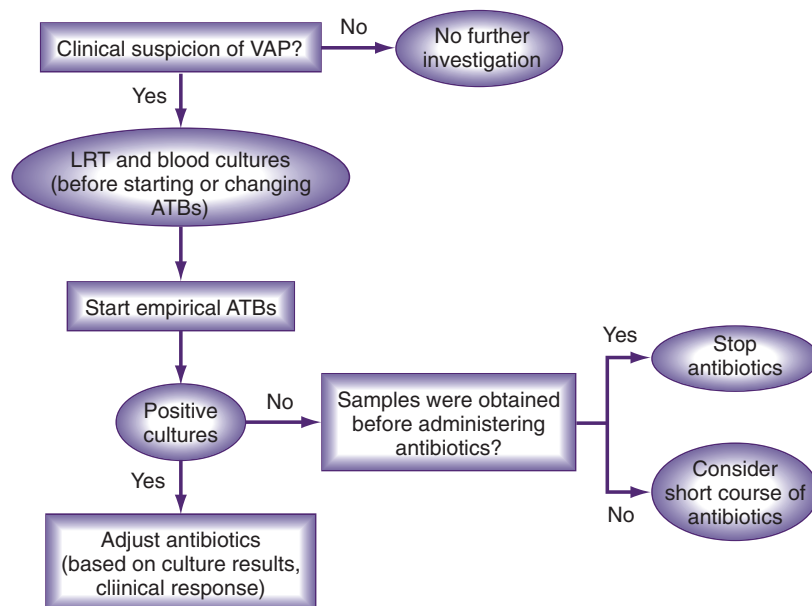


FIGURE 75-3 ■ Clinical noninvasive strategy for diagnosis and management of VAP. ATB, antibiotic; LRT, lower respiratory tract; VAP, ventilator-associated pneumonia. (Adapted from American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388-416.)

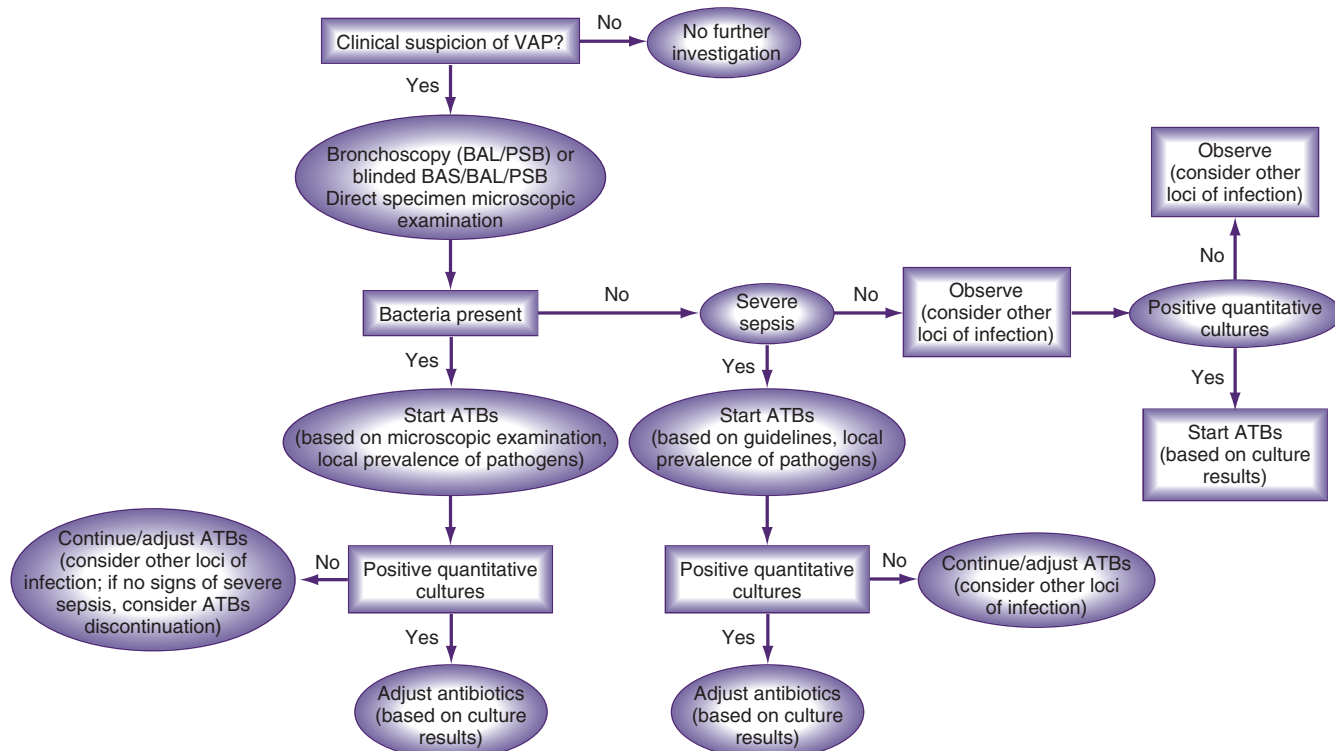


FIGURE 75-4 ■ Invasive and quantitative culturing strategy for diagnosis and management of VAP. ATB, antibiotic; BAL, bronchoalveolar lavage; BAS, bronchial aspirate; PSB, protected specimen brush; VAP, ventilator-associated pneumonia. (Adapted from American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388-416.)

the endotracheal aspiration group also had similar rates of targeted therapy and days alive without antibiotics. At least 40% of the screened patients were excluded because they were at risk for colonization with *Pseudomonas* spp. or MRSA or were immunosuppressed. Therefore, translation of these findings into clinical practice is challenging, because many ICU patients evaluated for suspected VAP fall into these categories. Last, in the latest meta-analysis,³⁰⁵ no differences using quantitative cultures versus qualitative cultures in mortality rates (RR = 0.91; 95% CI = 0.75 to 1.11), the number of days on MV, the length of ICU stay, or antibiotic changes were found. Likewise, there was no effect of invasive versus noninvasive diagnostic methods.

Practical Implementation of a Diagnostic Strategy in Suspected VAP

In clinical practice, the development of local clinical guidelines can combine both clinical and bacteriologic strategies (Table 75-2). The diagnostic protocol begins with clinical suspicion of a nosocomial

TABLE 75-2

Diagnostic Protocol to Combine Clinical and Bacteriologic Strategies for the Diagnosis of Ventilator-Associated Pneumonia

1. As soon as pneumonia or infection associated with mechanical ventilation is suspected and before initiating new empirical antibiotic treatment, collect samples as follows*:
 - Expectoration
 - Tracheobronchial aspirate (BAS)**
 - Bronchoalveolar lavage (BAL) or mini-BAL**
 - Protected brush specimen (PBS)**
2. Two blood cultures
3. In cases of evidence for parapneumonic effusion, obtain pleural fluid sample
4. Obtain *Legionella pneumophila* and *Streptococcus pneumoniae* antigens in urine
5. Other lab tests: complete blood cell count, serum electrolytes, liver and renal function tests, C-reactive protein, procalcitonin, arterial blood gases

*Samples should be sent to the microbiology department or, if not available, maintained in the refrigerator at 4°C (only respiratory samples) for a maximum of 1 hour for Gram staining, intracellular organism counting (only in BAL and mini-BAL), and quantitative cultures. The collection of lower respiratory secretion samples should not delay the initiation of empirical treatment in patients with severe sepsis.

**These techniques may be performed by bronchoscopy or blind procedures. Quantitative cultures are performed with the respiratory secretions obtained by BAS, BAL, or PBS. The cutoff count to diagnose pneumonia is the following: BAS 10⁶ CFU/mL, BAL 10⁴ CFU/mL, and PBS 10³ CFU/mL.

respiratory infection (Fig. 75-5). In mechanically ventilated patients, the presence of an infiltrate on chest radiograph differentiates between the possible presence of pneumonia and tracheobronchitis. The next step is to sample the lower respiratory tract (see Table 75-3) to identify the causative microorganism. Respiratory tract specimens can be obtained by expectoration, bronchial aspirate, BAL, or PSB. The latter two techniques can be performed with bronchoscopy or blindly. Several other samples should also be collected, as noted in Table 75-2. With clinical suspicion of pneumonia, CPIS²⁶⁸ should be calculated to improve the objective assessment of the clinical parameters (Table 75-1).

TREATMENT

Once the clinical decision to initiate antimicrobial therapy has been made, the following issues should be considered to achieve the best antimicrobial efficacy and reduce overuse of antibiotics:

- The most likely etiologic microorganisms
- Choice of the empirical antimicrobials likely to be active against these microorganisms
- Adjustment of therapy following microbiologic results and duration of treatment

Likely Etiologic Microorganisms

As detailed in previous paragraphs, microorganisms causing VAP originate from the oropharyngeal flora of the patient. Underlying chronic diseases, specific risk factors, acute inflammatory processes, and factors specific to each hospital or ICU can facilitate abnormal bacterial colonization of the oropharynx and may predispose patients to infection with specific organisms. Therefore, the selection of initial antimicrobial therapy must be tailored to the local prevalence of pathogens and antimicrobial patterns of resistance at each institution.¹⁰⁷ The dynamics of change of oropharyngeal flora during hospital stay can be described as follows (Fig. 75-6):

1. Healthy subjects are colonized with normal oropharyngeal flora in which pathogenic microorganisms, such as *S. pneumoniae*, group A streptococci, or meningococci may be transiently found.
2. Patients with chronic comorbidities or an acute inflammatory process have impairment of normal immune responses. As a result, *S. aureus* and Enterobacteriaceae can colonize the oropharynx.
3. Patients who have received antibiotic treatment become colonized with resistant pathogens, including ESBL + Enterobacteriaceae, *Enterobacter* spp., *P. aeruginosa*, or MRSA.

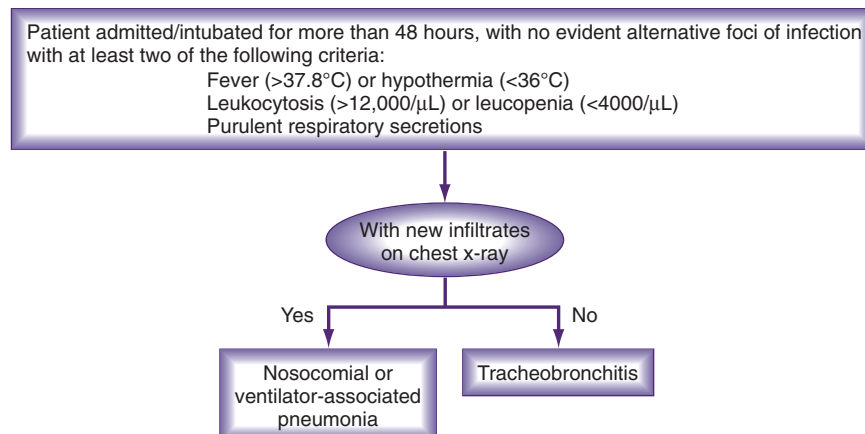


FIGURE 75-5 ■ Clinical suspicion of nosocomial respiratory infection.

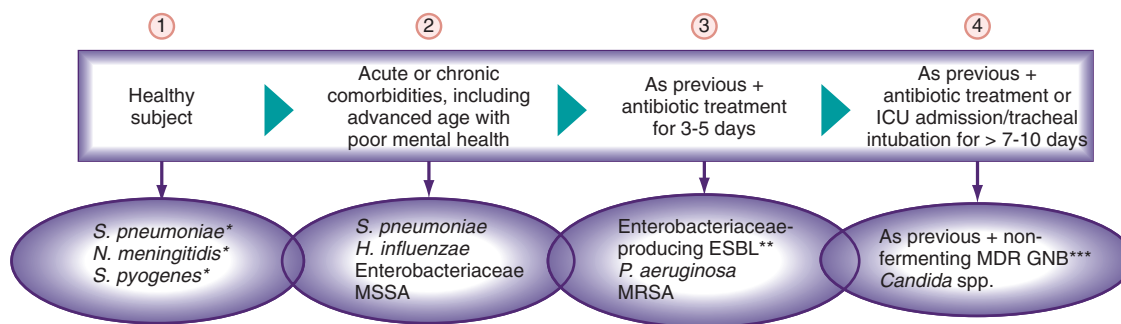


FIGURE 75-6 ■ Evolution of potentially pathogenic microorganisms present in oropharyngeal flora, related to comorbidity, antibiotic treatment, and colonization pressure. *Transitorily present in healthy carriers. **Producers of ESBL or with type ampC chromosomal β -lactamases. ****Pseudomonas aeruginosa*, *Stenotrophomonas* spp., *Acinetobacter* spp., *Burkholderia* spp. ESBL, extended-spectrum β -lactamase; GNB, gram-negative bacilli; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*.

4. Patients who have received broad-spectrum antibiotics for more than 7 days are often colonized by MDR microorganisms (i.e., *A. baumannii*, *S. maltophilia*, *B. cepacia*, and gram-positive microorganisms).

Changes in the oropharyngeal flora tend to occur progressively such that the presence of microorganisms during one stage often overlaps with the next stage.

Choice of Empirical Antimicrobials Likely to Be Active Against Causative Microorganisms

The latest guidelines of the American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) for the management of adult patients with nosocomial pneumonia recommend¹ that the selection of empirical antibiotic therapy for each patient should be based on the timing of onset and presence of risk factors for MDR pathogens. Risk factors for MDR pathogens defined by the ATS/IDSA guidelines are summarized in **Box 75-2**. An algorithm for the initial management of patients with nosocomial respiratory infection and selection of appropriate antimicrobials is shown in **Fig. 75-7**. The antibiotics recommended by the latest ATS/IDSA guidelines are shown in **Tables 75-3** and **75-4**. Adequate dosing of antibiotics for empirical therapy is summarized in **Table 75-5**. Broad-spectrum empirical antibiotic therapy should be rapidly deescalated as soon as microbiological data become available to limit the emergence of resistance in the hospital. **Fig. 75-7**, **Table 75-3**, and **Table 75-4** detail empirical therapy, which should be based on patient's risk of colonization by MDR organisms.

As for the need for dual therapy against Gram-negative pathogens, in a meta-analysis by Aarts et al.,³⁰⁶ 11 trials randomizing 1805 patients were evaluated. There was no mortality difference for patients receiving monotherapy versus combination therapy (RR = 0.94, 0.76-1.16). Likewise, there was no significant difference in treatment failure in patients with clinically suspected pneumonia (RR = 0.88, 0.72-1.07; **Fig. 75-5**) or microbiologically proven pneumonia (RR = 0.86, 0.63-1.16).

Nebulized Antibiotics

Intravenous administration of antibiotics for nosocomial pneumonia has several limitations, including insufficient lung distribution, development of adverse side effects, and selective pressure for development of MDR. Additionally, intravenous antibiotics are often underdosed in critically ill patients, due to sepsis-related higher volumes of distribution and hyperdynamic states. Administration of nebulized antibiotics is a potential therapeutic alternative^{307,308} to overcome these limitations. Additionally, systemic exposure to antibiotics and potential adverse

BOX 75-2

Risk Factors for Multidrug-Resistant Pathogens Causing Nosocomial Pneumonia

- Antimicrobial therapy in preceding 90 days
- Current hospitalization of 5 days or more
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for healthcare-associated pneumonia:
 - Hospitalization for 2 days or more in the preceding 90 days
 - Residence in a nursing home or extended care facility
 - Home infusion therapy (including antibiotics)
 - Chronic dialysis within 30 days
 - Home wound care
 - Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy

Adapted from American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388-416.

TABLE 75-3

Initial Empirical Antibiotic Treatment in Nosocomial and Ventilator-Associated Pneumonia of Early Onset in Patients Without Risk Factors for Infection by Multidrug-Resistant Pathogens

| PROBABLE MICROORGANISM | RECOMMENDED ANTIBIOTIC |
|--|----------------------------|
| <i>Streptococcus pneumoniae</i> | Ceftriaxone |
| <i>Haemophilus influenzae</i> | or |
| Methicillin-sensitive <i>Staphylococcus aureus</i> | Levofloxacin, moxifloxacin |
| Enteric gram-negative bacilli | or |
| <i>Escherichia coli</i> | Ampicillin/sulbactam |
| <i>Klebsiella pneumoniae</i> | or |
| <i>Enterobacter</i> spp. | Ertapenem |
| <i>Proteus</i> spp. | |
| <i>Serratia marcescens</i> | |

Adapted from American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388-416.

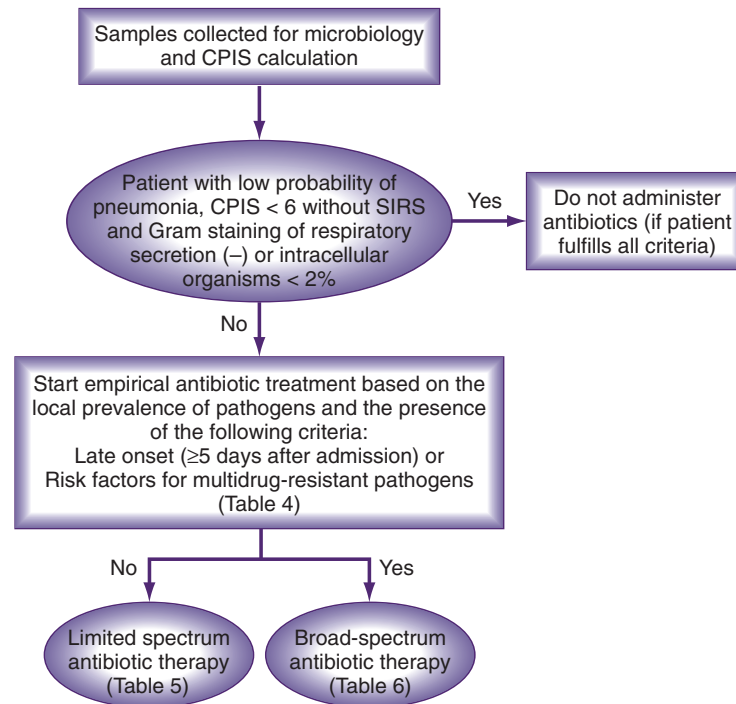


FIGURE 75-7 ■ Algorithm for the treatment of patients with suspicion of nosocomial respiratory infection. SIRS comprises at least two of the following: temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$; heart rate > 90 beats/min; respiratory rate > 20 breaths/min or $\text{PaCO}_2 < 32$ mm Hg; and leukocytes $> 12,000/\text{mm}^3$, $< 4000/\text{mm}^3$, or the presence of $> 10\%$ immature neutrophils. SIRS, systemic inflammatory response syndrome.

effects are dramatically reduced. Finally, nebulized antibiotics can reduce the risk of developing MDR infections.³⁰⁹

In laboratory models, nebulized amikacin reached pulmonary concentrations 30 times higher than intravenous administration. In a pivotal study by Lu et al.,³¹⁰ 20 patients with susceptible or intermediate resistant Gram-negative pathogens received nebulized ceftazidime and amikacin while 17 patients infected with susceptible strains received intravenous ceftazidime and amikacin. After 8 days of treatment, the cure rate was similar between groups. However, acquisition of treatment-associated antibiotic resistance was higher in the intravenous group. In a later study, Niederman et al.³¹¹ randomized 69 mechanically ventilated patients with Gram-negative VAP to receive aerosolized amikacin concomitantly with systemic antibiotics. They found that amikacin distributed well throughout the lung parenchyma, with high tracheal and alveolar levels, but with a serum concentration below the renal toxicity threshold.

Recently developed nebulizers increased the lung deposition of the aerosolized antibiotic dose by up to 60%. Several factors play a critical role in lung deposition of nebulized antibiotics during MV. First, the extent and severity of lung infection critically affect lung distribution of nebulized antibiotics.³¹² Second, vibrating plate nebulizers increase the efficiency of aerosol delivery to 40% to 60%.^{313,314-319} Finally, humidification^{317,320,321} and angular geometry of the ventilatory circuit should be taken into account during nebulization. In addition, ventilatory settings that ensure laminar inspiratory flow provide better distal lung deposition of aerosol particles.³²²⁻³²⁵

Antimicrobial Therapy in Special Situations

In geographic areas with a documented presence of community-acquired MRSA, severe pneumonia with radiologic images of

cavitation and presence of Gram-positive cocci in respiratory secretions, empirical treatment with linezolid or vancomycin may be appropriate. Recently, an outbreak of MRSA and linezolid-resistant *S. aureus* (LRSA) was reported in an intensive care department of a 1000-bed tertiary care university teaching hospital in Madrid, Spain, and was associated with nosocomial transmission and extensive usage of linezolid.¹⁰³ Tigecycline may be a useful alternative in this setting although clinical experience is scanty.

Infections by *L. pneumophila* serogroup 1 can be diagnosed by a *Legionella* urinary antigen test. This test should be routinely obtained if the hospital water supply is known to be colonized with *L. pneumophila* serogroup 1. A fluoroquinolone or a macrolide would be an appropriate treatment for *L. pneumophila* infection.

Modifications of Therapy and Duration of Treatment

A suggested flowchart for the follow-up of patients with nosocomial pneumonia is shown in Fig. 75-8. After 72 hours, treatment should be adjusted based on microbiological results. The initial β -lactam should be continued if the microorganism is susceptible to the empirical β -lactam originally prescribed. If not, another β -lactam should be introduced. The empirical antibiotic against MRSA should be discontinued if the presence of this pathogen is not confirmed by cultures. Discontinuation of the fluoroquinolone and especially the aminoglycoside should be considered after 3 to 5 days of treatment. The bactericidal activity of aminoglycosides and fluoroquinolones leads to a rapid reduction in the bacterial load during the first days of treatment. After this time, monotherapy may be sufficient. This approach would decrease the emergence of resistant mutants and minimize nephrotoxicity caused by aminoglycosides.

TABLE 75-4

Initial Empirical Antibiotic Treatment for Nosocomial and Ventilator-Associated Pneumonia of Late Onset or in Patients with Risk Factors for Infection by Multidrug-Resistant Pathogens and Any Degree of Severity

| PROBABLE MICROORGANISM | COMBINED ANTIBIOTIC TREATMENT |
|---|---|
| Microorganisms from Table 75-3 plus: | Antipseudomonal cephalosporin (ceftazidime or ceftipime)* |
| <i>Pseudomonas aeruginosa</i> | or |
| <i>Klebsiella pneumoniae</i> (ESBL+) [†] | Carbapenem (imipenem, meropenem)* |
| <i>Acinetobacter</i> spp. [‡] | or |
| Other nonfermenting gram-negative bacilli | β-lactam/β-lactamase inhibitor (piperacillin-tazobactam)* |
| Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) | + |
| <i>Legionella pneumophila</i> [§] | Antipseudomonal fluoroquinolone (ciprofloxacin, levofloxacin)** |
| | or |
| | Aminoglycoside** (amikacin) |
| | ± |
| | Linezolid or vancomycin*** |

*The choice of β-lactam is made as follows: patients who have not received any antipseudomonal β-lactam within the last 30 days should be administered piperacillin-tazobactam or an antipseudomonal cephalosporin. Patients who have received these drugs should be given empirical therapy with a carbapenem. Patients with infection by ESBL-producing microorganisms should be treated with carbapenem regardless of the results of the antibiogram.

**For combined empirical therapy for multidrug-resistant GNB, an antipseudomonal fluoroquinolone should be used in cases of renal failure or concomitant use of vancomycin. In other settings, combined empirical therapy is initiated with amikacin and maintained for a period of five days.

***Empirical therapy aimed against MRSA is initiated in patients with proven colonization (ψ), previous infection with this microorganism, or implementation of MV for more than six days. The antibiotic of choice is either vancomycin (except in patients allergic to this medication, with creatinine values ≥1.6 mg/dL, or in patients presenting signs of empirical treatment failure after 48 hours of antibiotic therapy) or linezolid. (Ψ) For epidemiologic surveillance, nasal and perineal cultures should be performed on admission and at 1-week intervals thereafter while remaining in the ICU.

[†]If an ESBL+ strain, such as *K. pneumoniae* or *Acinetobacter* spp. is suspected, a carbapenem is the first choice.

[‡]If *L. pneumophila* is suspected, the combination antibiotic regimen should include a macrolide (e.g., azithromycin), or a fluoroquinolone (e.g., ciprofloxacin, levofloxacin) should be used rather than an aminoglycoside.

ESBL, extended-spectrum β-lactamase; GNB, gram-negative bacilli.

The majority of infections can be effectively treated with 8 days or less of antimicrobial therapy. In a meta-analysis³²⁶ pooling data from four RCTs comparing short (7-8 days) with long (10-15 days) treatment periods, no difference in mortality was found. There was an increase in antibiotic-free days for the short-course treatment, and a trend to lower relapses in the long-course treatment was observed (OR = 1.67; 95% CI = 0.99-2.83; *P* = 0.06).

Four situations may justify prolonged treatment: (1) infection by intracellular microorganisms, such as *Legionella* spp.; (2) the presence of biofilms or prosthetic devices; (3) development of tissue necrosis, formation of abscesses, or infection within a closed cavity, such as empyema; and (4) the persistence of the original infection (such as perforation or endocarditis). If the clinical course from the pneumonia is favorable, as defined by defervescence, improvement in $\text{PaO}_2/\text{FiO}_2$, and reduction in C-reactive protein (CRP) levels within the first

TABLE 75-5

Recommended Initial Intravenous Antibiotic Dosage for Empirical Treatment of Patients with Nosocomial and Ventilator-Associated Pneumonia

| ANTIBIOTIC | DOSES | INTERVAL OF ADMINISTRATION | PERFUSION TIME |
|--|-------------|----------------------------|----------------|
| NON-ANTIPSEUDOMONAL CEPHALOSPORINS: | | | |
| Ceftriaxone | 2 g | 24 hours | 1/2-1 hour |
| Cefotaxime | 2 g | 6 hours | 1/2-1 hour |
| ANTIPSEUDOMONAL CEPHALOSPORINS: | | | |
| Ceftazidime | 2 g | 8 hours | 2-3 hours |
| Ceftipime | 1-2 g | 8 hours | 2-3 hours |
| Carbapenems: | | | |
| Imipenem | 0.5 or 1 g | 6 or 8 hours | 1 hour |
| Meropenem | 1 g | 8 hours | 2-3 hours |
| Piperacillin-tazobactam | 4 g-0.5 g | 6 hours | 2-3 hours |
| FLUOROQUINOLONES: | | | |
| Levofloxacin | 500 mg | 12 hours* | 1/2 hour |
| Ciprofloxacin | 400 mg | 8 hours | 1/2 hour |
| Amikacin | 15-20 mg/kg | 24 hours** | 1/2-1 hour |
| Vancomycin | 1 g | 8-12 hours*** | 1-3 hours |
| Linezolid | 600 mg | 12 hours | 1 hour |

*Administer this dose for three days and after continue with 500 mg/24 h.

**Adjust the dosage according to PK/PD parameters.

***Initiate this dose with 24 hours, measure trough blood levels prior to the following dosage, and adjust the levels according to values.

Dosages are based on normal renal and hepatic function.

3 to 5 days of antimicrobial therapy, treatment may be withdrawn after 7 days. If the causative microorganism is a nonfermenting gram-negative bacillus, the treatment can be extended beyond 14 days. A large prospective, multicenter, randomized trial study comparing the efficacy of 8-day and 15-day antibiotic regimens for treating VAP suggested that an 8-day regimen reduces antibiotic use and decreases the emergence of pulmonary MDR bacteria, without modification of the prognosis.³²⁷ However, this study observed that in cases of pneumonia produced by nonfermenting gram-negative bacilli, eradication of these microorganisms from bronchial secretions was lower with the shorter regimen.³²⁷ On the other hand, the 14-day treatment regimen was associated with a trend to colonization by MDR flora and a higher frequency of reinfection. Finally, in patients with clinical suspicion of ICU-acquired pneumonia who have a CPIS lower than 6 on the third day of treatment, antimicrobials may be withdrawn. In this setting, the patient likely does not have pneumonia or the pneumonia is sufficiently mild such that prolonged antibiotic treatment is not required.

Treatment Failure

At least 3 days of antibiotic treatment are necessary to achieve clinical improvement. Thus, treatment failure should be assessed between 3 and 5 days after the initiation of antibiotic therapy. The rate of treatment failure ranges between 30% and 50%, which highlights the severity and complexity of this pulmonary infection. In our previous observations,⁹² we developed a systematic definition of treatment failure comprising the following: (1) no improvement in $\text{PaO}_2/\text{FiO}_2$, or need for intubation due to pneumonia; (2) persistence of fever or hypothermia, together with purulent respiratory secretions;

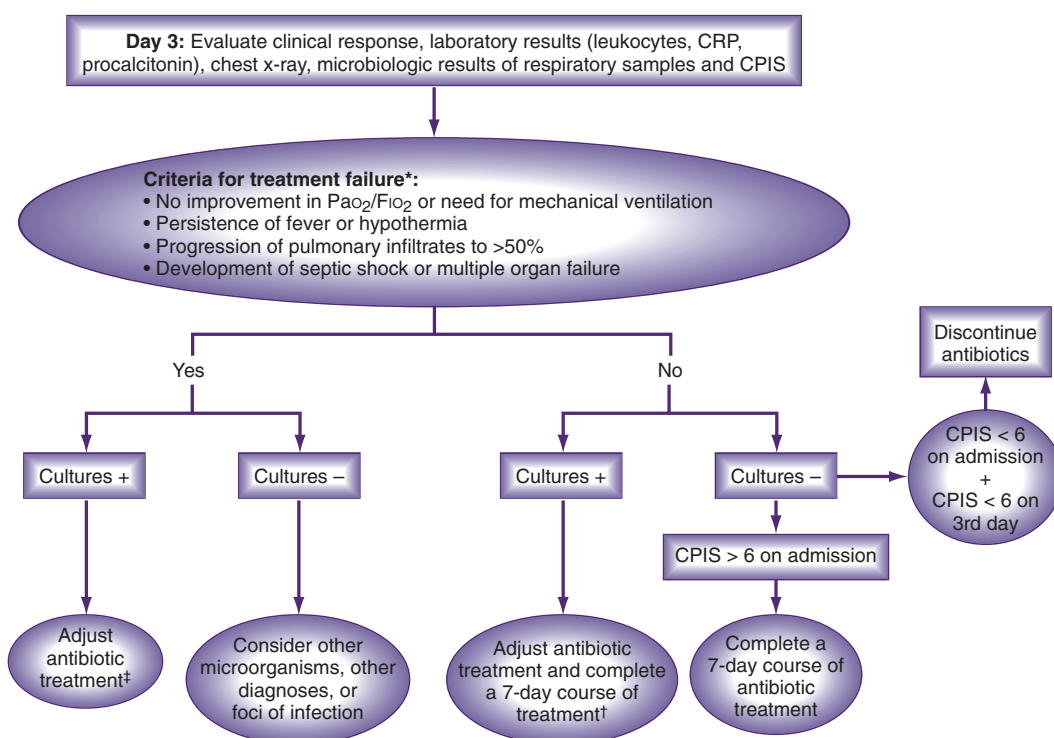


FIGURE 75-8 ■ Suggested flowchart for the follow-up of patients with nosocomial pneumonia and VAP. *Criteria of treatment failure taken from Ioannas M, Ferrer M, Cavalcanti M et al. Causes and predictors of non-response to treatment of the ICU-acquired pneumonia. Crit Care Med 2004;32:938-45. [†]In cases in which the etiologic agent is *Pseudomonas aeruginosa* or *Acinetobacter* spp., treatment should be maintained for 14 days. [‡]Patients with criteria of treatment failure and in whom MRSA is isolated should be administered linezolid. If a GNB is isolated, consultation is recommended. GNB, gram-negative bacilli; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilator-associated pneumonia.

(3) increase in the pulmonary infiltrates on chest radiograph of greater than or equal to 50%; or (4) occurrence of septic shock or multiple organ dysfunction syndrome. Thus, we found that no improvement in SOFA score and $\text{PaO}_2/\text{FiO}_2$ highly predicted worse 28-day mortality. Importantly, treatment failure could be a surrogate endpoint for clinical trials to compare novel treatments. Upon evidence of treatment failure, respiratory samples should be reobtained and the initial empirical therapy rapidly readjusted. CT scan or lung ultrasound^{328,329} may help to detect cavitation, pleural effusion, and other causes for treatment failure.

Implementation of Therapeutic Guidelines

Although guideline-recommended strategies may provide significant benefits for patients, implementation is often difficult to achieve.^{330,331} Soo-Hoo et al.³³¹ developed hospital protocols to manage patients with severe hospital-acquired pneumonia based on the 1996 ATS guidelines.³³² After the guidelines were introduced into clinical settings, the authors found that adequate antibiotic therapy was administered in more than 81% of the patients with pneumonia, compared with 46% before implementation ($P < 0.01$). Moreover, a lower mortality at 14 days was found after implementation of the guidelines ($P = 0.03$). Similarly, Ibrahim and coworkers developed a protocol to provide appropriate initial antibiotic treatment for patients with VAP and encouraged a 7-day course of treatment.³³³ Thus, patients with VAP, who were treated as directed by the protocol more often received adequate antimicrobial treatment than those treated empirically (94%, in comparison to 48% before implementation; $P < 0.001$). The length of treatment was reduced by 6 days, and the second episode of VAP was less likely to occur after implementation.

KEY POINTS

1. Nosocomial pneumonia is a common complication occurring in critically ill patients and is the leading cause of nosocomial infection-related death. Ventilator-associated pneumonia develops in tracheally intubated patients.
2. Etiologic agents for ventilator-associated pneumonia differ according to the population of ICU patients, duration of hospital stay, and prior antimicrobial therapy. Nosocomial pneumonia due to multidrug-resistant pathogens is associated with the highest morbidity and mortality.
3. Preventive strategies, grouped as bundles, should be implemented in hospital settings. Several preventive strategies have shown efficacy in decreasing the incidence of pneumonia. In particular, the most effective strategies focus on reduction of cross-transmission, diminishing the likelihood of aspiration across the tracheal tube cuff, and decreasing bacterial load in the oropharynx.
4. In the presence of clinical suspicion of nosocomial pneumonia, diagnostic strategies should include an early collection of respiratory samples *before* starting or changing antibiotics.
5. The choice of empirical treatment should be based on the most likely etiologic microorganisms and the antimicrobials likely to be active against these microorganisms. Response to therapy should be reassessed after 3-5 days and antimicrobials adjusted or de-escalated to reduce the burden of the disease.

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- Latest guidelines published by a joint committee of the American Thoracic Society and the Infectious Disease Society of America. Prior antibiotic treatments and recent stay in the hospital and healthcare-associated facility were identified as major risk factors for acquiring MDR pathogens. Moreover, the importance of choosing specific antimicrobials based on the local prevalence of pathogens and antibiotic susceptibility is also emphasized.*
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- Meta-analysis, pooling data from 6284 patients in 24 trials, that shows that the overall attributable mortality for ventilator-associated pneumonia is 13%, with higher mortality rates in surgical patients and patients with mid-range severity scores at admission (i.e., acute physiology and chronic health evaluation score [APACHE] 20-29 and simplified acute physiology score [SAPS 2] 35-58). Attributable mortality was close to zero in trauma, medical patients, and patients with low or high severity of illness scores.*
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■ References for this chapter can be found at expertconsult.com.

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According to the World Health Organization,¹ drowning is a serious and neglected public health threat claiming the lives of more than 372,000 people a year worldwide, or 40 people every hour of every day. More than 90% of these deaths occur in low- and middle-income countries. Whether it is small children slipping unnoticed into a pond, pool, or well; adolescents or others swimming under the influence of alcohol or drugs; passengers on vessels that capsize; or residents of coastal communities struck by floods, the toll of this global killer continues its quiet rise.

Fatal drowning is a frequent cause of death worldwide among boys 5 to 14 years of age. In the United States, drowning is the second leading cause of injury-related death among children 1 to 4 years of age, with a death rate of 3 per 100,000. In some countries, including Thailand, the death rate among 2-year-old children is more than 100 per 100,000.²

International data severely underestimate actual drowning figures, even for high-income countries.³ Epidemiologic data account for only 6% of the problem because drowning deaths are not registered in many countries. Almost all drowning victims are able to help themselves or are rescued in time by bystanders or professional rescuers. In areas where lifeguard services fully operate,² fewer than 1% of all persons rescued by lifeguards need cardiopulmonary resuscitation (CPR), and 0.3% of the rescues resulted in the death of the victim (0.34%).⁴ In one report of rescues by bystanders, almost 30% of persons rescued from drowning required CPR,⁵ demonstrating that a delay in intervention may lead to a more severe outcome than where lifeguards are on duty. Unfortunately, lifeguard or layperson rescues and first aid attendance are rarely considered in national databases, resulting in a distorted picture of drowning burden worldwide.

From 1972 to 2002 the Fire Department of Rio de Janeiro—Lifeguard Service (CBMERJ) made approximately 166,000 rescues on the beaches, and 8500 victims required attendance by the medical team in the Drowning Resuscitation Centre. With this scenario of a full lifeguard service in operation, approximately 290 rescues for each death (0.34%) were reported and one death for each 10 victims admitted for medical care in the Drowning Resuscitation Center (DRC).

The bias produced by not accounting for actual drowning figures affects not only the relative epidemiologic importance related to the problem of drowning⁶ but also gives the false impression that every drowning requires CPR and that to know how to resuscitate is the most important tool to save people from drowning.

Coastal drownings are estimated to cost more than \$273 million per year in the United States and more than \$228 million per year (in U.S. dollars) in Brazil. For every person who dies from drowning, another four receive care in the emergency department for nonfatal drowning.¹ Exposure-adjusted, person-time estimates for drowning are 200 times higher than deaths from traffic accidents.⁷

Key risk factors for drowning are male sex, age of less than 14 years, alcohol use, low income, poor education, rural residency, aquatic exposure, risky behavior, and lack of supervision. For people with epilepsy, the risk of drowning is 15 to 19 times the risk of those without.¹

Drowning deaths can be prevented in over 85% of cases by using a series of interventions.⁸ When preventive measures fail, responders need to be able to perform the necessary steps to interrupt the pathophysiologic processes associated with drowning. The first challenge is to recognize someone in the water at risk of drowning and appreciate

the need for rescue. Early self-rescue or rescue by others may stop the drowning process and prevent initial and subsequent water aspiration, respiratory distress, and medical complications. The drowning process happens quickly, but it is critical that rescuers take precautions not to become another victim by engaging in inappropriate or dangerous rescue responses.^{5,9} Removing the victim from a hostile environment has major potential for harm to the rescuer. The “drowning chain of survival”¹⁰ refers to a series of water safety interventions that when put into action by lay or professionals reduce the mortality associated with drowning.

DEFINITION

A new definition of drowning was adopted by the World Health Organization in 2002,¹¹ stating that “Drowning is the process of experiencing respiratory impairment from submersion or immersion in liquid.”

The drowning process is a continuum, beginning with respiratory impairment as the victim’s airway goes below the surface of the liquid (submersion) or when water splashes over the face (immersion). If the victim is rescued at any time, the process of drowning is interrupted, and this is called *nonfatal drowning*. If the victim dies at any time, this is a *fatal drowning*. Any submersion or immersion incident without evidence of respiratory impairment should be considered a water rescue and not a drowning. Terms such as “near-drowning,” “dry or wet drowning,” “secondary drowning,” “active and passive drowning,” and “delayed onset of respiratory distress” should not be used.¹¹ A uniform way to report data for studies on drowning and to allow comparison between different centers is to adopt the Utstein template for drowning resuscitation cases.¹²

PATHOPHYSIOLOGY

When water is aspirated into the airways, coughing occurs as an initial reflex response. In less than 2% of cases,^{13,14} laryngospasm may be present when the victim starts to inhale water. If the person is not rescued, aspiration of water continues, and hypoxemia leads to loss of consciousness and apnea. Apnea and hypoxia precede cardiac arrest. As a consequence, hypoxic cardiac arrest generally occurs after a period of bradycardia and pulseless electrical activity (PEA) and not by means of ventricular fibrillation.^{15,16} The process from immersion to cardiac arrest occurs in seconds to minutes depending on the scenario, but in unusual situations, such as when hypothermia precedes hypoxia, this process can last for up to an hour.¹⁷ In most drowning cases, cardiac function is initially relatively preserved and only ceases perfusion due to hypoxic insult after a period of apnea.^{4,9}

If the person is rescued in time during the drowning process, the clinical picture is determined by the reactivity of the airways and the amount of water that has been aspirated. Water in the alveoli causes surfactant destruction and wash-out. Salt and fresh water aspiration causes similar pathology.¹⁵ In either situation, the effect of the osmotic gradient on the alveolar-capillary membrane can disrupt its integrity, increase permeability, and exacerbate fluid, plasma, and electrolyte shifts.¹⁵ The clinical picture of damage is regional or generalized pulmonary edema (depending on the amount of water aspirated and airway reactivity) that may alter exchange of O₂ and CO₂.^{4,15,18} In animal experiments,¹⁸ aspiration of 2.2 mL of water per kilogram of body weight

leads to severe disturbance of oxygen exchange, decreasing arterial oxygen pressure (PaO₂) to approximately 60 mm Hg within 3 minutes. In humans, it seems that as little as 1 to 3 mL/kg of water aspiration produces profound alterations in pulmonary gas exchange and decreases pulmonary compliance by 10% to 40%.¹⁵ The combined effects of fluids in the lungs, loss of surfactant, and increased capillary-alveolar permeability can result in decreased lung compliance, increased right-to-left shunting in the lungs, atelectasis, and alveolitis.¹⁵

DROWNING CHAIN OF SURVIVAL

(FIG. 76-1)¹⁰

Prevent Drowning

The most effective way to reduce the number of drowning deaths is prevention. It has been estimated that 80% to 90% of all drownings are preventable.^{8,19} Drowning prevention requires multiple factors (Table 76-1).

Recognize Distress and Call for Help

The second element in the drowning chain is to recognize a person in distress in the water and know how to activate help.²¹ The Drowning Risk Assessment (DRA) identifies a person at high risk of drowning by a near-vertical body position, ineffective downward arm movements, ineffective pedaling or kicking leg actions, and little or no forward progress in the water. Professionals trained in DRA easily identify persons at risk of drowning. Sending someone to call for help upon recognizing a person in water distress is a key element that ensures early activation of professional rescue service and EMS.¹⁰

Provide Flotation to Stop the Process of Drowning¹⁰

The next priority is to interrupt the drowning process by providing flotation to the victim as an interim measure to reduce submersion risk. This buys valuable time for those on scene to initiate rescue efforts and for emergency services to arrive. Devices such as ring buoys are purposely designed to provide flotation; however, they are only available at very few locations where a drowning occurs. In most situations, improvised buoyancy aids, such as empty plastic bottles, containers, ice chests, or driftwood, should be used. It is critical that laypersons take precautions not to become another victim by engaging in inappropriate or dangerous rescue responses.^{5,9} Reaching out with, throwing, or dropping the buoyancy aid without entering the water is the preferred method of providing flotation to a drowning victim.²⁴ Also, because many victims cling to their would-be rescuer, it is better to approach a struggling victim with an intermediary object.

In-Water Resuscitation²⁵

If not interrupted, the drowning process leads first to unconsciousness and apnea, followed by cardiac arrest within minutes. During this short window of opportunity, immediate in-water ventilation may provide benefit if provided safely and effectively. For the unconscious victim, in-water resuscitation can increase the rates of discharge from hospital without sequelae by more than threefold. In-water ventilation is only possible if the rescuer is highly trained. Chest compression while the rescuer and victim are in deep water is futile, so assessment for a pulse does not serve any purpose. Victims with only respiratory arrest usually respond after a few rescue breaths. If there is no response, the

TABLE 76-1 Preventive Measures

Watch children carefully; 84% of drownings occur because of inadequate adult supervision. Begin swimming lessons from 2 years of age.
Avoid inflatable swimming aids such as “floaties” as they can give a false sense of security. Use lifejackets!
Never try to help rescue someone without being able to do it. Many people have died trying to do so.
Avoid drinking alcohol and eating lunch before swimming.
Don’t dive in shallow water, as cervical spine injury could occur.

BEACHES

Always swim in a lifeguard-supervised area.
Ask the lifeguard for safe places to swim or play.
Read and follow warning signs posted on the beach.
Do not overestimate your swimming capability—46.6% of drowning victims thought they knew how to swim.
Swim away from piers, rocks, and stakes.
Take lost children to the nearest lifeguard tower.
Over 80% of drownings occur in rip currents (the rip is usually the most falsely calm, deep place between two sand bars). If caught in a rip, swim transversally to the sand bar or let it take you away without fighting and wave for help.
If you are fishing on rocks, be careful about waves that may sweep you into the ocean.
Keep away from marine animals.

POOLS AND SIMILAR BODIES OF WATER

Over 65% of deaths occur in fresh water, even on the coast.
Fence off your pool and include a gate.
Recommended, approved fencing can decrease drowning by 50% to 70%.
Avoid toys around the pool.
Whenever infants or toddlers are in or around water, be within arm’s length, providing “touch supervision.”
Turn off motor filters when using the pool.
Always use portable phones in pool areas, so you are not called away to answer.
Don’t try to hyperventilate to increase submersion time.
Use warning sign of shallow water in the pool.
Learn CPR; over 42% of pools owners are not aware of first aid techniques. Be careful!

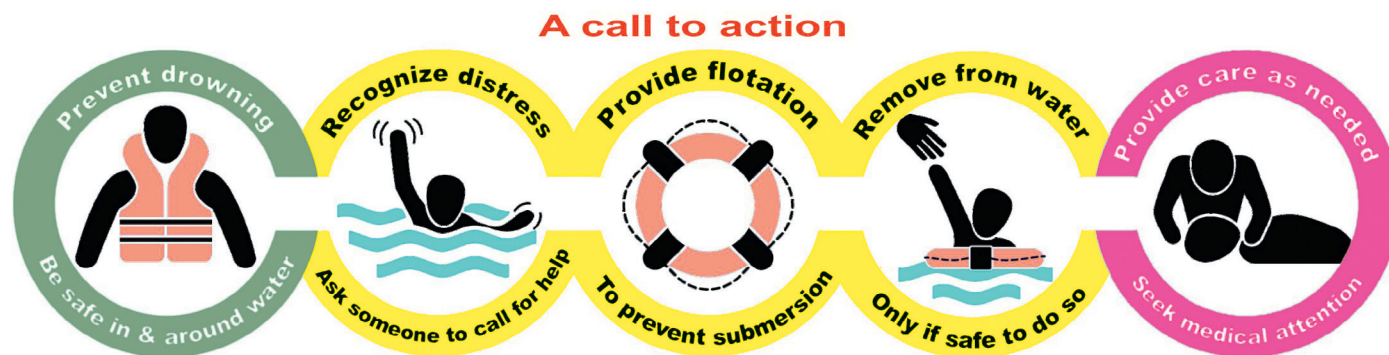


FIGURE 76-1 ■ Drowning chain of survival. (Adapted from Szpilman D, Morizot-Leite L, Vries W, et al. First aid courses for the aquatic environment. In: Bierens JJ, ed. Handbook on Drowning: prevention, rescue, and treatment. Berlin: Springer-Verlag; 2006, p. 342–7.)

victim should be assumed to be in cardiac arrest and be moved as quickly as possible to dry land where effective CPR can be initiated.

Cervical Spine Injury

Very few studies have examined how often in-water cervical spine injury (CSI) occurs.²⁶⁻²⁸ One such study retrospectively evaluated 46,060 water rescues on sand beaches and demonstrated that the incidence of CSI in this setting was very low (0.009%).²⁷ In another retrospective survey of more than 2400 drowning cases, only 11 (<0.5%) had CSI, and all had a history of obvious trauma from diving, falling from height, or a motor vehicle accident.²⁶ Considering this low incidence of CSI and the high risk to wasted time when ventilation is needed, routine cervical spine immobilization of water rescues without reference to whether a traumatic injury was sustained is not recommended.²⁹ Therefore, no attempt to immobilize the spine should be made without a strong indication and certainly not in cases where the victim appears lifeless.³⁰

Remove from Water: Rescue Only if Safe to Do So

The attempt to perform a rescue typically involves three phases: approach, contact, and stabilizing the victim. Removing the victim from water is essential to end the drowning process²⁵ and allows a setting for better assessment and care of the victim. Several strategies for removal can be used by bystander rescuers. The victim can be helped by directing them to the closest and safest place to get out of the water. If everything else fails, the lay rescuer may consider entering the water to attempt to rescue the victim by throwing, reaching, or wading to the victim.¹⁰ To mitigate risk to the bystander rescuer, the use of some type of flotation or a connecting rope is recommended, although sometimes these devices can also increase the risk.²⁴ To enter the water is a personal decision and may depend on the personal relationship with the victim (e.g., parents and children), water depth, distance to swim, and swimming skills.

The position of a drowning victim for transport out of the water is preferably as near to horizontal as possible but with the head still maintained above body level (keep horizontal if prolonged immersion or a history of immersion in cold water). The airways should be kept open at all times, if possible.³¹

Provide Care as Needed

Basic Life Support

Once on land, the victim should be placed supine with trunk and head at the same level. On beaches, this means parallel to the shore line. The standard checks for responsiveness and breathing are carried out.²⁵ If unconscious but breathing, the recovery position should be used.³¹ If the victim is not breathing, ventilation is essential.^{2,4,30} If the victim has a cardiac arrest from drowning, this is primarily due to lack of oxygen.^{4,9,30,32} For this reason, it is important that CPR follows the traditional Airway-Breathing-Circulation (ABC)^{32,33} sequence. Upper airway management is often challenging due to vomiting and the presence of pulmonary edema fluid that interferes with airway management, while at the same time pulmonary injury makes initial ventilation difficult because of decreased pulmonary compliance.^{30,35} Ventilation should be started with 5 initial breaths followed by 30 chest compressions and then continued with two breaths to 30 compressions until signs of life reappear, rescuer exhaustion occurs, or ALS becomes available. Because cardiac arrest in drowning victims is caused by asphyxia, cardiac compression-only CPR is useless.^{30,32}

The most frequent complication during drowning resuscitation is regurgitation of stomach contents, which occurs in more than 65% of victims who need rescue breathing alone, and in 86% of victims who require CPR.³⁶ The presence of vomitus in the airway can result in further aspiration injury and impairment of oxygenation.²⁵ Active efforts to expel water from the airway (abdominal thrusts or placing the victim head down) should be avoided as they only delay the initia-

tion of ventilation, increase the risk of vomiting by more than five-fold, and thereby lead to a significant increase in mortality.^{25,31}

A study has shown that less than 10% of all drowning victims are in ventricular fibrillation.³⁷ Given this, the effectiveness of an automated external defibrillator (AED) during drowning is low.

Advanced Life Support

Drowning Severity Classification. Early basic life support contributes to better outcomes from drowning and should be initiated as soon as possible.² Cardiopulmonary or isolated respiratory arrest comprises only approximately 0.5% of all rescues. In this situation, it is clear that CPR has to be started. For less serious situations, a classification system has been developed in Rio de Janeiro (Brazil) in 1972 and updated in 1997⁴ to assist lifeguards, ambulance personnel, and physicians in treatment of drowning victims. This classification was initially based on an analysis of 41,279 rescues, of which 2304 (5.5%) needed medical attention and then revalidated in 2002 by another 10-year study that included 46,080 rescues.³⁸ This classification (Fig. 76-2)² is stratified into 6 grades plus a rescue and a nonresuscitation condition encompassing support from the site of the accident to the hospital. The classification system recommends the most appropriate treatment and shows the likelihood of death based on the severity of injury. Severity is easily accessed by an on-scene rescuer, EMT, or physician using only clinical variables.⁴

To save time, medical equipment should be brought to the victim instead of the victim to the ambulance. Advanced medical treatment is given according to drowning classification.^{4,10} Recommendations for when to start and stop resuscitation are different from nondrowning-related cardiac arrest (Table 76-2).^{2,16}

For grade 6 cases (cardiopulmonary arrest⁴), resuscitation started by a layperson or lifeguard at the scene must be continued by the EMS system. The first priority should be adequate oxygenation and ventilation using bag-mask ventilation with 15 liters of oxygen until an orotracheal tube can be inserted. Meanwhile, cardiac compression should be continued. Once intubated, most victims can be oxygenated and ventilated effectively even in situations where copious pulmonary edema fluid fills the endotracheal tube. Suctioning of the orotracheal tube should be performed only when the presence of fluid makes effective ventilation impossible. Suctioning can disturb oxygenation and should be balanced against the need to ventilate and oxygenate. For cardiac monitoring, the presenting rhythm in cases of cardiac arrest following drowning is usually asystole or pulseless electrical activity (PEA). Ventricular fibrillation is rarely reported but may occur if there is a history of coronary artery disease, use of epinephrine, or in the presence of severe hypothermia.¹⁶ If ventricular fibrillation is present, defibrillation should be attempted. Peripheral venous access is the preferred route for drug administration in the prehospital setting. Endotracheal administration of drugs is not recommended for drowning.³⁴ Doses of 1 mg epinephrine IV (or 0.01 mg/kg) can be considered. After the resuscitation process is well organized, an orogastric tube can

TABLE 76-2 Drowning: When to Initiate CPR and When to Discontinue²

| QUESTION | RECOMMENDATIONS |
|----------------------|---|
| In whom to begin? | Give ventilatory support for respiratory distress/arrest to avoid cardiac arrest. Start CPR in all submersions <60 minutes who do not present with obvious physical evidence of death. |
| When to discontinue? | Basic life support should continue unless signs of life reappear, rescuers are exhausted, or advanced life support can take over. Advanced life support should be ongoing until patient has been rewarmed (if hypothermic) and asystole persists for more than 20 minutes. |



FIGURE 76-2 ■ Drowning severity classification and flow chart strategy decision based on evaluation of 87,339 rescues. ^{24,38}

be placed to reduce gastric distention and prevent further aspiration. This is particularly indicated if abdominal distention restricts ventilation. If initial resuscitation efforts are not successful, the victim should be transported to a hospital where advanced warming measures can be accomplished while resuscitation is continued during transport.

Grade 5 cases (isolated respiratory arrest⁴) are usually reversed by bystanders or lifeguards by the time advanced life support arrives at the scene. If not previously done, oxygenation and ventilation protocols as for grade 6 should be followed until spontaneous breathing is restored. If there is spontaneous ventilation, the protocol for grade 4 is followed. A grade 4 (acute pulmonary edema with hypotension⁴) patient may initially be able to maintain adequate oxygenation, although the respiratory rate is frequently elevated. Oxygenation goals are to achieve a prehospital peripheral saturation above 92% by administering oxygen by face mask at a rate of 15 L/min. Early intubation and mechanical ventilation are indicated for respiratory fatigue, even when good oxygenation is achieved using the face mask. Once intubated, most victims can be oxygenated and ventilated effectively. Patients should be sedated to tolerate intubation, and artificial mechanical ventilation providing a tidal volume of at least 5 mL/kg of body weight. FiO_2 can initially be 1.0 but should be reduced when possible. If hypotension is not corrected by oxygen, a rapid crystalloid infusion should be used.¹⁵

In grade 3 cases (acute pulmonary edema without hypotension), a therapeutic decision relates to whether there would be more benefit with initiating invasive ventilation rather than using face mask oxygenation. Only 27.6% of grade 3 drowning victims can be supported with noninvasive ventilatory support. Grade 2 patients (abnormal auscultation with rales in some pulmonary fields) usually require only oxygen by nasal cannula. In grade 1 and rescue cases, advanced medical attention and oxygen are not usually required.

As the majority of drowning victims has only mild distress or may not actually aspirate water, it is important for responders to know when to call EMS or seek medical assistance/hospital care (Table 76-3). Emergency department evaluation is recommended for all patients of grade 2 to 6 drowning.

Hospital. Decision making regarding admission to an intensive care unit (ICU) or hospital bed versus observation in an emergency

department or discharge home should include a thorough history of the incident and previous illness, physical examination, and diagnostic studies including chest radiography and ABG measurement. Electrolytes, blood urea nitrogen, creatinine, and hemoglobin also should be assessed, although perturbations in these laboratory tests are unusual. In some cases, a toxicologic screen for suspected alcohol, recreational drug use, or drug overdose might be warranted. Patients who experienced grade 3 to 6 drowning should be admitted to an ICU for close observation and therapy. Grade 2 patients can be observed in the emergency room for 6 to 24 hours, but grade 1 and rescue cases with no complaints or associated illness or trauma can be released home.

Drowning is sometimes precipitated by an injury or medical condition such as trauma, seizure, or cardiac arrhythmia. Such comorbidities should be considered⁴ after arrival in the emergency department, as they affect treatment options.

Respiratory Concerns. Grade 4 to 6 patients will usually arrive from prehospital advanced life support on mechanical ventilation with acceptable oxygenation. If not, the emergency department physician should follow standard ventilation protocols. Positive end-expiratory pressure (PEEP) should be added initially at a level of 5 cm H_2O and then increased by 2- to 3-cm H_2O increments as needed until the intrapulmonary shunt (QS:QT) is 20% or less, or $\text{PaO}_2:\text{FiO}_2$ of 250 or more is achieved. A clinical picture very similar to acute respiratory distress syndrome (ARDS) is common after significant drowning episodes (grade 3 to 6). Management is similar to that of other patients with ARDS, including efforts to minimize volutrauma and barotrauma. Lung-protective ventilation involving permissive hypocapnia probably is not suitable for drowning victims with grade 6 severity that may be associated with significant hypoxic-ischemic brain injury. In selected cases, CPAP may be provided by mask in cooperative adolescents or by nasal cannula in infants who are obligate nasal breathers, but usually this is not tolerated. If pulmonary and psychological status allows the patient to breathe without fighting, continuous positive airway pressure (CPAP) or a ventilatory pressure support mode (PSV) can be a good choice.

Pools, rivers, and beaches generally have insufficient bacteria colonization to induce pneumonia in the immediate postdrowning period.³⁹ Pneumonia is often initially misdiagnosed because of the early radiographic appearance of water in the lungs.⁴⁰ If the patient needs mechanical respiratory assistance, the incidence of ventilator-associated pneumonia increases from 34% to 52% in the third or fourth day of hospitalization as pulmonary edema is resolving.⁴⁰ Vigilance not only for pulmonary but also other infectious complications is important. Prophylactic antibiotics tend to only select out more resistant and more aggressive organisms.⁴² Daily monitoring of tracheal aspirates for Gram stain, culture, and sensitivity is advised. At the first sign of pulmonary infection, usually during the first 48 to 72 hours after drowning (as indicated by fever, sustained leukocytosis, persistent or new pulmonary infiltrates, and increased leukocyte numbers in tracheal aspirates), antibiotic therapy can be initiated using information, if available, on the predominant organism in the water where the drowning occurred. If there are reasons to suspect ventilator-associated pneumonia, antibiotics should be directed to the sensitivity of the predominant microorganisms in the ICU or by cultures if available. Fiberoptic bronchoscopy may be useful for evaluation of infection and for the rare occasions where therapeutic clearing of sand, gravel, or other solids is indicated. Corticosteroids for pulmonary injury should not be used except for bronchospasm.

The clinician must be aware of and constantly be vigilant for volutrauma and barotrauma during ventilation of drowning victims.³⁹ Spontaneous pneumothoraces are common (10%) secondary to positive-pressure ventilation and local areas of hyperinflation. Any sudden change in hemodynamic stability after mechanical ventilation is initiated should be considered to be due to pneumothorax or other barotrauma until proven otherwise.

Circulatory Issues. Cardiac dysfunction with low cardiac output is common immediately after severe drowning.¹⁵ Low cardiac output

TABLE 76-3

Who Needs Further Medical Help After Rescue from the Water

- (a) A patient who has experienced or required any of the following should be sent to a hospital:
 - Loss of consciousness, even for a brief period
 - Rescue breathing
 - Cardiopulmonary resuscitation
 - A serious condition such as heart attack, spinal injury, other injury, asthma, epilepsy, stinger, intoxication, delirium
- (b) The following persons may be considered for release from care at the scene if, after 10-15 minutes of careful observation while being warmed with blankets or other coverings as required, the patient has ALL of the following:
 - No cough
 - Normal rate of breathing
 - Normal circulation as measured by pulse in strength and rate and blood pressure (if available)
 - Normal color and skin perfusion
 - No shivering
 - Is fully conscious, awake and alert

In such cases, it is unwise for the patient to drive a vehicle, and the patient should be so advised. If any of these conditions does not apply or if the lifesaver has any doubt, then the patient should be advised to seek early medical attention.
- (c) There is always a risk of delayed lung complications. All immersion victims should therefore be warned that if they later develop cough, breathlessness, fever, or any other concerning respiratory symptoms, they should seek medical advice immediately. It is preferable that these persons not return to a home environment where they are alone for the next 24 hours.

is associated with high pulmonary capillary occlusion pressure, high central venous pressure, and high pulmonary vascular resistance and can persist for days after correction of oxygenation and perfusion abnormalities in drowning victims. This may add a cardiogenic component to drowning-associated pulmonary edema. Low blood pressure, if present, can be corrected with better oxygenation, rapid crystalloid infusion, and restoration of normal body temperature. Vasopressor infusion should be used only in refractory hypotension to improve cardiac output when replacement with crystalloid is inadequate to restore blood pressure. Urine output should be monitored by means of a Foley catheter. Echocardiography to assess cardiac function and ejection fraction can help to guide the clinician in titrating inotropic agents, vasopressors, or both if volume crystalloid replacement has failed.² In patients who are hemodynamically unstable or have severe pulmonary dysfunction, pulmonary artery catheterization may be considered to provide information concerning Starling forces in the lungs and may help in managing pulmonary edema. When pulmonary edema occurs after drowning, there is no evidence to support the use of any specific fluid therapy for salt and fresh water drowning,¹⁵ diuretics or water restriction.

Metabolic acidosis occurs in 70% of patients arriving at the hospital after a drowning episode.⁴ Acidosis should be corrected when pH is lower than 7.2 or bicarbonate is less than 12 mEq/L in spite of adequate ventilatory support. Significant depletion of bicarbonate is rarely present in the first 10 to 15 minutes of CPR, and its use is not indicated in the initial resuscitation period. In hypothermic patients, arterial blood gases do not need to be temperature corrected (the alpha-stat or pH-stat concept).⁴³

Neurologic System. The most important complication in grade 6 drowning, beyond reversible pulmonary injury, is anoxic-ischemic cerebral insult. Most late deaths and long-term sequelae of drowning are neurologic in origin.³⁹ Although the highest priority in resuscitation after drowning is restoration of spontaneous circulation, every effort in the early stages after rescue should also be directed at resuscitating the brain and preventing further neurologic damage. These steps include providing adequate oxygenation ($\text{SatO}_2\text{p} > 92\%$) and cerebral perfusion (mean arterial pressure around 100 mm Hg). Any victim who remains comatose and unresponsive after successful CPR or deteriorates neurologically should undergo careful and frequent neurologic function assessment for the development of cerebral edema and should be treated with the following measures:

- Raise the head of the bed by 30 degrees (if there is no hypotension).
- Maintain adequate mechanical ventilation.
- Ensure appropriate respiratory toilet without provoking hypoxia.
- Treat for seizure activity if present.
- Avoid overly rapid correction of metabolic alterations.
- Prevent interventions that increase intracranial pressure (ICP), including urinary retention, pain, hypotension, and hypoxia, by using sedation or muscular relaxants as necessary.
- Hyperthermia should be prevented in the acute recovery period.
- Frequently monitor blood glucose concentration, and maintain normoglycemic values.⁴⁴

Frequent monitoring of temperature is recommended in the emergency department and intensive care unit. Drowning victims with restoration of adequate spontaneous circulation who remain comatose should not be actively rewarmed to temperatures above 32°C to 34°C. If core temperature exceeds 34°C, therapeutic hypothermia (32°C–34°C) should be achieved as soon as possible and sustained for 12 to 24 hours. Although there is insufficient evidence to support a specific target PaCO_2 or oxygen saturation during and after resuscitation, hypoxemia should be avoided. Unfortunately, studies evaluating the results of cerebral resuscitation measures in drowning victims have failed to demonstrate that therapies directed at controlling intracranial hypertension and maintaining artificially high cerebral perfusion pressure (CPP) improve outcome. These studies have shown poor outcomes (i.e., death or moderate to profound neurologic sequelae) when

the intracranial pressure was 20 mm Hg or more and the CPP was 60 mm Hg or less, even when therapies were directed at controlling and improving these pressures.

Ice-Water Drowning. In some cases, hypothermia is just a reflection of prolonged submersion time and a bad prognosis. In other victims, early hypothermia is an important reason why survival without neurological damage is possible.^{30,45} Recent reports on drowning have documented good outcomes in postresuscitation patients who were kept hypothermic or treated with therapeutic hypothermia despite predicted poor outcome.^{32,46,47} Hypothermia associated with drowning can provide a protective mechanism that allows victims to survive prolonged submersion episodes.^{2,17} The rate of cerebral oxygen consumption is reduced by approximately 5% per each °C decrease in temperature within the range of 37°C to 20°C.⁴⁸

The paradox in drowning resuscitation is that the hypothermic victim needs to be warmed in order to effectively resuscitate but then may benefit from induced therapeutic hypothermia after successful resuscitation.² An important dictum that has been developed from experience with ice-water drownings and accidental hypothermia is that victims who appear dead after exposure to very cold temperatures should not be pronounced dead until they are at near-normal core temperature and remain asystolic.

Several studies have shown benefit from new therapeutic interventions for drowning victims such as extracorporeal membrane oxygenation,⁴⁶ artificial surfactant, and nitric oxide.⁴⁹

Unusual Complications. Important medical complications after drowning, other than those associated with neurologic function, are rare and are almost all restricted to patients with grade 6 severity. Rarely, some drowning victims who have normal chest radiography at initial assessment in the ED develop fulminant pulmonary edema as long as 12 h after the incident. Whether this late-onset pulmonary edema is ARDS, a neurogenic pulmonary edema secondary to hypoxia, or just an airway hyperreactive to water aspiration is unclear. Renal insufficiency or renal failure is rare in drowning victims but can occur secondary to anoxia, shock, or hemoglobinuria.

■ OUTCOME AND SCORING SYSTEMS

With advances in intensive care therapy, prognostication for drowning victims is now primarily based on neurologic outcome.⁹ Of the drowning victims with grade 1 to 5 severity, 95% return home without sequelae.⁴

In patients with grade 6 severity, prognostic variables are important when counseling family members in the early stages after the drowning incident and in deciding which patients are likely to have a good outcome with standard supportive therapy and which should be candidates for intensive cerebral resuscitation therapies.⁹

Victims who remain comatose or deteriorate neurologically should undergo intensive assessment and care.⁵⁰ Questions such as “How can we know for whom we should make the effort to resuscitate? How long should we continue to resuscitate? How should treatment differ? What should we expect as life quality after successful resuscitation?” need to be answered. Both at the rescue site and in the hospital, no single indicator for grade 6 severity appears to be an absolutely reliable predictor of outcome.² Prolonged submersion with successful resuscitation is not only possible in cold or icy water, as some anecdotal cases of warm-water drowning survival without sequelae have been described.^{4,45,51} Multiple studies^{2,4,9,12,16,17,19,25,48,50,51} have established that the outcome is almost solely determined by a single factor—duration of submersion. Basic and advanced life support enable victims to achieve their best outcome possible when the duration of cardiopulmonary arrest (submersion time included) is minimized. Most patients who show improvement and are alert (or are stuporous or obtunded but respond to stimuli 2 to 6 hours after the incident) have normal or near-normal neurological outcomes (Table 76-4).⁹

TABLE 76-4

Clinical Prognostic Score for the Immediate Period After Successful CPR Based on Glasgow Coma Score⁹

NEUROLOGIC PROGNOSTIC SCORE AFTER SUCCESSFUL CPR UPON DROWNING

| A: FIRST HOUR | B: AFTER 5 TO 8 H |
|---|---|
| Alert, 10 | Alert, 9.5 |
| Confused, 9 | Confused, 8 |
| Torpor, 7 | Torpor, 6 |
| Coma with normal brainstem functions, 5 | Coma with normal brainstem functions, 3 |
| Coma with abnormal brainstem functions, 2 | Coma with abnormal brainstem functions, 1 |
| A + B RECOVERY WITHOUT SEQUELAE | |
| Excellent, ≥ 13 | $\geq 95\%$ |
| Very good, 10-12 | 75% to 85% |
| Good, 8 | 40% to 60% |
| Regular, 5 | 10% to 30% |
| Poor, 3 | $\leq 5\%$ |

KEY POINTS

1. Drowning is a serious and neglected public health threat claiming the lives of 372,000 people per year worldwide.
2. Data account for only 6% of the cases, almost all resulting in death, giving the false impression that every drowning requires CPR and that knowing how to resuscitate is the most important tool.
3. Exposure-adjusted, person-time estimates for drowning deaths are 200 times higher than such estimates for deaths from traffic accidents.
4. The "drowning chain of survival" refers to a series of water-safety interventions that, when put into action, reduce the morbidity and mortality associated with drowning.
5. Drowning deaths can be prevented in over 85% of cases.
6. When prevention fails, the first challenge is to recognize someone in the water at risk of drowning, to appreciate the need for rescue, and to know how to help without becoming a second victim.
7. Almost all drowning victims are able to help themselves or are rescued in time. In areas where lifeguards fully operate, less than 1% of all persons rescued need cardiopulmonary resuscitation (CPR).

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Pulmonary parenchymal processes in children that an intensive care clinician may encounter include common and uncommon diseases of the lower airways, alveoli, and pulmonary interstitium. Among the more challenging conditions to manage in the intensive care unit (ICU) are those that include disease or dysfunction of all three of these components, such as bronchopulmonary dysplasia and congenital diaphragmatic hernia. This chapter will discuss the pathophysiology and management principles pertinent to each disease category, with emphasis given to common examples and conditions that are unique to pediatric patients.

■ DISEASES OF THE AIRWAYS

Status Asthmaticus

Although unusual anatomic conditions of the lower airways can occur in pediatric patients (Box 77-1), status asthmaticus and bronchiolitis are the most common causes of lower airways disease encountered in pediatric ICUs. Asthma is common in the industrialized world, and the overall mortality rate attributable to asthma in the United States is estimated at 2.6 deaths per million children per year.¹ Recurrent hospitalizations, previous ICU admissions, and the need for mechanical ventilatory support have been identified as risk factors for death from asthma.² Status asthmaticus is characterized by acute, severe airway obstruction due to bronchoconstriction that is refractory to initial management with supplemental oxygen, inhaled bronchodilators, and corticosteroids. This condition begins with a precipitant that triggers contraction of hyperresponsive bronchial smooth muscles, mucous secretion, and mucosal edema, all of which lead to the obstruction of the large and small airways (Fig. 77-1). Hyperinflation from airflow limitation and premature closure of the lower airways during expiration leads to increased end-expiratory lung volume³ and increased respiratory workload, which ultimately set the stage for alveolar hypoventilation and hypoxemia. Abrupt and profound acidosis can develop when respiratory compensation for accumulated inorganic acids ceases to occur.³ On physical examination, children with status asthmaticus can appear anxious or lethargic, will often demonstrate accessory muscle use, and depending on the quality of air entry, can demonstrate either cough with profound inspiratory and/or expiratory wheezing and prolongation of audible expiration or a silent chest. An exaggerated pulsus paradoxus can often be demonstrated, a finding that reflects the profoundly negative intrapleural pressures generated by these patients during spontaneous inspiration.

Therapy

Supportive therapy for patients with status asthmaticus begins with maintaining the airways, monitoring the quality of respirations, and ensuring euvoolemia. Standard medical therapies for these patients include bronchodilators and corticosteroids. Several adjunct therapies have also been investigated as possible rescue agents in difficult cases (Table 77-1). Short-acting β -agonist agents, which mediate airway smooth muscle relaxation via local β_2 receptors,³ are the most commonly used bronchodilators for status asthmaticus. Among these agents, albuterol is the most widely used. Unlike epinephrine and isoproterenol, albuterol is relatively β_2 -selective,³ and it is most commonly administered by nebulization. It is typically given at a dose of

0.15 mg/kg (up to 2.5 mg/dose) on an intermittent basis, but only a small fraction of the nebulized dose may actually be delivered to the lung, particularly in critically ill infants and children who are intubated with small tracheal tubes.⁴⁻⁶ Some studies have shown that small doses of a nebulized β agonist given in rapid sequential fashion produce sustained improvements in forced expiratory volume more often than when larger doses are given less frequently.^{7,8} Furthermore, evidence suggests that continuous nebulization of the drug may lead to more rapid and sustained improvement.⁹

A preparation of the therapeutically active isomer of albuterol (levalbuterol) has been widely available for at least a decade. Levalbuterol appears to be effective when administered to children with stable asthma, but it is not clear that it confers any particular therapeutic advantage over its racemic counterpart in the treatment of status asthmaticus.¹⁰ One recent double-blinded, randomized controlled trial (RCT) evaluated its use in children with acute exacerbations of the disease.¹¹ The investigators randomized 81 children between the ages of 6 and 18 years who failed an initial treatment protocol consisting of three 5-mg doses of inhaled racemic albuterol, two 500-mCg doses of inhaled ipratropium bromide, and an oral or parenteral corticosteroid load to receive equipotent doses of continuous inhaled racemic albuterol (20 mg/hour) or levalbuterol (10 mg/hour). Thereafter, enrolled patients were assessed, managed, and weaned from continuous bronchodilator therapy according to a standardized inpatient treatment protocol. Mean serum (S)-albuterol concentrations in each group were similar at the time the study drug was initiated but diverged following study drug administration and remained significantly different throughout the period of continuous therapy administration (baseline S-albuterol concentration was 14.2 ng/mL in the racemic group versus 11.7 ng/mL in the levalbuterol group; S-albuterol concentrations rose to 28.6 ng/mL at 6 hours in racemic group vs. 5.5 ng/mL in the levalbuterol group; $P < 0.001$). The investigators performed both an intention-to-treat and a per-protocol analysis and could not identify any difference between study groups in the study's primary outcome, the duration of time that patients required continuous albuterol therapy (median duration of continuous therapy 18.3 hours in the racemic group vs. 16.0 hours in the levalbuterol group; $P = 0.75$ by rank-sum test). Notably, the investigators did not find any between-group difference in the mean heart rate at any time point during the continuous albuterol therapy period.

Inhaled anticholinergic agents such as ipratropium have a recognized role in the management of severe bronchospasm in children with asthma. Addition of inhaled ipratropium to inhaled β agonists has been associated with favorable changes in pulmonary function, especially in children with severe asthma.^{12,13} For patients who do not respond to inhaled bronchodilators, it is possible to administer β agonist therapy intravenously. In some countries, the intravenous preparation of albuterol is available, which allows for an alternative administration route of this β_2 -selective agent. In the United States where intravenous albuterol is not available, terbutaline, which has some β_2 selectivity, is a reasonable alternative. Although terbutaline has not been associated with clinically significant cardiac toxicity in most pediatric patients,^{3,14} many clinicians advise monitoring the ECG and serum troponin levels during its administration.

For as long as the inflammatory basis for asthma has been recognized, corticosteroids have had an important role in the management

BOX 77-1**Anatomic Causes of Lower Airway Dysfunction**

Tracheomalacia, bronchomalacia
 Vascular anomaly
 Tracheoesophageal fistula
 Idiopathic
 Bronchiectasis
 Congenital lobar emphysema
 Cystic adenomatoid malformation
 Pulmonary sequestration
 Bronchogenic cyst

TABLE 77-1**Selected Pharmacotherapies for Status Asthmaticus****NEBULIZED THERAPIES**

Albuterol (0.5%) 0.15 mg/kg/dose (0.03 cc/kg/dose) inhaled q 1-6 h prn
 Continuous inhalation 0.5 mg/kg/hour
 Ipratropium 0.25-0.5 mg inhaled q 4-6 h
 Racemic epinephrine (2.25%) 0.25-0.5 cc inhaled q 1 h prn

SUBCUTANEOUS THERAPIES

Epinephrine (1:1000) 0.01 mg/kg/dose (0.01 cc/kg/dose) SC (max 0.5 cc/dose)

INTRAVENOUS THERAPIES

Terbutaline 10 mcg/kg IV \times 1, followed by 0.4-6.0 mcg/kg/min IV infusion
 Magnesium sulfate 25-50 mg/kg IV over 20 minutes (max 2 g/dose)
 Methylprednisolone 1 mg/kg/dose IV q 6 h

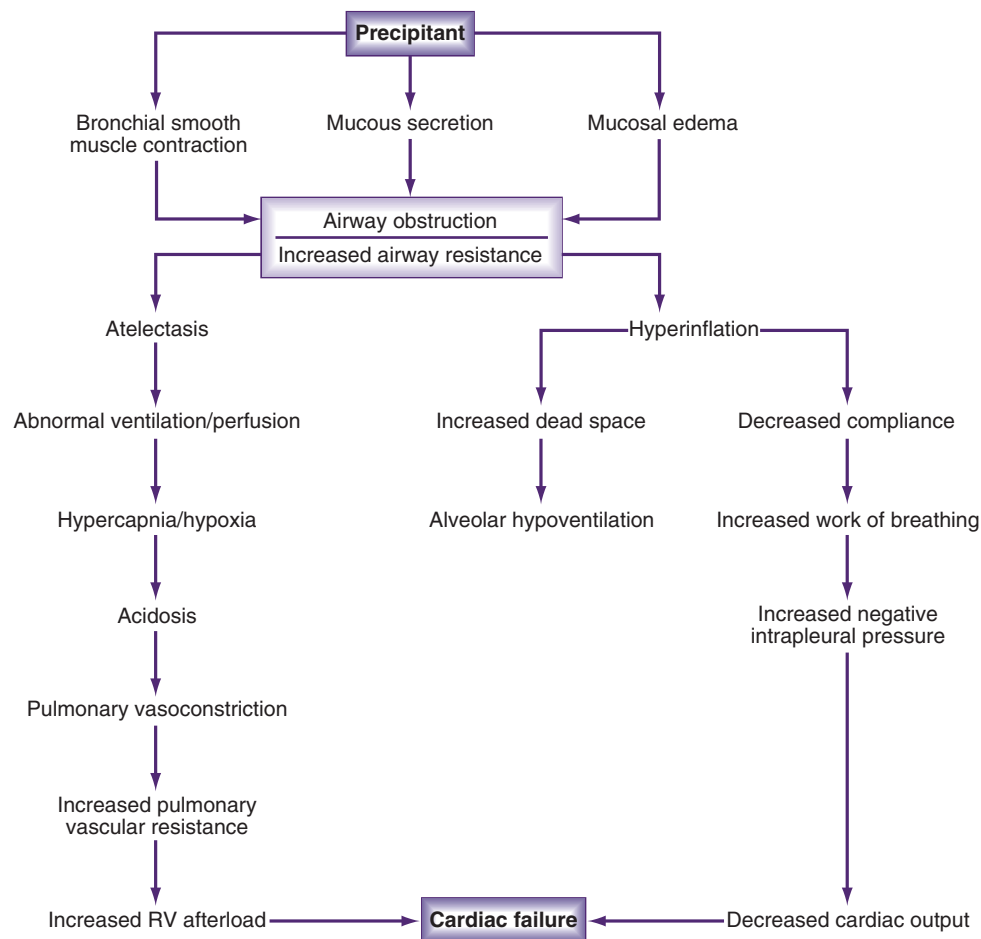


FIGURE 77-1 ■ Pathophysiology of status asthmaticus. (Modified from Helfaer M, Nichols D, Rogers M. Lower airways disease: bronchiolitis and asthma. In: Rogers M, editor. Textbook of pediatric intensive care. 3rd ed. Baltimore: Williams and Wilkins; 1996, p. 141.)

of status asthmaticus. The use of corticosteroids has been demonstrated to significantly improve airway obstruction in patients with severe acute asthma.¹⁵ The parenteral route is the method of choice for administering these agents to critically ill children, and it is important to understand that fatal anaphylaxis reactions to these drugs have been reported.^{16,17} Methylprednisolone is one of the most commonly used agents for acute severe asthma. Because of its half-life, steady-state levels can be achieved relatively quickly, and although dosing regimens

vary, it is probably most appropriate to dose the drug every 6 hours. There does not seem to be any advantage in administering massive doses of glucocorticoids to those with status asthmaticus.¹⁸ If methylprednisolone is not available, equipotent doses of another glucocorticoid may be used.

Magnesium has been investigated for use in status asthmaticus because of its potential to augment the effects of bronchodilators by causing relaxation of airway smooth muscles. A recent RCT in adults

showed that 2 g of IV magnesium sulfate improves pulmonary function when given as an adjunct to nebulized β agonists and IV corticosteroids in patients with especially low FEV1 (<20% of predicted).¹⁹ Although magnesium is occasionally added to standard therapy in pediatric patients with status asthmaticus, evidence supporting its use in this population is limited.²⁰

Enthusiasm for the use of methylxanthines (e.g., theophylline, aminophylline) in pediatric asthma has fluctuated over time. Theophylline is a preparation for enteral administration, and aminophylline is a compound for parenteral administration consisting of 80% theophylline (by weight) and 20% ethylenediamine, which is added to enhance solubility.²¹ These drugs act primarily as phosphodiesterase inhibitors, but they are believed to have a host of collateral effects that may contribute to the rationale for their use in acute asthma. These include endogenous catecholamine release,²² enhanced skeletal muscle contraction by sensitizing ryanodine receptors to intracellular calcium, and (even at low serum concentrations) attenuation of inflammatory gene expression by induction of histone deacetylase activity and suppression of NF- κ B activation.^{22,23} Importantly, methylxanthines are also nonselective adenosine receptor antagonists.^{22,24} Their interaction with the A_{2B} receptor, which is located on the bronchial tree and is known to mediate bronchospasm, may be of particular importance in producing their bronchodilatory effects. A recent RCT investigated the effects of aminophylline in 163 children with status asthmaticus. Aminophylline was administered to these children as an adjunct to nebulized β agonists, nebulized anticholinergics, and parenteral corticosteroids.²⁵ The results of this trial suggested that aminophylline improved pulmonary function and that it may have averted intubation in a portion of patients who received it.²⁵ Although aminophylline may have a role in the treatment of those with severe status asthmaticus who do not respond to standard therapies, the potential for its widespread use is limited by its narrow therapeutic index.³

Bronchiolitis

Bronchiolitis is a clinical term implying an invasion of the large and small airway respiratory epithelium by inflammatory cells in the setting of acute respiratory illness. The most common cause of bronchiolitis is respiratory syncytial virus (RSV), which is responsible for 45% to 80% of cases.²⁶ Parainfluenza viruses, human metapneumovirus (hMPV), enteroviruses, adenovirus, influenza viruses, and *Mycoplasma pneumoniae* can produce the syndrome as well. Hospitalization rates vary seasonally and regionally in infants and children with bronchiolitis arising from any of these causes. Recent temporal trends in the rates of hospitalizations for all-cause bronchiolitis indicate that between 2000 and 2009, there was a 17% decrease in the incidence of bronchiolitis-related hospitalizations among all children less than 2 years of age in the United States, while the proportion of hospitalized children with a history of prematurity and one or more chronic medical conditions increased 34% during the same time period (5.9% in 2000 vs. 7.9 in 2009; $P_{\text{trend}} < 0.001$).²⁷ Adjusting for inflation, total hospital charges increased from US\$1.34 billion in 2000 to US\$1.73 billion in 2009 ($P_{\text{trend}} < 0.001$), a finding illustrating the substantial contribution of bronchiolitis-related hospitalizations to overall health-care costs.²⁷

To put the epidemiology, pathophysiology, and clinical sequelae of bronchiolitis into a more meaningful context, it is useful to understand the taxonomy describing the genetic relationships among the important causative pathogens (Table 77-2).

Pneumovirinae: Human Metapneumovirus and Respiratory Syncytial Virus Bronchiolitis

In accordance with their genetic homology, RSV and hMPV share most of their encoded proteins²⁸ and establish infection in young children worldwide with astonishing reliability. RSV dependably causes yearly epidemics during the winter and spring months in most geographic regions. Infection with RSV is nearly universal among

TABLE 77-2

Taxonomy of Viruses That Are Important Causal Pathogens of Acute Bronchiolitis

| FAMILY | SUBFAMILY | VIRUS |
|-----------------|------------------------|---|
| Paramyxoviridae | <i>Pneumovirinae</i> | RSV ¹ hMPV ² |
| | <i>Paramyxovirinae</i> | Parainfluenza virus |
| Picornaviridae | | Enterovirus species A, B, C, D |
| | | Rhinovirus ³ species A, B, C |

¹Respiratory syncytial virus; ²Human metapneumovirus; ³Rhinovirus species A, B, and C are now classified within the genus *Enterovirus*.⁴⁵

infants and children by 2 years of age, and after 5 years of age, almost all children show serologic evidence of prior infection with hMPV.²⁹ Each of these viruses has developed a distinct repertoire of techniques to evade the host immune response. hMPV, for example, subverts the innate immune response by inhibiting Toll-Like Receptor (TLR) 4 and TLR 7–dependent activation of the cascade of cellular signaling events in airway epithelial cells that culminate in the expression of interferon- α and - β .²⁸

The various strategies RSV has evolved to sustain its presence in infected hosts serve as key mediators of important causal pathways connecting acute and/or recurrent infections with its enduring pathophysiologic consequences. In vitro experiments using immunofluorescence and flow cytometry on human nasal, tracheal, and bronchial epithelial cell lines confirm that RSV infection triggers distal airway epithelial cells to elaborate nerve growth factor (NGF) and its high-affinity receptor trkA, which is responsible for promoting the expression of antiapoptotic bcl-2 regulatory proteins.³⁰ Concurrently, infection of the distal airways triggers the downregulation of NGF's low-affinity receptor p75^{NTR}, which is normally responsible for initiating a molecular signaling cascade culminating in a proapoptotic paradigm mediated by NF- κ B, stress-activated c-Jun N-terminal protein kinases (JNK), and ceramide activation.^{30,31} By subverting these redundant components of the immune response, RSV is able to maintain a prolonged presence in distal airway epithelial cells, allowing them to accommodate ongoing viral replication and local viral propagation (Fig. 77-2).^{31,32} The approaches RSV takes to maintain an extended presence in an infected host are expressed in extrapulmonary settings as well. In 2011, Rezaee and colleagues were the first to demonstrate that RSV infects human bone marrow cells.³³ They established that RSV can efficiently infect and take refuge in human bone marrow cells, allowing the virus to modulate the immune response to acute infection and perhaps serve as a reservoir of latent disease.^{32,33}

RSV transmission can occur either by direct contact with contagious secretions or by exposure to aerosolized particles from the respiratory mucosa.³⁴ The incubation period varies from 2 to 8 days³⁴; symptoms tend to escalate over 3 to 5 days, and convalescence can be prolonged for up to several weeks in the most vulnerable small infants. A histologic examination shows that reappearance of ciliated respiratory epithelium commonly takes more than 2 weeks.³⁴ Viral shedding from the respiratory tract typically occurs over 3 to 8 days but may continue for up to 4 to 6 weeks in small infants. Symptoms typically begin with signs of upper respiratory illness including fever, coryza, and possibly, otitis media. Small infants commonly present with lethargy and central apnea³⁵ early in the course of illness. Cough and tachypnea soon develop as the illness progresses to the lower airways, usually 1 to 3 days following incubation.³⁴ Radiographic findings commonly include hyperinflation, peribronchial thickening, subsegmental consolidation, and multiple areas of atelectasis or infiltration, most frequently involving the right middle and right upper lobes. A large prospective study of RSV-infected hospitalized children found that

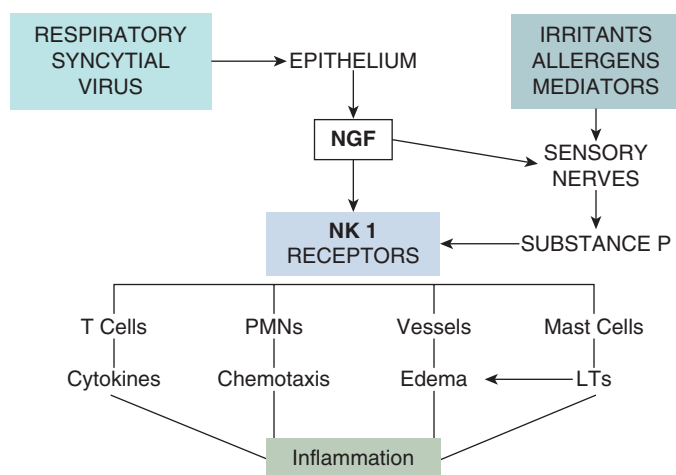


FIGURE 77-3 ■ Neuroinflammatory mechanisms incited by RSV infection, which can be reactivated by environmental exposures to produce recurrent wheezing. RSV preferentially invades and replicates in distal airway epithelial cells, increasing NGF production and upregulating the substance P receptor neurokinin (NK)-1 on a variety of immune cells. This process results in activation of neuroinflammatory pathways and longer term neural remodeling of infected airways. In small animals uninfected with RSV, NGF expression declines with age, whereas RSV infection greatly increases NGF expression across the age spectrum. Exposure to anti-NGF antibody inhibits the upregulation of NK-1 receptors.²²² LTs, leukotrienes; NGF, nerve growth factor. (From Piedimonte G. Pathophysiological mechanisms for the respiratory syncytial virus-reactive airway disease link. *Respir Res* 2002;3: S21–S25.)

Picornaviridae: Enteroviral Bronchiolitis and the Resurgence of Enterovirus D68

Within the genus *Enterovirus*, both *Rhinovirus* and *Enterovirus* species are among the important causal pathogens of bronchiolitis. Like RSV, human rhinovirus infection enhances expression of NGF and its trkA receptor in airway epithelial cells, an event with the dual consequence of creating a hospitable setting for ongoing viral replication and potentiating postinfectious airway hyperreactivity by setting the stage for neurokinin-1-mediated neural remodeling in distal airways.³² In rhinoviral infections, elaboration of NGF and upregulation of trkA also enhance viral attachment by increasing expression of intercellular adhesion molecule-1 (ICAM-1), the principal receptor by which rhinoviruses gains access to susceptible airway epithelial cells.⁴³

In 2014, the role of enteroviruses in the pathogenesis of bronchiolitis reestablished itself in the collective consciousness of pediatric clinicians with the widespread outbreak of severe lower respiratory illness caused by *Enterovirus* D68 (EV-D68). This virus was first recovered from the oropharynx of four children between 10 months and 3 years of age who were hospitalized in California with acute lower respiratory tract infection and wheezing during the autumn of 1962. Schieble and colleagues were subsequently able to isolate the virus in cell culture.⁴⁴ The virus was classified within the family Picornaviridae as a novel enteroviral serotype that became known as the “Fermon” strain of EV-D68.⁴⁴ Like the rhinoviruses, and unlike other enteroviruses, EV-D68 preferentially infects the respiratory tract rather than the GI tract and is transmitted principally through contact with respiratory secretions. During its 3- to 6-day incubation period, EV-D68 establishes its presence in the host respiratory epithelial cells through a sequence of events beginning with an attachment process mediated by the interaction between viral capsid components encoded by amino acid sequences VP1, 2, and 3 and sialic acid on the epithelial cell surface.⁴⁵

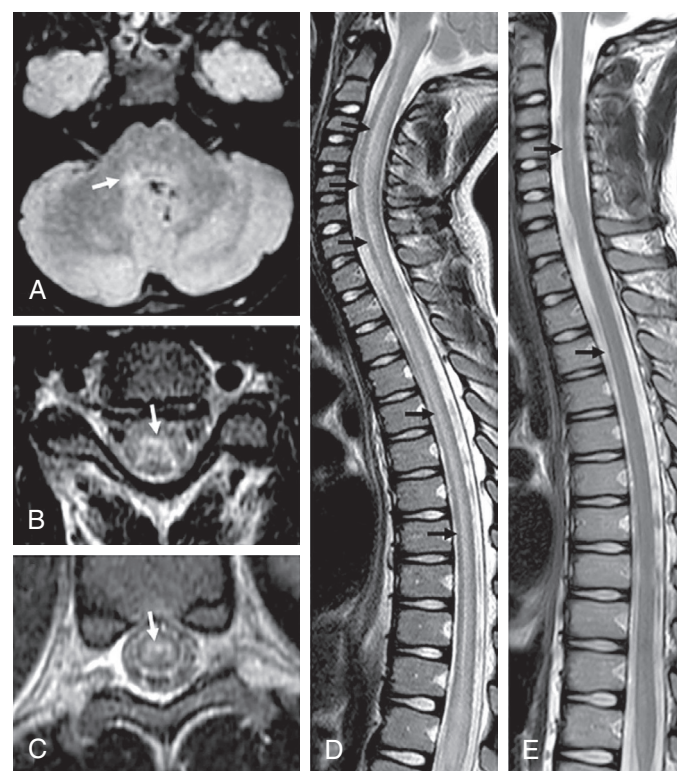


FIGURE 77-4 ■ Representative brain and spinal cord MR images in setting of EV-D68 infection with flaccid paralysis and cranial nerve dysfunction. Taken in the acute phase of illness, axial images **A**, **B**, and **C** show T2 hyperintensity in the right dorsal pons (white arrow, Panel **A**) and central hyperintensity in the central gray matter (white arrows, Panels **B** and **C**). Sagittal cord images show a progression from an extensive, ill-defined T2 hyperintensity in the acute phase of illness (black arrows, Panel **D**) to a signal hyperintensity that coalesces around the anterior horn cells 38 days into illness (black arrows, Panel **E**). (Modified from Maloney JA, Mirsky DM, Messacar K, et al. MRI findings in children with acute flaccid paralysis and cranial nerve dysfunction occurring during the 2014 enterovirus D68 outbreak. *Am J Neuroradiol* 2015;36:245–250; Fig. 4.)

Confirmed reports of respiratory illness attributed to EV-D68 were limited to 26 cases between 1970 and 2005; 75% of these occurred in children.⁴⁵ Another 95 confirmed cases were reported from the Philippines, Japan, the Netherlands, and the United States between 2008 and 2010. The widespread outbreak in the United States during 2014 is the largest to date, having involved over 1150 patients throughout the country. Traditionally, the symptom complex that was observed along with EV-D68 related respiratory disease included cough, dyspnea, wheezing, and increased work of breathing, with peripheral bandemia often noted on complete blood counts.⁴⁵ By historic standards, the 2014 cases presented with especially morbid disease, and 12 of the affected children died. Notably, the 2014 United States outbreak featured a cohort of 12 children in Colorado ranging from 1 to 16 years of age (median age 11.5 years) who developed acute onset of flaccid paralysis, cranial nerve dysfunction, and concordant spinal cord and brainstem abnormalities on magnetic resonance imaging (MRI), a median of 7 days after a prodromal febrile illness (Fig. 77-4).⁴⁶ The clinical findings in these cases resonated with case reports published between 2005 and 2014 that first suggested a possible association between EV-D68 infection and the development of acute motor neuropathy and/or anterior myelitis.^{47–49} Nasopharyngeal samples were positive for *Rhinovirus* or *Enterovirus* in 8 of the Colorado children; 5 of these 8 samples later revealed the presence of EV-D68. CSF

pleocytosis was present in all 10 children from whom it was obtained (median 55 cells/ μ L), yet *Enterovirus* could not be isolated from any of the CSF samples. Nonetheless, the pattern of neurologic involvement in these children and the absence of evidence for other candidate infections or autoimmune diseases implicate an *Enterovirus* (namely, EV-D68) as a possible cause. Follow-up of the Colorado cohort is still ongoing. While many have shown partial resolution of their neurologic findings, all 10 children who developed limb weakness were showing residual deficits as of December 1, 2014.⁴⁶

It is perhaps owing to more reliable diagnostic techniques that the prevalence of EV-D68–related respiratory illness seems to have increased over the past 40 years. Highly sensitive multiplex polymerase chain reaction (PCR) assays have certainly facilitated rapid diagnosis since they became available over the past decade, but because they target genetic sequences common to both *Enterovirus* and *Rhinovirus* species, they are unable to distinguish between the two.⁴⁵ A more specific diagnostic technique targeting the VP1 gene sequence has been available since 1999, and facilitated identification of EV-D68 as the causal pathogen of the U.S. outbreak that unfolded in 2014, allowing for crucially important early surveillance efforts.^{45,50}

Therapy

Many years of clinical experience with empiric use of symptomatic medical therapies have failed to determine a clear role for any of these agents in the management of bronchiolitis. Widespread use of bronchodilators and corticosteroids for the management of bronchiolitis is common despite the absence of evidence for meaningful improvement in relevant clinical outcomes for hospitalized and/or critically ill children.^{53–58} A few small studies have associated some short-term physiologic benefit with the use of corticosteroids and immune globulin in critically ill infants and children with bronchiolitis, but the efficacy of these therapies in altering outcomes in this population remains unproven.⁵³ Following from the observation that critically ill children with severe bronchiolitis demonstrate surfactant deficiency and dysfunction, a great deal of interest has surrounded the use of exogenous surfactant to modify the course of bronchiolitis in intubated patients. A number of small, underpowered trials have been conducted on this topic,^{59–61} but the available data do not provide a reliable estimate of surfactant's effects in this setting.⁶² Interpretation of this literature is complicated by the fact that the choice of surfactant preparation, the dosing regimen, and the mechanical ventilation strategy vary across studies.⁶² One recent multicenter RCT evaluated the impact of the semisynthetic surfactant Lucinactant (Discovery Laboratories, Warrington, PA) on duration of mechanical ventilation among children 2 years or less in age, with acute hypoxemic respiratory failure meeting criteria for acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS), a portion of whom had bronchiolitis.⁶³ This was a phase 2 trial designed to examine the safety, tolerability, and potential efficacy of Lucinactant for shortening the duration of mechanical ventilation through 14 days following study entry. The study randomized 165 infants from PICUs in the United States and Chile to receive intratracheal Lucinactant (175 mg/kg) or an equivalent volume of air placebo; an additional dose of Lucinactant could be administered to patients in the intervention group if they met predetermined redosing criteria. Unfortunately, the study protocol did not mandate a standardized approach to ventilator management or extubation readiness testing. It was not able to detect a significant decrease in the duration of mechanical ventilation that could be attributed to Lucinactant (least square mean: 4.0 days for Lucinactant group vs. 4.5 days in placebo group; $P = 0.25$). Fifty serious adverse events occurred in 34 patients in this study (20 Lucinactant patients vs. 14 placebo patients); two were attributed to study drug administration.

The latest guidelines issued by the American Academy of Pediatrics emphasize supportive care for hospitalized infants and children with viral bronchiolitis, and recommend against the routine use of aerosolized bronchodilators and systemic corticosteroids in this population.⁴² Supportive care of the patient with bronchiolitis consists of an ongoing assessment of airway patency, the adequacy of respirations, and

maintenance of adequate circulating volume. Supplemental oxygen is often required to reverse hypoxemia, and the clinician should be attentive to changes in mental status that could signal impending respiratory failure. Because future prospects for providing lasting immunity to RSV remain doubtful,³⁴ there is an ongoing need for large, multicenter studies to identify therapies that may benefit critically ill children with this disease.

Mechanical Ventilation

The need for mechanical ventilation in patients with lower airways disease commonly arises from failure of ventilation and the resulting hypercapnia. Hypoxemia and recurrent apnea, which are common in young infants with bronchiolitis, also frequently precipitate the institution of ventilatory support. Assuming adequate airway protection, oxygenation, and respiratory drive, it is probably best to avoid intubation in patients with lower airways disease unless the overall clinical status warrants the risk of augmenting airway hyperreactivity through airway instrumentation.⁶⁴ There are several adjunct therapies that may obviate the need for intubation when added to aggressively applied conventional therapies. An inspired mixture of helium and oxygen (heliox) has been used to alleviate airflow limitation in pediatric patients. Due to its low density and reduced Reynolds number, helium is able to convert turbulent gas flow to laminar flow in the airways, and its clinical effect is generally immediate. Because it is an inert gas, it can potentially reduce airways resistance without toxicity. When given as 60% to 80% of the total inspired gas mixture, helium can produce more efficient delivery of oxygen and nebulized drugs.⁶⁵

The use of heliox in patients with lower airways disease has generally produced inconsistent results. A small RCT in spontaneously breathing children with status asthmaticus demonstrated that administration of heliox improves respiratory mechanics by lowering the pulsus paradoxus, increasing peak flow, and decreasing the dyspnea index, which may decrease the need for mechanical ventilation.⁶⁶ In another small series, a 60:40 heliox mixture administered to 7 intubated patients resulted in a 15% to 50% reduction in peak inspiratory pressure and a 30% to 60% reduction in P_{aCO_2} .⁶⁷ A recent literature review on the use of heliox in patients of all ages with acute asthma concluded that it may be useful in the short-term management of these patients, but any advantage attributed to its use seems to have diminished over time.⁶⁸ There is little evidence available on the use of heliox in critically ill patients with bronchiolitis. This issue was prospectively investigated in a nonrandomized study of 38 nonintubated infants with RSV bronchiolitis admitted to an ICU.⁶⁹ Favorable changes in respiratory status through the first 4 hours of heliox administration and a significant decrease in length of ICU stay were seen among infants who received heliox therapy.⁶⁹ In a small randomized, crossover study of RSV-positive, nonintubated patients, clinical indicators of respiratory status improved during heliox administration, particularly among children with more severe disease.⁷⁰ However, many of these patients required another form of respiratory support, and the study was not designed to evaluate longer term outcomes such as length of ICU stay.⁷⁰

The application of noninvasive forms of mechanical support such as CPAP or bilevel positive pressure using either a nasal interface or full face mask has potential advantages in patients with adequate respiratory drive. Careful titration of applied CPAP (or PEEP) may prevent premature airways closure during expiration and decrease gas trapping (see later discussion). Patients who develop high levels of intrinsic PEEP due to hyperinflation manifest increased work of breathing and ultimately, respiratory muscle fatigue that may precipitate dramatic and rapid clinical deterioration. Noninvasive respiratory support may allow unloading of the muscles of respiration without adding to airway reactivity and has been used with success in managing asthma as well as bronchiolitis.^{71,72}

In patients with respiratory failure where noninvasive mechanical support is not feasible, intubation and mechanical ventilation are warranted. As tracheal intubation is performed in patients with airways

disease, the clinician should be watchful for complications arising from the transition to positive pressure ventilation. In spontaneously breathing children with severe airway obstruction, profoundly negative intrathoracic pressures develop in order to generate lung inflation. These conditions produce maximal venous return as right atrial pressure remains subatmospheric.⁷⁴ The transition to positive pressure ventilation in this setting increases juxtacardiac pressures and right ventricular afterload, resulting in decreased venous return, decreased left ventricular compliance, and decreased left ventricular end diastolic volume,⁷⁴ with risk of hypotension and cardiac arrest.³

In intubated patients with status asthmaticus or bronchiolitis, low elastic recoil and increased airway resistance due to bronchoconstriction, airway edema, and mucous plugging contribute to regional gas trapping and dynamic hyperinflation (Fig. 77-5, A). Gas trapping can also be exacerbated by the patient's forced expiratory efforts, during which increased abdominal pressure is transmitted to the pleural space, potentiating premature airways closure and the development of excess or intrinsic PEEP ("auto-PEEP"). The magnitude of the auto-PEEP reflects the degree of dynamic hyperinflation in patients with severe asthma.⁷⁵ Dynamic hyperinflation and auto-PEEP have an adaptive purpose in increasing the elastic recoil pressure of the lung to a level that would eventually allow complete evacuation of inhaled volume.⁷⁵ However, this increase in lung volume takes place at the

expense of an unfavorable change in pulmonary compliance. Other potential consequences of dynamic hyperinflation and auto-PEEP include air leak, hemodynamic compromise from sustained elevations in pulmonary vascular resistance, and increased inspiratory workload from the patient's attempts to drop the ventilator circuit pressure below the total PEEP level (applied or set PEEP plus auto-PEEP) in order to trigger a breath (Fig. 77-5, B). The development of gas trapping and auto-PEEP can be inferred if the flow versus time waveform on the ventilator console shows initiation of inspiratory flow before the expiratory flow from the preceding breath reaches zero. Alternatively, the ventilator can quantify auto-PEEP by allowing the alveolar pressure to equilibrate with pressure at the airway openings during an end-expiratory hold maneuver. The accuracy and reliability of each of these techniques rest on the premise that all lung units communicate with the airway openings, which may not be true if bronchial obstruction is severe.⁷⁶

Excessive gas trapping and auto-PEEP are managed through adherence to the basic principles of mechanical ventilatory support of patients with lower airways disease: (1) limitation of tidal volume, plateau pressure, and respiratory rate; (2) reducing inspiratory time; and (3) judiciously titrating applied PEEP. In spontaneously breathing mechanically ventilated patients, increases in applied PEEP can reduce auto-PEEP by reducing the tendency to premature airway closure during exhalation and restoring a pressure gradient between the alveoli and airway opening that favors a return toward normal end-expiratory lung volume. Reduction of auto-PEEP through this kind of maneuver can trigger ventilator breaths and decrease the inspiratory workload. It turns out that this concept can be difficult to optimize in practice. If increases in applied PEEP fail to improve respiratory mechanics or worsen gas trapping, the clinician may consider a trial of neuromuscular blockade in an effort to facilitate enforcement of permissive hypercapnia and further reductions in minute ventilation.

In summary, initial ventilator settings in patients with lower airways disease should be guided by observation, auscultation, careful ventilator waveform analysis, and attention to inspiratory plateau pressure. Ultimately, the choice of ventilator mode is not as important as a thorough understanding of how any mode might be strategically manipulated to alleviate the pathophysiology of gas trapping and auto-PEEP. It is generally preferable to allow patients to breathe in a spontaneous ventilator mode, using a strategy of permissive hypercapnia. In spontaneously breathing mechanically ventilated patients, applied PEEP can be titrated cautiously upward as needed to improve respiratory mechanics, to a level not exceeding 80% of auto-PEEP, or until the plateau pressure begins to exceed a tolerable limit, which is usually around 30 cm H₂O.^{76,77} If controlled ventilation is necessary, it is preferable to apply the lowest minute ventilation that provides adequate gas exchange.⁷⁸ The use of neuromuscular blocking agents should be limited to the shortest feasible course, because of their potentially detrimental effect on the relationship between ventilation and perfusion, and because of the risk of myopathy when these agents are administered together with corticosteroids.⁷⁹ High-frequency oscillatory ventilation (HFOV, see below) has been used to rescue a limited number of pediatric patients with asthma and bronchiolitis who demonstrate respiratory failure refractory to management with conventional ventilation.⁸⁰ One recent report recommends the use of high distending pressures to decrease airway resistance, low frequencies, longer expiratory times, and muscle relaxation in order to minimize gas trapping.⁸¹

Sedation is an important component of managing intubated patients with lower airways disease. Besides alleviating distress and promoting synchrony with the ventilator, sedative agents can be helpful adjuncts in limiting carbon dioxide production and reducing mechanical ventilatory requirements.⁷⁶ Ketamine, a dissociative anesthetic with sympathomimetic and bronchodilatory properties, is often used for sedation in intubated asthmatic children.⁸² Because of its favorable effects on airways reactivity, the inhalational anesthetic isoflurane (Forane®; Baxter Healthcare, Deerfield, IL) may be a useful adjunct to the management of severe status asthmaticus in intubated children

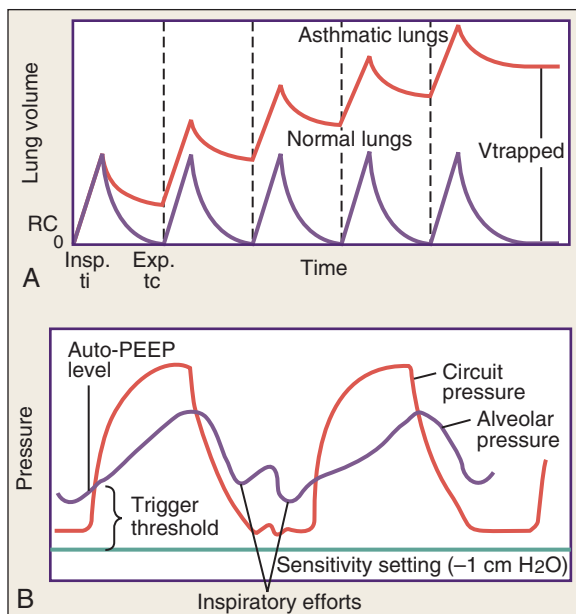


FIGURE 77-5 ■ A, Dynamic hyperinflation. Expiratory flow limitation in the asthmatic lung (upper tracing) causes incomplete evacuation of lung volume at end exhalation. Repetitive cycles of gas trapping lead to excess pressure accumulation at end exhalation ("auto-PEEP"), with a progressive shift toward ventilation on the less compliant (upper and outer) portion of the pressure-volume curve. (See also Fig. 77-6.) **B, Effect of auto-PEEP on inspiratory threshold load.** Ventilator circuit pressure, alveolar pressure, and trigger sensitivity setting are indicated. The difference between peak inspiratory circuit pressure and peak inspiratory alveolar pressure reflects the increased airway resistance. The difference between the end-expiratory circuit pressure and the end-expiratory alveolar pressure reflects the expiratory flow limitation and auto-PEEP. The pressure drop required to generate inspiratory flow ("trigger threshold") is the difference between the end-expiratory pressure and the sensitivity setting. In the presence of auto-PEEP, the patient must generate a larger inspiratory pressure drop in order to generate inspiratory flow. (A, From Stather DR, Stewart TE. Clinical review: Mechanical ventilation in severe asthma. *Crit Care* 2005;9:581-587.)

who are difficult to sedate or are unresponsive to other therapies. The mechanism underlying its bronchodilatory properties is not well understood.⁸³ Although isoflurane (Forane®; Baxter Healthcare, Deerfield, IL) has a better safety profile than halothane when used for this purpose, periodic monitoring of renal function may be advisable in children who require prolonged therapy with this agent.⁸³

■ DISEASES OF THE ALVEOLI

Viral Pneumonia

Defined as acute respiratory symptoms accompanied by parenchymal infiltrates on chest x-ray, pneumonia is a common syndrome in children and is most commonly caused by viral or bacterial pathogens.⁸⁴ Important viral pathogens responsible for pneumonia in infants and children include RSV, influenza, parainfluenza, and adenovirus. As we have seen, each of these agents is also capable of producing the clinical syndrome of bronchiolitis in infants and children. The precise infectious etiology for pediatric viral pneumonias may be suggested by the physical examination, the age of the patient, and seasonal incidence patterns. Confirmatory testing through microbiologic analysis is generally sought to facilitate therapeutic decision making and cohorting of similarly affected patients. RSV is the most common viral cause of lower respiratory tract infection in infants⁸⁵ and primarily affects the small airways. Parainfluenza viruses are also responsible for causing pneumonia in children and seasonal epidemics that commonly occur in autumn.⁸⁵ Primary infections tend to occur in young children 2 to 6 years of age, and recurrent infection is generally less severe, except perhaps in immunocompromised hosts.⁸⁵ Finally, adenoviruses have been reported to cause up to 20% of pneumonias in children less than 5 years of age, and the mortality rate attributable to the disease has been reported to be as high as 20%.⁸⁶ In neonates, adenovirus can produce an especially severe syndrome of disseminated disease and sepsis, which can present in the first 10 days of life.⁸⁶ The incubation period is 2 to 14 days,⁸⁵ and the virus can produce a profound and destructive lower respiratory process. Necrotizing bronchitis, purulent exudative alveolitis, and hyaline membrane formation have been identified on autopsy.⁸⁶ Survivors of severe adenoviral infections often demonstrate chronic sequelae such as recurrent wheezing and *bronchiolitis obliterans*, a syndrome of irreversible fibrosis characterized by a heterogeneous pattern of airway narrowing in some lung units and complete eradication of the airway lumen in others.^{86,87}

Influenza is a particularly important cause of pediatric pneumonia. Infection rates in healthy children are estimated at 10% to 40% each year, and approximately 1% of these children require hospitalization.⁸⁵ The course of up to 25% of infected children is complicated by lower respiratory tract disease.⁸⁵ Neonates and children up to 5 years of age, especially those who are immunocompromised, those with underlying lung disease, congenital heart disease, and other chronic conditions, seem to be at special risk for influenza pneumonia.⁸⁵ Neonates are at risk for especially severe influenza syndromes, which may also include apnea and sepsis.⁸⁵

The clinical course of influenza observed during the 2009 H1N1 pandemic diverged from what had typified prior seasonal patterns. It often featured rapidly progressive hypoxia and respiratory failure^{88,89} and was more frequently associated with concurrent shock in children and increased mortality.⁹⁰ Several case series of critically ill children and adults with the 2009 H1N1 infection included a cohort of patients who manifested particularly fulminant ARDS.^{88,89,91-93} Multicenter observational studies conducted across Canada,⁹² the United Kingdom,⁹³ and the United States⁹⁴ reported an ICU mortality rate of 7% to 9% for children with H1N1-associated respiratory failure. The cohort in the United States showed a propensity for early pulmonary co-infection with methicillin-resistant *Staphylococcus aureus* (MRSA), a finding that was strongly associated with mortality in previously healthy children who became critically ill with H1N1 disease (relative risk of death = 8; 95% CI, 3.1-20.6; $P < 0.0001$).⁹⁴

Therapy

Antiviral therapy for A and B strains of influenza are now available and can be considered for patients of appropriate age who are at high risk of complicated or severe disease.⁸⁵ When administered within 48 hours of disease onset, amantadine, which is approved for use in children less than a year old, may decrease the severity of influenza A disease, but data in young patients are limited.⁸⁵ Oseltamivir, an orally administered neuraminidase inhibitor active against both A and B strains of influenza, has been shown to decrease symptom duration when administered early in the disease process. When originally licensed for pediatric administration, oseltamivir was not approved for use in infants less than a year old.⁹⁵ However, increased experience with oseltamivir in smaller infants during the 2009 H1N1 influenza pandemic has produced some consensus on appropriate dosing guidelines in this age group.⁹⁶ The Centers for Disease Control and the American Academy of Pediatrics now recommend oseltamivir for treatment of influenza in infants and children of *any age* who are hospitalized, have a severe, progressive, or complicated trajectory of illness, or are at higher risk for influenza complications.⁹⁷ This drug can also be offered as postexposure chemoprophylaxis to high-risk, highly susceptible individuals 3 months or older or to control institutional outbreaks. Its inhalational counterpart zanamivir is also effective against A and B strains of influenza and is approved to treat active disease in children 7 years or younger as well as for chemoprophylaxis in children 5 years and younger. To date, viral resistance to either drug remains low.⁹⁷

Unlike RSV, influenza is commonly associated with secondary bacterial pneumonia that is typically caused by *Streptococcus pneumoniae* or *Staphylococcus aureus*, making it especially important to consider appropriate empiric antimicrobial therapy when clinically appropriate.^{98,99}

Bacterial Pneumonia

In infants less than 3 days of age, group B streptococcus is the major causal pathogen of vertically transmitted “early-onset” neonatal pneumonia. Among infants up to about 3 months of age, *Listeria monocytogenes* and gram-negative enteric organisms join the list of principal causes of bacterial pneumonia and sepsis. The pathogenesis in this age group can involve local overgrowth and invasion of colonizing organisms through respiratory mucosa or hematogenous transmission of a blood-borne organism to the lower respiratory tract.^{85,100} Widespread maternal intrapartum antibiotic prophylaxis has influenced the incidence of perinatal GBS infection as well as its antimicrobial resistance patterns.¹⁰¹ The incidence of GBS sepsis has declined among very low-birth-weight infants in the era of ampicillin prophylaxis, while the incidence of *E. coli* sepsis (largely resistant to ampicillin) has increased in the same time period.¹⁰¹ Perinatally acquired *Chlamydia trachomatis* is another important cause of lower respiratory tract infection in infants up to 12 weeks of age.¹⁰⁰ Although uncommon, periodic epidemics of infection with *Bordetella pertussis* occur among incompletely immunized infants and children.¹⁰⁰ Apnea and intermittent cyanosis progressing to respiratory failure and shock can develop in young infants infected with *B. pertussis*, and clinicians should have a relatively low threshold for admitting these patients to the ICU.

Among older infants and children, bacterial presence is commonly established in the lower respiratory tract as a result of oropharyngeal overgrowth of environmentally acquired pathogens and subsequent introduction of these secretions into the lower airways. Children with aspiration syndromes, immunodeficiencies, and malformations of the respiratory tract are at increased risk of lower respiratory bacterial infection.¹⁰⁰ Bacterial pathogens remain an important cause of potentially lethal pediatric pneumonias in the developing world, and they are the most important cause of severe pneumonia in Europe and North America, especially when complicated by parenchymal necrosis and/or parapneumonic effusion.⁸⁴ It is challenging to establish a causal role for specific bacteria when these agents are normally found in the

upper airway secretions, the specimen that is most commonly sampled for microbiologic diagnosis in children. The best data regarding the etiology of community acquired pneumonia come from lung puncture studies revealing that *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *S. aureus* are among the most important causes.⁸⁴ Since the introduction of a conjugate vaccine against *H. influenzae* type B (Hib) in 1988, the incidence of invasive disease in infants and young children attributed to this organism has declined by 99%.⁸⁵ Other serotypes of the organism, including nonencapsulated strains, are also capable of causing pneumonia in children.⁸⁵

A comprehensive review of necrotizing pneumonia cases occurring in predominantly immunocompetent children admitted to Boston Children's Hospital between 1990 and 2005 indicates that parenchymal necrosis appears to be an increasingly common complication of pediatric bacterial pneumonia.¹⁰² In this series, *S. pneumoniae* was the predominant inciting organism, accounting for 22% of cases. Since 2002, many more organisms, including methicillin-sensitive *S. aureus*, methicillin-resistant *S. aureus*, *Fusobacterium* species, *Pseudomonas* species, and other *Streptococcus* species, have emerged as important causes of necrotizing pneumonia, as well. Despite the short-term morbidity in these children, conservative management (consisting mainly of antibiotics and chest drainage) appeared sufficient to produce resolution of clinical symptoms within 2 months of hospital discharge, and marked improvement of imaging findings within 6 months.

Recent studies on the epidemiology of pediatric pneumonia complicated by parapneumonic effusions indicate that the incidence of empyema appears to have risen during the 1990s.¹⁰³⁻¹⁰⁵ During that period *S. pneumoniae* was isolated most commonly from patients with empyema, followed by *S. pyogenes* and *S. aureus*.^{104,105} As in the case of necrotizing pneumonia, temporal trends in the epidemiology of pediatric empyema in the United States show a shift in causative organisms after 2000, when the heptavalent pneumococcal conjugate vaccine (PCV) was licensed for widespread use. Since 2000, *S. aureus* has overtaken *S. pneumoniae* as the most common bacterial pathogen isolated from children with empyema, and the *S. aureus* isolates are often methicillin resistant.¹⁰³ In addition, nonvaccine serotypes (particularly serotypes 1, 3, and 19A) predominate among causes of pneumococcal empyema in the post-PCV era.^{104,106} The overall impact of widespread vaccination with PCV on the incidence of pediatric empyema across the United States is less clear. In Utah, where pneumococcal serotype 1 has always been prevalent, the incidence of pediatric empyema is still rising, while data from Texas Children's Hospital show a decrease in the incidence of empyema since the vaccine became available.^{103,104}

Therapy

In the clinical setting, one is often faced with having to select empiric antimicrobial therapy before arriving at a definitive viral or bacterial diagnosis. The presence of a focal alveolar process on chest radiographs, especially if accompanied by significant parapneumonic effusions, evidence of parenchymal necrosis, and/or abnormal peripheral blood counts and C-reactive protein all add considerably to the predictive value for the presence of bacterial disease.⁸⁴ Before demonstrating evidence of localized infection, neonates and young infants may demonstrate nonspecific but potentially ominous signs of lethargy, hypothermia, and apnea. Infants less than 3 months of age should be treated with a broad spectrum combination of antibiotics such as ampicillin and gentamicin, and consideration should be given to adding a third-generation cephalosporin in severe cases.⁸⁴ Investigation and empiric coverage for infection with *B. pertussis* should also be considered in infants with severe respiratory disease that features profound peripheral lymphocytosis, paroxysmal cough, and/or apnea.

For critically ill children with community-acquired bacterial pneumonia, reasonable coverage may be assured with a third-generation cephalosporin,^{84,100} although some centers advocate the use of clindamycin as a second empiric agent. A macrolide antibiotic can be added in cases where infection with atypical agents such as *Mycoplasma*

pneumoniae and *Chlamydia pneumoniae* is possible, particularly in patients with sickle cell disease.^{84,107} Although emerging resistance to penicillins in *S. pneumoniae* is widely recognized, high doses of cephalosporins are still appropriate in the majority of penicillin-nonsusceptible strains, as long as concurrent meningitis is not suspected, but the addition of vancomycin may be warranted in some cases.^{84,108} If infection with *S. aureus* is possible, an antistaphylococcal penicillin such as oxacillin should be added, unless local resistance patterns warrant the use of vancomycin.⁸⁴ In patients at risk for aspiration pneumonia and in immunocompromised children, special consideration should be given to administration of two antibiotics effective against gram-negative organisms (such as *Pseudomonas*) and to optimizing coverage for anaerobic organisms.

Management of pleural effusions is another important consideration in the care of patients with bacterial pneumonia. Although drainage of parapneumonic effusions is indicated under certain circumstances, satisfactory recovery may occur in many cases without intervention.¹⁰⁹ An evidence-based clinical practice guideline was developed for the medical and surgical treatment of parapneumonic effusions in adults.¹¹⁰ The panel issued management suggestions according to the underlying risk of poor clinical outcome based on effusion size and loculation, as well as chemical and microbiological analysis of the pleural fluid.¹¹⁰ Pleural fluid drainage was recommended for large effusions occupying less than 50% of the hemithorax, whether or not loculation or pleural thickening is present. Drainage was also recommended for purulent effusions, those with positive culture or Gram stain, or those with pH less than 7.20 as measured by a blood gas analyzer.¹¹⁰ In situations where drainage is indicated, more complex or invasive options such as thorascopic or "open" procedures are likely to be necessary for sufficient control of the effusion.¹¹⁰ The consensus panel's recommendations are based primarily on case series, historic controls, and expert opinion.¹¹⁰

Currently, the literature on parapneumonic effusions in children also does not provide robust evidence on which to base clinical interventions. The effect of image-guided needle aspiration versus percutaneous pigtail catheter drainage was examined in a 5-year retrospective study of pediatric parapneumonic effusions.¹¹¹ When comparing outcomes in the two groups, the authors found no difference in the length of stay but did report a significant decrease in the need for a second intervention in patients who received a chest drain.¹¹¹ Other independent predictors for a second intervention in their study population included loculation of pleural fluid and a pH of less than 7.2. A combination of low glucose and low pH in the pleural fluid specimen was especially predictive of the need for reintervention.¹¹¹ The decision to perform thoracostomy drainage in pediatric patients with parapneumonic effusion may depend on the clinical context in which it occurs. In cases where significant pleural fluid organization has taken place, some favor the administration of intrapleural thrombolytics to facilitate evacuation of fluid through the chest drain.¹¹² Studies assessing the efficacy of this practice have produced conflicting results. In one uncontrolled case series, 54 of 58 children (93%) with pneumonia complicated by empyema who received intrapleural tissue plasminogen activator (tPA) did not require additional surgical drainage.¹¹³ However, an RCT that enrolled 454 adults with empyema showed no outcome benefit attributable to the administration of intrapleural thrombolytics, compared to chest drainage and routine supportive care alone.¹¹⁴ In recent years, video-assisted thoracoscopic surgery (VATS) has gained popularity as a way to facilitate chest drainage through inspection of the pleural space, disruption of adhesions, and placement of chest drains in strategic locations.¹¹² To date, at least two prospective pediatric trials have failed to identify an outcome advantage attributable to VATS when compared to thrombolytic-enhanced chest drainage and routine supportive therapy for empyema.^{115,116}

In summary, it is certainly important to drain large parapneumonic effusions when they are suspected of causing hemodynamic instability in critically ill children. Pleural drainage may also be useful to relieve respiratory embarrassment that may contribute to respiratory failure or ongoing ventilator dependence. The best opportunity to achieve

sufficient drainage is probably in the first 48 to 72 hours, before organization of the effusion begins to take place. An RCT is necessary to resolve the issue of which pediatric patients with parapneumonic effusions would benefit from aggressive pleural drainage.

Acute Lung Injury and Acute Respiratory Distress Syndrome

What was once known as the *adult respiratory distress syndrome* is now called the *acute respiratory distress syndrome* (ARDS) in an effort to acknowledge its prevalence in the pediatric population. ARDS describes a diverse group of conditions for which the final common pathway involves the onset of permeability edema, parenchymal opacification, and significant oxygenation impairment. The syndrome can arise as a consequence of primary pulmonary disease or as a feature of systemic pathophysiology that is nonpulmonary in origin. Although ARDS had been described in adults for many years, consensus criteria for the diagnosis of the syndrome did not enter the scientific literature until 1994.¹¹⁷ The American European Consensus Conference's (AECC) establishment of highly sensitive diagnostic criteria for ARDS and acute lung injury (ALI), the less severe form of the disease, facilitated the conduct of large-scale RCTs that have added considerably to our understanding of the epidemiology, pathophysiology, and outcomes of both conditions. Published incidence estimates for ALI/ARDS vary and are best interpreted in the context of study design, case ascertainment methods, population demographics, and mechanical ventilation practices that were used at the time patients were identified as meeting criteria for either condition. The available data suggest that there are striking differences in the incidence of ALI and ARDS in children as compared to adults (Table 77-3).

As defined by AECC diagnostic criteria, ARDS is estimated to account for 1% to 4% of all PICU admissions, or ~10% of all children

requiring mechanical ventilatory support.^{118,119} Pneumonia, which was responsible for 35% of cases in a recent epidemiologic study, appears to have overtaken sepsis as the most common cause of pediatric ARDS.¹¹⁸ Reported mortality rates for children with ARDS have fluctuated over time, depending on the criteria used to identify cases, the presence of important comorbidities such as immunocompromise and nonpulmonary organ failures among patients in the cohort, and the quality and consistency of supportive care provided in the ICU. Data from contemporary epidemiologic investigations and the control groups of multicenter clinical trials conducted during the past decade indicate that mortality in the pediatric ALI/ARDS population ranges between 8% in both arms of a prone positioning trial¹²⁰ in which the investigators protocolized nearly every conceivable aspect of supportive therapy to 36% in the control arm of an RCT of exogenous surfactant administration.¹²¹ Among immunocompromised children, mortality may be as high as 60%.¹²¹⁻¹²⁴ As is the case in the adult literature, the lowest mortality rates for ALI/ARDS are reported in trials that evaluate the efficacy of a particular therapy while introducing it in the context of contemporary, evidence-based supportive care protocols.^{120,125,126}

The past 2 decades have seen the completion of many multicenter trials designed to investigate the effects of various adjuvant therapies in pediatric and adult ALI and ARDS (Table 77-4). So far, prone positioning¹²⁷ and tidal volume reduction during mechanical ventilation¹²⁸ stand as the only interventions proven to offer a significant mortality benefit to patients with ALI and ARDS. Having reached a point at which clinical trials are consistently unable to demonstrate outcome benefits for well-rationalized candidate therapies for ARDS, we now enter a new era obligating further refinement of diagnostic criteria, with an eye toward identifying relevant subgroups of ARDS patients who may stand to benefit from treatments whose merits may not be apparent in more unselected populations. The ARDS Definition Task Force and the Pediatric Acute Lung Injury Consensus Conference (PALICC) Group have each proposed updated diagnostic criteria for adult and pediatric patients that make an effort to address various aspects of the AECC consensus criteria that clinicians now recognize as potentially problematic.^{129,130} First, $\text{PaO}_2/\text{FiO}_2$ can be manipulated by altering ventilator settings. Second, acute lung injury can often coexist with hydrostatic pulmonary edema. Third, there is an increasing trend toward monitoring oxygenation in mechanically ventilated pediatric patients without indwelling arterial access. Finally, there exists considerable variability among radiologists in interpreting chest radiographs.¹³¹ Each group proposed eliminating the term *acute lung injury* in favor of simply classifying the degree of oxygenation impairment in ARDS patients as “mild,” “moderate,” or “severe”—in accordance with data indicating that mortality risk is concordant with the severity of oxygenation impairment in each category.¹²⁹ The PALICC group also defined a cohort of patients “at risk for” pediatric ARDS, a move intended to facilitate future research on preventative strategies.¹³⁰ It is evident from their final form (Table 77-5) that both new definitions foreclose the possibility that ARDS can be diagnosed in patients not requiring mechanical ventilation—a change that seems appropriate in light of the multiple lines of evidence suggesting a major role for mechanical ventilation in the pathogenesis of this disease.

Mechanical Ventilation

Mechanical ventilatory support of patients with ALI/ARDS is often necessary to provide adequate oxygenation. In relatively stable patients, noninvasive ventilation may be effective when instituted early in the disease process. This method has been used successfully in the management of acute hypoxic respiratory failure in a heterogeneous population of adult patients¹³² and in a more selected population of immunocompromised adult patients.¹³³ Each of these RCTs showed that early use of noninvasive ventilation decreased the need for intubation and reduced the risk of death in the ICU and in the hospital. Data on the use of noninvasive positive pressure ventilation in pediatric patients are limited, but several case series report success with the

TABLE 77-3

American-European Consensus Criteria for Acute Lung Injury (ALI) and the Acute Respiratory Distress Syndrome (ARDS)

| | ALI | ARDS |
|----------------------------|---|---|
| TIMING | ACUTE ONSET | ACUTE ONSET |
| Chest radiography | Bilateral pulmonary infiltrates | Bilateral pulmonary infiltrates |
| Edema | Pulmonary artery occlusion pressure ≤ 18 mm Hg or no clinical evidence of left atrial hypertension | Pulmonary artery occlusion pressure ≤ 18 mm Hg or no clinical evidence of left atrial hypertension |
| Oxygenation impairment | $\text{PaO}_2/\text{FiO}_2$ ratio $\leq 300^*$ | $\text{PaO}_2/\text{FiO}_2$ ratio $\leq 200^*$ |
| ESTIMATED INCIDENCE | | |
| Adults | 17.9-78.9 ^a cases per 100,000/year ²²³⁻²²⁵ | 14-58.7 ^b cases per 100,000/year ^{224,225} |
| Children | 2.95-12.8 ^c cases per 100,000 children/year ²²⁶⁻²²⁸ | 2.2-9.5 ^c cases per 100,000 children/year ^{226,227,229,230} |

*At altitudes exceeding 1000 m, $\text{PaO}_2/\text{FiO}_2$ should be adjusted for local barometric pressure ($\text{PaO}_2/\text{FiO}_2 \times (\text{barometric pressure}/760)$). ^aIncidence of ALI/ARDS in adults depends on age. Among adolescents, the incidence has been reported as low as 16/100,000.²²⁵ ^bThe incidence of ARDS among adults may be decreasing to as low as 38.9/100,000.²³¹ ^cHigh estimate for pediatric ALI and ARDS incidence comes from a cohort assembled between 1999 and 2000 who were ventilated with a mean (\pm SD) Vt of 9.3 ± 1.5 cc/kg.²²⁷ The most recent large, population-based cohort including children receiving lung-protective mechanical ventilation suggests an ARDS incidence of 3.9/100,000 children per year.²²⁹
Adapted from Bernard GR, et al. Am J Respir Crit Care Med 1994;149:818-824.

TABLE 77-4

Results of Selected Clinical Trials Evaluating Ventilation Strategies or Pharmacologic Therapies for Acute Lung Injury and the Acute Respiratory Distress Syndrome

| INTERVENTION | YEAR | NUMBER OF PATIENTS | FINDINGS | STUDY |
|--|--|--|---|---|
| Low tidal volume mechanical ventilation | 2000 | 861 | 22% relative mortality benefit | NIH Acute Respiratory Distress Syndrome Network ¹²⁸ |
| Increased recruitment vs. minimal alveolar overdistention in ALI and ARDS (PEEP titrated to Pplat 28-30 cm H ₂ O vs. PEEP 5-9 cm H ₂ O) | 2008 | 767 | No mortality benefit | Mercat et al. ²³² |
| Recruitment maneuvers, low tidal volumes, and high PEEP in ALI and ARDS (higher PEEP, Pplat ≤ 40 cm H ₂ O, Vt 6 cc/kg, and recruitment maneuvers vs. "conventional" PEEP, Pplat ≤ 30 cm H ₂ O, and Vt 6 cc/kg) | 2008 | 983 | No mortality benefit | Meade et al. ²³³ |
| HFOV at maximal Hz vs. conventional ventilation with higher PEEP, Vt 6 cc/kg, and Pplat ≤ 35 cm H ₂ O, "OSCILLATE" trial | 2013 | 548 ^c (of 1200) | Increase in hospital mortality with HFOV ^m | Ferguson et al. ¹⁴⁴ |
| HFOV vs. "usual" conventional ventilation (approximately 8 cc/kg ideal body weight), "OSCAR" trial | 2013 | 795 (of 1006) | No mortality benefit ⁿ | Young et al. ¹⁴⁵ |
| Prone positioning | 2001 2004 2005 ^a 2006 2009 2013 | 304 791 102 136 342 237 | No mortality benefit ⁱ No mortality benefit ^k No mortality benefit No mortality benefit ^o No mortality benefit ⁱ 51% relative mortality benefit^o | Gattinoni et al. ²³⁴ Guérin et al. ²³⁵ Curley et al. ¹²⁰ Manceb et al. ²³⁶ Taccone et al. ²³⁷ Guérin et al. ¹²⁷ |
| Conservative vs. liberal fluid administration strategy | 2006 | 1000 | No mortality benefit ^a | NIH Acute Respiratory Distress Syndrome Network ²³⁸ |
| Activated protein C | 2008 | 75 | No mortality benefit | Liu et al. ²³⁹ |
| Inhaled β agonist | 2011 | 282 | No mortality benefit | Matthay et al. ¹²⁵ |
| IV β agonist | 2012 | 324 | No mortality benefit ^f | Gao Smith et al. ²⁴⁰ |
| Surfactant | 1996 2004 2005 ^a 2009 2011 2012 ^a | 725 448 152 418 419 165 | No mortality benefit No mortality benefit Mortality benefit seen in surfactant group ^c No mortality benefit ^g No mortality benefit ⁱ No mortality benefit ^{h,j} | Anzueto et al. ²⁴¹ Spragg et al. ²⁴² Willson et al. ¹²¹ Kesecioglu et al. ²⁴³ Spragg et al. ²⁴⁴ Thomas et al. ⁶³ |
| Corticosteroids | 1998 2006 | 24 180 | Mortality benefit ^d No mortality benefit | Meduri et al. ²⁴⁵ NIH Acute Respiratory Distress Syndrome Network ²⁴⁶ |
| Inhaled nitric oxide | 1998 1999 ^a 2004 | 177 108 385 | No mortality benefit No mortality benefit No mortality benefit | Dellinger et al. ²⁴⁷ Dobyns et al. ²⁴⁸ Taylor et al. ²⁴⁹ |
| Ω-3 fatty acid, γ-linolenic acid, and antioxidant supplementation vs. isocaloric control supplement | 2011 | 272 | No mortality benefit | Rice et al. ²⁵⁰ |
| Early trophic vs. full enteral feeding | 2012 | 1000 | No mortality benefit | Rice et al. ¹²⁶ |

^aPediatric trial. ^bPatients prone for average of 17 hours/day and Vt of up to 10 cc/kg and PIP up to 40 cm H₂O were allowed. ICU mortality 58% in control arm; study ultimately underpowered. ^cStudy ultimately underpowered. ^dSmall study; crossover design. ^ePatients who received a fluid-conservative strategy had an improved oxygenation index and a significant increase in ventilator-free days during the first 28 days of therapy. ^fTrial terminated prematurely at interim analysis; patients in intervention arm had higher mortality rate than controls. ^gNonsignificant trend toward increased mortality and increased adverse effects in treatment arm. ^hPhase II trial. ⁱTrial enrolled patients with severe direct lung injury, a portion of whom met all criteria for ALI/ARDS. ^jPatients ventilated using (approximate) average Vt 10 cc/kg predicted body weight. ^kTrial enrolled patients with acute hypoxic respiratory failure, a portion of whom had ALI/ARDS. They were prone for median 8 hours/day and ventilated with (approximate) average Vt 8 cc/kg measured body weight. Concern for increased position-related adverse events in prone group. ^lTrial enrolled patients with moderate (PaO₂/FiO₂ 100-200) and severe (PaO₂/FiO₂ <100) ARDS. Patients prone for ≥20 hours/day; ventilated using Vt limited to ≤8 cc/kg and Pplat ≤30 cm H₂O. ^mTrial terminated prematurely for potential harm. Enrolled patients had PaO₂/FiO₂ ≤200 with an FiO₂ ≥0.5, and had ≤2 weeks of symptoms. HFOV delivered using the SensorMedics 3100B ventilator (CareFusion, San Diego, CA, USA). ⁿTarget enrollment reduced from 1006 at interim analysis. Enrolled patients had PaO₂/FiO₂ ≤200 on PEEP ≥5 cm H₂O. HFOV delivered using Novalung R100 ventilator (Metran, Kawaguchi, Japan). ^oAbsolute mortality reduction 16.8%. Adapted from Ventre KM, Arnold JH. Acute lung injury and the acute respiratory distress syndrome. In: Rogers M, editor. Textbook of Pediatric Intensive Care, 5th ed. Baltimore: Lippincott Williams and Wilkins, in press.

TABLE 77-5 The Acute Respiratory Distress Syndrome: Revised Diagnostic Criteria

| BERLIN DEFINITION | | PEDIATRIC ARDS (PARDS) DEFINITION [§] | |
|-----------------------------|---|---|--|
| Timing | Onset within 1 week of a known clinical trigger or new/worsening respiratory symptoms | Onset within 1 week of a known clinical trigger | |
| Chest imaging (x-ray or CT) | Bilateral opacities not fully explained by effusion, regional atelectasis, or nodules | New radiographic infiltrates consistent with acute pulmonary parenchymal disease | |
| Origin of edema | Respiratory failure not fully explained by cardiac failure or fluid overload ^{**} | Respiratory failure not fully explained by cardiac failure or fluid overload [*] | |
| Oxygenation impairment | | Noninvasive ventilation ^{††} | Invasive mechanical ventilation [‡] |
| Mild ARDS [*] | 200 < PaO ₂ /FiO ₂ ≤ 300 with PEEP or CPAP ≥ 5 cm H ₂ O [†] | PaO ₂ /FiO ₂ ≤ 300 SpO ₂ /FiO ₂ ≤ 264 | 4 ≤ OI < 8 OR 5 ≤ OSI < 7.5 8 ≤ OI < 16 OR 7.5 ≤ OSI < 12.3 OI ≥ 16 OR OSI ≥ 12.3 |
| Moderate ARDS [*] | 100 < PaO ₂ /FiO ₂ ≤ 200 with PEEP ≥ 5 cm H ₂ O | | |
| Severe ARDS [*] | PaO ₂ /FiO ₂ ≤ 100 with PEEP ≥ 5 cm H ₂ O | | |

^{*}At altitudes exceeding 1000 m, PaO₂/FiO₂ should be adjusted for local barometric pressure (PaO₂/FiO₂) × (barometric pressure/760).

^{**}Objective assessment such as echocardiography is needed to exclude hydrostatic edema in the absence of specific risk factor(s).

[†]Noninvasive positive pressure ventilation may be provided in mild ARDS.

^{††}Full face mask bilevel ventilation or CPAP ≥ 5 cm H₂O. No severity stratification for pARDS diagnosed in patients on noninvasive ventilatory support. If SpO₂/FiO₂ is used to quantify the degree of oxygenation impairment, FiO₂ should be titrated to keep SpO₂ 88%-97%.

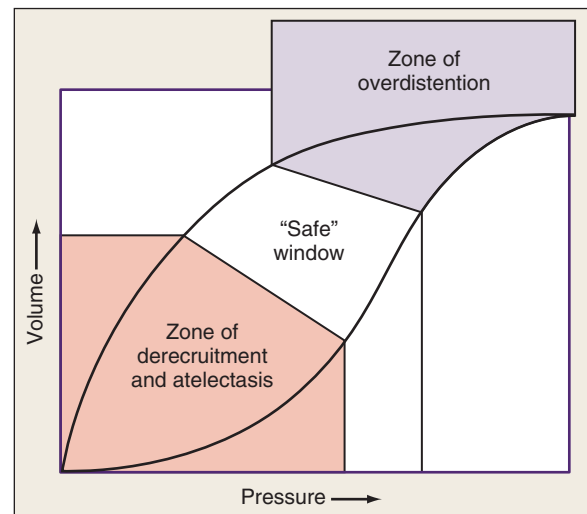
[‡]Diagnostic criteria exclude infants and children with perinatally related lung disease.

[§]Oxygenation index (OI) = 100 × (FiO₂ × mean airway pressure)/PaO₂; oxygen saturation index (OSI) = 100 × (FiO₂ × mean airway pressure)/SpO₂. If OSI is used to quantify the degree of oxygenation impairment, FiO₂ should be titrated to keep SpO₂ 88%-97%. Children with cyanotic congenital heart disease and those with chronic lung disease and dependence on invasive mechanical ventilation should not be stratified into pARDS severity groups.

Adapted from Ranieri M, et al., JAMA 2012;307:2526-2533 and Pediatric Acute Respiratory Distress Syndrome: Consensus Recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med* 2015 (16) DOI 10.1097.

application of this technique in children with alveolar disease.^{134,135} In one study, noninvasive bilevel positive airway pressure was used to support pediatric patients with pneumonia, acute chest syndrome and sickle-cell disease, underlying chronic hypoventilation syndromes, and postoperative hypoventilation with atelectasis.¹³⁴ The authors reported favorable changes in respiratory rate, heart rate, and oxygenation among all patients receiving noninvasive support, and 91% of respiratory failure episodes in their study were reversed without the need for intubation.¹³⁴

When noninvasive techniques are not appropriate or have failed, tracheal intubation is warranted. It is established that mechanical ventilation can have a profound influence on the course of disease and on the overall clinical outcome.^{77,136-139} Chief among these is the landmark multicenter study conducted by the ARDS Network (ARDSnet) investigators, which established that ALI/ARDS patients randomized to receive tidal volumes of 6 cc/kg ideal body weight had a mortality reduction of 22% relative to those who received ventilation using "traditional" tidal volumes of 12 cc/kg ideal body weight.⁷⁷ This trial also demonstrated a greater reduction in plasma levels of the pro-inflammatory cytokine interleukin-6 among those patients randomized to receive lower tidal volumes, suggesting that reducing the magnitude of phasic stretch during mechanical ventilation can actually attenuate the systemic inflammatory response. Over the past decade, much attention has been given to the provision of "lung-protective" mechanical ventilation in patients with ALI/ARDS. Lung-protective ventilation involves (1) the preservation of end-expiratory lung volume by judicious use of PEEP in order to minimize atelectrauma; (2) the minimization of cyclic stretch; and (3) the avoidance of parenchymal overdistention at end inspiration by limiting tidal volume and transpulmonary pressure (Fig. 77-6).^{77,136-139} Consensus recommendations recently issued by the PALICC group call for limiting tidal volumes to 3 to 6 mL/kg predicted body weight for infants and children with the most impaired pulmonary compliance and maintaining pH between 7.15 and 7.30. More "physiologic" tidal volumes (5 to 8 mL/kg predicted body weight) are allowed for those with more favorable compliance, provided the inspiratory plateau pressure remains 28 to 32 cm H₂O or less.¹³⁰

**FIGURE 77-6 ■ Pressure-volume relationships in acute lung injury.**

The lower curve shows the pressure-volume relationships during inspiration. The upper curve shows the pressure-volume relationships during exhalation. Note that during exhalation (as compared to inspiration), larger lung volumes can be maintained at lower transpulmonary pressures. Combining moderate to high end-expiratory pressures with small tidal volumes minimizes the potential for cyclic derecruitment (lower left) and overdistention (upper right). (From Froese AB. High-frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time! *Crit Care Med* 1997;25:906-908.)

When oxygenation failure is refractory to noninjurious strategies of conventional ventilation, HFOV is an alternative modality with a long history of use in the pediatric population. During HFOV, lung recruitment is maintained by application of a relatively high mean airway pressure with superimposed pressure oscillations at a frequency

of 3 to 15 Hz.¹³⁹ Because maximal recruitment is maintained throughout the respiratory cycle and ventilation is achieved using very small phasic changes in pressure and volume, this technique allows the lung to be ventilated above the critical opening pressure of injured lung units while avoiding end-inspiratory overdistention of more compliant lung units (see Fig. 77-3).¹⁴⁰⁻¹⁴² This “open lung” strategy of mechanical ventilation can capitalize on pulmonary hysteresis in order to achieve satisfactory gas exchange at lower alveolar pressures (see Fig. 77-3). In 1994, a prospective multicenter, randomized clinical study compared HFOV and conventional mechanical ventilation in pediatric patients with diffuse alveolar disease or air leak syndromes.¹⁴³ Patients in the HFOV arm showed rapid and sustained improvements in oxygenation without suffering adverse effects on ventilation.¹⁴³ Ultimately these patients showed a decreased incidence of ventilator-associated lung injury as evidenced by a decreased need for supplemental oxygen at 30 days and demonstrated improved outcomes compared to their cohorts in the conventional arm, particularly when HFOV was instituted within 72 hours of intubation.¹⁴³ The oxygenation index (OI), defined as $(\text{mean airway pressure} \times \text{FiO}_2 \times 100) / \text{PaO}_2$, used often in the pediatric literature to quantify oxygenation failure, was shown to discriminate between survivors and nonsurvivors in the first 72 hours of therapy.¹⁴³ Furthermore, the time at which changes in the OI were found to occur seemed to influence the likelihood of survival: an OI equal to or more than 42 at 24 hours predicted mortality with an odds ratio of 20.8, a sensitivity of 62%, and a specificity of 93%.¹⁴³ In the time since this study was published, other investigators have helped to establish that the OI seems to be a time-sensitive predictor of survival in patients with hypoxic respiratory failure and that OI trends can be used to facilitate decisions about the need for extracorporeal support in patients with acute hypoxic respiratory failure.¹²²

There has been a recent tempering of enthusiasm for offering HFOV to adult ARDS patients, after two recent large-scale multicenter clinical trials involving a total of 1343 patients were unable to demonstrate a mortality benefit from HFOV in this population.^{144,145} The Oscillation for Acute Respiratory Distress Syndrome Treated Early (“OSCILLATE”) trial¹⁴⁴ enrolled patients within 72 hours of meeting eligibility criteria. This trial used a “maximally protective” high mean airway pressure HFOV strategy and was terminated well before reaching its goal of recruiting 1200 patients, after a planned interim analysis revealed that the HFOV group had an in-hospital mortality rate of 47% compared to 35% for the conventional ventilation group (RR for mortality with HFOV 1.33; 95% CI, 1.09-1.64; $P = 0.005$). Nearly half of the patients in each study arm had a diagnosis of sepsis. As compared to their counterparts in the control group, a significantly higher proportion of patients randomized to the HFOV group required vasoactive medications (91% vs. 84%; $P = 0.01$), neuromuscular blocking agents (83% vs. 68%; $P < 0.001$), and higher median doses of midazolam (199 mg/day [IQR 100-382] vs. 141 mg/day [IQR 68-240]; $P < 0.001$). Whether or not these data provide “definitive” information regarding the relative benefits and potential harms of HFOV, they could be pointing toward a few important insights. First, early institution of a high mean airway pressure HFOV strategy may not be advisable for patients whose underlying diagnosis (e.g., sepsis) and perceived supportive care requirements (e.g., deep sedation and neuromuscular blockade) may render them vulnerable to problematic levels of hemodynamic instability. Second, the study’s use of an HFOV management protocol that called for an initial mean airway pressure setting of 30 cm H₂O with incremental adjustment according to the FiO₂ may deserve consideration. In septic patients who are early in their clinical course, initiating HFOV at a mean airway pressure of 30 cm H₂O and adjusting upward from that point could exacerbate hemodynamic instability by creating conditions in which alveolar pressure exceeds pulmonary vascular pressure throughout the respiratory cycle. This would set the stage for increased right ventricular afterload and impaired left ventricular compliance. Ultimately, HFOV may be a technique better suited for patients with diffuse alveolar disease that is coupled with increased chest wall compliance—conditions that commonly coexist in infants and young children with ALI/ARDS.

DISEASES OF THE INTERSTITIUM

The interstitial lung diseases (ILD) in children are a diverse group of rare conditions that involve alteration of the alveolar wall, infiltration and fibrosis of the pulmonary interstitium, and loss of functional alveolar-capillary units.¹⁴⁶ The major clinical findings include abnormal gas exchange, tachypnea, and crackles, as well as the potential for both restrictive and obstructive pulmonary physiology.¹⁴⁷ In children, as in adults, the morbidity and mortality of ILD can be high,^{148,149} but the frequency distribution and prognostic implications of specific conditions appear to be very different in the two populations. Our collective sense of the prevalence of specific ILD subtypes in the pediatric population has shifted in recent years, following the publication of an international consensus statement on pediatric ILD classification (Box 77-2) and a follow-up report issued by the European Respiratory Society’s task force on chronic ILD in immunocompetent children.^{150,151} Advances in our understanding of the genetic determinants of surfactant metabolism and the development of sensitive diagnostic techniques have helped establish that inherited abnormalities of surfactant function are an important contributor to particular histologic signatures of ILD that were once classified as idiopathic (Table 77-6; Fig. 77-7).

As a group, the ILDs can be conceptualized as a diverse array of conditions arising from disordered alveolar repair following injury. The histopathologic features of the ILDs (see Table 77-6) help make clear that disruption in what would otherwise be a highly reliable program for regenerating the alveolar architecture appears to play a central role in the pathogenesis of ILD.¹⁵² Under favorable conditions, type II cells play a key role in repopulating the alveolar epithelial surface following local injury. After injury has taken place, surviving type II cells are capable of spreading over exposed basement membranes, proliferating, and even transdifferentiating into type I cells. Prolonged basement membrane exposure can alter the usual interactions between alveolar epithelial cells and mesenchymal cells, resulting in the maladaptive elaboration of cytokines, growth factors, oxidants, proteases, and antiapoptotic factors that encourage the proliferation of fibrillar collagen, elastic fibers, fibronectin, and proteoglycans.¹⁵² Nearby alveolar epithelial cells can actually translate this array of ambient molecular signals into a provocation compelling them to lose their apical-basal polarity, dissolve their intercellular adhesions, restructure their cytoskeleton, and assume a mesenchymal phenotype.^{152,153}

The highly metabolic nature of type II alveolar epithelial cells renders them vulnerable to dysfunction resulting from the cytoplasmic accumulation of mutant or dysfunctional proteins, which can be enough to overwhelm regulatory defenses and precipitate cell death.¹⁵² Surfactant synthesis and metabolism are key functions of the type II cell; the “life cycle” of surfactant is illustrated in Figure 77-7. Surfactant manufacture begins in the endoplasmic reticulum (ER), which is responsible for folding polypeptides into an appropriate geometric conformation to assure their proper function as mature proteins.

BOX 77-2

Histopathologic Classification of Pediatric Idiopathic Interstitial Pneumonias*

Idiopathic pulmonary fibrosis
Desquamative interstitial pneumonia (DIP)
Respiratory bronchitis-interstitial lung disease (RB-ILD)
Acute interstitial pneumonia
Cryptogenic organizing pneumonia†
Nonspecific interstitial pneumonia (NSIP)
Lymphoid interstitial pneumonia

*Chronic pneumonitis added as a category in 2007 by European Respiratory Society Task Force.¹⁵¹

†Previously known as *bronchiolitis obliterans organizing pneumonia*.

Adapted from Fan LL, Deterding RR, Langston C. Pediatric interstitial lung disease revisited. *Pediatr Pulmonol* 2004;38:369-378.

TABLE 77-6

Children's Interstitial Lung Disease (chILD) Network Classification Scheme for Pediatric Interstitial Lung Disease

| SUBCATEGORY | SPECIFIC DISEASE |
|--|--|
| DISORDERS MORE PREVALENT IN INFANCY | |
| Diffuse developmental disorders | Acinar dysplasia Congenital alveolar dysplasia |
| Growth abnormalities featuring deficient alveolarization | Alveolar capillary dysplasia with misalignment of pulmonary veins ACD/MPV ¹ Pulmonary hypoplasia Chronic lung disease of prematurity Lung disease related to chromosomal disorders Lung disease related to congenital heart disease |
| Conditions of uncertain etiology | Neuroendocrine cell hyperplasia of infancy (NEHI) Pulmonary interstitial glycogenolysis |
| Surfactant dysfunction disorders | Surfactant protein B (SFTPB) mutations Surfactant protein C (SFTPC) mutations ABCA3 ² mutations TTF-1/NKX2.1 mutations (?) ³ Surfactant dysfunction disorders not always with known genetic etiology |
| | Pulmonary alveolar proteinosis Chronic pneumonitis of infancy Desquamative interstitial pneumonia Nonspecific interstitial pneumonia |
| DISORDERS RELATED TO SYSTEMIC DISEASE PROCESSES | |
| | Immune-mediated connective tissue disorders Storage diseases Sarcoidosis Langerhans cell histiocytosis Malignant infiltrates |
| DISORDERS IN IMMUNOCOMPETENT HOSTS | |
| | Infectious/postinfectious processes Related to environmental agents Hypersensitivity pneumonitis; toxic inhalation Aspiration syndromes Eosinophilic pneumonia |
| DISORDERS IN IMMUNOCOMPROMISED HOSTS | |
| | Opportunistic infections Related to therapeutic intervention Related to transplantation and/or rejection Diffuse alveolar damage of unknown etiology |
| DISORDERS MIMICKING INTERSTITIAL LUNG DISEASE | |
| | Arterial hypertensive vasculopathy Congestive cardiac disease Veno-occlusive disease Lymphatic disorders |

¹Fatal course, featuring severe pulmonary hypertension in early neonatal period. Histopathologically associated with severe medial hypertrophy of branch pulmonary arteries, with dilated pulmonary veins and venules. One-third of cases demonstrate pulmonary lymphangectasia. Pulmonary capillaries are situated in splayed alveolar walls and distanced from alveolar epithelium. Associated with FOXP1 gene mutations and deletions.⁶⁷ ²ATP-binding cassette A3 transporter gene. ABCA3 has an important role in transporting surfactant phospholipids into lamellar bodies. ³Thyroid transcription factor gene/autosomal dominant inheritance. This gene has a crucial role in pulmonary branching morphogenesis, alveolar type II cell differentiation, and surfactant homeostasis. Mutations and deletions are associated with "brain-lung-thyroid syndrome," which has been associated with dysregulated surfactant protein synthesis and ABCA3 gene expression.²⁵¹

Adapted from Dishop M. Paediatric interstitial lung disease: Classification and definitions. *Paediatr Res Rev* 2011;12:230–237.

Surfactant protein C's (SP-C) polyvaline domain makes it particularly vulnerable to misfolding and aggregating into amyloid filaments.¹⁵² The C-terminal domain of its precursor molecule (pro-SP-C) mediates the folding process in a way that minimizes the tendency of the polyvaline domain to interfere with achievement of the proper SP-C protein conformation. Accordingly, mutations in the SP-C gene affecting the C-terminal domain of pro-SP-C can subvert this important adaptive function, setting the stage for cytoplasmic accumulation of aberrant protein material.¹⁵² In general, diseases causing accumulation of mutant proteins within the alveolar epithelial cell are well represented among the etiologic agents of pediatric ILD.

The Children's ILD (chILD) Research Cooperative recently proposed a novel classification scheme for pediatric ILD, based on pathologic specimens collected from 187 North American children less than 2 years of age who underwent lung biopsy between July 1999 and July 2004 for diffuse parenchymal disease.¹⁵⁶ The disease entities identified in this cohort ranged from primary congenital abnormalities of the alveolar-capillary unit, to acquired syndromes of chronic interstitial disease referable to infection, recurrent aspiration, or symptomatic cardiovascular disease (see Table 77-6).¹⁴⁶

Given the wide variety of potential etiologies in ILD, a systematic approach to the diagnostic workup is important.¹⁴⁸ While history and

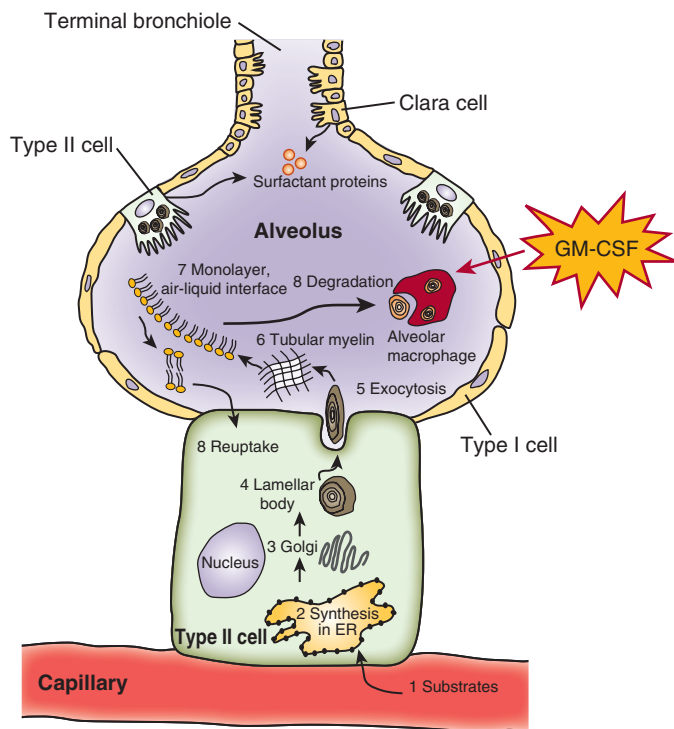


FIGURE 77-7 ■ Surfactant production and metabolism. Surfactant proteins are manufactured in alveolar type II cells and Clara cells located on terminal bronchioles. Synthetic steps taking place within alveolar type II cells are shown. Surfactant synthesis begins in the endoplasmic reticulum, is further modified in the Golgi apparatus, and its components are stored in lamellar bodies until exocytosed into the alveolar space (step 5). There, surfactant forms a lattice (known as “tubular myelin”) that is transported to form a monolayer of surfactant film at the air-liquid interface. Surfactant phospholipids are engulfed and degraded by alveolar macrophages (step 8) or are shuttled back to type II cells for recycling (step 8). GM-CSF has an important role in surfactant homeostasis. Its interaction with a specific receptor triggers alveolar macrophage maturation to a degree that is required for efficient surfactant clearance. (Adapted from Han S, Mallampalli R. The role of surfactant in lung disease and host defense against pulmonary infections. *Ann Am Thorac Soc* 2015; 12:765-774.)

physical exam have a role in the initial evaluation of children with suspected ILD, noninvasive tests such as serologies, cultures, chest radiographs, high-resolution chest CT scans, pulmonary function testing, barium swallow, pH studies, and echocardiograms will more often allow the clinician to arrive at a specific diagnosis.^{147,148} In those children in whom an etiology is still unclear, more invasive studies such as bronchoalveolar lavage, cardiac catheterization, and lung biopsy should be considered.¹⁴⁸ Results of biopsy specimens may be important to guide decision making in critically ill children who are not responding to therapy.

Therapy

As many of the etiologies for pediatric ILD may begin with an inflammatory response to lung injury, treatment of children with this condition commonly involves the use of antiinflammatory agents such as corticosteroids. A favorable response to corticosteroids among children with ILD may be evident in only 40% of cases,¹⁵⁷ and this variability may reflect the diverse potential causes of the disease. In cases where concerns about long-term administration of corticosteroids arise,

steroid-sparing antiinflammatory agents such as azathioprine, cyclophosphamide, methotrexate, cyclosporine, and intravenous gamma globulin have been used.¹⁴⁷ There is also a great deal of experience with the use of hydroxychloroquine in the management of pediatric ILD, although its use has been associated with the development of hepatic toxicity and retinopathy in children.¹⁵⁷ For patients manifesting alveolar proteinosis, many demonstrate improvement following whole lung lavage.^{158,159} In keeping with its role in promoting surfactant clearance by triggering an appropriate level of alveolar macrophage maturation¹⁶⁰ (see Fig. 77-7), granulocyte monocyte-colony stimulating factor (GM-CSF) has been administered to these patients with some success,¹⁶¹ although patients with alveolar macrophage dysfunction on the basis of circulating GM-CSF antibodies present a particular therapeutic challenge.

■ COMPLEX PARENCHYMAL DISEASES

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a term used to describe histopathologic changes in the lungs of neonates exposed to mechanical ventilation who go on to demonstrate radiologic abnormalities and supplemental oxygen dependence at 36 weeks' post menstrual age.¹⁶² Heterogeneous alveolar consolidation, squamous metaplasia of airway epithelium, hyperplasia of mucous glands, peribronchial fibrosis, airway smooth muscle hypertrophy, and vascular lesions of pulmonary hypertension typified BPD-related histopathologic changes when the disease was first described by Northway and colleagues in 1967.^{163,164} The past two decades have witnessed a shift in the histopathologic features of BPD away from cystic, metaplastic, and fibroproliferative changes toward a more uniform distribution of lung aeration across fewer, larger, and more simplified alveoli, with a concomitant impairment in the growth and development of the pulmonary microvasculature that often evolves into clinically significant pulmonary hypertension.^{165,166} Evolution of the BPD phenotype likely documents the effects from more than 20 years of widespread intratracheal surfactant administration to preterm infants, as well as a trend toward the use of lung-protective ventilatory strategies and other improvements in the supportive care of these patients. Fifteen years ago, a consensus conference refined the diagnostic criteria for BPD, reframing it as a disease with mild, moderate, or severe manifestations, depending on the intensity of respiratory support that an infant requires at the point of assessment (Table 77-7).¹⁶⁷ The revised criteria better represent the array of clinical manifestations seen in contemporary BPD and should facilitate the execution of clinical trials to identify subpopulations of infants who are likely to benefit from specific therapies. In the current era, BPD is most likely to develop in premature infants who are born at a gestational age when alveolar development is not yet complete whose birth weight ranges from below 1000 g to 1200 g.^{163,168} The National Institute of Child Health and Development (NICHD) Neonatal Research Network recently assembled a cohort of 9575 infants born between 2003 and 2007 at 22 to 28 weeks' gestational age and ranging in birth weight from 401 g to 1500 g. Using the newer severity-based diagnostic criteria, the investigators found a 68% incidence of BPD in these infants.¹⁶⁹

Clinically, the BPD syndrome is associated with airways hyperactivity and intermittent airway obstruction, leading to increased work of breathing, recurrent wheezing, chronic abnormalities of gas exchange, and potentially significant pulmonary hypertension.¹⁶³ Focal airway collapse consistent with tracheomalacia and/or bronchomalacia has also been documented in these infants,¹⁷⁰ and their pathogenesis in this context is not well understood. The spectrum of pathology observed in BPD patients is believed to derive from an inflammatory response to lung injury, as numerous investigations have identified mediators of inflammation in the BAL fluid of infants with chronic lung disease.¹⁷¹ Pulmonary edema from cardiogenic and noncardiogenic causes, infectious issues, and exposure to high concentrations of supplemental oxygen are other factors important in the pathogenesis

TABLE 77-7 Consensus Diagnostic Criteria for Bronchopulmonary Dysplasia (BPD)

| | | GESTATIONAL AGE | |
|---------------------------------|----------|---|--|
| | | <32 WEEKS | ≥32 WEEKS |
| Time point of assessment | | 36 weeks' post menstrual age or discharge to home* | >28 days but <56 days' postnatal age or discharge to home* |
| Supplemental oxygen requirement | | >21% for ≥28 days | >21% for ≥28 days |
| Disease severity | Mild | Breathing room air at 36 weeks' post menstrual age or at discharge* | Breathing room air by 56 days' postnatal age or at discharge* |
| | Moderate | Requires <30% oxygen at 36 weeks' post menstrual age or at discharge* | Requires <30% oxygen at 56 days' postnatal age or at discharge* |
| | Severe | Requires >30% oxygen, with or without mechanical ventilation or CPAP at 36 weeks' post menstrual age or at discharge* | Requires >30% oxygen with or without mechanical ventilation or CPAP at 56 days' postnatal age or at discharge* |

*Whichever comes first.

Adapted from Kinsella JP, Greenough A, Abman SH. Bronchopulmonary dysplasia. *Lancet* 2006;367:1421–1431.

of BPD. Premature infants may be at special risk from exposure to high concentrations of supplemental oxygen because they are deficient in the antiproteases and antioxidant enzymes that have a role in modulating the injurious effects from the proliferation of reactive oxygen species.¹⁶²

While our present understanding of the pathogenesis of chronic lung injury in the neonate mirrors what has been learned from older children and adults, it is also important to recognize that in preterm infants, perinatally or postnatally acquired inflammatory lung injury takes place against a background of disrupted alveolar development. This is a key distinction between BPD and ARDS or acute lung injury that develops in mature infants and older children and likely accounts for the persistence of pulmonary morbidity in the BPD population into early adolescence.¹⁶⁶ In any event, preterm neonates with respiratory failure may be especially susceptible to ventilator-associated lung injury because surfactant deficiency, high chest wall compliance, and a dynamic FRC that is near closing capacity in this age group may potentiate cycles of derecruitment and reinflation that have been shown to promote the development of lung injury in humans and animal models, including surfactant-deficient preterm animals.^{136–138,172,173} Mechanical ventilatory techniques aiming to promote alveolar recruitment and maintain lung volume have in fact decreased the incidence of ventilator-associated lung injury in neonates. Numerous large prospective RCTs have found a lower incidence of chronic lung disease among high-risk infants supported with HFOV compared to cohorts who are supported with conventional phasic ventilation, with no apparent increase in the development of intracranial hemorrhage or other significant morbidities.^{174–176} A growing appreciation of the role of invasive mechanical ventilation in the pathogenesis of BPD has also created interest in whether the need for mechanical ventilatory support may be obviated through the strategic use of CPAP immediately after birth.^{177–180} The first studies showed that early initiation of CPAP and modest reductions of target oxygen saturations (91%–94%) could reduce the incidence of BPD.¹⁸¹ In a follow-up of this study, the NICHD Neonatal Research Network carried out an RCT involving 1316 neonates born at 24 to 28 weeks' gestational age.^{182,183} Using a 2 × 2 factorial design, the investigators compared (1) immediate intubation and surfactant administration against initiation of CPAP in the delivery room, allowing surfactant administration only for infants meeting predetermined criteria; and (2) target oxygen saturations of 85% to 89% against saturations of 91% to 95%. The first comparison tested the hypothesis that infants managed with early CPAP administration and adherence to a limited ventilation protocol would have a reduction in the incidence of BPD or death. The second tested the hypothesis that infants managed using a lower target saturation range would have a reduction in the incidence of severe retinopathy of prematurity or death. There were no significant differences between groups with respect to the first comparison, the rate of death or

development of BPD (defined as a supplemental oxygen requirement persisting to 36 weeks' corrected gestational age). Remarkably, 33% of infants in the early CPAP arm never received surfactant.¹⁸² Examining the impact of low versus high target saturations, the investigators found no difference between the groups in the composite primary outcome (rates of death or development of severe retinopathy). The incidence of BPD was also comparable between groups. However, while severe retinopathy developed less frequently among survivors in the low saturation group (8.6% vs. 17.9%; $P < 0.001$), death before discharge occurred more commonly among infants in this group (19.9% of the lower saturation group compared to 16.2% in the higher saturation group; $P = 0.04$).¹⁸³ While these results challenge the paradigm that intubation, surfactant administration, and commitment to a longer course of invasive ventilation are required elements of supportive care in preterm infants, they also raise an important note of caution that pursuing a strategy of moderate “permissive hypoxemia” does not appear to impact the incidence of BPD and may in fact reduce the incidence of severe retinopathy of prematurity at the expense of higher mortality.¹⁸³

Therapy

In the past 10 years, methylxanthines have emerged as having a potentially important role in the prevention of BPD. A large, multicenter RCT found that 36% of 963 very low-birth-weight infants who received caffeine in the first 10 days of life remained dependent on supplemental oxygen at 36 weeks postmenstrual age, compared to 47% in the placebo group ($P < 0.001$).¹⁸⁴ Positive pressure respiratory support was also discontinued 1 week earlier in the intervention group ($P > 0.001$). For those infants in whom BPD cannot be prevented, medications that may be useful in producing short-term improvements in their pulmonary mechanics include bronchodilators, corticosteroids, and diuretics.^{162,163,185} Aerosolized β agonists may be useful in the management of smooth-muscle mediated bronchospasm in infants with chronic lung disease, but the consequent decrease in airway smooth muscle tone may aggravate airway collapse in infants with tracheomalacia or bronchomalacia.¹⁷⁰ Diuretics may be especially helpful in the management of these infants because many demonstrate a tendency to accumulate fluid in the pulmonary interstitium on the basis of alterations in pulmonary vascular resistance, plasma oncotic pressure, capillary permeability, and impaired lymphatic drainage.¹⁷¹ Judicious use of diuretics can also facilitate the delivery of adequate nutrition to the infant with chronic lung disease.¹⁷¹ Inhaled nitric oxide (iNO) has also been studied for its potential role in treating refractory hypoxemia in infants with chronic lung disease. Case series have documented improvements in oxygenation with the use of iNO, even including infants with intercurrent infection, with a sustained response reported in some patients.^{186,187} Sildenafil (Revatio®, Pfizer, Inc., New York, NY) is an oral preparation that has been used for years as an off-label

adjunct therapy for managing BPD-related pulmonary hypertension. This drug selectively inhibits phosphodiesterase type 5, allowing the circulation of increased amounts of cyclic guanosine monophosphate, the second messenger in the molecular signaling cascade that triggers NO-induced vasorelaxation. Results from a 16-week clinical trial examining the use of sildenafil in treatment in naïve children aged 1 to 17 years pulmonary arterial hypertension ("STARTS-1")¹⁸⁸ aroused concerns that lower sildenafil doses did not show efficacy in improving exercise duration. As well, data emerging from the follow-up study suggested that children taking a higher dose of sildenafil may have a higher risk of death than those taking a lower dose.¹⁸⁹ In 2014, the FDA issued a recommendation on the matter, advising clinicians who remain inclined to offer sildenafil for treatment of children with PAH to consider whether the benefits of treatment outweigh its possible risks, on a case-by-case basis.^{191,192}

Lower respiratory tract infection is one of the most common reasons for hospital readmission in the first year of life for infants with BPD and accounts for a significant fraction of these pulmonary exacerbations.¹⁶⁸ Other potential causes for BPD exacerbations include aspiration syndromes, worsening pulmonary hypertension, and the evolution of clinically important systemic-to-pulmonary collateral vessels.¹⁶³ Therefore, the diagnostic approach to infants with BPD who demonstrate unexplained deterioration may include dynamic airway studies as well as echocardiography and, in certain cases, cardiac catheterization.¹⁶³ Treatment of these episodes is supportive and often includes empiric antibiotic coverage for potential infectious causes.

Congenital Diaphragmatic Hernia

Management of infants with congenital diaphragmatic hernia (CDH) is one of the greatest clinical challenge that the ICU clinician encounters. The Bochdalek hernia is the most common form and occurs when abdominal contents herniate into the thoracic cavity through a posterolateral diaphragmatic defect, usually at around the 10th week of gestation. This phase of gestation concurrently includes the branching of bronchi and pulmonary arteries, and this crucial process may be interrupted by the growing mass of herniated viscera.¹⁹³ On the other hand, the discovery that administering the teratogen nitrofen to midgestation rats results in diaphragmatic defects in the developing fetus as well as a spectrum of anomalies in other organ systems similar to what is seen in humans with CDH suggests that the pathogenesis of this syndrome may originate from fetal exposure to an agent that causes generalized maldevelopment from that point forward.¹⁹⁴⁻¹⁹⁷ Small animal models of CDH have since demonstrated that nitrofen disrupts fetal lung development by reducing fetal trophoblastic expression of retinol binding protein and transthyretin, proteins responsible for ushering maternal retinol into the fetal circulation, where it plays an important role in organ morphogenesis.¹⁹⁸

The complex pathology associated with CDH in humans includes a hypoplastic and abnormally muscularized pulmonary arterial tree.¹⁹³ Other congenital anomalies are associated with CDH in up to 39% of cases. Congenital cardiac disease is the most commonly associated feature and most frequently involves some degree of cardiac hypoplasia, although a wide variety of structural cardiac anomalies may be associated with CDH.¹⁹⁹ Genitourinary, gastrointestinal, neurologic, and skeletal defects are also commonly described.¹⁹³ Adjunct medical therapies have not managed to improve the survival of these infants, whose mortality rate is traditionally reported in the range of 50%. Nonetheless, there are experienced centers reporting more encouraging results in recent years by adopting strategic forms of mechanical support in these patients that incorporate much of what has been learned about modulating the pulmonary and hemodynamic consequences of mechanical ventilation.

Therapy

In infants with CDH, as in those with BPD, ICU management is directed at managing their lower airways disease, alveolar disease, and

abnormal pulmonary vascular reactivity. Initial medical stabilization of infants with CDH includes tracheal intubation and nasogastric decompression. It is preferable to obtain preductal (i.e., right radial) arterial access, when possible. Information from preductal blood gases should guide clinical intervention because it reflects the status of cerebral circulation. Initially, echocardiography is suggested to rule out structural cardiac disease, and it may be repeated as necessary throughout the clinical course to determine evidence of ongoing right-to-left shunting as well as estimates of right ventricular pressure and function in response to therapy.¹⁹³ iNO has been used with varying results, and a role for the drug in reducing the need for ECMO or in improving survival among these patients was not established by a large, RCT on the use of iNO in neonates with pulmonary hypertension.²⁰⁰ The evidence supporting the use of iNO in the management of infants with CDH is limited to small case series and individual case studies.²⁰¹⁻²⁰³ In CDH, as in BPD, deficient alveolar development may explain the limited potential benefit from iNO.¹⁸⁷ A limited number of reports have addressed the possibility of targeting an array of potential mechanisms behind pulmonary hypertension in CDH, including interference with calcium-mediated platelet activation and vasoconstriction (prostaglandin analogues), inhibition of endothelin-mediated vasoconstriction (bosentan), and inhibition of phosphodiesterase metabolism (sildenafil, milrinone), but none has been able to establish a clear outcome benefit for any of these agents in infants with this disease.²⁰⁴ At least one source has raised concern about the potential for hepatotoxicity when bosentan is used in infants.²⁰⁵

Recommendations for the optimal timing of surgical repair in infants with CDH have evolved over time. It was once considered appropriate to refer these infants for immediate repair. Growing experience with the mechanical support of CDH patients, along with the observation that pulmonary vascular resistance and reactivity as well as pulmonary compliance often become more favorable within days after birth, have since created a trend toward delaying surgical repair until a satisfactory level of physiologic stability can be achieved.^{193,206}

Mechanical Ventilation

Given what is presently known about ventilator-associated lung injury, it is logical to apply lung-protective ventilation strategies to infants with chronic lung disease as well as to infants with CDH. Although the technique has not been traditionally applied to neonates, permissive hypercapnia is in fact well tolerated by most infants with these conditions.²⁰⁷⁻²⁰⁹ Because of the heterogeneity of airspace involvement in BPD and CDH, regional hyperinflation can easily occur. Therefore, it makes sense to maintain end-expiratory lung volume with a careful titration of PEEP and limit tidal volume to 4 to 6 cc/kg in order to ventilate at the area of maximal compliance on the pressure-volume curve.²¹⁰ While managing these patients, monitoring of tidal volume at the endotracheal tube is important because compressible volume losses in the ventilator circuit can be significant. Judicious use of sedation and the use of spontaneous ventilation (such as flow-triggered pressure support) may improve matching of ventilation to perfusion and may allow optimal patient-ventilator synchrony.

A review of infants with CDH revealed a significant increase in survival from 44% to 69% during the period in which permissive hypercapnia was used to manage these infants, with even higher survival rates noted in infants without coexisting heart disease (Table 77-8).²¹¹ Neither the introduction of ECMO nor delaying surgical repair was associated with significant increases in survival in this single-center historic experience.²¹¹ Other case series have also reported favorable results using kinder and gentler ventilatory strategies, rather than more aggressive techniques that attempt to control pulmonary vascular resistance.^{206,212,213} These observations suggest that ventilator-associated lung injury contributes to excess mortality in infants with CDH,^{206,211} and it is possible that a survival benefit attributable to ECMO may emerge as lung-sparing mechanical ventilation is more widely applied.²¹¹ At least one single-center experience

TABLE 77-8

Therapeutic History and Outcomes for Congenital Diaphragmatic Hernia, Children's Hospital, Boston

| YEAR | ECMO | SURGERY | VENTILATION | PARALYSIS | ANALGESIA | MONITORING | SURVIVAL, ISOLATED CDH | | |
|----------------|--------|-----------|------------------------|-----------|--------------------|------------|------------------------|------|---------|
| | | | | | | | ECMO | CMV* | OVERALL |
| 1981-84 | N/A | Immediate | Hyper | Yes | High-dose fentanyl | Postductal | N/A | 73% | 73% |
| 1984-87 | Postop | Immediate | Hyper | Yes | High-dose fentanyl | Postductal | 50% | 67% | 61% |
| 1987-91 | Preop | Delayed | Hyper | Yes | High-dose fentanyl | Postductal | 48% | 80% | 57% |
| 1991-94 | Preop | Delayed | Permissive hypercapnia | No | Epidural | Preductal | 71% | 100% | 84% |
| <i>P</i> value | | | | | | | NS | 0.02 | 0.02 |

*Conventional mechanical ventilation.

From Wilson JM, Lund DP, Lillehei CW, Vacanti JP. Congenital diaphragmatic hernia—a tale of two cities: the Boston experience. *J Pediatr Surg* 1997;32:401–405.

suggests that epidural analgesia in the postoperative period facilitates spontaneous ventilation and may further improve pulmonary outcomes in these infants.²¹¹

Over the past decade, experience with the use of HFOV in infants with CDH has grown. For those clinicians who opt to use HFOV in this population, it is essential to understand that infants with CDH do not have inherently recruitable lungs, and attempts to improve gas exchange by applying high levels of mean airway pressure can increase the dead space fraction and may result in both lung injury and potentially dangerous elevations in pulmonary vascular resistance.²¹⁴ Therefore, centers experienced with the use of HFOV in infants with CDH generally recommend trying to limit the mean airway pressure to 16 cm H₂O or less.²¹⁴ The Hospital for Sick Children in Toronto has developed an HFOV protocol for infants with CDH that emphasizes maintaining a preductal SaO₂ of less than 85%, tolerating hypercarbia with a compensated pH, and initiation of HFOV when the peak inspiratory pressure on conventional ventilation exceeds 25 cm H₂O. Since implementing this set of guidelines in 1995, they have reported improvement in the survival of CDH infants.²¹⁴

WEANING THE PEDIATRIC PATIENT FROM MECHANICAL VENTILATION

Although it is clear that it is best to discontinue mechanical ventilatory support as soon as this is feasible, a great deal of controversy surrounds ventilator mode selection, the pace of weaning, and timing of separation from mechanical support in children. In the largest pediatric study presently available in the literature, the use of specific weaning modes and ventilator weaning protocols was evaluated against standard care (no defined ventilator weaning protocol) for mechanically ventilated infants and children.²¹⁵ Patients with alveolar disease as well as lower airways disease were included, while those less than 2 years of age with status asthmaticus and those with CDH were excluded. In this study, 182 intubated, spontaneously breathing children who met standardized bedside criteria for extubation readiness were randomized to the protocolized application of pressure support ventilation (PSV), volume support ventilation (VSV), or no protocol.²¹⁵ There were no significant differences among the three treatment groups in extubation failure rates, and most children were weaned from the ventilator in 2 days or less.²¹⁵ In children who were successfully extubated, the median duration of ventilator weaning did not significantly differ according to the mode of ventilation.²¹⁵ Separating infants or children with complex and/or chronic pulmonary disease from mechanical ventilation is challenging and requires an appreciation of the components of pulmonary dysfunction and timely recognition of acceptable mechanics and gas exchange in spontaneously breathing patients. For example, patients with alveolar hypoplasia are expected to be tachypneic at baseline, and this complicates the use of commonly applied criteria for extubation readiness. In these cases, weaning from mechanical

ventilation can be guided by an ongoing assessment of exhaled tidal volume (measured at the airway opening), work of breathing, serum pH, and evidence of appropriate daily weight gain as pressure support is decreased.

Numerous investigators have taken an interest in whether sedation practices in patients with acute respiratory failure could represent a potentially modifiable risk for extended dependence on mechanical ventilatory support. Studies carried out in adults have associated “dynamically managed” patient sedation protocols that seek to maintain a minimally sedated, spontaneously breathing patient with reductions in the duration of mechanical ventilation.²¹⁶⁻²²⁰ The recently published Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) trial evaluated whether a goal-directed, nurse-controlled sedation protocol would reduce the duration of mechanical ventilation in infants and children with acute respiratory failure.²²¹ This was a cluster randomized trial in which 31 participating U.S. PICUs were randomly designated as “intervention” sites, where sedation practices were strictly protocolized, or “usual care” sites (the control condition), where sedation practices and extubation readiness assessment remained discretionary. The trial enrolled 2449 children from 2 weeks to 17 years of age requiring invasive mechanical ventilation for acute airway and/or parenchymal disease. Intervention sites used a management protocol consisting of targeted sedation, routine arousal assessment, dynamic sedation titration, and extubation readiness testing. The study found no difference between the two PICU groups in the primary outcome, duration of mechanical ventilation (median 6.5 days [IQR 4.1–11.2 days] in intervention PICUs vs. median 6.5 [IQR 3.7–12.1 days] in control PICUs). The number of adverse events attributable to sedation practices (inadequate pain or sedation management, significant iatrogenic withdrawal, unplanned extubation or invasive line removal) was comparable in the two groups. Long-term follow-up is forthcoming.

CONCLUSION

A fundamental understanding of age-specific diagnostic and treatment considerations is required when caring for pediatric patients with pulmonary disease. Although the capacity for physiologic compensation in infants and children is remarkably efficient, they are also prone to sudden and profound clinical deterioration, warranting the application of sophisticated supportive measures in the ICU. In recent years, work in the laboratory as well as the clinical arena has brought about an appreciation that in airway disease, alveolar disease, and complex conditions such as BPD and CDH, gentler strategies of mechanical ventilation may have a central role in improving functional outcomes. Thoughtful application of therapies proven to reverse pulmonary pathophysiology while promoting spontaneous ventilation as much as possible is likely to enhance already favorable survival statistics for even the most critically ill pediatric patients.

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Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342(18):1301-1308.

Landmark multicenter trial showing that in adult patients with ALI and ARDS ($PaO_2/FiO_2 \leq 300$), mechanical ventilation limiting tidal volumes to 6 cc/kg ideal body weight and plateau pressure ≤ 30 cm H₂O results in decreased mortality and more ventilator-free days when compared with tidal volumes of 12 cc/kg ideal body weight and plateau pressure ≤ 50 cm H₂O.

Courtney SE, Durand DJ, Asselin JM, Hudak ML, Aschner JL, Shoemaker CT. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. *N Engl J Med* 2002;347(9):643-652.

Large multicenter, well-controlled trial demonstrating significant benefit of HFOV compared to conventional ventilation in very low-birth-weight infants. Infants who received HFOV were successfully extubated earlier and were more likely to survive without need for supplemental oxygen at 36 weeks' postmenstrual age. No increase was observed in the occurrence of intracranial hemorrhage or other complications referable to prematurity.

Curley MA, Wypij D, Watson RS, Grant MJ, Asaro LA, Cheifetz IM, Dodson BL, Franck LS, Gedeit RG, Angus DC, et al: Protocolized sedation vs. usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. *JAMA* 2015;313(4):379-389.

Multicenter cluster randomized trial in which 31 U.S. PICUs were randomly designated as "intervention sites" where a goal-directed, nurse-controlled sedation protocol was implemented for mechanically ventilated patients, or "usual care" sites, where sedation and extubation readiness assessment practices remained discretionary. The study found no differences between the two PICU groups in the primary outcome, the median number of days on mechanical ventilation. The number of adverse events attributable to sedation practices was comparable in the two groups. Long-term

follow-up assessing emotional outcomes and health care resource use in the two study arms will be forthcoming.

Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, Zhou Q, Matte A, Walter SD, Lamontagne F, et al: High-frequency oscillation in early acute respiratory distress syndrome ["OSCILLATE"]. *N Engl J Med* 2013; 368(9):795-805.

Multicenter, randomized controlled early intervention trial that enrolled 548 adult patients within 72 hours of meeting clinical criteria for moderate-severe ARDS to either HFOV (experimental condition) or conventional ventilation targeting a tidal volume of 6 cc/kg ideal body weight, plateau pressure ≤ 35 cm H₂O, and high PEEP (control condition). For patients randomized to HFOV, the initial mean airway pressure setting was 30 cm H₂O regardless of the mean airway pressure they required on conventional ventilation. Mean airway pressure was thereafter adjusted according to FiO_2 . To minimize tidal volume on HFOV, the maintenance frequency setting was the highest level that would allow arterial pH > 7.25 . Nearly half of the patients in each study arm had sepsis. This study was terminated early, after a planned interim analysis revealed that the HFOV group had an in-hospital mortality rate of 47% compared to 35% in the control group. As compared to their counterparts in the control arm, a significantly higher proportion of patients randomized to the HFOV group required vasoactive medications, neuromuscular blocking agents, and higher median doses of midazolam during the first week of the trial.

The Neonatal Inhaled Nitric Oxide Study Group (NINOS). Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. *Pediatrics* 1997;99(6):838-845.

Multicenter trial in which infants with isolated congenital diaphragmatic hernia and hypoxic respiratory failure were randomized to receive inhaled nitric oxide or 100% oxygen. The study was unable to show a survival benefit or reduction in need for extracorporeal membrane oxygenation among those infants who received nitric oxide.

■ References for this chapter can be found at expertconsult.com.

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DEFINITION AND CLINICAL MANIFESTATIONS

Acute coronary syndromes account for nearly 2 million hospitalizations annually in the United States, and if patients who die before reaching the hospital are included, the mortality may be as high as 25%. Acute coronary syndromes are a family of disorders that share similar pathogenic mechanisms and represent different points along a common continuum. They include ST elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), and unstable angina (UA) pectoris. The common link among the various acute coronary syndromes is the rupture of a vulnerable, but previously quiescent, coronary atherosclerotic plaque. Exposure of the plaque contents to the circulating blood pool triggers the release of vasoactive substances and activation of platelets as well as the coagulation cascade. The extent of resultant platelet aggregation, thrombosis, vasoconstriction, and microembolization dictates the clinical manifestations of the syndrome.

Acute coronary syndromes have traditionally been classified into Q-wave myocardial infarction, non-Q-wave myocardial infarction (NQMI), and UA. More recently, the classification has shifted and has become based on the initial electrocardiogram; patients are divided into three groups: (1) those with ST-elevation (STEMI), (2) those without ST elevation but with enzyme evidence of myocardial damage (non-ST elevation MI or NSTEMI), and (3) those with UA. Classification according to a presenting electrocardiogram coincides with current treatment strategies since patients presenting with ST elevation benefit from immediate reperfusion and should be treated with fibrinolytic therapy or urgent revascularization. In contrast, fibrinolytic agents are not effective in other patients with acute coronary syndromes.

PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES

Myocardial ischemia results from an imbalance between oxygen supply and demand and usually develops in the setting of obstructive atherosclerotic coronary artery disease, which limits the blood supply. The pathophysiology of unstable coronary syndromes and myocardial infarction (MI) usually involves a dynamic partial or complete occlusion of an epicardial coronary artery because of acute intracoronary thrombus formation.

The inciting event underlying the development of acute coronary syndromes is the rupture of an atherosclerotic plaque.¹ The possible sequelae of plaque rupture include thrombus formation with a total occlusion and with STEMI, dissolution of the thrombus, and healing of the fissure, with clinical stabilization and subtotal occlusion, which can lead to either non-STEMI or UA.

Atherosclerotic plaques are composed of a lipid core, which includes cholesterol, oxidized low-density lipoproteins (LDLs), macrophages, and smooth muscle cells, covered by a fibrous cap. Plaque rupture occurs when external mechanical forces exceed the tensile strength of the fibrous cap. After plaque rupture, the clinical consequences depend largely on the balance between prothrombotic and antithrombotic forces.^{2,3} The lipid core contains tissue factors and other thrombogenic materials that lead to platelet activation and aggregation. Fibrinolytic

factors, such as tissue plasminogen activator, prostacyclin, and nitric oxide, act to counteract the potential for thrombosis. A major factor in the outcome of plaque rupture is blood flow. With a subtotal occlusion, high-grade stenosis, or vasospasm, a thrombus begins to propagate downstream in the arterial lumen. In contrast to the initial thrombi that are platelet rich, these thrombi contain large numbers of red cells enmeshed in a web of fibrin. The former would be expected to respond best to antiplatelet therapy and the latter to antithrombotic and fibrinolytic therapy.

STEMI

Epidemiology

STEMI comprises approximately 25% to 40% of MI presentations. In-hospital mortality and 1-year mortality rates from STEMI have decreased significantly with improvements in reperfusion therapy and guideline-directed medical therapy (GDMT); current in-hospital mortality can be as low as 4% to 6%, and 1-year mortality ranges from 7% to 18%.^{4,5} Nonetheless, not all eligible patients with STEMI receive reperfusion therapy; registry data from 2004 to 2006 estimated a miss rate of 7%, with the majority of those patients being elderly. Women, diabetics, and patients with renal disease appear to have worse outcomes when presenting with STEMI. Approximately 23% of patients with STEMI in the United States have diabetes mellitus, and three-fourths of all deaths among patients with diabetes mellitus are related to coronary artery disease. Patients with chronic renal disease, particularly those on dialysis, are less likely to receive GDMT; only 45% of eligible patients on dialysis received reperfusion therapy, and only 70% received aspirin on admission. At discharge, only 67% of patients on dialysis were prescribed aspirin, and only 57% were prescribed beta blockers.^{5,6} Women and patients on dialysis tend to have higher bleeding complications associated with antithrombotic therapy.^{6,7}

Diagnosis and Treatment of STEMI

Symptoms suggestive of MI may be similar to those of ordinary angina but are usually greater in intensity and duration. Nausea, vomiting, and diaphoresis may be prominent features, and malaise and even stupor attributable to low cardiac output can occur. Compromised left ventricular function may result in pulmonary edema with the development of pulmonary bibasilar crackles and jugular venous distention; a fourth heart sound can be present with small infarcts or even mild ischemia, but a third heart sound is usually indicative of more extensive damage.

A consensus group to standardize the definition of MI defines the changes diagnostic of STEMI as new ST elevation at the J-point in at least two contiguous leads of ≥ 2 mm (0.2 mV) in men or ≥ 1.5 mm (0.15 mV) in women in leads V2-V3, and ≥ 1 mm (0.1 mV) in other contiguous chest leads or the limb leads.^{7,8} However, there are several circumstances in which interpreting an ECG may be difficult. A new left bundle branch block (LBBB) has been referred to as a "STEMI equivalent" and has been treated. A multicenter, longitudinal study published in 2011 challenged this notion. In that study, 36/892 (4%) patients presenting with possible ACS had an LBBB presumed to be new, and of these, only 14 of the 36 were diagnosed with ACS.⁹ Similar

SIZE OF TREATMENT EFFECT

Estimate of Certainty (Precision) of Treatment Effect

| | Class I <i>Benefit >>> Risk</i> <i>No additional studies needed</i> Procedure/Treatment SHOULD be performed/administered | Class IIa <i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i> IT IS REASONABLE to perform procedure/administer treatment | Class IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; Additional registry data would be helpful</i> IT IS NOT UNREASONABLE to perform procedure/administer treatment | Class III <i>Risk ≥ Benefit</i> <i>No additional studies needed</i> Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL |
|---|---|---|--|---|
| Level A <i>Multiple (3–5) population risk strata evaluated</i> <i>General consistency of direction and magnitude of effect</i> | <ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses | <ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses | <ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses | <ul style="list-style-type: none"> Recommendation that procedure or treatment not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses |
| Level B <i>Limited (2–3) population risk strata evaluated</i> | <ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Limited evidence from single randomized trial or non-randomized studies | <ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies | <ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or non-randomized studies | <ul style="list-style-type: none"> Recommendation that procedure or treatment not useful/effective and may be harmful Limited evidence from single randomized trial or non-randomized studies |
| Level C <i>Very limited (1–2) population risk strata evaluated</i> | <ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard-of-care | <ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard-of-care | <ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard-of-care | <ul style="list-style-type: none"> Recommendation that procedure or treatment not useful/effective and may be harmful Only expert opinion, case studies, or standard-of-care |

FIGURE 78-1 ■ Classification of recommendation and level of evidence. (From Gibbons RJ, Smith S, Antman E. American College of Cardiology/American Heart Association Clinical Practice Guidelines: Part I. C. Circulation. 2003;107:2979-2986.)

findings have been reported elsewhere.¹⁰ In the GUSTO-1 trial, of the 26,003 North American patients presenting with possible ACS, 131 (0.5%) with confirmed acute myocardial infarction had an LBBB.¹¹

Patients presenting with suspected myocardial ischemia should undergo a rapid evaluation, continuous monitoring, and reassessment. The 2013 ACCF/AHA Guidelines for the Management of ST-Elevation Myocardial Infarction emphasize the importance of choosing some type of reperfusion therapy as soon as possible when appropriate (Fig. 78-1). In addition to conventional antiplatelet therapy, an early decision to perform percutaneous coronary intervention (PCI), transfer to a PCI-capable facility, or administer fibrinolytic therapy should be made. The previous 2004 guidelines statement still holds: “the appropriate and timely use of some form of reperfusion therapy is likely more important than the choice of therapy.”¹² The current guidelines regarding reperfusion timing and strategy are listed in Table 78-1.

The 2013 ACCF/AHA Guidelines for the Management of STEMI emphasize the importance of early reperfusion by stating that for patients presenting to a non-PCI-capable hospital, every effort should be made to get that patient to a PCI-capable hospital within 120 minutes of first medical contact (FMC). In addition, EMS transport directly to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI, with an ideal FMC-to-device-time system goal of 90 minutes or less. See Figure 78-2 for the management of patients with STEMI who are candidates for reperfusion therapy.

Fibrinolytic Therapy

Early reperfusion of an occluded coronary artery is indicated for all eligible candidates. Overwhelming evidence from multiple clinical trials demonstrates the ability of fibrinolytic agents administered early in the course of an acute MI to reduce infarct size, preserve left ventricular function, and reduce short-term and long-term mortality.¹³⁻¹⁵ Patients treated early derive the most benefit.¹⁵ Fibrinolytics should be

TABLE 78-1

Strategy and Timing of Reperfusion Therapy for STEMI

| RECOMMENDATION | COR | LOE |
|--|-----|-----|
| Reperfusion therapy should be administered to all eligible patients with STEMI with symptom onset within the prior 12 hours | I | A |
| Primary PCI is the recommended method of reperfusion when it can be performed in a timely fashion by experienced operators | I | A |
| In the absence of contraindications, fibrinolytic therapy should be administered to patients with STEMI at non-PCI-capable hospitals when the anticipated first medical contact-to-device time at a PCI-capable hospital exceeds 120 minutes because of unavoidable delays | I | B |
| When fibrinolytic therapy is indicated or chosen as the primary reperfusion strategy, it should be administered within 30 minutes of hospital arrival | I | B |

Adapted from O’Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA Guidelines for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:e362-e425.

PCI, percutaneous coronary intervention; COR, class of recommendation; LOE, level of evidence.

considered within the first 12 hours of symptom onset when it is anticipated that primary PCI cannot be performed within 120 minutes from the FMC.⁶

Indications for and contraindications to fibrinolytic therapy are listed in Table 78-2. Because of the small, but nonetheless significant, risk of a bleeding complication (most notably, intracranial hemorrhage), the selection of patients with acute MI for the administration

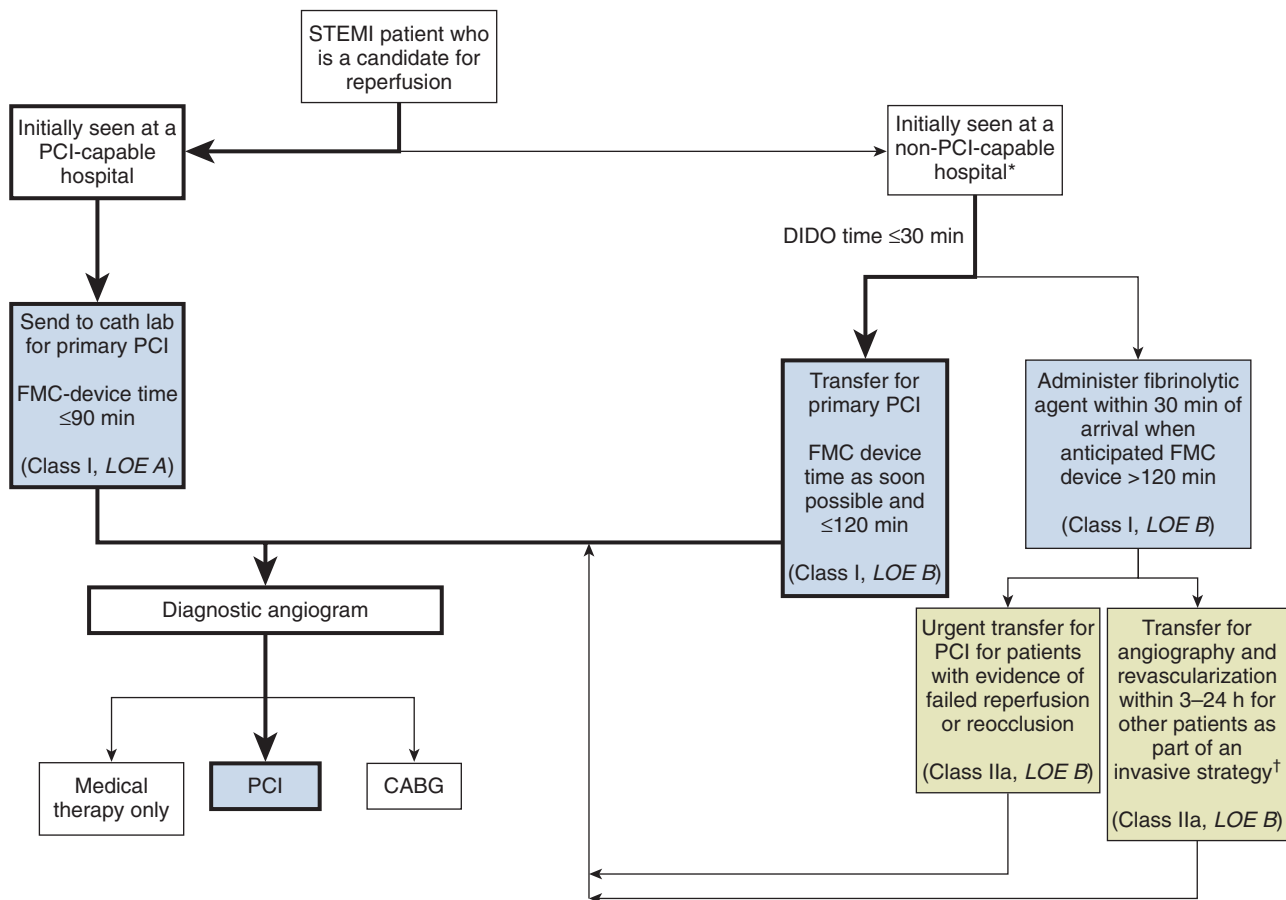


FIGURE 78-2 ■ Reperfusion therapy for patients with STEMI. (O’Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guidelines for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362-e425-27.)

of a fibrinolytic agent should be undertaken with prudence and caution. This is of special importance in ICU patients, who may have a predisposition to bleeding complications because of multiple factors. In this setting, emergent coronary angiography (with PCI as clinically indicated) is usually preferable.

Commonly administered fibrinolytics include the fibrin-specific agents tenecteplase, reteplase, and alteplase; the nonfibrin specific agent streptokinase is infrequently used. After the administration of fibrinolytics for STEMI, the patient should be monitored for signs and symptoms of adequate reperfusion, as indicated by relief of symptoms and/or hemodynamic/electrical instability coupled with the resolution of the highest initial ST elevation (preferably 50%, but at least some).^{16,17} Complete (or near complete) ST segment resolution at 60 or 90 minutes after fibrinolytic therapy is a useful marker of a patent infarct artery.¹⁸⁻²⁰ If signs of adequate reperfusion are not evident within 90 minutes (“failed fibrinolysis”), patients should be urgently transferred to a PCI-capable facility.⁶ Patients with STEMI and signs of shock or severe heart failure should be immediately transferred to a PCI-capable facility irrespective of when the MI occurred or when fibrinolytics were given.²¹ Diagnostic coronary angiography and possible PCI within 3 to 24 hours after fibrinolytics are given is referred to as a pharmacoinvasive strategy and should be considered, even if there is evidence of reperfusion and the patient remains hemodynamically stable. This recommendation is supported by case-control studies and randomized controlled trials with small sample sizes that showed a reduction in death, recurrent MI, recurrent ischemia, new or worsening HF, or shock at 30 days with routine angiography compared to patients who

underwent an ischemia-guided approach to coronary angiography after fibrinolysis.²²⁻²⁴

The greatest benefit from angioplasty following fibrinolysis is seen in high-risk patients. This is likely driven by a reduction in the incidence of a recurrent infarction or ischemia.^{25,26} In contrast to the treatment of STEMI, fibrinolysis has shown no benefit and an increased risk of adverse events when used for the treatment of UA/NSTEMI.²⁷ Based on these findings, there is currently no role for fibrinolytic agents in these latter syndromes.

Primary PCI in Acute Myocardial Infarction

The major advantages of primary PCI over fibrinolytic therapy include a higher infarct artery patency, with a higher rate of normal flow, lower rates of recurrent ischemia, reinfarction, the need for emergency repeat revascularization, and a lower risk of intracranial hemorrhage.^{14,28} Coronary angiography also affords the ability to stratify risk based on the severity and distribution of coronary artery disease. Data from several randomized trials have indicated that PCI is preferable to fibrinolytic therapy for AMI patients at a higher risk.²⁸

More important than the method of revascularization is the time to revascularization and that this should be achieved in the most efficient and expeditious manner possible.²⁹ It is important to keep in mind that early, complete, and sustained reperfusion after myocardial infarction is known to decrease the 30-day mortality rate. The preferred method for reperfusion in STEMI is PCI if it can be done in a timely manner, defined as the first contact to device time of less than 90

TABLE 78-2

Indications for and Contraindications to Fibrinolytic Therapy in ST Elevation Myocardial Infarction

INDICATIONS FOR FIBRINOLYTIC THERAPY WHEN THERE IS A >120-MINUTE DELAY FROM FIRST MEDICAL CONTACT TO PRIMARY PCI

- Presentation within 12 hours of symptom onset
- Evidence of ongoing ischemia 12 to 24 hours after symptom onset, and a large area of myocardium at risk or hemodynamic instability
- Fibrinolytics are contraindicated for the treatment of ST depression (NSTEMI), except if true posterior myocardial infarction or when associated with ST elevation in lead aVR

CONTRAINDICATIONS

Absolute

- Any prior ICH
- Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
- Known malignant intracranial neoplasm (primary or metastatic)
- Ischemic stroke within 3 months (EXCEPT acute ischemic stroke within 4.5 hrs)
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed-head or facial trauma within 3 months
- Intracranial or intraspinal surgery within 2 months
- Severe uncontrolled hypertension (unresponsive to emergency therapy)
- For streptokinase, prior treatment within the previous 6 months

Relative

- History of chronic, severe, poorly controlled hypertension
- Significant hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg)
- History of prior ischemic stroke >3 mo
- Dementia
- Known intracranial pathology not covered in absolute contraindications
- Traumatic or prolonged (>10 min) CPR
- Major surgery (<3 wk)
- Recent (within 2 to 4 wk) internal bleeding
- Noncompressible vascular punctures
- Pregnancy
- Active peptic ulcer
- Oral anticoagulant therapy

CPR, cardiopulmonary resuscitation; MI, myocardial infarction; PCI, percutaneous coronary intervention.

minutes. If a patient initially presents to a non-PCI-capable hospital and door in–door out time is anticipated to be less than 30 minutes, then the transfer to a PCI-capable hospital should be arranged if the FMC to device time is anticipated to be less than or equal to 120 minutes. If the FMC to device time is longer than 120 minutes, fibrinolytics should be considered, with probable transfer to a PCI-capable facility following fibrinolytic therapy for STEMI. Practical considerations regarding transport to a PCI-capable facility should be reviewed carefully before foregoing thrombolytics for PCI. Achieving reperfusion in timely matter correlates with improvement in the ultimate infarct size, left ventricular function, and survival.^{16,17} The ultimate goal is to restore adequate blood flow through the infarct-related artery to the infarct zone, as well as to limit microvascular damage and reperfusion injury. The latter is accomplished with adjunctive and ancillary treatments that will be discussed below.

Coronary Stenting

Primary balloon angioplasty for acute myocardial infarction results in a significant reduction in mortality but is limited by the possibility of an abrupt vessel closure, recurrent in-hospital ischemia, reocclusion of the infarct-related artery, and restenosis. The use of coronary stents has been shown to reduce restenosis and adverse cardiac outcomes in both routine and high-risk PCI and has now become routine in acute coronary syndromes.³⁰ Whether to use a bare metal stent or a drug-eluting

stent in acute MI is a question that has not yet been addressed definitively by clinical trials; selection is currently based on both patient and angiographic characteristics. Restenosis rates are lower with drug-eluting stents, and with advances in technology, stent thrombosis rates are decreasing. In patients with a high bleeding risk, the inability to comply with 1 year of dual antiplatelet therapy (DAPT), or anticipated invasive or surgical procedures in the next 1 year, bare metal stents are preferred.⁶

Adjunctive Therapy to Primary PCI

Aspirin

Aspirin is the best known and the most widely used of all the antiplatelet agents because of the low cost and relatively low toxicity. Aspirin inhibits the production of thromboxane A₂ by irreversibly acetylating the serine residue of the enzyme prostaglandin H₂ synthetase. Aspirin has been shown to reduce the mortality in acute infarction to the same degree as fibrinolytic therapy, and its effects are additive to fibrinolytics.³¹ In addition, aspirin reduces the risk of reinfarction.^{32,33} Unless contraindicated, all patients with a suspected acute coronary syndrome (STEMI, NSTEMI, UA) should be given aspirin as soon as possible. A 162- to 325-mg dose should be given initially. The maintenance dose is typically 81 mg daily, and aspirin should be continued indefinitely unless contraindicated.

Adenosine Diphosphate Receptor P2Y₁₂ Blockers

P2Y₁₂ inhibitors include clopidogrel, prasugrel, and ticagrelor. A loading dose of a P2Y₁₂ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI.⁶

Clopidogrel is a pro-drug that is converted in the liver to the active thiol metabolite via the cytochrome P450 (CYP) 3A, 1A, 2B, and 2C subfamilies. The active metabolite binds irreversibly to the P2Y₁₂ component of the ADP receptor on the platelet surface, preventing the activation of the GPIIb/IIIa receptor complex and reducing platelet aggregation for the remainder of the platelet's lifespan, which is approximately 7 to 10 days. The onset of the inhibition of platelet aggregation (IPA) is dose-dependent, with a 300 to 600-mg loading dose achieving the inhibition of platelets within 2 hours. A 600-mg loading dose of clopidogrel provides more rapid platelet inhibition and is preferred to a 300-mg loading dose.³⁴

Prasugrel is a thienopyridine that irreversibly binds to the P2Y₁₂ component of the ADP receptor with a more rapid onset of action.⁴¹ Like clopidogrel, prasugrel is a prodrug metabolized to both an active and inactive metabolite, but a higher proportion is metabolized to an active metabolite, resulting in a higher level of inhibition of platelet aggregation than clopidogrel. The onset of inhibition of platelet aggregation is dose-dependent and can be achieved in less than 30 minutes with a loading dose of 60 mg, but peak effect occurs in approximately 4 hours.⁴² In the randomized, double-blind TRITON-TIMI 38 trial, patients treated with prasugrel had a significant reduction in nonfatal MI when compared to those treated with clopidogrel.⁴³ The rate of major bleeding was higher in the prasugrel group (2.4% vs. 1.8%, $P = 0.03$), as was the rate of life-threatening bleeding. A post hoc analysis of the TRITON-TIMI 38 trial identified either harm or no benefit in patients with a history of TIA or stroke (net harm), age over 75 years (no net benefit), and body weight less than 60 kg (no net benefit). The FDA has labeled a history of TIA and/or stroke as a contraindication to prasugrel use.⁴⁴

Ticagrelor is a reversible, nonthienopyridine P2Y₁₂ receptor antagonist that does not require metabolic conversion to the active drug. The PLATO trial compared ticagrelor to clopidogrel in 18,000 patients presenting with ACS, 38% of whom had a STEMI; the primary endpoint (MI, stroke, or cardiovascular death) occurred less often with ticagrelor (9.4% vs. 10.8%, $P < 0.05$), although there were more strokes and episodes of intracranial hemorrhage with ticagrelor.⁴⁵ Interestingly, ticagrelor was less effective in North America than in the rest of the world, probably due to an interaction with the aspirin maintenance dose (more patients in the United States took a median aspirin dose

≥300 mg/dL).⁴⁶ Hence, when a ticagrelor is used with aspirin as a component of dual antiplatelet therapy, the dose of aspirin should not exceed 100 mg.⁴⁷

Dual antiplatelet therapy with aspirin and P2Y₁₂ inhibition is given to all patients undergoing PCI, as described above. However, data suggest that even patients not undergoing PCI benefit from the addition of clopidogrel to aspirin.⁴⁸ On the basis of these data, patients presenting with MI should be considered for clopidogrel regardless of whether or not they underwent reperfusion therapy. Ticagrelor and prasugrel have not been evaluated in STEMI patients treated with fibrinolysis, and there is concern about the potential for increased bleeding in this patient population.⁵⁰

Glycoprotein IIb/IIIa Receptor Antagonists

Glycoprotein IIb/IIIa receptor antagonists inhibit the final common pathway of platelet aggregation, blocking the crosslinking of activated platelets, and are often used as percutaneous interventions.⁵¹⁻⁵⁴ In the era of dual antiplatelet therapy using P2Y₁₂ inhibitors and aspirin, the role of the addition of a glycoprotein IIb/IIIa inhibitor in primary angioplasty for STEMI is uncertain. “Upstream” (prior to PCI) use of a GP IIb/IIIa receptor antagonist has failed to show benefit and is no longer recommended. Current guidelines suggest that when a patient with an ST elevation MI is treated with a thienopyridine and aspirin plus an anticoagulant, such as UFH or bivalirudin, the use of a glycoprotein IIb/IIIa inhibitor at the time of PCI cannot be recommended as routine but may be beneficial and is typically considered on an individual patient basis. For example, the use of a glycoprotein IIb/IIIa inhibitor at the time of PCI may be appropriate if the patient has a large thrombus burden or if there was insufficient loading with a P2Y₁₂ receptor antagonist.⁵⁵

Anticoagulants in Patients Undergoing PCI

For patients undergoing PCI who have already been treated with aspirin and a P2Y₁₂ inhibitor, both unfractionated heparin and bivalirudin are acceptable anticoagulant regimens.⁵⁵ Bivalirudin is a direct thrombin inhibitor that inhibits both clot-bound and circulating thrombin. It is an alternative to unfractionated heparin in patients with a history of heparin-induced thrombocytopenia. Previous studies have concluded that bivalirudin is at least equivalent to heparin plus a glycoprotein IIb/IIIa inhibitor in reducing ischemic events.⁶⁰⁻⁶² More recent trials which reflect contemporary practices such as DAPT use, a radial approach to PCI, and decreased use of IIb/IIIa glycoprotein inhibitors, have concluded that compared to bivalirudin, heparin reduces the incidence of major adverse ischemic events in the setting of primary PCI, with no increase in bleeding complications.⁶³ See [Table 78-3](#) for doses of antiplatelet and anticoagulant therapy for the management of STEMI.

Coronary Artery Bypass Graft (CABG) Surgery in Patients with STEMI

Subsets of patients who present with STEMI are better served with CABG. Patients with failed PCI or whose coronary anatomy is not amenable to PCI but who have ongoing symptoms of ischemia, cardiogenic shock, severe HF, or other high-risk features should be considered for CABG.⁶⁵ CABG is also recommended in patients who require not only revascularization but also the repair of a mechanical defects, such as a ventricular septal defect, free wall rupture, or papillary muscle rupture.⁶ The previously reported increased mortality in CABG patients who recently had a STEMI needs to be balanced against the need for revascularization. Consideration must be given to the timing of urgent CABG in relation to the administration of antiplatelet agents in patients with a recent STEMI. [Table 78-4](#) provides a summary of these recommendations. The risk of major bleeding and mediastinal reexploration was previously reported to be quite high in patients who had received clopidogrel 5 to 7 days before CABG. However, a 2009 trial with randomized patients to clopidogrel either continued until the day of CABG, stopped 3 days before CABG, or stopped 5 days

TABLE 78-3

Adjunctive Antiplatelet and Anticoagulant Therapy to Support Reperfusion with Primary PCI

| DRUG | DOSING | COR | LOE |
|---|--|----------|-----|
| ANTIPLATELET THERAPY | | | |
| Aspirin | 162-325 mg loading 81 mg maintenance | I | B |
| Clopidogrel | 600 mg loading 75 mg maintenance | I | B |
| Prasugrel | 60 mg loading 10 mg maintenance | I | B |
| Ticagrelor | 180 mg loading 90 mg twice a day maintenance | I | B |
| GP IIb/IIIa RECEPTOR ANTAGONISTS IN CONJUNCTION WITH UFH OR BIVALIRUDIN IN SELECTED PATIENTS | | | |
| Abciximab | 0.25-mg/kg IV bolus, then 0.125 mcg/kg/min (maximum 10 mcg/min) | IIA | A |
| Tirofiban | 25-mcg/kg IV bolus, then 0.15 mcg/kg/min CrCl < 30 mL/min, reduce infusion by 50% | IIA | B |
| Eptifibatide | 180-mcg/kg IV bolus, then 2 mcg/kg/min; a second 180-mcg/kg bolus is administered 10 min after the first bolus CrCl < 50 mL/min, reduce infusion by 50% Avoid in patients on hemodialysis | IIA | B |
| ANTICOAGULANT THERAPY | | | |
| UFH | With a GP IIb/IIIa receptor antagonist: 50 to 70-U/kg IV bolus to achieve therapeutic ACT With no GP IIb/IIIa receptor antagonist planned: 70 to 100-U/kg bolus to achieve therapeutic ACT | I | C |
| Bivalirudin | 0.75-mg/kg IV bolus, then 1.75-mg/kg/h infusion with or without prior treatment with UFH* [†] | I | B |
| Fondaparinux | Not recommended as the sole anticoagulant for primary PCI | III Harm | B |

Adapted from O’Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA Guidelines for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362-e425.

*Reduce infusion to 1 mg/kg/h with estimated CrCl < 30 mL/min.

[†]Preferred over UFH with GP IIb/IIIa receptor antagonist in patients at high risk of bleeding.

COR, class of recommendation; LOE, level of evidence.

TABLE 78-4

Timing of Urgent CABG in Patients with STEMI in Relation to the Use of Antiplatelet Agents

| DRUG | RECOMMENDATION | COR | LOE |
|---------------------------|--|-----|-----|
| Aspirin | Aspirin should not be withheld before urgent CABG | I | C |
| Clopidogrel or ticagrelor | Discontinue at least 24 hours before urgent on-pump CABG | I | B |
| Eptifibatide or tirofiban | Discontinue at least 2 to 4 hours before urgent CABG | I | B |
| Abciximab | Discontinue at least 12 hours before urgent CABG | I | B |

Adapted from O’Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA Guidelines for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362-e425.

COR, class of recommendation; LOE, level of evidence.

before CABG demonstrated a significant increase in bleeding and blood product utilization only in the group who continued clopidogrel until the day of surgery. Those whose clopidogrel was held either 3 or 5 days in advance had a similar rate of major bleeding, which was low and comparable to historical controls.⁶⁶ Retrospective, nonrandomized studies have reported similar rates of CABG-related bleeding in comparable patients receiving either clopidogrel or ticagrelor prior to surgery.⁶⁷ A subset of subjects in the TRITON-TIMI 38 studies who had CABG after STEMI as opposed to PCI had a significantly increased rate of TIMI minor and major bleeding after CABG surgery (21.9% vs. 4.1%, $P < 0.004$).⁶⁸ This should be taken into consideration when choosing a P2Y₁₂ receptor antagonist in STEMI patients who may need CABG.

Other Medical Therapies

Nitrates

Nitrates have a number of beneficial effects in acute myocardial infarction. They reduce myocardial oxygen demand by decreasing preload and afterload and may also improve myocardial oxygen supply by increasing subendocardial perfusion and collateral blood flow to the ischemic region.⁶⁹ Patients with ST elevation due to an occlusive coronary artery spasm may have a dramatic resolution of ischemia with nitrates. In addition to their hemodynamic effects, nitrates also reduce platelet aggregation. Despite these benefits, the GISSI-3 and ISIS-4 trials failed to show a significant reduction in mortality from routine acute and chronic nitrate therapy.^{70,71} Nonetheless, nitrates remain the first-line agents for the symptomatic relief of angina pectoris and when a myocardial infarction is complicated by hypertension or congestive heart failure. Nitrates should be avoided in patients with right ventricular infarct, hypotension (SBP < 90 mm Hg or if the SBP is > 30 mm Hg below baseline), or phosphodiesterase-5-inhibitor use within the previous 24 to 48 hours.

Beta Blockers

Beta blockers are beneficial both in the early management of myocardial infarction and as long-term therapy. In the prethrombolytic era, early intravenous atenolol was shown to significantly reduce reinfarction, cardiac arrest, cardiac rupture, and death.⁷² However, more recent data have shown that while the early administration of intravenous beta blockers followed by oral dosing may lower the reinfarction rate at 4 weeks, there may be an increase in the risk of developing heart failure and cardiogenic shock when compared to the placebo.⁷³ Based on these findings, routine use of intravenous beta blockers in the absence of systemic hypertension is no longer recommended.⁷⁴ However, oral beta blockers should be administered to patients within the first 24 hours of having a STEMI as long as the following conditions are not present: signs of heart failure; cardiogenic shock or a low-output state; significant AV conduction disease; or active wheezing due to reactive airway disease.⁶ Unless contraindicated, beta blockers should be continued beyond the hospitalization.

Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors

The RAAS inhibitors include angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blocker (ARB), and aldosterone antagonists.

Immediate intravenous ACE inhibition, particularly with enalaprilat, has not been shown to be beneficial,⁸⁰ but oral ACE inhibition should be started early in the hospital course. An ACE-I should be administered within the first 24 hours to all patients with a STEMI and LV dysfunction or heart failure.⁶ Possible contraindications to ACE-I use include hypotension, shock, or a history of renal failure or hyperkalemia with ACE-I or ARB use. Baseline renal function should be taken into consideration when initiating an ACE or and ARB, but renal failure is not an absolute contraindication to their use. Patients should be started on low doses of oral agents and titrated to maximally tolerated doses. STEMI patients who are intolerant to

an ACE-I should be given an ARB. In particular, valsartan has been shown to be noninferior to captopril in the VALIANT (Valsartan in Acute Myocardial Infarction) trial.⁸¹ Aldosterone has also been implicated in deleterious LV remodeling after MI. Early initiation (<7 days post MI) of the aldosterone antagonist eplerenone has a proven mortality benefit and should be given to patients with STEMI and no contraindications who are already receiving an ACE inhibitor and beta blocker and who have an EF less than or equal to 40% and either symptomatic HF or diabetes mellitus.^{6,82} Contraindications to the use of an aldosterone antagonist include creatinine greater than 2.5 mg/dL in men and more than 2.0 mg/dL in women or potassium higher than 5.0 mEq/L.

Lipid-Lowering Agents

Multiple studies have shown that statin use in patients after ACS can prevent death, recurrent MI, and stroke.^{83,84} Use of a high-intensity statin is preferred and should be initiated before discharge to improve compliance.^{5,6} In patients with ACS, high-intensity statin therapy should be given regardless of the LDL level. Among the currently available statins, only high-dose atorvastatin (80 mg daily) has been shown in clinical trials to reduce death and ischemic events among patients with ACS.^{85,86} Contraindications to statin use include a history of statin-induced rhabdomyolysis or significant myopathy and/or acute liver injury.

Calcium Channel Blockers

Randomized clinical trials have not demonstrated that routine use of calcium channel blockers improves survival after myocardial infarction.⁸⁷ In fact, meta-analyses suggest that high doses of the short-acting dihydropyridine nifedipine increased mortality in myocardial infarction.⁸⁸ Adverse effects of calcium channel blockers include bradycardia, atrioventricular block, and an exacerbation of heart failure.

Oxygen

The routine use of oxygen in patients with ACS who are not hypoxic (oxygen saturation <90%) is no longer recommended. A pooled Cochrane analysis of 3 trials showed no mortality benefit when supplemental oxygen was given to normoxic patients with confirmed MI and even suggested possible harm (increased mortality) from routine oxygen use.⁹⁰ The AVOID trial randomized 441 patients with confirmed STEMI to supplemental oxygen or none regardless of oxygen saturation. In patients who received supplemental oxygen, there was an increase in the rate of recurrent myocardial (5.5% vs. 0.9%, $P = 0.006$) and an increase in the frequency of cardiac arrhythmia (40.4% vs. 31.4%; $P = 0.05$). At 6 months, the oxygen group had an increase in the myocardial infarct size on CMR ($n = 139$; 20.3 g vs. 13.1 g; $P = 0.04$). Supplemental oxygen therapy in patients with STEMI but without hypoxia is no longer recommended.⁹¹

UA AND NSTEMI

UA and NSTEMI should be considered as part of the spectrum of ACS with elevated cardiac troponin differentiating NSTEMI from UA. The key to the initial management of patients with acute coronary syndromes who present without ST elevation is risk stratification. The overall risk of a patient is related to both the severity of preexisting heart disease and the degree of plaque instability. Risk stratification is an ongoing process, which begins with hospital admission and continues through discharge (see Fig. 78-3).

The risk of acute coronary syndromes increases with age. ST segment depression on the electrocardiogram identifies patients at a higher risk for clinical events.⁹² However, a normal 12-lead ECG does not exclude an NSTEMI and is seen in approximately 1% to 6% of patients with ACS.^{93,94} For example, a left circumflex coronary artery occlusion can be “electrically silent” and may only be detected using posterior leads V7-V9. An isolated posterior infarction can occur with a left circumflex or right coronary artery occlusion and manifest as tall R waves in the anterior leads V1-V3; ST elevation may be seen in

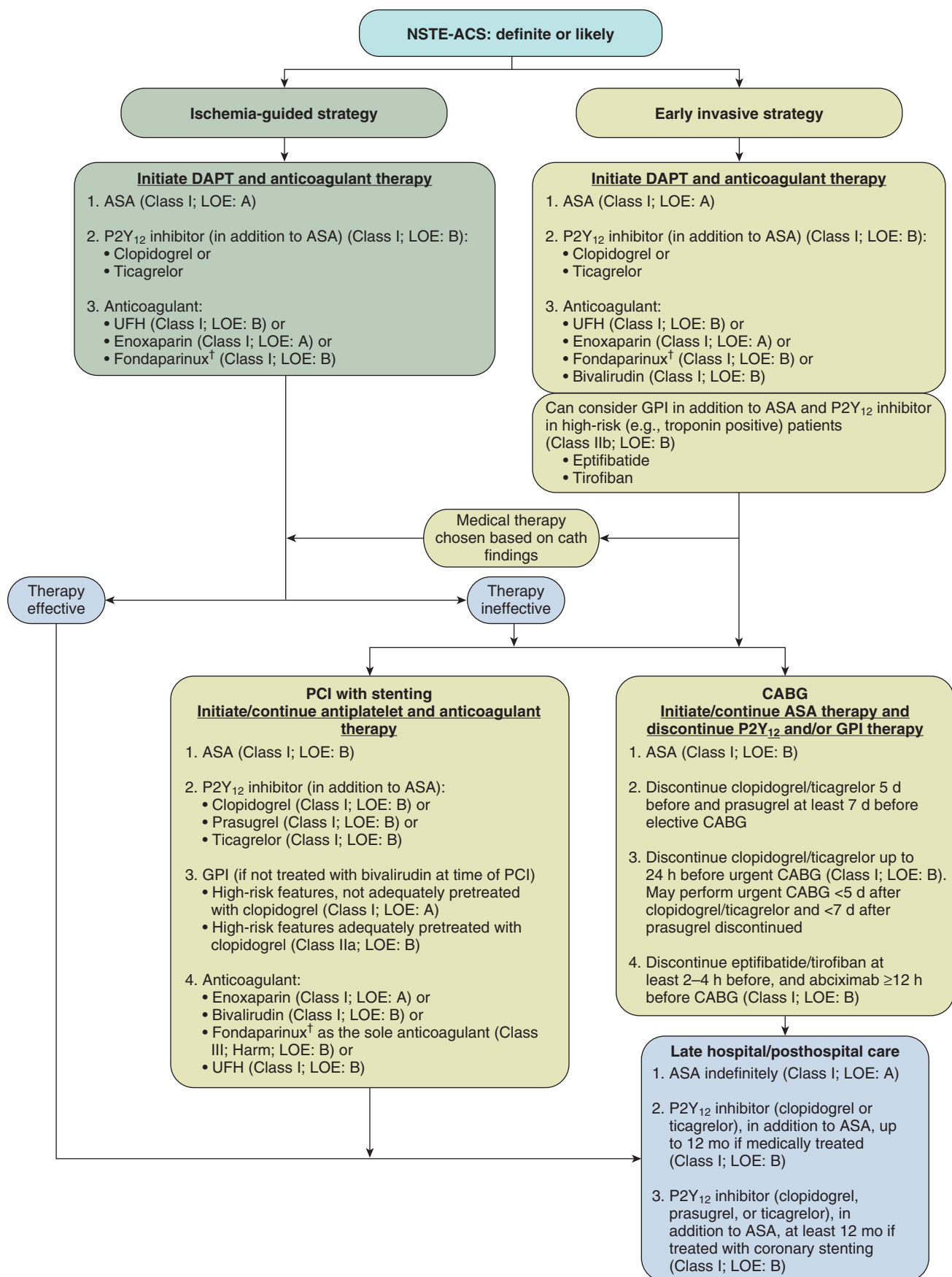


FIGURE 78-3 ■ Algorithm for management of patients with definite or likely NSTEMI-ACS. (From Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guidelines for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:e344-426.)

TABLE 78-5 Non-ACS Causes of ST-T Wave Changes on ECG

| DISEASE/CONDITION | ECG FINDING |
|-------------------------------|--|
| Left ventricular aneurysm | ST elevation in precordial leads, Q waves, TWI (low amplitude) |
| Pericarditis or myocarditis | Widespread concave ST elevation and PR depression throughout most of the leads. Reciprocal ST depression and PR elevation in lead aVR (\pm V1) |
| Right bundle branch block | ST depressions and T wave inversions in the right precordial leads |
| Left ventricular hypertrophy | Down-sloping ST segments into an inverted T wave in the lateral leads ("LV strain pattern") ST elevations and tall positive T waves are also common findings in leads V1 and V2 |
| Hyperkalemia | Peaked T waves |
| Prinzmetal angina | ST elevation in an anatomic distribution |
| Stress-induced cardiomyopathy | ST elevation |
| Brugada pattern | ST elevation in V1-V3 |
| CNS disease | Deep T wave inversions ST depression |
| Early repolarization | J-point elevation of ≥ 0.1 mV in two adjacent leads Widespread concave ST elevation, most prominent in the mid- to left precordial leads (V2-V5) No reciprocal ST depression to suggest STEMI (except in aVR) |

posterior leads (V7-V9) but typically does not exceed 1 mm. If there is a high clinical suspicion for ACS, a repeat ECG should be done in 15- to 30-minute intervals for the first hour.⁹⁵ Nonspecific ST and T wave changes can be seen on ECG in the absence of ACS. See Table 78-5 for non-ACS causes of ST-T wave changes.

Cardiac Biomarkers in NSTEMI

Biochemical markers of cardiac injury are predictive of outcome. The preferred biomarker for the diagnosis of myocardial necrosis is troponin. Cardiac troponin T and cardiac troponin I are sensitive markers of cardiac injury, particularly when used with the recommended diagnostic cut point of the 99th percentile of healthy controls.^{96,97} Elevated levels of troponin T are associated with an increased risk of cardiac events and a higher 30-day mortality.⁹⁸ Conversely, low levels are associated with low event rates, although the absence of troponin elevation does not guarantee a good prognosis and is not a substitute for good clinical judgment. Troponins are elevated in MI as early as 2 to 4 hours after symptom onset and may persist for several days after the initial event.

An elevated cardiac troponin level in the absence of overt ischemic heart disease is a common finding in both acute and nonacute processes. When serum cardiac troponin is present but the clinical information does not suggest ACS, the clinician should look for other causes.

Early Invasive Approach Versus Ischemia-Guided Approach to Treatment of NSTEMI

Two pathways have emerged in the management of patients with an NSTEMI and are referred to as an *early invasive approach* or an *ischemia-guided approach*. An early invasive approach is defined as a coronary angiogram within 24 hours of admission with PCI if

appropriate. An early invasive approach is clearly indicated in patients with NSTEMI who have refractory angina, hemodynamic or electrical instability, severe heart failure, or worsening mitral regurgitation and who lack serious comorbidities or contraindications to performing cardiac catheterization.⁹⁵ An early invasive strategy should not be considered for patients who are deemed low risk or who have significant comorbidities such as bleeding, advanced liver or renal failure, end-stage lung disease, or advanced-stage cancer such that the risk of PCI outweighs the benefit. Whenever considering an invasive strategy, the patient's ability to tolerate anticoagulation, antiplatelet, or antithrombotic therapy must be considered.

Risk stratification is the key to managing patients with NSTEMI acute coronary syndromes. An initial strategy of medical management with attempts at stabilization is warranted in patients with a lower risk, but patients at higher risk should be considered for cardiac catheterization.

Guideline-Directed Medical Therapy for UA/NSTEMI

Standard medical therapy for the early management of patients presenting with UA/NSTEMI includes analgesics, nitrates, and antiplatelet and antithrombotic therapy. Other medications that should be considered include high-dose statin, beta blockers, and renin angiotensin blockers. See Table 78-6 for a summary of recommendations for the use of medications in UA/NSTEMI.

Initial Antiplatelet/Anticoagulant Therapy in Patients with Definite or Likely NSTEMI

Antiplatelet Therapy

Antiplatelet therapy includes aspirin, P2Y₁₂ receptor inhibitors, and glycoprotein IIb/IIIa inhibitors. As previously noted, aspirin is a mainstay of therapy for acute coronary syndromes. A loading dose of 162 mg to 325 mg non-enteric-coated aspirin is the initial antiplatelet therapy. Both the VA Cooperative Study Group^{32,99} and the Canadian Multicenter Trial¹⁰⁰ showed that aspirin reduces the risk of death or myocardial infarction by approximately 50% in patients with UA or NSTEMI. Aspirin also reduces events after resolution of an acute coronary syndrome, and 81 mg should be continued indefinitely. In patients who are aspirin-intolerant (allergy or significant GI intolerance), a loading dose of clopidogrel followed by a daily maintenance dose should be administered.⁶

Similar to patients with STEMI, patients with NSTEMI and UA benefit from the use of P2Y₁₂ receptor inhibitors, in addition to aspirin. This benefit, a decrease in cardiovascular death, MI, or stroke, is seen not only in patients who undergo PCI but also in patients who are managed medically.¹⁰¹ This benefit may come with a 1% absolute increase in major, non-life-threatening bleeds ($P = 0.001$) as well as a 2.8% absolute increase in major/life-threatening bleeds associated with CABG within 5 days ($P = 0.07$) as seen in the CURE trial.¹⁰¹ Patients undergoing PCI in this trial had a 31% reduction in cardiovascular death or MI ($P < 0.002$)¹⁰²; however, because PCI was performed in only 23% of patients in the CURE trial during the initial hospitalization, the study provides convincing evidence that clopidogrel is beneficial in patients who are managed medically in addition to those undergoing PCI.

Prasugrel has a more rapid onset of action and can achieve a greater level of platelet inhibition when compared to clopidogrel. It can be a useful alternative to clopidogrel considering that approximately 20% to 25% of the population may be resistant to clopidogrel.¹⁰³ The use of prasugrel is not recommended for "upfront" therapy in patients with NSTEMI undergoing PCI due to an increase in bleeding complications without a significant reduction in composite endpoints.¹⁰⁴

Ticagrelor, a small molecule that binds reversibly to the P2Y₁₂ platelet receptor, exhibited greater efficacy than clopidogrel in the PLATO trial.¹⁰⁵ Major bleeding events did not differ between the groups, although bleeding not related to coronary-artery bypass

TABLE 78-6 Recommendations for the Use of Medications in NSTEMI/UA

| THERAPY | COR | LOE |
|--|-----|-----|
| OXYGEN | | |
| Oxygen only if SpO ₂ < 90% or respiratory distress | I | C |
| NITRATES | | |
| Sublingual nitroglycerin | I | C |
| IV nitroglycerin for persistent ischemia, HF, or hypertension | I | B |
| Nitrates are contraindicated if phosphodiesterase was recently used | III | B |
| ANALGESICS | | |
| Morphine sulfate for ongoing ischemic pain despite maximal medical therapy | IIb | B |
| NSAIDs (except aspirin) should not be initiated or should be discontinued | III | B |
| BETA BLOCKERS | | |
| Oral β -blockers should be initiated within the first 24 hours, in the absence of contraindications* | I | A |
| Use of metoprolol succinate, carvedilol, or bisoprolol is recommended in patients with NSTEMI and reduced systolic function with stabilized heart failure | I | C |
| IV β -blockers are contraindicated in patients with risk factors for or evidence of shock | III | B |
| STATIN THERAPY | | |
| Initiate or continue high-intensity statin therapy [†] in patients with no contraindications | I | A |
| Obtain a fasting lipid profile | IIa | C |
| RENIN ANGIOTENSIN ALDOSTERONE INHIBITORS | | |
| ACE inhibitors should be started and continued indefinitely in all patients with an LVEF < 40% and those with HTN, DM, or stable CKD unless contraindicated | I | A |
| ARBs should be given to ACE-I intolerant patients with an LVEF < 40% | I | A |
| Aldosterone blockade is recommended in patients post MI without significant renal dysfunction (Cr > 2.5 mg/dL in men or > 2.0 mg/dL in women) or hyperkalemia (K > 5.0 mEq/L) who are and have an LVEF < 40%, diabetes mellitus, or HF who are receiving therapeutic doses of ACE-I and β -blocker | I | A |

Adapted from Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC Guidelines for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e344-e426.

*Decompensated heart failure, low-output state, risk for cardiogenic shock, bradycardia, evidence of AV nodal conduction disease.

[†]Atorvastatin or rosuvastatin.

grafting occurred more often with ticagrelor. Ticagrelor has a faster onset of action when compared to clopidogrel and has a faster recovery of platelet function. Patients with NSTEMI in PLATO trial comparing clopidogrel to ticagrelor showed a reduction in the composite outcome of death from vascular causes, MI, or stroke (reduction: 11.7%-9.8%; HR: 0.84; $P < 0.001$) in patients treated with ticagrelor.¹⁰⁵ Table 78-7 summarizes the dosing of clopidogrel, prasugrel, and ticagrelor in the treatment of NSTEMI/UA.

Anticoagulant Therapy

Heparin is an important component of primary therapy for patients with unstable coronary syndromes without ST elevation. When added to aspirin, heparin has been shown to reduce refractory angina and the development of MI,³² and a meta-analysis of the available data indicates that the addition of heparin reduces the composite endpoint of death or MI.¹⁰⁶

Unfractionated heparin, however, can be difficult to administer, because the anticoagulant effect is unpredictable in individual patients. Therefore, the APTT (activated partial thromboplastin time) must be monitored closely. The potential for heparin-associated thrombocyto-

TABLE 78-7 Dosing of Clopidogrel, Prasugrel, and Ticagrelor in Patients with NSTEMI

| DRUG | LOADING DOSE | MAINTENANCE DOSE |
|-------------------------|------------------|------------------|
| Clopidogrel | 300 mg or 600 mg | 75 mg |
| Prasugrel [†] | Not recommended* | 10 mg |
| Ticagrelor [‡] | 180 mg | 90 mg BID |

Adapted from Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC Guidelines for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; 130:e344-e426.

*Due to a significant increase in spontaneous bleeding, life-threatening bleeding, and fatal bleeding in the patients loaded with prasugrel compared with patients loaded with clopidogrel.

[†]Net harm in patients with a history of cerebrovascular events and no clinical benefit in patients older than 75 years of age or those with low body weight (<60 kg) (Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001-2015.)

[‡]The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

penia is also a safety concern. The recommended regimen is weight based and adjusted using a standardized nomogram.

Low-molecular-weight heparins (LMWHs) have several advantages. Since they bind less avidly to heparin-binding proteins, there is less variability in the anticoagulant response and a more predictable dose-response curve, obviating the need to monitor APTT. The incidence of thrombocytopenia is lower (but not absent, and patients with heparin-induced thrombocytopenia with antiheparin antibodies cannot be switched to LMWH). LMWH is less susceptible to inactivation by platelet factor 4. Finally, LMWHs have longer half-lives and can be given by subcutaneous injection.

Several trials have documented beneficial effects of LMWH therapy in unstable coronary syndromes.^{107,108} Specific considerations with the use of LMWH include a decreased clearance in renal insufficiency and the lack of a commercially available test to measure the anticoagulant effect. Enoxaparin is dosed by weight and in the presence of impaired renal function (CrCl < 30 mL/min) the dose should be reduced.

Direct Thrombin Inhibitors

Bivalirudin is a direct thrombin inhibitor (DTI). As opposed to heparin, bivalirudin binds directly to both circulating and clot-bound thrombin and inhibits the conversion of fibrinogen to fibrin in the final step of the clotting cascade. Direct thrombin inhibitors have several theoretic advantages over heparin. Heparin binds to a number of tissue and plasma proteins, which alters its bioavailability and clearance. Heparin may also have a platelet-activating effect in ACS. Last, DTIs do not bind to platelet factor 4 and therefore avoid the problem of heparin-induced thrombocytopenia.

Bivalirudin is the only DTI indicated for use in ACS. Bivalirudin appears to be equivalent to glycoprotein IIb/IIIa inhibitors plus heparin but with a lower bleeding rate.¹⁰⁹ However, patients who get bivalirudin alone without a thienopyridine prior to angiography or PCI may have a higher rate of composite ischemic events than patients who received heparin plus a glycoprotein IIb/IIIa inhibitor (9.1% vs. 7.1%).¹¹⁰ Therefore, it is not recommended that bivalirudin be administered alone, particularly if there is a going to be a delay to angiography.

Glycoprotein IIb/IIIa Antagonists

Given the central role of platelet activation and aggregation in the pathophysiology of unstable coronary syndromes, attention has been focused on platelet glycoprotein IIb/IIIa antagonists, which inhibit the final common pathway of platelet aggregation. Meta-analyses have found a relative risk reduction of 11% in NSTEMI.⁵² Additional analysis suggests that glycoprotein IIb/IIIa inhibition is most effective in high-risk patients, those with either EKG changes or elevated troponin.^{52,111}

The benefits appear to be restricted to patients undergoing percutaneous intervention, which may not be entirely surprising.

The studies mentioned above were conducted prior to the era of dual antiplatelet therapy. As mentioned previously, it is common practice to administer a P2Y₁₂ inhibitor and aspirin in conjunction with an anticoagulant in patients with ACS. For patients with UA/NSTEMI undergoing an initial invasive approach, the most recent data suggest that either a glycoprotein IIb/IIIa inhibitor or P2Y₁₂ inhibitors can be given in addition to aspirin and an anticoagulant if the patient is considered low risk (troponin negative). However, if the patient is considered high risk (troponin positive, recurrent ischemic features) both a glycoprotein IIb/IIIa inhibitor and clopidogrel can be given in addition to aspirin and an anticoagulant.⁵⁵ In patients with intermediate/high-risk features (e.g., positive troponin) treated with an early invasive strategy, a GP IIb/IIIa inhibitor may be considered, with tirofiban and eptifibatide preferred.⁹⁵

Complications of Acute Myocardial Infarction

Ventricular Free Wall Rupture

Ventricular free wall rupture typically occurs during the first 5 days after an infarction and within 2 weeks in over 90% of cases. The incidence of LV free wall rupture in all comers with STEMI is low (about 1%). Not surprisingly, the incidence in those who die following STEMI is much higher, ranging from 7% to 26%.¹¹²⁻¹¹⁴ The classic patient is elderly, female, and status postanterior wall infarction. Early use of fibrinolytic therapy reduces the incidence of cardiac rupture, but late use may actually increase the risk. Pseudoaneurysm with leakage may be heralded by chest pain, nausea, and restlessness, but frank free wall rupture presents as a catastrophic event with shock and electromechanical dissociation. Pericardiocentesis may be necessary to relieve acute tamponade, ideally in the operating room since the pericardial effusion may tamponade the bleeding. Salvage is possible with expeditious thoracotomy and repair, either with a patch or by direct suturing.¹¹⁵ For those patients who make it to the operating room for repair, mortality approaches 60%.⁶

Ventricular Septal Rupture

Septal rupture presents as severe heart failure or cardiogenic shock, with a loud pansystolic murmur and parasternal thrill. Ventricular septal rupture most commonly occurs within 24 hours of reperfusion in patients with a STEMI.¹¹⁶ The hallmark finding is a left-to-right intracardiac shunt ("step up" in oxygen saturation from the right atrium to right ventricle), but the diagnosis is most easily made with echocardiography. Rapid institution of supportive pharmacologic measures and mechanical support, such as intraaortic balloon pumping is necessary. Operative repair is the only viable option for long-term survival. Even if surgical repair is done promptly, mortality remains high, ranging from 20% to 87%.¹¹⁶⁻¹¹⁹

Acute Mitral Regurgitation

Ischemic mitral regurgitation is usually associated with inferior myocardial infarction and ischemia or infarction of the posterior papillary muscle, although an anterior papillary muscle rupture can also occur. Papillary muscle rupture has a bimodal incidence, either within 24 hours or 3 to 7 days after an acute myocardial infarction. It presents dramatically with pulmonary edema, hypotension, and cardiogenic shock. When a papillary muscle ruptures, the murmur of acute mitral regurgitation may be limited to early systole because of a rapid equalization of pressures in the left atrium and ventricle. More important, the murmur may be soft or inaudible, especially when the cardiac output is low.¹²⁰

Echocardiography is extremely useful in the differential diagnosis, which includes free wall rupture, ventricular septal rupture, and infarct extension with pump failure. Hemodynamic monitoring with pulmonary artery catheterization may also be helpful. Management includes an afterload reduction with an intraaortic balloon pumping as a temporizing measure. Inotropic or vasopressor therapy may also be needed

to support cardiac output and blood pressure. Definitive therapy, however, is a surgical valve repair or replacement, which should be undertaken as soon as possible since clinical deterioration can be sudden.^{120,121}

RIGHT VENTRICULAR INFARCTION

Right ventricular infarction occurs in up to 30% of patients with an inferior infarction and is clinically significant in 10%.¹²² The combination of a clear chest x-ray with jugular venous distention in a patient with an inferior wall MI should lead to the suspicion of a coexisting right ventricular infarct. The diagnosis is substantiated by a demonstration of ST-segment elevation in the right precordial leads (V_{3R} to V_{5R}) or by characteristic hemodynamic findings on the right heart catheterization (elevated right atrial and right ventricular end-diastolic pressures with normal to low pulmonary artery occlusion pressure and low cardiac output). Echocardiography can demonstrate a depressed right ventricular contractility.¹²³ Patients with cardiogenic shock on the basis of right ventricular infarction have a better prognosis than those with left-sided pump failure.¹²¹ This may be due in part to the fact that the right ventricular function tends to return to normal over time with supportive therapy, although such therapy may need to be prolonged.¹²⁴

In patients with right ventricular infarction, right ventricular preload should be maintained with fluid administration. In some cases, however, fluid resuscitation may increase pulmonary capillary occlusion pressure but may not increase cardiac output, and overdistention of the right ventricle can compromise left ventricular filling and cardiac output.¹²⁴ Inotropic therapy may be more effective in increasing cardiac output in some patients, and monitoring with serial echocardiograms may also be useful to detect a right ventricular overdistention. Maintenance of atrioventricular synchrony is also important in these patients to optimize right ventricular filling.¹²³ For patients with continued hemodynamic instability, intraaortic balloon pumping may be useful, particularly because elevated right ventricular pressures and volumes increase wall stress and oxygen consumption and decrease right coronary perfusion pressure, exacerbating right ventricular ischemia. Reperfusion of the occluded coronary artery is also crucial.¹²⁵

CARDIOGENIC SHOCK

Epidemiology and Pathophysiology

Cardiogenic shock, resulting either from left ventricular pump failure or mechanical complications, represents the leading cause of in-hospital death after myocardial infarction.^{126,127} Cardiogenic shock should be considered in the presence of persistent hypotension (systolic blood pressure <90 mm Hg or mean arterial pressure 30 mm Hg lower than baseline) with reduced cardiac index (<1.8 L/min/m² without support or <2.2 L/min/m² with support) and adequate or elevated filling pressures.¹²⁸ Patients may have cardiogenic shock at initial presentation, but shock most often evolves over several hours.^{129,130}

Cardiac dysfunction in patients with cardiogenic shock is usually initiated by a myocardial infarction or ischemia. The myocardial dysfunction resulting from ischemia worsens the ischemia, creating a downward spiral (Fig. 78-4). Compensatory mechanisms that retain fluid in an attempt to maintain cardiac output may add to the vicious cycle and further increase diastolic filling pressures. The interruption of this cycle of myocardial dysfunction and ischemia forms the basis for the therapeutic regimens for cardiogenic shock. Early recognition of cardiogenic shock and timely management (revascularization) are paramount to improved mortality.

Initial Management

Maintenance of adequate oxygenation and ventilation is critical. Many patients require intubation and mechanical ventilation if only to reduce the work of breathing and facilitate sedation and stabilization before cardiac catheterization. Electrolyte abnormalities should be corrected,

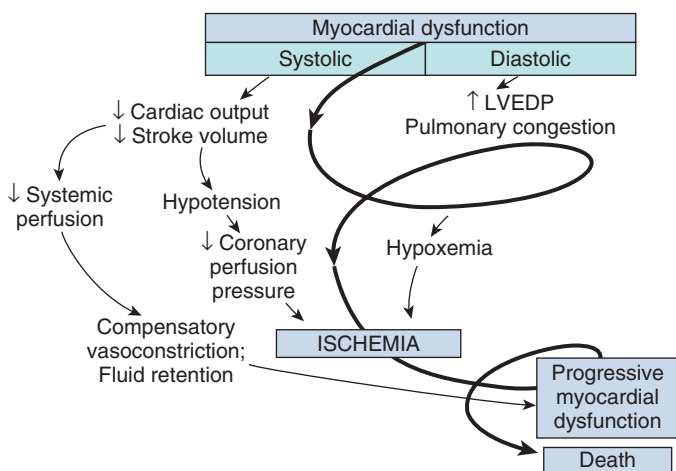


FIGURE 78-4 ■ The “downward spiral” in cardiogenic shock.

Stroke volume and cardiac output fall with left ventricular (LV) dysfunction, producing hypotension and tachycardia that reduce coronary blood flow. Increasing ventricular diastolic pressure reduces coronary blood flow, and increased wall stress elevates the myocardial oxygen requirements. All of these factors combine to worsen ischemia. The falling cardiac output also compromises systemic perfusion. Compensatory mechanisms include sympathetic stimulation and fluid retention to increase preload. These mechanisms can actually worsen cardiogenic shock by increasing myocardial oxygen demand and afterload. Thus, a vicious circle can be established. LVEDP, left ventricular end-diastolic pressure. (Adapted with permission from Hollenberg SM, Kavinsky CJ, Parrillo JE. Cardiogenic shock. *Ann Intern Med* 1999;131:47–59.)

and morphine (or fentanyl if systolic pressure is compromised) used to relieve pain and anxiety. Arrhythmias and a heart block may have important effects on cardiac output and should be corrected promptly with antiarrhythmic drugs, cardioversion, or pacing. Amiodarone is the preferred antiarrhythmic drug for sustained ventricular or atrial tachyarrhythmias in the setting of cardiogenic shock.

Both pharmacologic and mechanical forms of circulatory support should be used to reverse hypotension and maintain organ and coronary artery perfusion. Patients are commonly diaphoretic, and relative hypovolemia may be present in as many as 20% of patients with cardiogenic shock, so fluid boluses, titrated to clinical endpoints of heart rate, urine output, and blood pressure, should be considered as an initial measure unless frank pulmonary edema is present. Patients who do not respond rapidly to initial fluid boluses or those with poor physiologic reserves should be considered for invasive hemodynamic monitoring. Optimal filling pressures vary from patient to patient; hemodynamic monitoring can be used to construct a Starling curve at the bedside, identifying the filling pressure at which the cardiac output is maximized. Maintenance of an adequate preload is particularly important in patients with a right ventricular infarction.

Vasopressor and inotropic agents remain the mainstay of first-line therapy in the management of cardiogenic shock. Catecholamine agents, such as norepinephrine, epinephrine, dopamine, dobutamine, and phenylephrine, have both vasopressor and inotropic effects, but it is useful to distinguish vasopressor effects (those aimed at maintaining blood pressure) and inotropic effects (those aimed at increasing myocardial contractility and thus cardiac output) to allow for a titration of dose to effect. When the arterial pressure remains inadequate, therapy with vasopressor agents may be required to maintain coronary perfusion pressure, to break the vicious cycle of progressive hypotension with further myocardial ischemia. The most commonly used vasopressors include norepinephrine, phenylephrine, and epinephrine. Norepinephrine acts on both alpha-1 and beta-1 adrenergic receptors, thus producing potent vasoconstriction, as well as a modest increase in

cardiac output,¹³¹ and is the preferred first-line agent. A subgroup analysis of a multicenter randomized trial comparing norepinephrine to dopamine in patients with shock demonstrated a lower 28-day mortality with norepinephrine ($P = 0.03$).¹³² Phenylephrine, a selective alpha-1 adrenergic agonist, acts as a potent vasoconstrictor that augments systemic vascular resistance (SVR) without greatly affecting contractility or CO. Phenylephrine may be used when tachyarrhythmias limit therapy with other vasopressors. Epinephrine has a potent beta-1 adrenergic receptor activity and moderate beta-2 and alpha-1 adrenergic receptor effects. The net effect can be an increase in cardiac output and decreased systemic vascular resistance (SVR), with escalating doses causing a greater increase in SVR. Epinephrine is typically used in addition to norepinephrine in septic shock, and for the management of hypotension following coronary artery bypass grafting.

Vasopressor infusions need to be titrated carefully in patients with cardiogenic shock to maximize coronary perfusion pressure with the least possible increase in myocardial oxygen demand. Hemodynamic monitoring, with serial measurements of cardiac output and filling pressures (and other parameters, such as mixed venous oxygen saturation) can allow for titration of the dosage of vasoactive agents to the minimum dosage required to achieve the chosen therapeutic goals.¹³³ However, reperfusion therapy should not be delayed for the placement of a pulmonary artery catheter.

Following the initial stabilization and restoration of adequate blood pressure, tissue perfusion should be assessed. If tissue perfusion is adequate but significant pulmonary congestion remains, diuretics may be employed. Vasodilators can be considered as well, depending on the blood pressure.

If tissue perfusion remains inadequate, cardiovascular support with inotropic agents should be initiated. There is no firm guideline-based recommendation regarding which inotropic agent to use in the setting of cardiogenic shock. Typically used inotropes include dobutamine, dopamine, and norepinephrine (which can act as both a vasopressor and inotrope). Dobutamine, a selective β_1 -adrenergic receptor agonist, can improve myocardial contractility and increase cardiac output. Dobutamine may exacerbate hypotension in some patients and can precipitate tachyarrhythmia. Dobutamine is typically reserved for patients with an SBP over 80 mm Hg. Epinephrine can increase cardiac output but often at the expense of a substantial increase in myocardial oxygen demand. In some situations, a combination of a vasopressor and an inotrope can be more effective than either agent used alone. Phosphodiesterase inhibitors such as milrinone are less arrhythmogenic than catecholamines, but have the potential to cause hypotension, and should be used with caution in patients with tenuous clinical status.

Mechanical Support in Cardiogenic Shock

Intraaortic balloon counterpulsation (IABP) reduces the systolic afterload and augments diastolic perfusion pressure, increasing cardiac output and improving coronary blood flow.¹³⁴ These beneficial effects, in contrast to those of inotropic or vasopressor agents, occur without an increase in oxygen demand. IABP does not, however, produce a significant improvement in blood flow distal to a critical coronary stenosis.^{134,135} The timing and utility of IABP in patients with STEMI complicated by cardiogenic shock, however, remain uncertain.^{136,137} The IABP-SHOCK II trial, a multicenter, randomized open-label multicenter trial, allocated 600 patients with cardiogenic shock complicated by acute MI to either IABP or no IABP at the time of PCI. There was no difference in all-cause mortality at 30 days (39.7% vs. 41.3%, $P = 0.69$) or 12 months (52% vs. 51%), nor was there any significant difference in any of the subgroups.¹³⁸ Some randomized patients in this trial received an IABP after PCI when they were hemodynamically stable and might not have been expected to derive great benefit. In addition, 10% of patients in the control group crossed over to IABP therapy. IABP is widely available, is easy to place, and has a lower cost compared to other support devices; as such, IABP may still have a role in the stabilization of selected patients with cardiogenic shock.

In appropriate settings, more intensive support with mechanical assist devices may also be implemented. Such devices include left ventricular and biventricular assist devices, percutaneous left atrial-to-femoral arterial ventricular assist device (Tandem Heart™), percutaneous transvalvular left ventricular assist device (Impella™), and percutaneous cardiopulmonary bypass support with the use of an extracorporeal membrane oxygenator (ECMO). The percutaneous LVADs provide better hemodynamics compared with IABP, with higher cardiac indices and mean arterial pressures, as well as lower filling pressures, and improve metabolic parameters. However, there is conflicting evidence regarding mortality.^{139,140}

Reperfusion Therapy

Although fibrinolytic therapy reduces the likelihood of the subsequent development of shock after the initial presentation, it is clearly less effective in patients with cardiogenic shock than in those without¹⁴¹ and has not been shown to reduce mortality in patients with established cardiogenic shock.^{13,142}

To date, emergency percutaneous revascularization is the only intervention that has been shown to reduce mortality rates consistently in patients with cardiogenic shock. An extensive body of observational and registry studies has shown consistent benefits from revascularization.^{143,144} These data have been confirmed in the SHOCK study, a randomized, multicenter international trial that assigned patients with cardiogenic shock to receive optimal medical management (including IABP and fibrinolytic therapy) or to cardiac catheterization with revascularization using PTCA or CABG.^{21,145} The trial enrolled 302 patients and was powered to detect a 20% absolute decrease in 30-day all-cause mortality rates. Mortality at 30 days was 46.7% in patients treated with early intervention and 56% in patients treated with initial medical stabilization, but this difference did not quite reach statistical significance ($P = 0.11$).²¹ At 6 months, the absolute risk reduction with early invasive therapy in the SHOCK trial was 13% (50.3% compared with 63.1%, $P = 0.027$), and this risk reduction was maintained at 12 months (mortality 53.3% vs. 66.4%, $P < 0.03$).¹⁴⁵ The subgroup analysis showed a substantial improvement in mortality rates in patients younger than 75 years of age at both 30 days (41.4% vs. 56.8%, $P = 0.01$) and 6 months (44.9% vs. 65.0%, $P = 0.003$).¹⁴⁵ Put into perspective with the results from other randomized, controlled trials of patients with acute myocardial infarction, an important point emerges: despite the moderate relative risk reduction (0.72, CI 0.54-0.95) the absolute benefit is important, with 9 lives saved for 100 patients treated at 30 days (number needed to treat, 10.8), and 13.2 lives saved for 100 patients treated at 1 year in the SHOCK trial (number needed to treat 7.6). Based on these data trials, the presence of cardiogenic shock in the setting of acute MI is an indication for emergency revascularization, either by percutaneous intervention or CABG.⁶

See Table 78-8 for a summary of complications due to acute myocardial infarction.

TABLE 78-8 Complications Due to Acute Myocardial Infarction

| |
|---|
| Cardiogenic shock |
| Mechanical |
| Rupture of the left ventricular free wall |
| Rupture of the interventricular septum |
| Acute mitral regurgitation |
| Left ventricular aneurysm |
| Ventricular arrhythmia |
| Bradycardia or AV nodal block |
| Pericarditis |
| Bleeding |

KEY POINTS

1. The definition of myocardial infarction (MI) has evolved. Now, the patient's clinical presentation is considered in conjunction with highly sensitive and specific serum markers, the electrocardiogram (ECG), advanced imaging techniques, and pathologic samples.
2. Atypical presentations of acute myocardial infarction (AMI) are seen in up to 30% of infarct patients. The rate of atypical presentation is highest among the very elderly in whom mental status change, syncope, and other nonspecific symptom/sign complexes are seen. Atypical presentations are more likely to be encountered in the ill critical care patient.
3. The ECG is diagnostic (i.e., ST segment elevation or new left bundle branch block [LBBB]) for AMI in only 50% of patients ultimately diagnosed with an acute infarction. The remainder of these AMI patients demonstrate normal, nonspecifically abnormal, abnormal but not diagnostic, and confounding patterns.
4. Cardiac troponin is the diagnostic marker of choice. While highly specific, serial measurements should be obtained to identify MI properly.
5. Echocardiography (ECHO) is a valuable noninvasive tool. It can be utilized under many clinical circumstances to help identify MI and its complications.

ANNOTATED REFERENCES

Thygesen K, Alpert JS, White HD, on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation* 2007;116:2634-2653.

This article is vital to the understanding of MI. Not only is myocardial infarction defined, but the subtypes of AMI encountered in the critical care environment are also delineated. The "typical rise and fall" description of the serum marker pattern encountered in AMI is discussed; this portion of the paper is vital to understanding AMI and differentiating MI-related troponin elevations from noninfarction serum marker abnormalities.

Hoekstra JW, O'Neill BJ, Pride YB, et al. Acute detection of ST-elevation myocardial infarction missed on standard 12-lead ECG with a novel 80-lead real-time digital body surface map: primary results from the multicenter OCCULT MI trial. *Ann Emerg Med* 2009;54:779-788.

This paper investigates the use of the additional ECG lead concept taken to extreme: the use of ECG body mapping. In the discussion, the authors note that the traditional 12-lead ECG can and does "miss" some ACS events, including STEMI. They found that the ECG body map provided an incremental increase in STEMI detection as compared to the 12-lead; in fact, an increase in STEMI diagnosis by 28% was reported. Importantly, in patients with an ECG body map, only STEMI have adverse outcomes similar to those of 12-lead STEMI patients, yet these patients are managed much less aggressively in the early phase of presentation.

Lim W, Whitlock R, Khara V, et al. Etiology of troponin elevation in critically ill patients. *J Crit Care* 2010;25:322-328.

A small but interesting study exploring the etiology of elevated troponin values in the ICU patient. These investigators found that approximately half of the ICU patients with elevated troponin values experienced AMI; sepsis and renal failure accounted for the next most frequently encountered cause of elevated troponin.

Body R. Emergent diagnosis of acute coronary syndromes: today's challenges and tomorrow's possibilities. *Resuscitation* 2008;78:13-20.

This article nicely summarizes the pros and cons of the various diagnostic studies and diagnostic strategies in the evaluation of patients suspected of AMI.

Goodacre S, Pett P, Arnold J, et al. Clinical diagnosis of acute coronary syndrome in patients with chest pain and a normal or nondiagnostic electrocardiogram. *Emerg Med J* 2009;26:866-870.

This paper investigates the patient with a nondiagnostic ECG who is ultimately diagnosed with ACS. It importantly makes the point that the ECG is a fallible study, and when the clinical situation suggests the diagnosis, ACS cannot be excluded based upon a normal or nondiagnostic ECG.

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■ CLASSIFICATION AND EPIDEMIOLOGY

Supraventricular arrhythmias include rhythms arising from the sinus node and the adjacent atrial tissue (inappropriate sinus tachycardia, sinoatrial reentry tachycardia), both the right and left atria (atrial tachycardia, flutter, and fibrillation), the atrioventricular (AV) node (AV nodal reentry tachycardia, accelerated ectopic junctional rhythm), and the AV node, with involvement of an accessory pathway or multiple pathways (AV reentry tachycardia) (Fig. 79-1).

Atrioventricular Nodal Reentry Tachycardia and Atrioventricular Reentry Tachycardia

AV nodal reentry tachycardia and AV reentry tachycardia are usually referred to as *paroxysmal supraventricular tachycardias*. They are often seen in young patients with little or no structural heart disease, although a congenital heart abnormality giving rise to increased atrial pressure and dilatation (e.g., Ebstein's anomaly, atrial septal defect, Fallot's tetralogy) can coexist in a small percentage of patients with these arrhythmias.¹ The first presentation is common between age 12 and 30 years, and the prevalence is approximately 2.5 per 1000. Women are twice as likely as men to present with AV nodal reentry tachycardia.

Atrial Flutter and Fibrillation

Atrial fibrillation is the most common supraventricular arrhythmia, affecting 1% to 2% of the general population, especially the elderly. It is usually associated with cardiovascular pathologies, among which hypertension and congestive heart failure prevail.² About a third of patients, however, present with no underlying heart disease and are considered to have "lone" atrial fibrillation. The incidence of isolated atrial flutter is largely unknown and is believed to be in the range of 0.037% to 0.88% per 1000 person-years, but at least half of these patients also have atrial fibrillation as a coexistent arrhythmia.

Atrial Tachycardia

Atrial tachycardia affects 0.34% to 0.46% of patients with arrhythmias. It is common in younger individuals following surgical correction of congenital heart disease and in the elderly, in whom it often occurs in association with atrial fibrillation.

Other Supraventricular Tachycardias

Inappropriate sinus tachycardia and sinoatrial reentry tachycardia are less well-defined clinical and electrocardiographic entities, and their prevalence and associated conditions are not well characterized. Sinoatrial reentry tachycardia is found incidentally in 1.8% to 16.9% of patients undergoing electrophysiologic studies for other supraventricular tachyarrhythmias.

■ CLINICAL PRESENTATION

The leading symptom of most supraventricular tachyarrhythmias, particularly AV nodal reentry tachycardia and AV reentry tachycardia, is rapid, regular palpitations, usually with an abrupt onset; they can

occur spontaneously or be precipitated by simple movements. A common feature of tachycardias that involve circulation through the AV node is termination by the Valsalva maneuver. In younger individuals with no structural heart disease, the rapid heart rate can be the main pathologic finding. Other symptoms may include anxiety, dizziness, dyspnea, neck pulsation, central chest pain, weakness, and occasionally polyuria due to the release of atrial natriuretic peptide in response to increased atrial pressures (more common in atrial tachycardia and AV nodal reentry tachycardia). Prominent jugular venous pulsations due to atrial contractions against closed AV valves may be observed during AV nodal reentry or AV reentry tachycardia.

True syncope is relatively uncommon unless uncontrolled tachycardia over 200 beats per minute is sustained for a long period, especially in patients who remain standing. Syncope has been reported in 10% to 15% of patients, usually just after onset of the arrhythmia or in association with a prolonged pause following its termination. However, in older patients with concomitant heart disease such as aortic stenosis, hypertrophic cardiomyopathy, and cerebrovascular disease, significant hypotension and syncope may result from profound hemodynamic collapse associated with only moderately fast ventricular rates.

It is essential to recognize that patients presenting with AV reentry tachycardia may also present with atrial fibrillation. If an accessory pathway has a short antegrade effective refractory period (<250 msec), it may conduct impulses to the ventricles at an extremely high rate and cause ventricular fibrillation. The incidence of sudden death is 0.15% to 0.39% per patient-year, and this may be the first manifestation of the disease in younger individuals.

Irregular palpitations may be due to atrial premature beats, atrial flutter with varying AV conduction block, atrial fibrillation, or multifocal atrial tachycardia. Although highly symptomatic, these arrhythmias usually have a benign hemodynamic prognosis. However, in patients with depressed ventricular function, uncontrolled atrial fibrillation can reduce cardiac output and precipitate hypotension and congestive heart failure. Atrial fibrillation in association with slow AV conduction or complete block (Frederick's syndrome) may result in hemodynamic collapse. Inappropriate sinus tachycardia and nonparoxysmal accelerated junctional rhythm are characterized by relatively slow heart rates and gradual onset and termination.

■ ELECTROCARDIOGRAPHY

Whenever possible, a 12-lead electrocardiogram (ECG) should be taken during the tachycardia. If a patient with an arrhythmia is hemodynamically unstable, a monitor strip should be obtained from the defibrillator before electrical discharge.

Narrow-Complex Tachycardias

The typical ECG feature is narrow QRS complexes less than 120 msec. In this case, the tachycardia is almost always supraventricular, and the differential diagnosis relates to its mechanism (Fig. 79-2).

Wide-Complex Tachycardias

The differential diagnostic features of wide-complex tachycardias favoring a supraventricular origin of the arrhythmia include, but are not limited to, preexistent bundle branch block; rate-dependent

aberrancy; antidromic AV reentry tachycardia, when an accessory pathway conducts and excites the ventricles antegradely; and prominent electrolyte abnormalities (e.g., hypokalemia) or heart muscle disease (cardiomyopathy), all of which may result in QRS widening (Fig. 79-3). If the diagnosis of supraventricular tachycardia cannot be proved, the patient should be treated as if ventricular tachycardia is present. Immediate direct current (DC) cardioversion is the treatment for any hemodynamically unstable tachycardia.

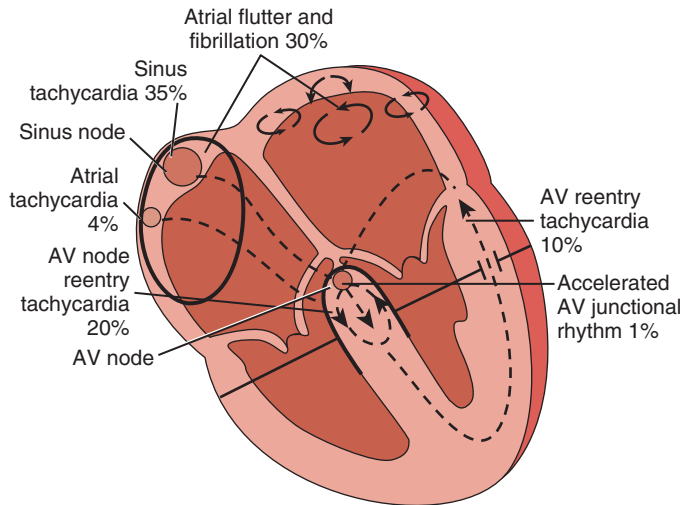


FIGURE 79-1 ■ Supraventricular tachyarrhythmias encountered in the emergency setting. AV, atrioventricular.

ATRIOVENTRICULAR NODAL REENTRY TACHYCARDIA

Mechanism

In AV nodal reentry tachycardia, there are two functionally and anatomically different pathways within the AV node: one is characterized by a short effective refractory period and slow conduction, and the other has a longer effective refractory period and faster conduction. In sinus rhythm, the atrial impulse that depolarizes the ventricles usually conducts through the fast pathway. If the atrial impulse (e.g., an atrial premature beat) occurs early, when the fast pathway is still refractory, the slow pathway takes over in propagating the atrial impulse to the ventricles; the impulse then travels back through the fast pathway, which by then has recovered its excitability, thus initiating the most common “slow-fast,” or typical, AV nodal reentry tachycardia.

Electrocardiographic Presentation

In sinus rhythm, the ECG is usually normal unless other unrelated abnormalities are present. During AV nodal reentry tachycardia, the rhythm is regular, with narrow QRS complexes and a rate of 140 to 250 beats per minute. The atria are activated retrogradely, producing inverted P waves in leads II, III, and aVF. Because atrial and ventricular depolarization occur simultaneously, the P waves are often obscured by the QRS complexes and cannot be detected on the surface ECG (Fig. 79-4, A). However, in about one third of cases of slow-fast AV nodal reentry tachycardia, a terminal positive deflection may be present in lead aVR or V₁ (or both), imitating right bundle branch block, or pseudo-S waves may be noted in the inferiorly oriented leads; these findings reflect retrograde activation of the atria. Tachycardia using these pathways in reverse (“fast-slow,” or long RP, tachycardia) is less common, occurring in 5% to 10% of cases.

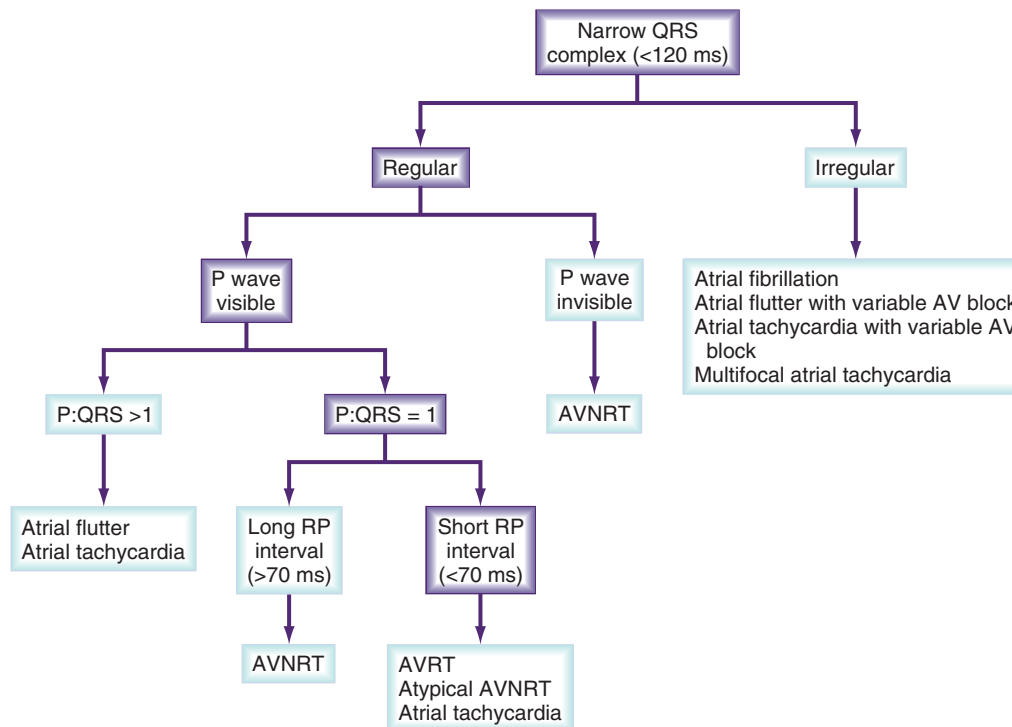


FIGURE 79-2 ■ Differential diagnosis for narrow QRS complex (presumably supraventricular) tachycardias. Note that ventricular tachycardia may present with narrow QRS complexes (e.g., fascicular tachycardia). AV, atrioventricular; AVNRT, atrioventricular nodal reentry tachycardia; AVRT, atrioventricular reentry tachycardia.

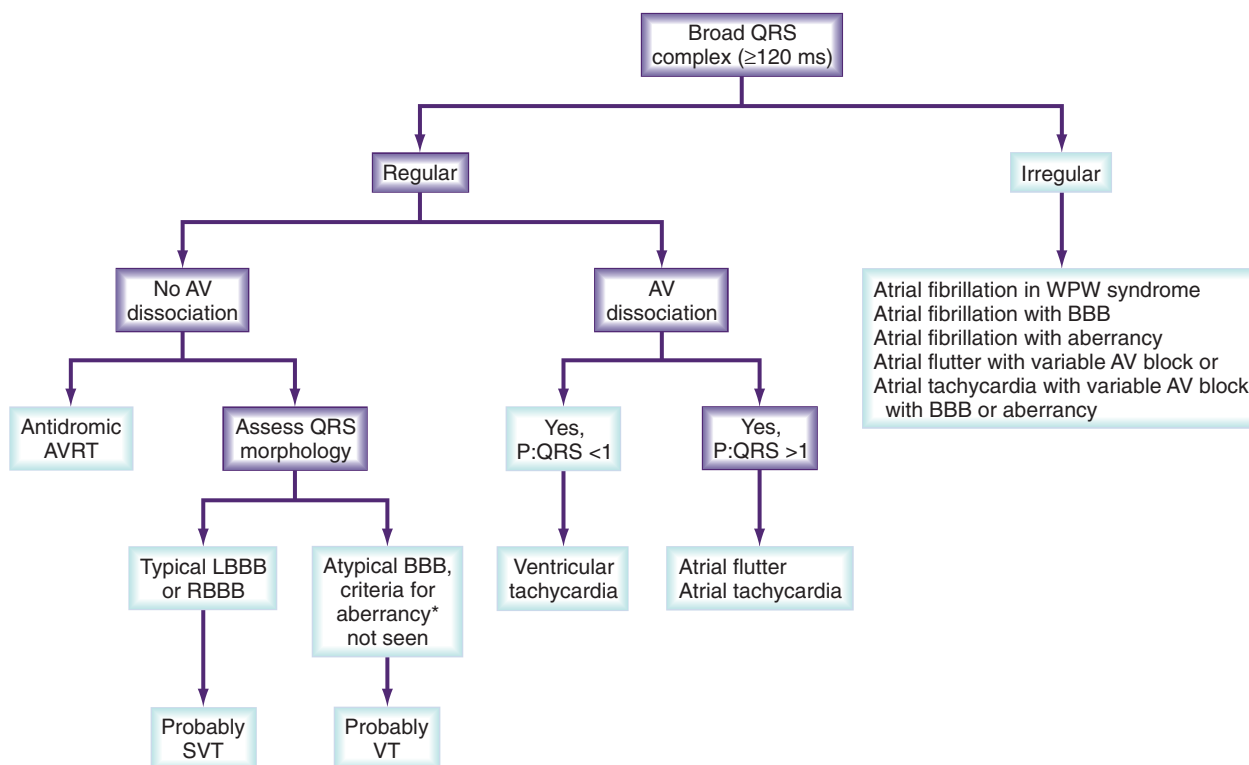


FIGURE 79-3 ■ Differential diagnosis for wide QRS complex tachycardias. AV, atrioventricular; AVRT, atrioventricular reentry tachycardia; BBB, bundle branch block; LBBB, left bundle branch block; RBBB, right bundle branch block; SVT, supraventricular tachycardia; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White. *Criteria for aberrancy: rate dependency, triphasic QRS complexes, rSR in V_1 with R >, QRS width <140 msec, QRS deflections are discordant in precordial leads, absence of fusion complexes and capture beats.

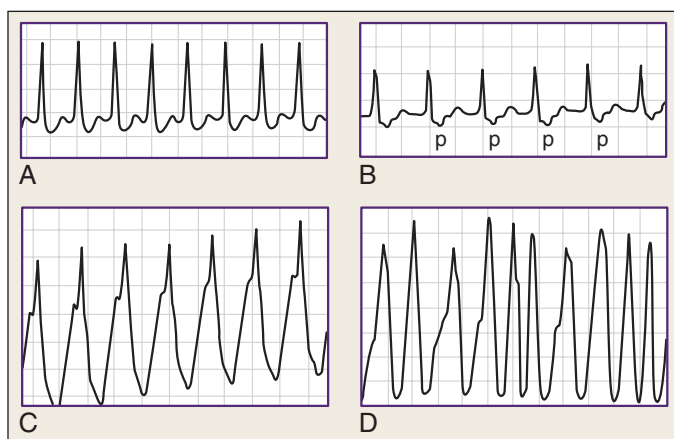


FIGURE 79-4 ■ **A**, Atrioventricular nodal reentry tachycardia, slow-fast type. Note narrow QRS complexes and absence of P waves. **B**, Atrioventricular reentry orthodromic tachycardia. Retrograde inverted P waves follow QRS complexes in leads II, III, and aVF. **C**, Atrioventricular reentry antidromic tachycardia with wide QRS complexes. Electrocardiogram during sinus rhythm with a QRS complex morphology identical to that seen during tachycardia may be helpful in the diagnosis. **D**, Atrial fibrillation in preexcitation syndrome with a fast ventricular rate response.

ATRIOVENTRICULAR REENTRY TACHYCARDIA

Accessory Pathways

AV reentry tachycardia occurs as a result of an anatomically distinct AV connection termed an *accessory pathway*, produced by incomplete separation of the atria and ventricles during fetal development. The most common AV accessory pathway (often called a *Kent bundle*) is located around the mitral or tricuspid annulus. In about 10% of cases, there are multiple pathways.

Accessory pathways are capable of conduction in either or both directions. Accessory pathways that are capable of antegrade conduction are referred to as *manifest*, demonstrating a delta wave during sinus rhythm when the atrial impulses conduct over the accessory pathway without encountering AV delay. The PR interval is short (<120 msec), and the QRS complex is wide; this occurs because the atrial impulse enters nonspecialized ventricular myocardium, and depolarization progresses slowly at first, giving rise to the delta wave before it is overtaken by a depolarization wavefront propagating via the normal conduction tissue. An accessory pathway that is capable of only retrograde conduction is termed *concealed* and does not produce a short PR interval or delta wave during sinus rhythm.

Mechanism and Electrocardiographic Presentation

The reentry circuit of orthodromic AV reentry tachycardia involves the AV node and an accessory pathway, with the impulses conducting from

the atria to the ventricles over the AV node and traveling in the reverse direction through the accessory pathway (see Fig. 79-4, B). In antidromic AV reentry tachycardia, the reentrant impulses conduct antegradely from the atria to the ventricles via an accessory pathway and retrogradely via the AV node or a second accessory pathway (see Fig. 79-4, C). Antidromic AV reentry tachycardia is uncommon (<10% of cases). Atrial fibrillation is usually encountered in patients with antegradely conducting pathways (see Fig. 79-4, D).

Acute Management

In an emergency, distinguishing between AV nodal reentry tachycardia and AV reentry tachycardia may be difficult, but it is usually not critical because both tachycardias respond to the same treatment. If the patient is hemodynamically stable, vagal maneuvers, including carotid sinus massage, the Valsalva maneuver, and facial immersion in cold water (diving reflex), can terminate tachycardia in about 50% of patients (Box 79-1).^{3,4} Commercially available gel packs can be used as cold compresses instead of facial immersion, but the most important elements are wet nostrils and breath-holding.

Pharmacologic Termination

AV blocking agents, such as adenosine, verapamil, diltiazem, and beta-blockers, are effective in terminating both AV nodal reentry and AV reentry tachycardia (Table 79-1).¹

Adenosine

Intravenous (IV) adenosine is effective in diagnosing, rate slowing, and often terminating narrow-complex tachycardias.⁵ Adenosine usually terminates AV nodal reentry tachycardia and AV reentry tachycardia but rarely interrupts the atrial flutter circuit and does not suppress automatic atrial tachycardia; it can, however, produce high-degree AV block during which the tachycardia persists (Fig. 79-5). It has no effect on most ventricular tachycardias. Adenosine is advantageous compared with verapamil because of its rapid onset and absence of a negative inotropic effect in patients with poor left ventricular function and those with significant hypotension.

Adenosine is administered as a very rapid 3- to 6-mg IV bolus; if this is ineffective, another 6- to 12-mg bolus can be given 2 to 5 minutes later. Adenosine is metabolized very quickly, with an effective half-life

of 10 seconds. Adverse effects, including dyspnea, facial flushing, and chest tightness, are therefore short-lived, but in about 12% of patients, adenosine may shorten the atrial effective refractory period and provoke atrial flutter or fibrillation or accelerate conduction over the accessory pathway and produce a rapid ventricular response. In a proportion of patients, ventricular premature beats and nonsustained ventricular tachycardia may occur after the successful termination of

BOX 79-1

Vagal Maneuvers to Terminate Tachycardia

CAROTID SINUS MASSAGE

Ensure that there is no significant carotid artery disease (carotid bruits).

Monitor the electrocardiogram continuously.

Place the patient in the supine position with the head slightly extended.

Start with right carotid sinus massage.

Apply firm rotatory or steady pressure to the carotid artery at the level of the third cervical vertebra for 5 sec.

If no response, massage the left carotid sinus.

Generally, right carotid sinus massage decreases sinus node discharge, and left carotid sinus massage slows atrioventricular conduction.

Do not massage both carotids at the same time.

A single application of carotid sinus pressure is effective in about 20% to 30% of patients with paroxysmal supraventricular tachycardias; multiple applications terminate tachycardia in about 50% of patients.

Asystole is a potential but rare complication.

VALSALVA MANEUVER

Valsalva maneuver involves an abrupt voluntary increase in intrathoracic and intraabdominal pressures by straining.

Monitor the electrocardiogram continuously.

Place the patient in the supine position.

The patient should not take a deep inspiration before straining.

Ideally, the patient blows into a mouthpiece of a manometer against a pressure of 30 to 40 mm Hg for 15 sec.

Alternatively, the patient strains for 15 sec while breath-holding.

Transient acceleration of tachycardia usually occurs during the strain phase as a result of sympathetic excess.

On release of strain, the rate of tachycardia slows because of the compensatory increase in vagal tone (baroreceptor reflex); it may terminate in about 50% of patients.

Termination of tachycardia may be followed by pauses and ventricular ectopics.

TABLE 79-1 Acute Pharmacologic Rate Control in Atrial Tachyarrhythmias

| DRUG | ROUTE OF ADMINISTRATION | DOSE | ONSET | POTENTIAL ADVERSE EFFECTS |
|-------------|-------------------------|--|-----------|--|
| Verapamil | Intravenous | 5-10 mg (0.075-0.15 mg/kg) over 2 min; if no response, additional 5-10 mg after 15-30 min; 3-10 mg every 4-6 h for rate control | 3-5 min | Hypotension, bradycardia, heart block, possible deterioration of ventricular function in the presence of organic heart disease |
| Diltiazem | Intravenous | 0.25 mg/kg over 2 min; if no response, additional 0.35 mg/kg after 15-30 min; followed by 5-15 mg/h infusion for rate control | 2-7 min | |
| Esmolol | Intravenous | 0.5 mg/kg over 1 min, followed by 0.05-0.2 mg/kg/min for 4 min; if no response after 5 min, 0.5 mg/kg for 1 min, followed by 0.1 mg/kg for 4 min; infusion 0.05-0.2 mg/kg/min for rate control | 2-3 min | Hypotension, bradycardia, heart block, possible deterioration of ventricular function in the presence of organic heart disease |
| Metoprolol | Intravenous | 2.5-5 mg over 2 min followed by repeat doses if necessary (total 10-15 mg) | 5 min | |
| Atenolol | Intravenous | 2.5 mg over 2 min, followed by repeat doses if necessary (total 10 mg) or infusion 0.15 mg/kg for 20 min | 5-10 min | |
| Propranolol | Intravenous | 1 mg over 1 min (total 10-12 mg; 0.15 mg/kg) | 5 min | |
| Digoxin | Intravenous | 0.5-1 mg, followed by 0.25 mg every 2-4 h (maximum, 1.5 mg) | 30-60 min | Bradycardia, atrioventricular block, atrial arrhythmias, ventricular tachycardia |

Intravenous amiodarone can also be effective for rate control, especially in patients with poor left ventricular function, but there is insufficient evidence to support this recommendation. The rate-slowing effect of amiodarone is usually delayed by 1-2 hours.



FIGURE 79-5 ■ **A**, Adenosine usually terminates atrioventricular reentry tachycardias. **B** and **C**, It rarely interrupts the atrial flutter circuit or suppresses automatic focal atrial tachycardia but produces high-degree atrioventricular block during which the tachycardia persists.

the supraventricular tachycardia.⁶ Some individuals, particularly heart transplant recipients, are unusually sensitive to adenosine and require a lower dose (1 mg).

Verapamil and Diltiazem

Verapamil is administered as a 5- to 10-mg IV bolus over 2 minutes, and the effect on the tachycardia should occur in 5 to 10 minutes. If necessary, a second bolus of 10 mg can be given 30 minutes after the initial dose. Vagal maneuvers can be effective at this stage. Verapamil should not be used for wide-complex tachycardias. IV verapamil is contraindicated in patients with poor left ventricular function or heart failure, and it should not be administered after pretreatment with oral, or especially IV, beta-blockers. It should not be used for atrial fibrillation associated with preexcitation syndrome because it may result in acceleration of conduction over an antegradely conducting accessory pathway (especially with a short effective refractory period), resulting in a rapid ventricular response and ventricular fibrillation. Diltiazem is an alternative to verapamil, but diltiazem has been associated with lower effective rates.⁷ Diltiazem has the same contraindications as verapamil.

DC cardioversion or pharmacologic conversion with IV ibutilide, propafenone, or flecainide is appropriate for termination of atrial fibrillation with preexcitation.

Beta-Blockers

Among beta-blockers, esmolol, administered as an IV infusion at a rate of 50 to 200 $\mu\text{g/kg/min}$, is the agent of choice because of its rapid onset. More readily available IV metoprolol, atenolol, and propranolol can also be considered (see Table 79-1). Excessive bradycardia caused by AV node blocking agents can be countered with IV injection of atropine, 0.6 to 2.4 mg in divided doses of 0.6 mg.

Other Antiarrhythmic Agents

Because adenosine, verapamil, diltiazem, and beta-blockers are so highly effective in terminating AV nodal reentry tachycardia and AV reentry tachycardia, specific antiarrhythmic drugs such as propafenone, flecainide, sotalol, ibutilide, and amiodarone are seldom needed in the acute setting. Digoxin is not useful because it is often ineffective



FIGURE 79-6 ■ Accelerated junctional rhythm with independent sinus node activity.

and may facilitate conduction over the accessory pathway, shorten the atrial effective refractory period, and promote atrial fibrillation.

Atrial Pacing

In patients with implantable devices, antitachycardia pacing functions can be used to terminate the arrhythmia. However, there is also a risk of inducing atrial fibrillation with a rapid ventricular response in a patient with an antegradely conducting accessory pathway.

Long-Term Management

Patients with AV nodal reentry tachycardia and AV reentry tachycardia should be referred to a cardiologist for electrophysiologic evaluation and long-term management. Both pharmacologic and nonpharmacologic alternatives, including ablation of an accessory pathway, are widely available.

ACCELERATED ATRIOVENTRICULAR RHYTHM

Accelerated AV rhythm is produced by abnormal automaticity in the AV node. It is a narrow QRS complex tachycardia (unless bundle branch block is present), with a ventricular rate ranging from 70 to 250 beats per minute. AV dissociation is also present because the atria are activated normally by the sinus node impulse, while the ventricles are depolarized from an accelerated junctional site (Fig. 79-6). This arrhythmia is commonly due to digitalis toxicity, and drug withdrawal is the usual therapy. If the rate of the AV node pacemaker is not fast, atropine can be given to increase the sinus node discharge rate until the sinus node resumes its dominance.

ATRIAL FIBRILLATION AND ATRIAL FLUTTER

Atrial fibrillation with a fast ventricular response is the most common supraventricular arrhythmia encountered in the emergency department in both younger adults with first-onset arrhythmia and older patients presenting with decompensation. Atrial flutter shares these clinical presentations and requires similar initial therapy. The acute management of both arrhythmias is, therefore, considered together.

Atrial Flutter

Mechanism

Classification of atrial flutter is based on the ECG presentation and electrophysiologic mechanisms. The most common type is typical isthmus-dependent atrial flutter. Incisional reentry atrial flutter occurs after surgical correction for congenital heart disease. There are also various forms of atypical flutters, such as atypical right atrial isthmus-dependent flutter (double-wave and lower loop reentry) and left atrial flutter, in which the circuit contains the pulmonary vein or mitral valve annulus.⁸

Typical, or isthmus-dependent, atrial flutter involves a macroreentrant right atrial circuit around the tricuspid annulus. The wavefront circulates down the lateral wall of the right atrium, through the eustachian ridge between the tricuspid annulus and the inferior vena cava,

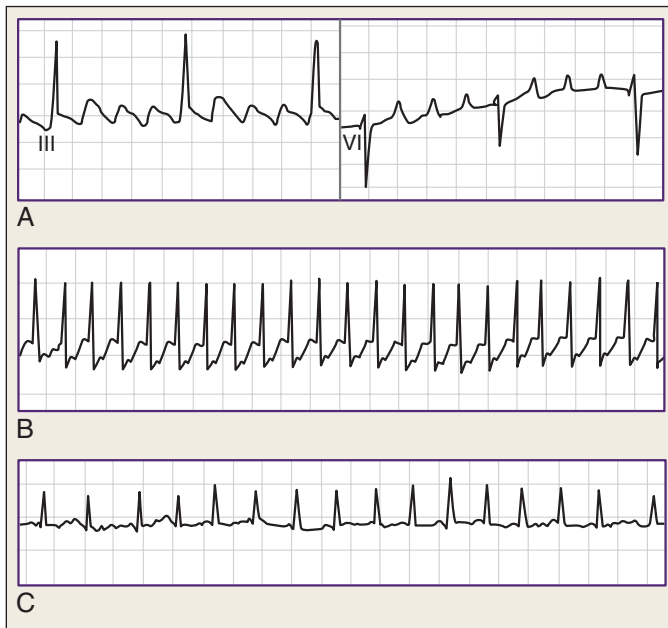


FIGURE 79-7 ■ **A**, Typical counterclockwise atrial flutter. F waves are negative in leads II, III, aVF, and V_{5-6} and positive in leads V_{1-2} . **B**, Atrial flutter with 1:1 atrioventricular conduction and a ventricular rate of 270 beats per minute in a patient treated with flecainide. **C**, Atrial fibrillation with fast, uncontrolled ventricular rate.

and up the interatrial septum, giving rise to the most frequent pattern, referred to as *counterclockwise flutter*. Reentry can also occur in the opposite direction (clockwise or reverse flutter).

Electrocardiographic Presentation

Atrial flutter is usually an organized atrial rhythm with an atrial rate typically between 250 and 350 beats per minute. In the more common counterclockwise flutter, F waves are negative in leads II, III, aVF, and V_{5-6} and positive in leads V_{1-2} (Fig. 79-7, A). Clockwise atrial flutter is typically characterized by positive F waves in leads II, III, and aVF and negative waves in leads V_{1-2} .

Treatment with propafenone, flecainide, and amiodarone to prevent recurrent atrial fibrillation without adding an AV blocking agent (beta-blocker or nondihydropyridine calcium antagonist) can organize the arrhythmia into typical atrial flutter with AV conduction of 1:1 or 2:1, producing a ventricular rate response of 150 beats per minute or higher (see Fig. 79-7, B). The probability of 1:1 conduction is increased in the presence of an accessory pathway with a short effective refractory period.

Long-Term Management

The precise mechanism of atrial flutter is important for long-term management (e.g., catheter ablation) but has little influence on the initial approach. Patients with all types of atrial flutter should be referred for electrophysiologic evaluation with a view to ablation. Atrial fibrillation may develop even after successful ablation, and the patient should be followed up carefully.

Atrial Fibrillation

Electrocardiographic Presentation

Atrial fibrillation is defined as rapid oscillations or fibrillatory f waves that vary in size, shape, and timing (see Fig. 79-7, C). The ventricular response rate is variable and depends on the rate and regularity of atrial activity, the refractory properties of the AV node itself, and the balance

between sympathetic and parasympathetic tone. RR intervals are irregular unless the patient has complete AV block or a paced rhythm.

Classification

The clinical classification of atrial fibrillation includes first detected, paroxysmal (up to 7 days), persistent (more than 7 days), long-standing persistent (>1 year), and permanent (accepted) forms of the arrhythmia. Classification is essential for deciding between rhythm restoration and rate control. First-onset atrial fibrillation, if the duration of the episode is less than 48 hours, is a clear indication to restore sinus rhythm by either electrical or pharmacologic means. Because atrial fibrillation may be asymptomatic, the “first detected episode” should not be regarded as necessarily the true onset of the arrhythmia, in which case formal anticoagulation (see later discussion) and rate control may be preferred. Persistent or permanent atrial fibrillation should be treated initially by rate control and anticoagulation when appropriate.

Long-Term Management

Recognition of the pulmonary veins as the source of atrial premature beats or rapid atrial tachycardia that triggers atrial fibrillation or drives the atria prompted the development of ablation techniques that may “cure” the arrhythmia. In symptomatic permanent or persistent atrial fibrillation, AV node ablation and permanent pacing are effective in rate and symptom control. Any patient with first-onset or recurrent atrial fibrillation should be referred to a cardiologist for long-term management.

Acute Management

Acute therapy for atrial flutter and atrial fibrillation depends on the clinical presentation. Emergency electrical cardioversion is indicated for patients with hemodynamic collapse and progressively deteriorating left ventricular systolic function.

Direct-Current Cardioversion

Atrial flutter can be converted with DC shock energy as low as 25 to 50 J, but because a 100-J shock is virtually always successful, it should be considered as the initial shock strength. In recent-onset atrial fibrillation, sinus rhythm can be restored by a shock of 100 J, but it is generally recommended that cardioversion be started with an initial shock energy level of 200 J or greater. In patients with an arrhythmia of unknown duration, heavier individuals, and those with chronic obstructive lung disease and pulmonary emphysema, an initial setting of 300 to 360 J is appropriate. Success may occur on the third or subsequent attempt at an intensity that initially proved ineffective.

Rate Control

Rate control is pertinent to all atrial tachyarrhythmias, particularly if restoration of sinus rhythm is deferred. IV verapamil, diltiazem, and beta-blockers can rapidly control the ventricular response rate in atrial fibrillation² (see Table 79-1), but their efficacy may be less in atrial flutter. The decrease in the ventricular rate (approximately 20%-30%), time to maximal effect (20-30 minutes), conversion rate (12%-25%), and adverse reactions (usually hypotension and bradycardia, although left ventricular dysfunction and high-degree heart block may also occur) are reportedly similar with both classes of drugs. Beta-blockers are preferable if thyrotoxicosis is suspected as a cause of the arrhythmia.

IV digoxin is no longer the treatment of choice when rapid rate control is essential because of the delayed onset of its therapeutic effect (>60 minutes). However, because of its positive inotropic action, digoxin may be safer to use in patients with poor ventricular function and moderately fast ventricular rates. Digoxin may convert flutter to fibrillation, in which rate control is easier to accomplish.

There is evidence that IV amiodarone may be effective in rate control when other AV node blocking agents have no effect on the ventricular response or are contraindicated.

TABLE 79-2 Antiarrhythmic Drugs for Pharmacologic Conversion of Atrial Tachyarrhythmias

| DRUG | ROUTE OF ADMINISTRATION | DOSE | POTENTIAL ADVERSE EFFECTS |
|--------------|---------------------------------------|--|--|
| Flecainide | Oral or intravenous | Loading oral dose 200-300 mg or slow injection 1.5-2 mg/kg over 10-20 min; if no response, infusion 1.5 mg/kg for 1 h, then 0.1-0.25 mg/kg over 24 h | Rapidly conducted atrial flutter, possible deterioration of ventricular function in the presence of organic heart disease, monomorphic ventricular tachycardia |
| Propafenone | Oral or intravenous | Loading oral dose 450-600 mg or 1.5-2 mg/kg over 10-20 min, followed by infusion 5-10 mg/kg if needed | |
| Ibutilide | Intravenous | 1 mg over 10 min; if no response, additional 1 mg | QT prolongation, torsades de pointes, hypotension |
| Amiodarone | Intravenous (preferably central line) | 5-7 mg/kg over 30-60 min, followed by infusion 20 mg/kg for 24 h (total 1200-1800 mg) | Hypotension, bradycardia, QT prolongation, torsades de pointes (?), gastrointestinal upset, constipation, phlebitis |
| Procainamide | Intravenous | 1000 mg over 30 min, followed by 2 mg/min infusion | QRS widening, torsades de pointes, rapid atrial flutter |
| Vernakalant | Intravenous | 3 mg/kg over 10 min; after 15-min break, 2 mg/kg unless arrhythmia terminated | Hypotension, postfibrillation bradycardia |

Pharmacologic Cardioversion

If the arrhythmia is hemodynamically stable and of recent onset, pharmacologic cardioversion can be effective.

Flecainide and Propafenone. Pharmacologic cardioversion of atrial fibrillation can be accomplished with the IC class of antiarrhythmic drugs—flecainide or propafenone—administered orally as a single dose of 300 or 600 mg, respectively (Table 79-2).² Placebo-controlled randomized studies show an efficacy rate of 60% to 80% between the third and eighth hour after drug ingestion.^{9,10} Both oral and IV routes of administration are equally effective, although with IV injection, restoration of sinus rhythm can be achieved more quickly.

Flecainide is given as a slow IV injection of 2 mg/kg over 10 to 30 minutes, up to the maximum dose of 150 mg. Propafenone is administered as a slow IV injection of 1.5 to 3 mg/kg, up to 300 to 600 mg. Because these drugs can significantly slow the atrial rate (from 300-350 beats/min to 200 beats/min), which may result in 1:1 AV conduction, beta-blockers or calcium antagonists with negative dromotropic effects on AV node conduction (verapamil, diltiazem) should be used concomitantly. Other cardiovascular effects include reversible QRS widening and (rarely) left ventricular decompensation. Because of their negative inotropic effects, flecainide and propafenone are contraindicated in patients with severe structural heart disease and a poor ejection fraction.

Class IC drugs are usually ineffective for the conversion of atrial flutter because they slow conduction within the reentrant circuit and prolong the flutter cycle length but rarely interrupt the circuit. These drugs pose the risk of increased (e.g., 2:1 or 1:1) AV conduction. Reported efficacy rates are as low as 13% to 40% with IV flecainide and propafenone.

Ibutilide. The class III agent, ibutilide, is administered intravenously as a 10-minute injection of 1 to 2 mg and is particularly effective in terminating atrial flutter, with a success rate of about 60%. Its administration may be associated with excessive QT interval prolongation, however, because of rapid delayed rectifier potassium current (I_{Kr}) blockade, which may increase the risk of torsades de pointes.^{11,12} It is less effective in atrial fibrillation. Higher doses of ibutilide administered as two successive infusions of 1 mg are usually required to terminate fibrillation. The advantage of ibutilide is that it may be effective in the conversion of arrhythmias of up to 30 days' duration, but the success rate drops significantly to 20% to 30%. The safety of ibutilide in patients with poor left ventricular function is unknown.

Amiodarone. Amiodarone administered intravenously at a dose of 5 mg/kg for 1 hour, followed by an infusion of 20 mg/kg over 24 hours, is effective in converting both atrial fibrillation and flutter, but

the effect is significantly delayed.^{13,14} However, because of its ability to control the ventricular rate, low likelihood of torsades de pointes, and absence of a negative inotropic effect, amiodarone can be used safely in patients with significant structural heart disease and those who are critically ill.

Procainamide and Sotalol. Procainamide administered as a slow IV injection of 1000 mg over 20 to 30 minutes, followed if necessary by an infusion of 2 mg/min over 1 hour, converts atrial flutter or fibrillation of less than 48 hours' duration, but its efficacy is limited in longer lasting arrhythmias.¹⁵ It is less effective than propafenone, flecainide, and ibutilide.

Sotalol is not indicated for the pharmacologic cardioversion of atrial flutter or fibrillation because its efficacy does not exceed 11% to 13%; however, it may satisfactorily control the ventricular rate.

Vernakalant. This drug is given by a short IV infusion (3 mg/kg over 10 minutes). If after a 15-minute waiting period the arrhythmia persists, a second infusion of 2 mg/kg may be given over 10 minutes. In recent-onset (<72 hours) atrial fibrillation, about 50% of cases will terminate on average 12 minutes from the start of the first infusion. Vernakalant may be given to patients with underlying structural heart disease but not to patients with grades II/IV congestive heart failure. Proarrhythmia effects are uncommon, but hypotension and posttermination bradycardia may occur.¹⁶

The choice of an antiarrhythmic agent for cardioversion is illustrated in Figure 79-8.

Atrial Pacing

Burst overdrive atrial pacing can terminate atrial flutter in about 80% of cases and is feasible after cardiac surgery, when patients frequently have epicardial atrial pacing wires, or in patients with implantable dual-chamber pacemakers and defibrillators. High-frequency (50 Hz or 3000 beats/min) atrial pacing is available in some of the latest models for the termination of early-onset atrial fibrillation, but its efficacy has not yet been established. Atrial burst overdrive pacing may induce sustained atrial fibrillation, although short periods of fibrillation often precede conversion to sinus rhythm.

Anticoagulation

Anticoagulation is imperative if the arrhythmia persists for more than 24 to 48 hours or if its duration is unknown. Atrial flutter and atrial fibrillation pose similar risks of thromboembolism, and the same criteria for anticoagulation should be applied in patients with either arrhythmia. In hemodynamically stable arrhythmias of more than 48 hours' or of unknown duration, rate control and 3 weeks' anticoagulation with warfarin (international normalized ratio 2.0 to 3.0) should

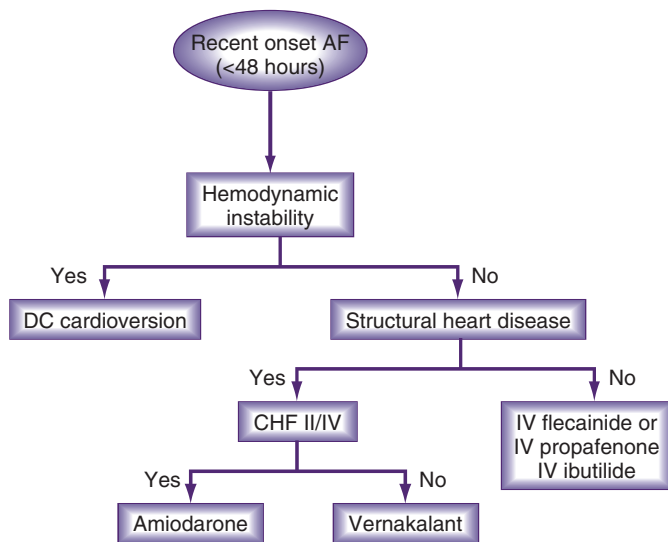


FIGURE 79-8 ■ Choice of antiarrhythmic for pharmacologic cardioversion of atrial fibrillation.

be considered before any intervention (electrical or pharmacologic cardioversion, catheter ablation).¹⁷

Transesophageal Echocardiography–Guided Cardioversion

If, for any reason, deferral of cardioversion is not indicated, the transesophageal echocardiography–guided approach, with short-term anticoagulation using low-molecular-weight heparin, is a safe and effective alternative.¹⁸ It may be clinically beneficial in patients with recent-onset arrhythmias or in individuals at high risk of bleeding complications during prolonged anticoagulation therapy.¹⁹ Compared with unfractionated heparin, low-molecular-weight heparin therapy does not involve prolonged IV administration or laboratory monitoring and, therefore, has the potential to greatly simplify cardioversion-related anticoagulation therapy in low-risk individuals. Postcardioversion anticoagulation should be considered if atrial fibrillation has been present for 48 hours or more, or if thromboembolic risk factors are present.^{17,20}

■ ATRIAL TACHYCARDIA

Mechanism

The mechanism of atrial tachycardia is attributed to enhanced automaticity, triggered activity, or intraatrial reentry. Macroreentrant atrial tachycardia often occurs after surgery for congenital heart disease. Focal atrial tachycardia typically originates along the crista terminalis in the right atrium, in the pulmonary veins entering the left atrium, or around one of the atrial appendages.

Electrocardiographic Presentation

The heart rate varies from 120 to 250 beats per minute, P waves precede the QRS complexes, and PP intervals are regular (see Fig. 79-5, B). The PR interval is linked to the rate of the tachycardia and is longer than in sinus rhythm at the same rate. P-wave morphology is usually different from that observed during sinus rhythm and depends on the site of origin. Left atrial tachycardia presents with negative P waves in leads I, aVL, V₅, and V₆. Automatic atrial tachycardia may present as an incessant variety, leading to tachycardia-induced cardiomyopathy.

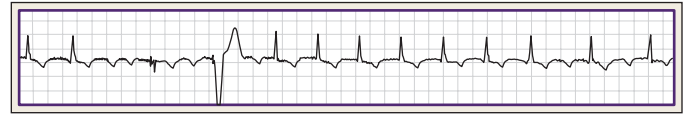


FIGURE 79-9 ■ Atrial tachycardia with varying atrioventricular block due to digitalis toxicity.

Atrial Tachycardia with Atrioventricular Block

Tachycardia with AV block occurs commonly in patients with organic heart disease, and in 50% to 75% of cases, it is due to digitalis toxicity (Fig. 79-9). Digoxin-specific antibody fragments are available for the reversal of life-threatening overdose.

Multifocal Atrial Tachycardia

This tachycardia presents as rapid, irregular atrial activity with discrete P waves of varying morphology and is considered a transitional rhythm between atrial tachycardia and fibrillation. However, it may occur in patients with chronic severe pulmonary disease as a result of theophylline or beta-agonist overdose. Elimination of the causative factor may reduce the need for antiarrhythmic therapy. IV verapamil can accomplish rate control.

Acute Management

DC cardioversion converts atrial tachycardia based on the reentry mechanism or triggered activity, but it may not terminate automatic tachycardia. Similarly, atrial overdrive pacing may slow the tachycardia rate but seldom suppresses the automatic focus.

It is generally accepted that beta-blockers and calcium antagonists, particularly verapamil, can either terminate the tachycardia or produce rate control. Adenosine can terminate atrial tachycardia, but the most common response to adenosine is to create AV block and, thereby, reveal the unaffected tachycardia (see Fig. 79-5, B and C).

Flecainide, propafenone, sotalol, and amiodarone are effective in converting atrial tachycardia. If the arrhythmia occurs as a result of digitalis intoxication, therapy includes the cessation of digoxin and IV administration of potassium.

Long-Term Management

Patients with atrial tachycardia should be referred to a cardiologist because the arrhythmogenic focus can be found and ablated in up to 86% of cases.

■ INAPPROPRIATE SINUS TACHYCARDIA

Inappropriate sinus tachycardia is a persistent increase in resting heart rate unrelated or out of proportion to the level of physical or emotional stress. It is found predominantly in women and is not uncommon in health professionals. Sinus tachycardia due to intrinsic sinus node abnormalities such as enhanced automaticity or abnormal autonomic regulation of the heart, with excess sympathetic and reduced parasympathetic input, is not unusual. The main therapy is beta-blockers, although ivabradine, a drug that blocks the main current responsible for diastolic depolarization in the sinus node, is being increasingly used in Europe.²¹ In general, sinus tachycardia is a secondary phenomenon, and the underlying cause should be actively investigated. Depending on the clinical setting, acute causes include fever, hypotension, infection, anemia, thyrotoxicosis, hypovolemia, acute heart failure, acute pulmonary embolism, and shock. Sinus tachycardia may be associated with the abuse of drugs such as amphetamines.

KEY POINTS

1. Supraventricular tachycardia (SVT) is characterized by narrow QRS complexes, but differentiating SVT from ventricular tachycardia may be necessary when bundle branch block, rate-dependent aberrancy, and antidromic atrioventricular (AV) reentry tachycardia are present.
2. If the diagnosis of SVT cannot be proved, the arrhythmia should be treated as ventricular tachycardia.
3. Immediate direct-current (DC) cardioversion is the treatment for any hemodynamically unstable tachycardia.
4. In hemodynamically stable paroxysmal junctional tachycardias (AV nodal reentry tachycardia and AV reentry tachycardia), vagotonic maneuvers should be tried first because they may terminate tachycardia in about 50% of patients without the need to resort to pharmacologic therapy.
5. Intravenous (IV) adenosine, verapamil, and esmolol are first-line drug therapies for paroxysmal junctional tachycardias, but adenosine and verapamil should not be used for wide complex tachycardias and atrial fibrillation with preexcitation.
6. DC cardioversion or pharmacologic conversion with IV ibutilide or flecainide is appropriate for the termination of atrial fibrillation associated with preexcitation syndrome.
7. IV verapamil, diltiazem, esmolol, metoprolol, and propranolol can rapidly accomplish rate control in atrial fibrillation but may be less effective in atrial flutter.
8. Beta-blockers are preferable in atrial fibrillation associated with thyrotoxicosis.
9. Pharmacologic cardioversion of atrial fibrillation in the absence of severe underlying heart disease can be attained using oral or IV flecainide or propafenone, vernakalant, and IV ibutilide, but the last is more effective in atrial flutter.
10. Propafenone, flecainide, and vernakalant may result in atrial flutter with slow atrial rates and 2:1 or 1:1 AV conduction; verapamil, diltiazem, or beta-blockers should be available to treat this complication. Ibutilide can significantly prolong the QT interval and cause polymorphic ventricular tachycardia that, if sustained, may require DC cardioversion.
11. IV amiodarone should be considered as first-line drug therapy in patients with severely impaired left ventricular function.
12. Accelerated AV rhythm and atrial tachycardia with AV block commonly occur as a result of digitalis toxicity; digitalis withdrawal is the usual therapy.
13. Anticoagulation is indicated if atrial fibrillation or flutter persists for more than 48 hours or if the duration is unknown; anticoagulation and rate control should be the initial therapy in these patients.
14. An alternative approach is transesophageal echocardiography, to exclude the presence of atrial thrombi or dense spontaneous echocontrast, and short-term anticoagulation with low-molecular-weight heparin, followed by DC or pharmacologic cardioversion.
15. Patients with paroxysmal junctional tachycardias, atrial tachycardia, atrial flutter, and first-onset or recurrent atrial fibrillation should be referred to a cardiac electrophysiologist/cardiologist for assessment and long-term management planning; effective nonpharmacologic therapies are available for these arrhythmias.

ANNOTATED REFERENCES

Albers GW, Dalen JE, Laupacis A, et al. Antithrombotic therapy in atrial fibrillation. *Chest* 2001;119:194S–206S.

This paper focuses on the prevention of stroke in nonrheumatic atrial fibrillation and flutter and provides expert recommendations regarding risk stratification, anticoagulation strategies, cardioversion (including transesophageal echocardiography-guided cardioversion), and long-term management of patients at risk of thromboembolism. It contains a complete review of the evidence base for anticoagulation in atrial fibrillation.

Blomström-Lundqvist C, Scheiman MM, Aliot EM, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to develop guidelines for the management of patients with supraventricular arrhythmias). *J Am Coll Cardiol* 2003;42:1493–1531.

These practice guidelines describe a range of generally accepted approaches to the diagnosis and management of supraventricular tachyarrhythmias (excluding atrial fibrillation) and provide insight into the multiple mechanisms defined by electrophysiologic studies, with a focus on both acute and long-term therapies.

Camm AJ. Atrial fibrillation: is there a role for low-molecular-weight heparin? *Clin Cardiol* 2001;24:115–119.

This review paper summarizes evidence emerging from clinical studies that clearly supports both the use of transesophageal echocardiography-based cardioversion protocols and the introduction of low-molecular-weight heparin for anticoagulation in atrial fibrillation. Clinical settings in which low-molecular-weight heparin may offer advantages over unfractionated heparin and warfarin are discussed.

Fuster V, Rydén LE, Asinger RV, et al. Task force report: ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. *Eur Heart J* 2001;22:1852–1923.

These guidelines incorporate a comprehensive review of the latest information about the classification, epidemiology, mechanisms, and clinical presentations of atrial fibrillation. Practical approaches to acute and long-term management of this arrhythmia are discussed at length. An extensive list of references covers various aspects of atrial fibrillation.

Mehta D, Wafa S, Ward DE, Camm AJ. Relative efficacy of various physical manoeuvres in the termination of junctional tachycardia. *Lancet* 1988;1:1181–1185.

This paper compares the ability of four vagotonic physical maneuvers to terminate paroxysmal supraventricular tachycardias that involve the AV node as part of their reentrant circuits. It shows that these tachycardias can be terminated without resorting to pharmacologic therapy in more than half of patients. The paper provides a detailed methodologic description and explains the physiologic effects of vagotonic maneuvers.

References for this chapter can be found at expertconsult.com.

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Cardiac arrhythmias are common in critically ill patients and a frequent reason for hospital admission to areas with capability for continuous electrocardiographic monitoring and personnel trained in their recognition and management (e.g., ICUs and telemetry units).

Arrhythmias are supraventricular if they originate above the atrioventricular (AV) node in atrial tissue or pulmonary veins. They may compromise stroke volume and create hemodynamic instability by excessive heart rate and/or reduced ventricular filling after losing the atrial contribution to preload. However, in the absence of accessory conduction pathways bypassing the AV node (e.g., Wolf-Parkinson-White syndrome), supraventricular arrhythmias are rarely life threatening and may be managed without immediate urgency by pharmacologic or electrical means. In contrast, arrhythmias that originate in ventricular structures, such as ventricular tachycardia (VT) and ventricular fibrillation (VF), may be life threatening and require immediate treatment.

NORMAL ELECTROPHYSIOLOGY

Anatomic Synopsis

The electrical impulse originates in the sinoatrial (SA) node, located high on the right atrium near its junction with the superior vena cava (Fig. 80-1). The impulse propagates through muscle fibers and specialized internodal pathways (composed of Purkinje-type fibers) to converge on the AV node, located in the interatrial septum near the tricuspid valve. The impulse then travels through the bundle of His, its left and right branches, and the Purkinje system to activate simultaneously both ventricles. A ring of fibrous tissue interposed between the atria and the ventricles prevents spread of the impulse through muscle fibers, enabling the AV node to function as relay and filter, preventing 1:1 conduction under conditions of very rapid atrial activation, such as atrial flutter (rate ~300/s) or atrial fibrillation (rate ~600/s).

Action Potential and Pacemaker Activity

Action Potential

Action potentials initiate and propagate the electrical impulse, ultimately reaching cardiomyocytes signaling Ca^{2+} -induced Ca^{2+} release from the sarcoplasmic reticulum to activate contractile proteins. Action potentials result from a coordinated sequence of depolarization and repolarization of polarized cells following opening and closing of ion channels, carrying electrical currents through the plasma membrane. The main currents result from influx of Na^+ and Ca^{2+} (inward currents) and efflux of K^+ (outward currents).¹⁻³

Cells from the Purkinje system and muscle tissue have stable resting potential of approximately -90 mV (negative inside), largely the result of a K^+ current known as *inward rectifier* (I_{K1}). I_{K1} “anchors” the membrane potential to a voltage close to the equilibrium potential of potassium and is turned off during depolarization. Triggering an action potential requires depolarization between -70 and -80 mV—that is, the activation threshold for fast voltage-gated Na^+ channels driving a Na^+ current (I_{Na})³—and typically occurs upon arrival of another action potential. The I_{Na} drives the membrane potential toward the Na^+ equilibrium potential, reversing the membrane potential to approximately

$+20$ mV (overshoot). This sequence is *phase 0* of the action potential, which is followed by repolarization in four phases (Fig. 80-2).

Phase 1 is early repolarization after rapid inactivation of I_{Na} and rapid activation and inactivation of a “transient” K^+ current (I_{To}) carried by two subpopulations of K^+ channels driving a “fast” recovering (I_{Tof}) and a slowly recovering (I_{Tos}) current. I_{Tof} appears to be the predominant contributor to I_{To} in ventricular myocardium.⁴ Because K^+ channels carrying I_{To} are expressed in the subepicardium and mid-myocardium but not in the subendocardium, I_{To} contributes to repolarization inhomogeneity.⁵

Phase 2 is mid-repolarization (plateau phase), which results predominantly from a Ca^{2+} current carried by the slow and prolonged opening of L-type voltage-gated Ca^{2+} channels ($\text{I}_{\text{Ca-L}}$).^{6,7} These channels open during *phase 0* at a membrane potential of -30 to -40 mV; they are inactivated by increased cytosolic Ca^{2+} and are strongly regulated by neurotransmitters.

Phase 3 is late repolarization, which follows closing of Ca^{2+} channels and opening of K^+ channels with slow activation kinetics that carry currents known as *delayed rectifiers* (I_{K}), which have a rapid (I_{Kr}) and a slow (I_{Ks}) component.^{8,9} Both are implicated in heritable forms of the long QT syndrome.¹⁰ Opening of I_{K1} —the main contributor to the resting potential—also contributes to repolarization.

Phase 4 is the return to resting membrane potential, the interval during which ionic balance is restituted, largely through the Na^+/K^+ pump.

Pacemaker Activity

Cells of the SA and AV nodes lack voltage-gated Na^+ channels; therefore, phase 0 is carried by $\text{I}_{\text{Ca-L}}$.¹¹ Because of their slower opening kinetics, phase 0 is slanted and in part responsible for the slower SA and AV nodes’ conduction velocity (~ 50 cm/s) relative to the His-Purkinje system (~ 400 cm/s) and muscle cells (~ 100 cm/s). Pacemaker activity of SA and AV node cells results from slow phase 4 depolarization (known as *prepotential* or *pacemaker potential*) to about -40 mV. Slow depolarization involves a background Na^+ current ($\text{I}_{\text{Na-B}}$), a decay of K^+ currents, and the opening of T-type voltage-gated Ca^{2+} channels ($\text{I}_{\text{Ca-T}}$). Cells of the His-Purkinje system have latent pre-potential activity and can become active when SA or AV node activity is depressed or their impulses are blocked (i.e., “escape rhythm”). Muscle cells exhibit pre-potential activity only under abnormal circumstances.

The preceding description is brief and oversimplified. Various other ion channels, antiporters, pumps, and receptors modulate the action potential. An example is the nonselective cationic channel gated at resting potential by intracellular Ca^{2+} . This channel produces an inward Na^+ current (I_{NS})¹² that may contribute to delayed afterdepolarizations after Ca^{2+} release from the sarcoplasmic reticulum. $\text{I}_{\text{k(atp)}}$ is a K^+ current carried through channels inhibited by adenosine triphosphate (ATP) and opened under conditions of ischemia and hypoxia. $\text{I}_{\text{k(atp)}}$ is the main contributor to action potential shortening and the characteristic ST-segment elevation observed during myocardial ischemia.^{13,14}

The sarcolemmal $\text{Na}^+/\text{Ca}^{2+}$ exchanger is another important modulator of the action potential. Because it exchanges one Ca^{2+} for three Na^+ , it generates a current ($\text{I}_{\text{Na/Ca}}$) whose direction depends on Na^+ and Ca^{2+} gradients and the membrane potential.^{14,15}

Adrenergic receptor stimulation may also modulate the action potential by modifying channel activity.¹⁶⁻¹⁸ For example, β -adrenoceptor

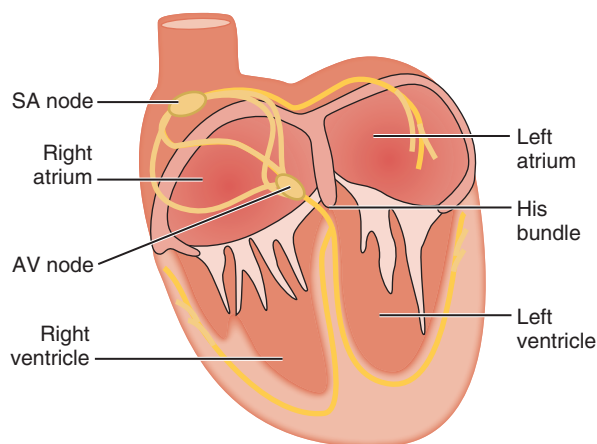


FIGURE 80-1 ■ Conduction system of the heart. AV, atrioventricular; SA, sinoatrial.

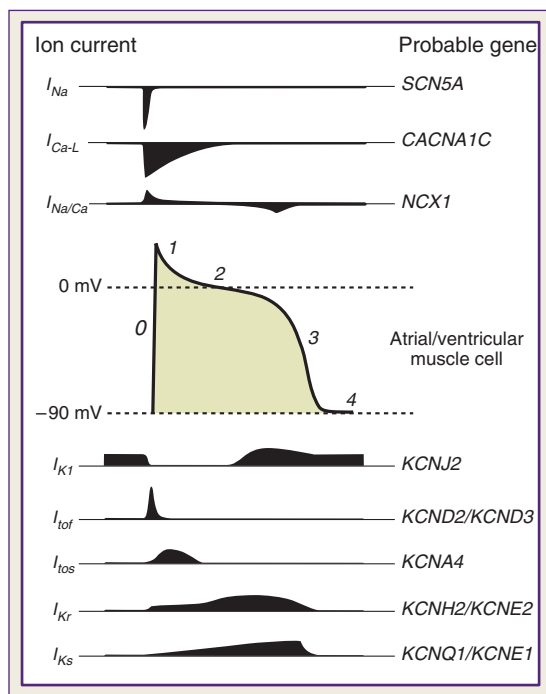


FIGURE 80-2 ■ Action potential of a cardiac muscle cell, depicting the main underlying inward and outward currents and respective gene products. Distinctive phases of the action potential are numbered. Voltage (mV) refers to the potential on the intracellular side of the plasma membrane relative to an outside reference. Notice that the resting potential is negative inside at approximately -90 mV, indicating the cell at rest is polarized (phase 4). The beginning of the action potential is signaled by rapid reduction in such potential, with the inside voltage reaching 0 mV (depolarization) and then becoming transiently positive (overshoot) during phase 0, to be followed by phase 1, 2, and 3 as voltage returns to resting potential on phase 4.

stimulation increases I_{Ca-L} activity and Ca^{2+} influx, enhancing inotropic action. β -Adrenoceptor stimulation also activates K^+ channels, shortening the action potential duration.¹⁹ α_1 -Adrenoceptor stimulation acting via G-protein on the Na^+/K^+ pump, K^+ channels, and phospholipase C and can alter impulse initiation and repolarization—an effect linked to triggered arrhythmias via early and delayed afterdepolarizations and abnormal automaticity during ischemia and reperfusion.^{20,21}

Cardiomyocytes can also react to mechanical forces through stretch-activated ion channels and other mechanisms, including mechanical modulation of Ca^{2+} handling and interaction with other mechanosensitive cells.^{22,23} These mechanisms are in part involved in commotio cordis,²⁴ precordial thump,²⁵ and fist pacing.²⁶

MECHANISMS OF VENTRICULAR TACHYARRHYTHMIAS

Abnormalities in impulse generation and conduction are responsible for the genesis and maintenance of ventricular tachyarrhythmias.

Abnormalities in Impulse Generation

Abnormalities in impulse generation are generally the result of automaticity or triggered activity.

Automaticity

Automaticity is the emergence of ectopic pacemaker activity resulting from enhanced normal automaticity or development of abnormal automaticity.

Enhanced normal automaticity occurs when cells whose pacemaker potentials are normally suppressed by the SA node (e.g., AV node or His-Purkinje system) fire at rates that escape such suppression. This phenomenon may result from effects on phase 4 prepotentials yielding earlier development of action potentials (i.e., less maximal polarization, faster depolarization, or lower threshold potential) or from shortening of the action potential duration with earlier return to phase 4. Enhanced normal automaticity is usually the result of adrenergic stimulation.

Abnormal automaticity refers to impulses originating in cells without intrinsic pacemaker potential and typically occurs by generation of depolarizing currents during phase 4 (e.g., ischemia).²⁷ Abnormal automaticity can develop in atrial and ventricular muscle cells and in specialized tissues other than the SA and AV node. Examples include accelerated idioventricular rhythms and some VTs developing 24 to 72 hours after acute myocardial infarction.²⁸

Triggered Activity

Triggered activity refers to arrhythmias that arise from afterdepolarizations, defined as alterations in membrane potential that occur during repolarization without an external trigger.²⁹ Afterdepolarizations are considered early if they develop during phase 2, phase 3, or early phase 4 of the action potential and are characterized by transient retardations in repolarization (Fig. 80-3). Early afterdepolarizations of sufficient magnitude can trigger an “extra” action potential and are typically associated with conditions that prolong the action potential (e.g., increased sympathetic tone, exogenous catecholamines, hypoxia, acidosis, bradycardia, etc.), enabling increased Ca^{2+} entry through I_{Ca-L} ³⁰ and potentially triggering torsades de pointes.

Afterdepolarizations are considered delayed if they develop in late phase 4 and can also reach the threshold for triggering an action potential (see Fig. 80-3). The main underlying abnormality is intracellular Ca^{2+} overload that triggers Ca^{2+} release from the sarcoplasmic reticulum³⁰ and depolarizing currents (i.e., inward $I_{Na/Ca}$ currents). Delayed afterdepolarizations are classically associated with digitalis toxicity; however, they can also occur with myocardial stretch, hypertrophy, catecholamines, ischemia, and reperfusion. In heart failure, increased expression of the Na^+-Ca^{2+} exchanger along with abnormalities in the ryanodine receptor predispose to delayed afterdepolarizations.

Abnormalities in Impulse Conduction (Reentry)

Abnormalities in impulse conduction leading to reentry account for the vast majority of sustained ventricular tachyarrhythmias. Reentry occurs when a propagating impulse reenters and reexcites a region of previously excited tissue after its refractory period is over. Several

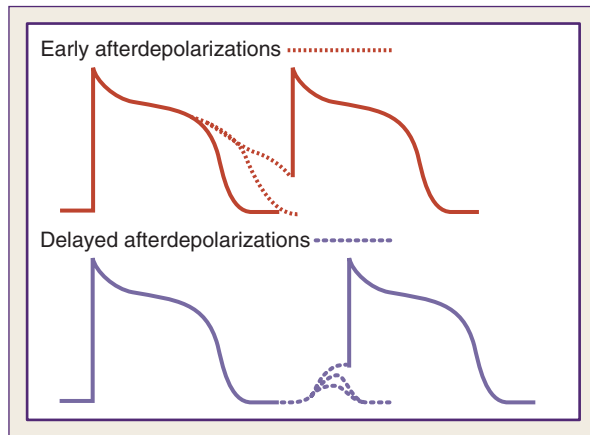


FIGURE 80-3 ■ Afterdepolarizations (dotted lines). Early afterdepolarizations are retardations in repolarization with prolongation in action potential duration (upper figure). Delayed afterdepolarizations represent spontaneous depolarizations that occur after repolarization is over (lower figure). Afterdepolarizations that reach threshold trigger an action potential.

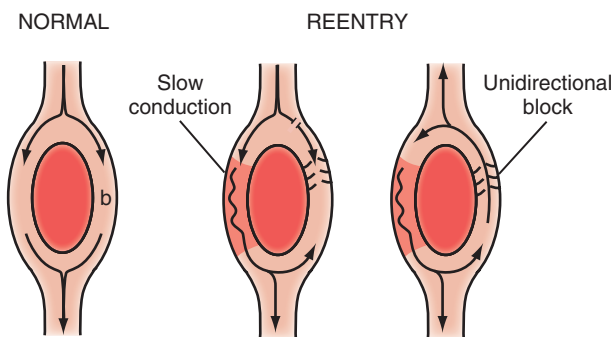


FIGURE 80-4 ■ Ring model of reentry.

forms of reentry have been described, including circus movement, phase 2, and reflection.³¹

Circus Movement

Circus movement is the most widely studied reentry model and encompasses four distinct models: ring, leading circle, figure of eight, and spiral wave.

The *ring model* is the simplest³² and is useful for illustrating the basic mechanism of reentry (Fig. 80-4). The ring model requires two contiguous paths separated by unexcitable tissue. One path (*b* in Fig. 80-4) has a zone of unidirectional block whereas the other path (*a* in Fig. 80-4) allows slow but bidirectional conduction. Once the impulse that is traveling path *a* reaches path *b*, it propagates retrogradely to subsequently reenter path *a*. To establish reentry, the circling impulse wavelength must be shorter than the reentry circuit path length, allowing its leading edge to find tissue in an excitable state. The circling impulse wavelength is the product of the conduction velocity and refractory period; conditions that slow conduction or shorten refractoriness favor reentry.

Reentry is usually triggered by the arrival of a premature beat. Unidirectional block may result from increased refractoriness caused by anatomic abnormalities (e.g., fibrosis, accessory pathway, bundle branch block) or functional defects (e.g., ischemia, action of drugs). The ring model commonly involves AV accessory pathways and the AV node.

The leading circle model is similar to the ring model but without requiring anatomic obstacles and can develop in structurally uniform myocardium by a properly timed premature impulse.³³

The figure-of-eight model was first described in experimental myocardial infarction. It encompasses two reentry circuits moving alongside a functional conduction block (ischemia or infarct) in opposite directions, forming a pretzel-like configuration.³⁴

The spiral wave model is a more complex version of the leading circle model. This model involves a core and filaments and can be described as reentry in two dimensions.³⁵ It has been used to explain monomorphic and polymorphic VTs as well as VF. In monomorphic VT, the spiral wave is anchored and unable to drift, whereas in polymorphic VTs such as torsades de pointes, the spiral is thought to drift. In VF, the spiral wave is thought to break up into multiple rotating spiral waves that continuously extinguish and recreate. Yet, some authors have proposed a single rapidly shifting spiral, and others have postulated a stationary rotor whose frequency of excitation is exceedingly high, resulting in multiple areas of intermittent block.³⁶

Phase 2

Phase 2 reentry refers to local reexcitation consequent to repolarization heterogeneity with areas of markedly shortened repolarization—essentially obliterating phase 2 of the action potential—next to areas of normal repolarization. Local reexcitation may precipitate VT during myocardial ischemia.³⁷ Action potentials of normal duration may alternate with ones of shorter duration during myocardial ischemia, yielding beat-to-beat alternans (temporal dispersion) and site-to-site alternans (spatial dispersion) and promote regions with conduction block and regions with injury current, leading to reentry and ventricular tachyarrhythmias. The degree of spatial and temporal dispersion progresses during ischemia, suggesting this mechanism may be an important trigger of VT and VF during acute myocardial ischemia.³⁸ In the surface ECG, dispersion of the action potential duration manifests as T-wave alternans, a predictor of VF.³⁹

Reflection

Reflection refers to a back-and-forth propagation of the impulse over the same functionally unexcitable tissue, with recurrent activation of the proximal region as a result of electrotonic currents.⁴⁰ The area of unexcitable tissue can result from ischemia and lead to extrasystolic activity. Reflection differs from classic reentry in that the impulse travels along the same pathway in both directions.

CONDITIONS PREDISPOSING TO VENTRICULAR ARRHYTHMIAS

Channelopathies

The term *channelopathies* has been coined to identify a group of diseases caused by abnormalities in ion channels.^{41,42} These abnormalities distort the action potential, primarily accentuating the inherent instability of repolarization and increasing the risk of polymorphic VT of the torsades de pointes type. Channelopathies may be hereditary or acquired.

Hereditary Channelopathies

Most hereditary channelopathies originate from mutations in genes encoding for Na⁺, K⁺, and Ca²⁺ channels and are largely represented by the congenital long QT syndrome (LQTS),⁴³⁻⁴⁷ Brugada syndrome,⁴⁸⁻⁵¹ and catecholaminergic polymorphic ventricular tachycardia (CPVT).⁵²⁻⁵⁴ Less common channelopathies include the short QT syndrome (SQTs)⁵⁵ and early repolarization syndrome (ERS).⁵⁶⁻⁵⁸ All contribute with varying penetrance to sudden cardiac arrest in young individuals.^{59,60}

Long QT Syndrome (LQTS). The LQTS was first described in 1957 by Jervell and Lange-Nielsen in patients with long QT intervals, episodes of torsades de pointes, and deafness.⁶¹ The syndrome is transmitted by autosomal recessive inheritance and is known as the *Jervell*

and Lange-Nielsen syndrome. In 1963 and 1964, Romano and colleagues⁶² and Ward⁶³ independently reported patients with an almost identical disorder but without deafness. The syndrome is transmitted by autosomal dominant inheritance and is known as the *Romano-Ward syndrome*. The two syndromes are primarily responsible for LQTS1 and account for nearly 50% of all genotyped families. LQTS2 accounts for nearly 40% and LQTS3 for about 5%. The remaining types are much less frequent⁶⁴ and are listed in Table 80-1.

The common mechanistic thread is a perturbed balance between I_{Na} and I_K during phase 2 of the action potential, yielding prolongation of repolarization, slowed I_{Ca-L} inactivation, late Ca^{2+} influx, and early afterdepolarizations predisposing to torsades de pointes.⁶⁵

LQTS should be suspected in young individuals who present with syncope or episodes of sudden cardiac arrest precipitated by exercise, emotional distress, or conditions that prolong the QT interval. A family history of unexplained syncope or sudden cardiac arrest should raise

suspicion. The diagnosis should be suspected when the corrected QT interval ($QT_c = QT_{(ms)} \cdot \sqrt{R - R_{(s)}}$) exceeds 470 ms in males (normal <422 ms) and 480 ms in females (normal <432 ms). Genetic testing for identifying the various LQTS subtypes is becoming readily available.⁶⁴

In addition to LQTS, recent population studies have shown that even milder prolongation of the QT_c in adults (>450 ms in men and >470 ms in women) increases the risk of sudden cardiac arrest.⁶⁶

Recently, mutations in the calmodulin genes *CALM1* and *CALM2* have been shown to cause an extremely severe form of LQTS, with QT prolongation greater than 600 ms, T-wave alternans, cardiac arrest in infancy, and intermittent 2:1 atrioventricular block.^{67,68}

The management starts with discontinuing all drugs known to prolong the QT interval and correcting electrolyte imbalances and metabolic conditions that could trigger torsades de pointes. Restriction of participation in athletic activities is generally recommended along with use of β -blockers and antiarrhythmic agents (e.g., mexiletine or

TABLE 80-1 Congenital Long QT Syndromes

| TYPE | FREQUENCY (%) | GENE CHROMOSOME | PROTEIN | MECHANISM, MUTATION EFFECT | GENETIC TRANSMISSION | CLINICAL FEATURES | SYNDROME TYPE |
|--------|---------------|---------------------------|---|---|---------------------------------|---|---------------|
| LQTS1 | 40-55 | <i>KCNQ1</i> 11p15.5 | α -subunit, I_{Ks} | Loss-of-function ↓ K efflux | Autosomal recessive or dominant | Broad-based and late-onset T wave with (recessive) or without (dominant) bilateral sensory-neural deafness; ↑ risk of fatal arrhythmia | RWS, JLNS |
| LQTS2 | 35-45 | <i>KCNH2</i> 7q35-36 | I_{Kr} α -subunit, <i>HERG</i> , <i>KV11.1</i> | Loss-of-function ↓ K efflux | Autosomal dominant | Widely split and low-amplitude T wave; no associated defects | RWS |
| LQTS3 | 2-8 | <i>SCN5A</i> 3p21-24 | α -subunit, I_{Na} | Gain-of-function ↑ Na influx | Autosomal dominant | Late-onset, biphasic or peaked T wave; no associated defects | RWS |
| LQTS4 | <1 | <i>ANKK</i> 4q25-27 | Ankyrin-B | Loss-of-function ↑ Na and ↓ Ca within cell | Autosomal dominant | Variable QT-interval prolongation; no associated defects | RWS |
| LQTS5* | <1 | <i>KCNE1</i> 21q22.1-2 | β -subunit, I_{Ks} | Loss-of-function ↓ K efflux | Autosomal recessive or dominant | With (recessive) or without (dominant) bilateral sensory-neural deafness; ↑ risk of fatal arrhythmia | RWS, JLNS |
| LQTS6† | <1 | <i>KCNE2</i> 21q22.1 | Membrane protein, I_{Kr} | Loss-of-function ↓ K efflux | Autosomal dominant | Auditory/acoustic stimulus can provoke syncopal attacks | RWS |
| LQTS7 | <1 | <i>KCNJ2</i> 17q23 | α -subunit, I_{K1} | Loss-of-function ↓ K efflux | Autosomal dominant | Mild prolongation of QT interval, prominent Q wave, bidirectional VT; periodic paralysis, dysmorphic features, and cardiac arrhythmias | AS |
| LQTS8 | <1 | <i>CACNA1C</i> 12p13.3 | α -subunit, I_{Ca} | Gain-of-function ↑ Ca influx | Autosomal dominant | Exaggerated QT-interval prolongation; neurocognitive impairment, congenital structural heart disease, developmental abnormalities, and immunodeficiencies | TS |
| LQTS9 | <1 | <i>CAV3</i> 3p25 | Caveolin-3 protein | Loss-of-function ↑ Na influx | Autosomal dominant | LQTS3-like phenotype | RWS |
| LQTS10 | <0.1 | <i>SCN4B</i> 11q23.3 | β -subunit, I_{Na} | Loss-of-function ↑ Na influx | Autosomal dominant | LQTS3-like phenotype | RWS |
| LQTS11 | <0.1 | <i>AKAP9</i> 7q21-q22 | Regulatory protein of α subunit, I_{Ks} | Loss-of-function ↓ K efflux | Autosomal dominant | No other associated clinical features | RWS |
| LQTS12 | <0.1 | <i>SNTA1</i> 20q11.2 | Scaffolding protein (I_{Na}) | Loss-of-function ↑ Na influx | Autosomal dominant | No other associated clinical features | RWS |
| LQTS13 | <0.1 | <i>KCNJ5</i> 11q24.3 | K ⁺ channel subunit Kir3.4 | Loss-of-function ↓ K efflux | Autosomal dominant | Syncopal episodes, heart failure, atrial tachycardia, paroxysmal atrial fibrillation, hypokalemia, atrioventricular block, CA | |

**KCNQ1* and *KCNE1* gene products are assembled to form a complete I_{Ks} channel. †*HERG* and *KCNE2* gene products are assembled to form a complete I_{Kr} channel. AS, Andersen syndrome; JLNS, Jervell and Lange-Nielsen syndrome; RWS, Romano-Ward syndrome; TS, Timothy syndrome.

flecainide). In selected cases an implantable defibrillator, cardiac sympathetic denervation, or both may be necessary.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). CPVT is a highly malignant arrhythmogenic disorder that may present with sudden cardiac arrest induced by exercise or emotion, typically in children or adolescents without structural heart disease.⁵⁴ CPVT is associated with two main mutations that affect Ca^{2+} handling by the sarcoplasmic reticulum. One involves an autosomal dominant mutation on the ryanodine receptor gene *RyR2* (i.e., CPTV type 1). The mutation reduces the affinity of FKBP12.6 for *RyR2*, lowering the threshold for Ca^{2+} release from the sarcoplasmic reticulum.⁵³ β -Adrenergic stimulation intensifies Ca^{2+} release and in part explains the effects of exercise and emotion.

The second is an autosomal recessive mutation on the calsequestrin 2 gene *CASQ2* (CPVT type 2). Within the sarcoplasmic reticulum, the *CASQ2* protein serves as the major Ca^{2+} reservoir. The mutation causes a negatively charged domain that alters Ca^{2+} binding.⁵²

The electrocardiogram at rest is typically normal, with occasional U waves and bradycardia. β -Blockers are the cornerstone of therapy, with an implantable cardioverter defibrillator (ICD) indicated in high-risk individuals. Flecainide inhibits the *RyR2* receptor and can suppress or terminate the arrhythmias. Familial screening is indicated once the diagnosis is established.

Short QT Syndrome (SQTS). SQTS is a more recently described syndrome⁵⁵ characterized by tall and peaked T waves with QT intervals less than or equal to 300 milliseconds insensitive to changes in heart rate in structurally normal hearts. Individuals are at risk of developing atrial fibrillation and VF. A family history may be present including sudden death at a young age.

The shortened QT interval results from increased outward K^{+} currents during phase 2 and phase 3 of the action potential associated with autosomal dominant mutations in the *KCNH2*, *KCNJ2*, and *KCNQ1* genes.

ICD implantation is a class I recommendation in survivors of cardiac arrest and in patients with spontaneous sustained VT with or without syncope. Among various drugs, quinidine and sotalol could be effective by prolonging the QT interval.⁵⁵

Brugada Syndrome. Another important hereditary channelopathy is the Brugada syndrome described in 1992 by the Brugada brothers,⁴⁸⁻⁵¹ who reported sudden cardiac arrests in individuals with structurally normal hearts but ST-segment elevation in V_1 to V_3 and a QRS resembling right bundle branch block.

Brugada syndrome exhibits predominantly an autosomal dominant pattern of inheritance, with an average worldwide prevalence of 5:10,000.⁶⁹ Mutations have been identified in ten genes.⁷⁰ Loss of function caused by a mutation in the *SCN5A* gene (encoding for the I_{Na} α -subunit) accounts for approximately 20% of cases. The other 80% depend on mutations involving *GPD1-L*, *CACNA1C*, *CACNB2*, *SCN1B*, *KCNE3*, *SCN3B*, *MOG1*, *KCNE5*, and *KCND3*.⁷⁰

The predominant genetic mechanism in the *SCN5A* gene is an accelerated inactivation of I_{Na} leaving I_{To} unopposed, resulting in rapid repolarization with shortened action potential duration. In addition, the predominant epicardial expression of I_{To} allows normally depolarized endocardium to reexcite, prematurely repolarizing the epicardium and generating reentry, which in turn can precipitate polymorphic ventricular tachycardia.

The ST-segment elevation can adopt various shapes related to severity of the $\text{I}_{\text{Na}}/\text{I}_{\text{To}}$ imbalance. With increasing severity, saddleback, coved, and triangular shapes are recognized.⁶⁵ These changes are dynamic and can change in the same affected individual as shown in Figure 80-5.

Brugada syndrome exhibits variable expressivity, reduced penetrance, and “mixed phenotypes” wherein families may include members with Brugada syndrome as well as members with SQTS, LQTS, atrial fibrillation, disease of the conduction system, and even structural heart disease.⁶⁹

Genetic testing can be useful when there is personal and family history along with the characteristic electrocardiographic pattern identified at rest or after drug challenge.

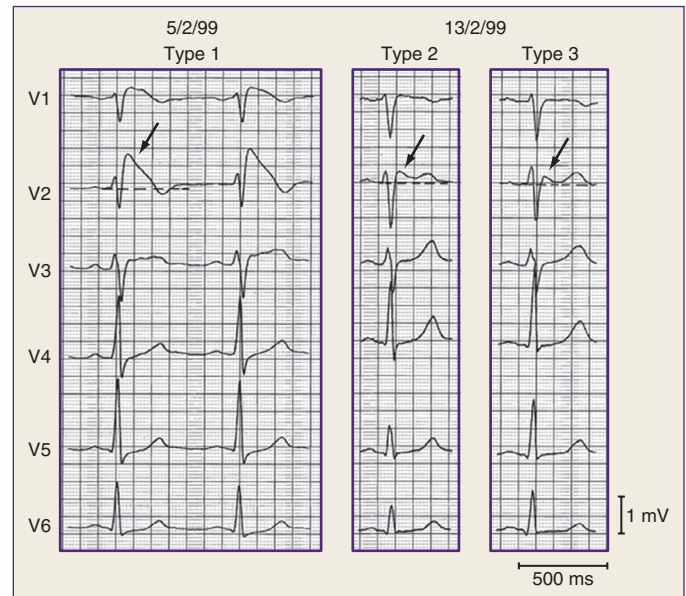


FIGURE 80-5 ■ Representative tracings in a patient with Brugada syndrome, demonstrating dynamic changes in V_1 to V_2 after resuscitation from cardiac arrest. Type 1 refers to the coved-type ST-T configuration, whereas type 2 and type 3 refer to the saddleback ST-T configuration. (From Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Corrado D, et al. Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome: consensus report. *Circulation* 2002;106:2514–9.)

Patients with Brugada syndrome may have concealed or intermittent forms, unmasked (or precipitated) by febrile states, vagotonic agents, α -adrenergic agonists, β -adrenergic blockers, tricyclic or tetracyclic antidepressants, a combination of glucose and insulin and hypokalemia, and alcohol and cocaine toxicity.⁷¹ Concealed Brugada syndrome can be unmasked by class IC antiarrhythmic drugs; e.g., ajmaline (1 mg/kg intravenous in 5 minutes), flecainide (2 mg/kg intravenous in 10 minutes), or procainamide (10 mg/kg intravenous in 10 minutes). Such testing carries a 0.5% risk of precipitating VF. Ajmaline is favored because of its shorter half-life.⁷² The test is considered positive if an additional 1-mm ST-segment elevation (0.08 seconds after the J point) occurs in leads V_1 , V_2 , and V_3 . The test has high specificity and high sensitivity (94% and 80%, respectively).⁷³

The preferred management of Brugada syndrome is an ICD.⁵⁰ However, quinidine and hydroquinidine can prevent spontaneous changes in the electrocardiogram (ECG) and reduce the risk of VT and VF, presumably through inhibition of I_{To} .^{74,75} Ablation of the substrate located in the anterior epicardial region of the right ventricular outflow tract recently has been shown to reduce the episodes of VF in patients with ICD.⁷⁶

Early Repolarization and Early Repolarization Syndrome. Early repolarization is generally defined by a J-point elevation on the ECG greater than 0.1 mV in two adjacent leads with a slurred or notched morphology. This common condition affects 1% to 5% of individuals.⁵⁶ Early repolarization was previously thought to be a completely benign finding; however, studies and case reports seem to suggest a higher risk of arrhythmias, mainly idiopathic ventricular fibrillation, in such patients.^{57,58}

Early repolarization is mainly sporadic; however, genetic inheritance is being noted in the literature, and a wide array of both loss and gain of function genetic mutations have been reported.^{74,77} Some studies have stratified the risk of developing arrhythmia based on the patterns of early repolarization on ECG. Type 1 is associated with early

repolarization in the lateral leads. This pattern is thought to be largely benign. Type 2 is associated with early repolarization in the inferior or inferolateral leads and is associated with a moderate level of risk. Type 3 is associated with early repolarization in the inferior, lateral, and right precordial leads and appears to be associated with the highest relative risk.⁷⁸ Type 4, also known as Brugada syndrome, is described in detail earlier in this chapter.

It is important to differentiate between early repolarization in which only the classic ECG findings are found in an asymptomatic individual with early repolarization syndrome (ERS), which includes the classic ECG findings of early repolarization in a survivor of sudden cardiac death with evidence of VF after an extensive workup has ruled out any other cardiac abnormalities.

A class 1 recommendation for patients with asymptomatic early repolarization on the ECG is to observe. In this patient population in the acute setting of VF requiring defibrillation, isoproterenol was shown to be effective in suppressing the episode.⁷⁹ ICD is a class 1 recommendation in patients with ERS who are survivors of SCD.

Acquired Channelopathies

Acquired channelopathies are common with advanced heart failure and are an important factor affecting the expression of ion channels regardless of the primary etiology.⁸⁰ Downregulation of I_{To} and I_{K1} can occur, causing QT prolongation, possibly an adaptive response allowing a longer interval for excitation-contraction. Yet it predisposes to inhomogeneous repolarization, early afterdepolarizations, and triggered arrhythmias. Upregulation of the Na^+/Ca^{2+} exchanger can also occur, a response in part to downregulation of the sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA2a),⁸¹ yielding larger $I_{Na/Ca}$ and predisposing to delayed afterdepolarizations and triggered arrhythmias.

An increasingly important mechanism of acquired channelopathies is the use of drugs that prolong the QT interval; most are associated with drugs that block I_{Kr} , which is carried by subunits of the human ether-à-go-go (*HERG*) gene.⁸² The list of such drugs is long and includes antiarrhythmic and nonantiarrhythmic drugs. The University of Arizona Health Sciences Center maintains a list of drugs categorized based on their potential to induce torsades de pointes (available at www.crediblemeds.org), including drugs with known risk, drugs with possible risk, drugs with conditional risk, and drugs to avoid in congenital LQTS.

The importance of drug-induced LQTS has mandated pharmaceutical companies to screen early in the process of drug development, mostly for effects on the *HERG* gene product.⁸²

Other Conditions

The QT interval may be prolonged by cocaine abuse, organophosphate compounds, subarachnoid hemorrhage, stroke, myocardial ischemia, fasting using liquid-protein-modified diets, autonomic neuropathy, and human immunodeficiency virus disease.⁸³⁻⁸⁷ Electrolyte abnormalities can not only prolong but also shorten the QT interval. Some of these conditions and others not associated with channelopathies are discussed next.

Electrolyte Abnormalities

Electrolyte abnormalities rarely precipitate but often contribute to ventricular tachyarrhythmias, mostly in relation to abnormalities in serum K^+ , Mg^{2+} , and Ca^{2+} .

Hypokalemia (serum $K^+ < 3.5$ mM) makes the resting membrane potential more negative, rendering cells less excitable and reducing the firing rate of pacemaker cells. Hypokalemia also prolongs the QT interval and flattens the T wave,¹⁰ consequent to a dependency of I_{Kr} conductivity on the square root of extracellular K^+ , resulting in a prolongation of repolarization at lower serum K^+ ; this effect is more pronounced in the mid-myocardial region (greater I_{Kr}/I_{Ks} ratio).

Hyperkalemia (serum K^+ greater than 5.5 mM) makes the resting membrane potential less negative, rendering cells more excitable. By increasing I_{Kr} , hyperkalemia accelerates repolarization and shortens

the action potential, explaining the characteristic peak and tall T-waves. With severe hyperkalemia, the rise rate of phase 0 is reduced, slowing conduction and leading—at very high serum K^+ levels—to widespread blocks (i.e., widened P-waves and widened QRS interval). A very rapid serum K^+ rise can precipitate VF, probably by reentry after developing areas of conduction block.

Mg^{2+} is a cofactor of the Na^+/K^+ pump and hence important for maintaining intracellular K^+ and the resting membrane potential. Mg^{2+} also modulates the effects of various K^+ and Ca^{2+} channels. Hypomagnesemia is associated with QT prolongation and increased risk of ventricular arrhythmias. This effect is usually compounded by other electrolyte deficits including hypokalemia and hypocalcemia.

Serum Ca^{2+} is also important. Hypocalcemia increases the QT interval, predisposing to VT, whereas hypercalcemia exerts the opposite effects reducing the QT interval. Changes in intracellular calcium contribute to arrhythmias associated with acute ischemia and reperfusion and may be important in the genesis of VT induced by exercise and by digitalis.

Hypothermia

Moderate (32°C to 35°C) and severe ($<32^\circ\text{C}$) hypothermia can predispose to ventricular tachyarrhythmias by QT prolongation and QT dispersion.⁸⁹ Typically, patients with hypothermia develop J waves (also known as *Osborn waves*) in the ECG, which reflects accentuation of the inhomogeneity of repolarization caused by the predominant distribution of I_{To} in subepicardial and mid-myocardial regions.⁹⁰

Hypoglycemia

Acute hypoglycemia can trigger VT and VF in patients with diabetes mellitus.⁹¹ The mechanism involves QT prolongation by direct suppression of repolarizing K^+ currents. In addition, the neuroendocrine stress response to hypoglycemia, via release of catecholamines, favors intracellular Ca^{2+} entry and reduction in serum K^+ , further compounding the risk, especially in patients with coronary artery disease, acute myocardial infarction, left ventricular hypertrophy, autonomic neuropathy, congestive heart failure, and in those taking medications that prolong the QT interval.

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

ARVC is characterized by progressive replacement of the right ventricular muscle cells by fibrous tissue and fat.⁹² ARVC may be familial with autosomal dominant inheritance.⁹³ Patients present with palpitations and syncope, an important cause of sudden cardiac arrest in subjects younger than 35 years, especially when related to exercise.⁹⁴

The ECG is abnormal in 90% of cases, showing T-wave inversions beyond lead V_1 and epsilon waves in leads V_1 to V_3 . The QRS complex may be widened (>110 milliseconds) with complete or incomplete right bundle branch block morphology. Ventricular premature beats with left bundle branch configuration are present.

CLINICAL DIAGNOSIS

The first element to recognize is wide QRS complexes. They may indicate the origin in ventricular tissue; however, supraventricular ectopic activity can produce wide QRS complexes in the presence of preexistent or rate-dependent bundle branch blocks or aberrant pathways. The diagnostic clue is dissociation from atrial activity; this feature is often difficult to establish, necessitating reliance on other indirect features as discussed later. Ventricular arrhythmias present in several forms.

Premature Ventricular Contractions (PVCs)

PVCs are isolated ventricular ectopic beats. The QRS is typically wide with opposing T-wave polarity and a full compensatory pause. PVCs may present one after each normal QRS in the form of bigemini and also as couplets (two consecutive PVCs).

Ventricular Tachycardia (VT)

VT is defined as three or more consecutive ventricular ectopic beats with a rate typically greater than 100 bpm, often ranging between 130 and 170 bpm. QRS complexes are 120 ms or longer. However, wide QRS complex tachycardias can also be supraventricular when the impulse originates above the bifurcation of the His bundle but is conducted with aberrancy (see later).⁹⁵ VTs are classified as *monomorphic* if all QRS complexes have similar morphology and *polymorphic* if they have variable morphology. VTs are considered *nonsustained* if they last less than 30 seconds and *sustained* if they last 30 seconds or longer.

Nonsustained VTs are rarely symptomatic but are an independent risk factor for sudden cardiac death in patients with severe congestive heart failure.⁹⁶ Most sustained VTs present with palpitations, chest discomfort, and weakness or with more severe symptoms such as dizziness, angina, syncope, seizures, and even sudden cardiac death.

Monomorphic Ventricular Tachycardia

Monomorphic VTs are the most common types of VTs and are usually associated with structural heart disease. The mechanism is commonly reentry operating within or around damaged myocardium. Examination of the jugular veins may show cannon A waves, indicative of AV dissociation.

A standard 12-lead ECG reveals a wide-complex tachycardia with regular complexes of similar morphology. A representative tracing is shown in Figure 80-6. Establishing the diagnosis requires excluding the possibility of supraventricular tachycardia (SVT) with aberrancy. It is appropriate to assume that a wide-complex tachycardia is VT until proven otherwise in patients with myocardial ischemia, heart failure, and hemodynamic instability. SVT with aberrancy should be suspected if there is a history of previous aberrant rhythms, accessory pathways, and baseline or rate-induced bundle branch block. The ECG should be examined for evidence of AV dissociation (i.e., P waves and QRS complexes at uncoupled rates), which is specific for VT. Use of an esophageal lead could be useful by amplifying atrial potentials.

Some special forms of VT tend to be mistaken for SVT with aberrancy.⁹⁷ These include bundle branch reentrant tachycardia, in which the impulse travels down the right bundle branch, across the interventricular septum, and up the left bundle branch.⁹⁸ The morphology resembles SVT with left bundle branch block (LBBB) and is common among patients with nonischemic dilated cardiomyopathy.⁹⁹ Right ventricular outflow tract tachycardia is another condition caused by triggered activity from delayed afterdepolarizations that most commonly originate in the right ventricular outflow tract.¹⁰⁰ The tachycardia usually presents with LBBB morphology and right axis deviation. Right ventricular outflow tract tachycardias occur in structurally normal hearts, typically in young individuals, and are responsive to verapamil

or adenosine.¹⁰¹ Finally, there are fascicular tachycardias that originate from either fascicle of the left bundle branch. They occur in structurally normal hearts, mimic SVT with aberrancy, and are responsive to β -blockers and verapamil.¹⁰²

ECG algorithms are available to help differentiate VT from SVT. A widely accepted four-step algorithm was developed by Brugada et al. in the early nineties and reported to have 98.7% sensitivity and 96.5% specificity for VT.¹⁰³ However, more recent studies found the Brugada criteria to have lower sensitivity and specificity when used by emergency department physicians and cardiologists.¹⁰⁴ Vereckei et al. proposed a simpler criterion based on analysis of aVR and reported greater sensitivity and specificity.¹⁰⁵ The aVR lead is useful because in normal sinus rhythm and in supraventricular tachycardias the ventricular activation wavefront moves away from aVR, typically yielding a QS complex and not an R wave, which is the step one criterion in the new algorithm (Fig. 80-7).

Polymorphic Ventricular Tachycardia

Polymorphic VTs have irregular rhythms, usually compromise hemodynamic function, and may quickly degenerate into VF. Variation in QRS morphology represents changes in the electrical axis. One special form of polymorphic VT is torsades de pointes. This is a descriptive term denoting a rotating electrical axis in 180 degrees along an imaginary axis ("twisting points"); it is typically associated with LQTS. Representative tracings are shown in Figure 80-8.

Accelerated Idioventricular Rhythm (AIVR)

AIVR is a form of automatic ventricular arrhythmia characterized by regularly wide QRS complexes with a rate between 50 and 120 bpm. It is often slightly faster than the underlying sinus rhythm. AIVR does not produce symptoms, and the treatments for VT do not apply.¹⁰⁶ The presence of AIVR may indicate underlying myocardial ischemia.

Ventricular Fibrillation (VF)

VF is recognized by the abrupt onset of irregular waveforms of varying contour, duration, and amplitude without identifiable QRS and T waves accompanied by the inability of the heart to generate blood flow, precipitating unconsciousness within seconds. VTs or SVTs that conduct through accessory pathways (e.g., Wolff-Parkinson-White syndrome) may be the initiating rhythm. Generalized seizures and agonal breathing may follow.

ACUTE MANAGEMENT

PVCs and episodes of nonsustained VT are of little hemodynamic significance in the structurally normal heart and may occur associated with use of stimulants, electrolyte abnormalities, hypoxemia,



FIGURE 80-6 ■ ECG tracing (lead II, III, and V₁) showing couplets followed by an 11-beat episode of nonsustained monomorphic ventricular tachycardia. ECG, electrocardiography.

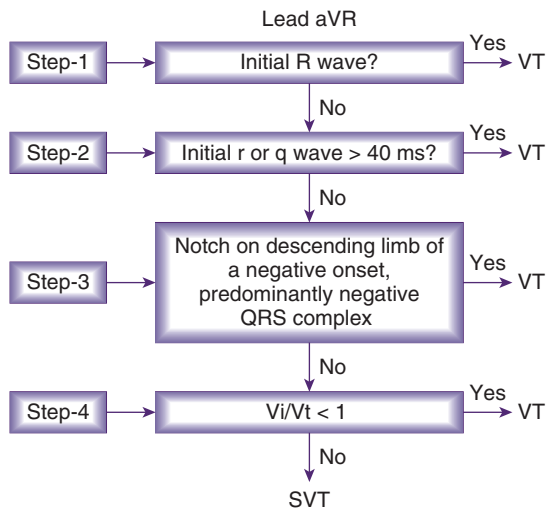


FIGURE 80-7 ■ aVR algorithm for distinguishing wide-complex monomorphic ventricular tachycardia (VT) from supraventricular tachycardia. VT is diagnosed whenever the analysis of aVR yields a positive answer to each successive step. In step 4, Vi and Vt refer to ventricular activation velocity measured as the vertical excursion (in millivolts) during the initial (Vi) and terminal 40 ms (Vt) of the QRS complex. When the initial or terminal 40 ms displays both positive and negative deflections, the sum of their absolute values (disregarding polarity) is used to calculate Vi and Vt, with the Vi/Vt ratio determining whether the rhythm is VT or supraventricular tachycardia. (From Vereckei A, Duray G, Szenasi G, Altemose GT, Miller JM. Application of a new algorithm in the differential diagnosis of wide QRS complex tachycardia. *Eur Heart J* 2007;28:589–600.)

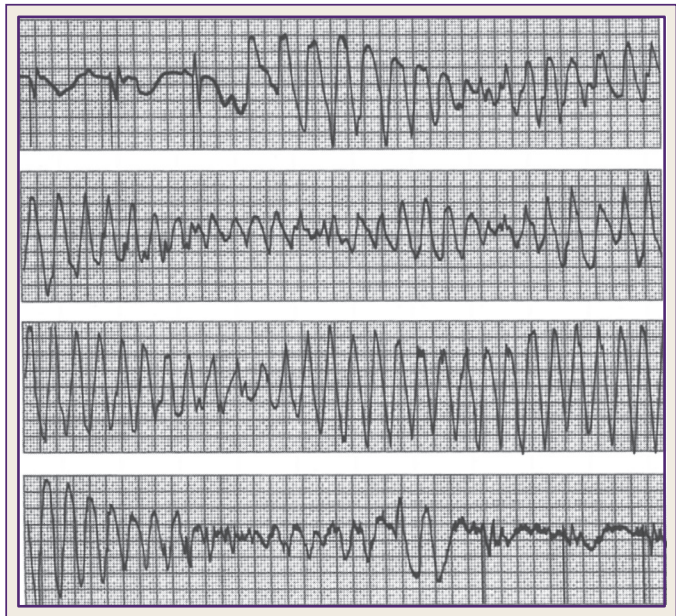
catecholamine discharge, and medications, to name a few conditions. Management should focus on removing contributing factors. The risk of progression to sustained VT is low. Even the notorious R-on-T phenomenon has been shown to be of prognostic significance for the development of VF only in patients with a predisposing substrate such as Brugada syndrome.¹⁰⁷ Antiarrhythmic drugs are typically not required. Persistence of nonsustained VT after an episode of critical illness should prompt assessment of underlying cardiac substrate and possible triggers.

The management of sustained ventricular tachyarrhythmias requires concurrent diagnostic and therapeutic interventions. This requirement is particularly the case in pulseless VT, polymorphic VT, and VF when delivery of unsynchronized electrical shocks and advanced cardiac life support cannot be delayed. In less urgent situations, treatment should focus on identifying the substrate and the triggering events. Arrhythmogenic conditions commonly present in critically ill patients include hemodynamic and respiratory abnormalities, endogenous or exogenous adrenergic states, acid-base and electrolyte imbalances, the presence of proarrhythmic drugs, prolongation of the QT interval, ongoing myocardial ischemia, and mechanical stimulation of cardiac structures. Often, the treatment of these factors suffices to terminate the arrhythmic episode. Specific antiarrhythmic interventions should take into consideration the type of rhythm and the degree of hemodynamic stability.

Ventricular Arrhythmias with Preserved Blood Flow

Monomorphic Ventricular Tachycardia

Direct-current synchronized cardioversion and intravenous antiarrhythmic agents are acceptable first-line options. Antiarrhythmic agents have the advantage of exerting a persistent effect after termination of the event and that anesthetic agents are not required; however,



A



B

FIGURE 80-8 ■ Torsades de pointes. **A**, Patient with a demand ventricular pacemaker developed QT prolongation (≈ 640 milliseconds, seen during paced rhythm) after treatment with amiodarone for recurrent ventricular tachycardia (VT). An episode of torsades de pointes developed that spontaneously terminated with resumption of a paced ventricular rhythm. **B**, Tracing from a young boy with congenital long QT syndrome and marked prolongation of the QTU interval (≈ 600 milliseconds). TU alternans is noted before a late premature complex, occurring on the downslope of the TU wave, initiates an episode of VT. (From Braunwald E, Zipes D, Libby P, editors. *Heart disease: a textbook of cardiovascular medicine*, 6th ed. Philadelphia: Saunders; 2001, p. 868.)

patients may experience adverse effects including hypotension and increased susceptibility to arrhythmias, given that most agents cause QT prolongation.

The American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) 2006 Guidelines for management of patients with ventricular arrhythmias¹⁰⁸ recognize various drugs available in IV formulation for VT, including flecainide, propafenone, sotalol, procainamide, lidocaine, and amiodarone, with availability contingent on the specific country. The same 2006 Guidelines recommend IV procainamide (or ajmaline in some European countries) as a reasonable initial choice for patients with stable sustained monomorphic VT.^{109,110} Close monitoring is recommended, as IV procainamide can cause transient hypotension,¹¹¹ especially in patients with severe left ventricular dysfunction. For patients with sustained monomorphic VT who are hemodynamically unstable, are refractory to electrical shocks, or have recurrent episodes despite procainamide or other agents, IV amiodarone is considered a reasonable choice.^{112,113} The initial effect of amiodarone is to slow down AV nodal conduction and block adrenergic stimulation. However, effects

on ventricular conduction and refractoriness develop more gradually, achieving the maximal effect only after weeks or months of treatment.^{114,115}

When sustained monomorphic VTs are associated with an acute ischemic substrate (i.e., unstable angina or myocardial infarction), lidocaine is considered a reasonable initial choice.¹¹⁶ Calcium channel blockers such as verapamil and diltiazem should not be used to terminate wide-QRS-complex tachycardia of unknown origin, especially when myocardial dysfunction is present.

Addition of a second antiarrhythmic agent is discouraged to avoid compounding proarrhythmic effects. Thus, a single agent should be used, followed by direct-current synchronized electrical cardioversion if optimal dosing fails.

Direct-current synchronized cardioversion should be considered first-line treatment in patients who are unstable or in those with borderline blood pressure who could experience further deterioration by the vasodilator and antiinotropic effects of antiarrhythmic agents. Monophasic waveform electric shocks at an initial energy of 100 J or higher are effective with comparable or lower energy levels expected to be effective using biphasic waveform electric shocks. Transvenous pacing with override pacing can terminate monomorphic VT and should be considered in instances of failed cardioversion or frequent recurrence despite antiarrhythmic medication.

Ventricular Arrhythmias with Cessation of Effective Blood Flow

Cessation of blood flow occurs with pulseless VT, VF, and polymorphic VT. The immediate priority is to reestablish an organized electrical activity with mechanically competent pump function, typically requiring the unsynchronized delivery of electric shocks with cardiopulmonary resuscitation contingent on the duration of the arrhythmia and the response to electrical shocks.

Ventricular Fibrillation and Pulseless Ventricular Tachycardia

Current resuscitation algorithms¹¹⁷ consider VF and pulseless VT as rhythms requiring delivery of electric shocks upon their recognition through an automated external defibrillator or through manual defibrillators along with quality chest compressions. If VT/VF persists after the third shock, IV amiodarone is recommended. The energy level of the initial electric shock depends on the specific device. For biphasic waveform defibrillators, the energy level typically ranges from 150 to 200 J. Equal or higher energy levels are recommended for the second and subsequent shocks. If the available defibrillator uses monophasic waveforms, the energy level should be 360 J for all shocks. The probability of survival after VF and pulseless VT is inversely related to the time elapsed between the onset of the arrhythmia and the delivery of electric shocks.¹¹⁸

Electrical storm is a rather uncommon but highly lethal phenomenon defined as recurrent episodes of VF, occurring mainly in the course of an acute myocardial infarction. Conventional antiarrhythmic drug therapy—including lidocaine and procainamide—often fails to secure a stable sinus rhythm.

Polymorphic Ventricular Tachycardia

Polymorphic VT with cessation of effective blood flow is treated as VF with unsynchronized shocks at the same energy as for VF. As with all ventricular arrhythmias, substantial effort must be directed at identifying and correcting the causes.

Polymorphic VT with a normal QT interval is most frequently associated with acute myocardial ischemia but also with cardiomyopathies,

idiopathic polymorphic VT, and catecholaminergic VT. In this setting, use of IV beta-blockers¹¹⁹ or IV amiodarone¹²⁰ is effective. Coronary angiography should be considered for recurrent polymorphic VT when ischemia is suspected.¹²¹

Polymorphic VT with prolonged QT interval is usually associated with bradycardia. The management includes discontinuation of drugs that prolong the QT interval, correction of electrolyte abnormalities, and avoidance of catecholamines. In the setting of congenital LQTS, beta-blockers (or sympathetic interruption), pacing, and implantation of an internal cardioverter defibrillator device should be considered. In the acquired forms of LQTS, IV magnesium, overdrive pacing, and beta-blockers after pacing are recommended interventions.

CONCLUSION

Ventricular tachyarrhythmias are important and common manifestations of cardiac and extracardiac abnormalities in critically ill patients. In addition to the traditional assessment based on ECGs and hemodynamic manifestations, understanding and recognition of the processes that affect ion channels, pumps, exchangers, and signaling mechanisms are important for proper management. Awareness of prevalent, clinically relevant, mutations that affect cardiac channels has increased. The intensivist should be alert and prepared to identify these conditions and provide the necessary initial treatment and referral when appropriate. Initial enthusiasm for antiarrhythmic agents has diminished as the proarrhythmic effects of various compounds have become evident. Some drugs are no longer recommended as first-line agents, whereas others have become components of accepted algorithms. More emphasis is currently being placed on understanding arrhythmogenic mechanisms and on correcting the precipitating and maintaining factors.

KEY POINTS

1. Hereditary and acquired abnormalities in cardiac ion channels can alter the action potential, mostly by prolonging repolarization, and predispose to ventricular tachyarrhythmias, especially *torsades de pointes*.
2. Ventricular arrhythmias are the result of abnormalities in impulse generation (automaticity and triggered activity) and impulse conduction (reentry).
3. Proper management of ventricular tachyarrhythmias requires assessment of precipitating and maintaining conditions; often, the removal of these conditions is all that is needed.
4. A long QT interval in the baseline electrocardiogram should prompt a diligent search for possible drugs, metabolic abnormalities, or hereditary channelopathy.
5. Ventricular tachyarrhythmias in critically ill patients are often precipitated by cardiac, metabolic, and respiratory processes.
6. AV dissociation is a reliable sign that a wide-complex tachycardia is ventricular; this may be evident on the surface 12-lead ECG or after analyzing an esophageal lead.
7. Direct-current synchronized cardioversion should be considered first-line treatment in patients with VT who are hemodynamically unstable or have heart failure.

References for this chapter can be found at expertconsult.com.

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■ CONDUCTION DISTURBANCES

Bradyarrhythmias and conduction blocks are common in the intensive care unit (ICU). A broad range of clinical presentations and pathologic findings occurs in this group of arrhythmias. Some bradyarrhythmias are benign and asymptomatic and do not require treatment. Other atrioventricular (AV) blocks and arrhythmias are life threatening and warrant immediate intervention.

Normal Cardiac Conduction

Normal depolarization and impulse conduction are central to maintaining cardiac output. Two types of cells are found in the heart: (1) cells responsible for impulse generation and conduction, and (2) cells responsible for contraction. Depolarization of the myocardium begins in the sinoatrial (SA) node. The SA node is located in the posterior and superior portion of the right atrium and is innervated by the sympathetic and parasympathetic nervous systems.

The impulse is generated by a specialized group of cells with the ability to depolarize spontaneously. Initial depolarization of the SA node is not seen on the electrocardiogram (ECG). The P wave is generated when the impulse spreads throughout the atria. There is no specific conduction system in the atria to convey the SA node impulse to the AV node.¹ The impulse is transmitted by depolarization of adjacent atrial myofibrils. Approximately halfway through the P wave, the impulse reaches the AV node. The second half of the P wave is due to left atrial depolarization.

In a normal heart, the atria and ventricles are electrically isolated from each other except at the AV node. The AV node is located in the atrial septum near the apex of the triangle of Koch. The AV node is innervated by the sympathetic and parasympathetic nervous systems. Conduction through the AV node accounts for the majority of the PR interval. After emerging from the AV node, the impulse is conducted through the bundle of His. From there, the impulse travels down the right and left bundle branches and their fascicles to the Purkinje network, which causes ventricular contraction.

Failure of Impulse Conduction

Failure of conduction can occur anywhere along the conduction pathway. AV node block is most often caused by medications, increased parasympathetic tone, or ischemia. AV node blocks are usually reversible, except when infarction permanently damages a portion of the conduction pathway. Infranodal blocks are rarely caused by physiologic abnormalities. Structural heart disease and anatomic disruption of the conduction system are the main causes of infranodal heart block. Rare causes of infranodal block include disruption of the bundle of His from aortic valve calcification, Lenègre's disease (idiopathic degeneration of Purkinje fibers), and Chagas' disease.²

Once AV block is identified, it is helpful to determine the site of conduction pathology. The anatomic site can be identified in most cases by synthesizing the type of AV block, the width of the QRS complex, and the QRS morphology. When the QRS complex is narrow (<120 milliseconds), the site of pathology is most likely supraventricular. When the QRS complex is wide, the most likely site of AV block is infranodal. Bundle branch and fascicular blocks produce various QRS

morphologies that may aid in determining the specific anatomic location of the pathology.

Clinical Presentation

Syncope and presyncope are the most dramatic symptoms of conduction disturbances; palpitations, dyspnea, angina, and fatigue are seen as well. Many patients are asymptomatic. A significant number of patients develop bradydysrhythmias after an acute myocardial infarction (MI) (Table 81-1).³

Diagnostic Evaluation

A high-quality ECG is paramount for the appropriate evaluation of P waves and various intervals. Routine monitoring in the ICU is usually accomplished with a single- or three-lead display at the bedside. The lead chosen should clearly delineate the P waves and QRS complexes. Complex arrhythmias may require Lewis leads, intraatrial leads, or esophageal ECG monitoring. Calipers significantly aid in the diagnosis of AV blocks and are helpful to "march out" P waves and intervals. Holter or continuous loop monitoring can also be an important tool in the evaluation of AV block.⁴ These monitors allow one to evaluate the cardiac conduction system during a patient's activities of daily living. A monitoring period of at least 24 hours is recommended, so that both daytime and nighttime activities are included.

Sinus Node Abnormalities

Sinus Bradycardia

Sinus bradycardia is defined as a sinus rhythm with a heart rate less than 60 beats per minute. Sinus bradycardia is divided into two categories: appropriate and inappropriate. Appropriate bradycardia is seen in young, healthy individuals and endurance athletes; the heart rate increases appropriately with exercise. Pathologic sinus bradycardia does not increase appropriately with exercise. Medications are the most common cause of inappropriate sinus bradycardia; autonomic influences, electrolyte abnormalities, and intrinsic structural disorders are others. In older individuals, sinus bradycardia can result from a decrease in the sinus node firing rate, which is a normal part of the aging process. Ischemia may also increase vagal tone and result in a slower heart rate.

Sinus Arrest

Sinus arrest occurs when the pacemaker cells in the SA node fail to depolarize. Pauses of less than 3 seconds may be seen in up to 11% of normal individuals and should not cause concern.⁵ There is a higher incidence of sinus pause in athletes. Pauses longer than 3 seconds are usually considered pathologic and should be evaluated.

SA exit block and sinus arrest appear similar on ECGs, but they should be distinguished, if possible. The duration of the pause in exit block is a multiple of the P-P interval. High-grade exit block cannot be distinguished from sinus arrest. The treatment is the same for both conditions.⁶

Noninvasive testing includes ECG, carotid sinus massage, and a tilt table test. Carotid sinus massage is useful to diagnose carotid sinus hypersensitivity. Risks of carotid sinus massage include transient ischemic attack and stroke, and the test should not be performed on patients with carotid bruits. The tilt table test is helpful to determine whether

TABLE 81-1

Incidence of Bradydysrhythmias in Acute Myocardial Infarction

| RHYTHM | INCIDENCE (%) |
|---------------------------------|---------------|
| Any bradydysrhythmia | 25-30 |
| Sinus bradycardia | 25 |
| Junctional escape rhythm | 20 |
| Idioventricular escape rhythm | 15 |
| First-degree AV node block | 15 |
| Second-degree AV block type I | 12 |
| Second-degree AV block type II | 4 |
| Third-degree block | 15 |
| Right bundle branch block | 7 |
| Left bundle branch block | 5 |
| Left anterior fascicular block | 8 |
| Left posterior fascicular block | 0.5 |

AV, atrioventricular.

syncopal episodes are due to autonomic dysfunction. Invasive diagnostic testing of the SA node can also be performed, although this is rarely necessary.

The treatment of sinus node dysfunction can be temporary or permanent. Atropine or an isoproterenol drip can be used in the ICU as a bridge to permanent pacemaker placement. Temporary pacing is indicated for patients who fail to respond to medical therapy.

Carotid Sinus Hypersensitivity

Carotid sinus hypersensitivity is diagnosed when ventricular asystole greater than 3 seconds' duration (usually due to a sinus pause or arrest) or a drop in systolic blood pressure greater than 50 mm Hg occurs in response to carotid massage. If symptoms occur, a 30 mm Hg drop in systolic blood pressure defines a positive response. Treatment is permanent pacing in symptomatic patients only.⁷

Postsurgical Bradydysrhythmias

Bradyarrhythmias are common after cardiac surgery. Valve surgery and septal myectomy can cause significant damage to the conduction system. Prolonged ischemia during heart transplantation may also result in sinus node or conduction system damage. The decision to place a permanent pacer should not be made until 5 to 7 days postoperatively, however, because the bradyarrhythmia may be temporary. Medication administered during surgery or reversible ischemia is often implicated. Permanent pacing is required in 3.2% to 8.5% of patients after valve surgery and approximately 10% of patients after heart transplantation.⁸

Atrioventricular Node Dysfunction

There are many causes and several manifestations of AV node dysfunction. Box 81-1 lists the causes of AV node abnormalities.

First-Degree Atrioventricular Block

First-degree AV block is characterized by a prolonged PR interval greater than 200 milliseconds in adults and 180 milliseconds in children who are not taking medications that can prolong the PR interval (Fig. 81-1). All of the P waves are conducted to the ventricles, and the PR interval is typically fixed. Potential causes of first-degree AV block include delayed conduction through the atria from the SA node to the AV node, a delay in AV node conduction, or prolonged infranodal conduction.

BOX 81-1

Causes of Atrioventricular Node Dysfunction

Drugs
 Digoxin
 Beta-blockers
 Certain calcium channel blockers
 Membrane-active antidysrhythmic drugs
 Primary cardiac disease
 Ischemic heart disease
 Idiopathic fibrosis of the conduction system
 Congenital heart disease
 Calcific valvular disease
 Cardiomyopathy
 Metabolic
 Hyperkalemia
 Hypermagnesemia
 Infiltrative disease
 Infectious/inflammatory disease
 Collagen vascular disease
 Endocrine
 Addison's disease
 Trauma
 Radiation
 Tumors
 Neurally mediated
 Carotid sinus syndrome
 Vasovagal syndrome
 Neuromyopathic disorders

Adapted from Wolbrette DL, Naccarelli GV. Bradycardias: sinus nodal dysfunction and atrioventricular conduction disturbances. In: Topol EJ, editor. Textbook of cardiovascular medicine. Philadelphia: Lippincott-Raven; 1998: 1655.

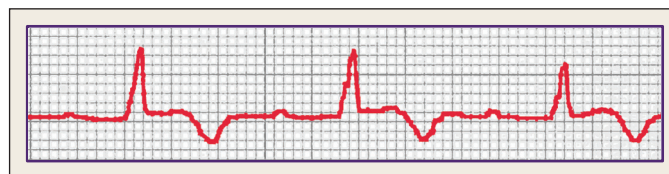


FIGURE 81-1 ■ Electrocardiogram from a patient with first-degree atrioventricular block. The PR interval is approximately 290 milliseconds. All P waves are being conducted to the ventricles. The PR interval is constant.

Conduction delays from the SA node to the AV node are typically due to structural causes, such as right atrial enlargement or an ostium primum atrial septal defect. A delay in AV node impulse conduction is the most common cause of first-degree AV block. Patients with delayed conduction in the AV node often have a PR interval greater than 300 milliseconds. Infranodal causes of first-degree AV block are rare and are typically associated with a wide QRS complex due to disease in the fascicles or the bundle of His. First-degree AV block can also occur when each of these conduction times is at the upper limit of normal and summate to produce an overall prolongation of the PR interval.⁷

First-degree AV block is typically benign and asymptomatic. It can be seen in 0.5% of young adults without heart disease. In older people, first-degree block is most often the result of idiopathic degenerative disease. A prolonged PR interval is often an incidental finding when an ECG is ordered for other reasons. It rarely warrants further workup or treatment.

Second-Degree Atrioventricular Block Type I

Second-degree AV block type I, or a Wenckebach (or Mobitz type I) rhythm, is defined by a progressive prolongation of the PR interval with each successive beat, with eventual failure of a P wave to conduct

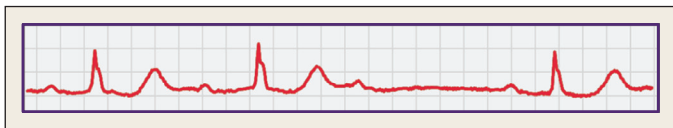


FIGURE 81-2 ■ Electrocardiogram rhythm strip from a patient with second-degree atrioventricular block type I. Note progressive prolongation of the PR interval until failure of conduction occurs. Also note the reciprocal RP shortening. The pattern of conduction is 3:2.

to the ventricles (Fig. 81-2). This results in a dropped beat and failure of the ventricles to depolarize. The P waves occur at regular intervals. As the PR interval lengthens, the RR interval becomes shorter, which eventually results in decremental conduction. There is a reciprocal relationship between the RP interval and the PR interval.

The pathophysiology of second-degree AV block type I is similar to that of first-degree AV block, except that intraatrial block is usually not a cause. For all practical purposes, second-degree AV block type I is caused by a block in AV node conduction. The QRS complex is generally narrow.

QRS complexes are typically grouped in twos, threes, fours, and so on. Group beating is characteristic of Wenckebach rhythms. The rhythm is described by recording the number of P waves and QRS complexes involved in the pattern of block (e.g., 4:3 or 3:2). During a dropped beat, a P wave is observed with no corresponding QRS complex. Second-degree AV block type I is a stable rhythm and has a much better prognosis than does a Mobitz type II rhythm. If the Wenckebach rhythm is due to medication, resolution of the block can be monitored with an ECG. Once the medication is discontinued, a shortening of the PR interval and a lengthening of the RP interval, with a corresponding improvement in AV node conduction, may be observed.

Second-Degree Atrioventricular Block Type II

Second-degree AV block type II (or Mobitz type II block) is characterized by a sudden nonconducted P wave without a change in the PR interval. A P wave with no corresponding QRS complex is observed on the ECG (Fig. 81-3). This is an inherently unstable rhythm, and serious pathology may be present. In contrast to the Mobitz type I rhythm, type II is described as a high degree of AV block, with P wave-to-QRS ratios of 3:1 or 4:1. A Mobitz type II rhythm is almost always due to an infranodal conduction disturbance. The conducted QRS complexes are often wide, and a bundle branch block pattern is often observed. Second-degree AV block can result from an anterior wall MI. Type II second-degree AV block can progress to complete heart block.

2:1 Atrioventricular Block

When conduction of every other P wave is blocked, 2:1 AV block is present. The PR interval of the conducted beat remains fixed. QRS complexes are regular and occur at half the atrial rate. A 2:1 AV block can be caused by a Mobitz I (usually with a narrow QRS complex) or Mobitz II (with a wide QRS complex) rhythm, and the two entities are difficult to distinguish.

Third-Degree Atrioventricular Block

Third-degree AV block is characterized by complete AV dissociation. There is no conduction of the atrial signal through to the ventricle, so the atrial and ventricular systems operate independently. On an ECG, the P waves “march through” and are not associated with ventricular contraction. The PR intervals are irregular. The ventricular complexes may be junctional (narrow QRS complex; rate, 40–60 beats per minute) or ventricular (wide QRS complex; rate, <40 beats per minute). Depending on the escape heart rate, patients may present with tachypnea, dyspnea on exertion, fatigue, cyanosis, or syncope (Fig. 81-4).

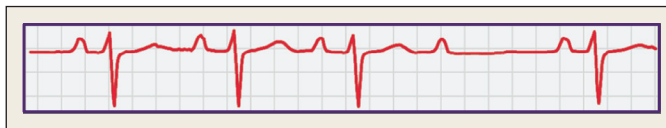


FIGURE 81-3 ■ Electrocardiogram demonstrating second-degree atrioventricular block type II. The PR interval is constant before and after the blocked P waves. The QRS complex is widened.

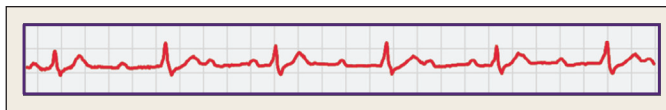


FIGURE 81-4 ■ Complete heart block. The PR intervals are irregular because the ventricles and atria represent two independent sources of depolarization.

Third-degree block can be divided into congenital and acquired causes. Sixty percent of patients with congenital heart block are female. Patients with congenital third-degree block often have an escape rhythm with an adequate rate.⁹ Acquired third-degree block occurs most frequently in the seventh decade of life and usually requires permanent pacing; these patients are often male. Specific causes include medications, ischemia, progression from Mobitz type II rhythm, and infarction. Acute MI results in third-degree heart block in 14% of patients with inferior wall infarcts and 2% of patients with anterior infarcts. Third-degree block is usually observed within 24 hours after an MI. Third-degree block as a complication of an inferior MI is usually temporary and may require only temporary pacing. Complete heart block as a result of an anterior MI usually requires a permanent pacer.

Treatment involves correction of underlying disorders and immediate transcutaneous or transvenous pacing in unstable patients. If the primary cause cannot be medically managed, permanent pacing is required.

Diagnostic Pitfalls

Determining the degree of AV node block is usually straightforward if an adequate ECG has been obtained. There are circumstances, however, in which one may be misled to an incorrect diagnosis.

Third-degree block is occasionally misdiagnosed as second-degree block type II if there appears to be a constant PR interval. This may occur for short periods on an isolated rhythm strip. The clinician must, therefore, examine a strip for an appropriate length of time to make the correct diagnosis. Vagal maneuvers can also be attempted and may identify a second-degree AV block that is really a third-degree AV block.

With isorhythmic AV dissociation, the P waves and QRS complexes occur at a similar rate. The P waves may never “march out” long enough to determine whether they are all conducting. Interventions such as vagal maneuvers to change the P to QRS relationship may aid in diagnosis.

When second-degree AV block is fixed (2:1, 3:1, 4:1), some P waves may be concealed during the repolarization phase of the ECG. This may occur in an acute MI or with ischemia. Vagal maneuvers and examination of multiple leads may be necessary to correctly identify the AV block.

When complete AV dissociation occurs with accelerated junctional or ventricular rhythms, it is possible that some of the atrial impulses would be conducted if the heart rate were slower. It is best to designate these rhythms as complex AV dissociation.

Therapy

Medical therapy for AV block consists of atropine, adrenergic agents, digoxin immune Fab (if appropriate), and pacing. Atropine decreases

vagal tone and is useful for hypervagotonia but not AV node ischemia. It is more useful in inferior wall MI than in anterior wall MI. Atropine will not improve third-degree AV block or a Mobitz type II block if the pathology is below the AV node, and it is ineffective in heart transplant patients. Atropine should be used with caution in patients with Mobitz type II rhythms because a paradoxical decrease in heart rate can occur.

Digoxin immune Fab should be used in symptomatic patients with digoxin-induced AV block. The number of vials required is approximately equal to the patient's weight (in kilograms) times the digoxin serum level (in ng/mL), divided by 100.

PACEMAKERS

Although pacemakers are reliable, patients occasionally present with abnormalities in one or more pacemaker functions that may impact their current illnesses. Intensivists can expect to routinely encounter patients with pacemakers, and it is helpful to be familiar with the basics of their functions and malfunctions.

The North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group created a code consisting of five letters to describe pacemaker functions, known as the NBG pacemaker code (Table 81-2).¹⁰ The first three letters describe the antibradycardia functions, the fourth describes the programmability of rate responsiveness, and the fifth describes any antitachycardia functions. A pacemaker may carry one classification (e.g., DDD) but be capable of several modes of function, depending on how it is programmed. Indications for permanent pacing were updated by the American College of Cardiology in 2002.¹¹

The pacemaker itself consists of two components: a pulse generator and wire leads connecting the generator to the heart. The pulse generator consists of a lithium-based battery and the circuitry to detect and analyze the cardiac rhythm and produce the output. The battery can last more than 10 years, depending on the type of programming; at the end of its life, it produces a gradual rate decrease, not an abrupt drop-off.¹²

Pacemakers also contain a reed switch that can be used to assess the pacemaker's pacing ability. When an external magnet is placed over the pulse generator, the reed switch closes, disabling the sensing mechanism. The unit then fires asynchronously without regard for the patient's underlying rhythm. The pacing rate is unique to each model and manufacturer, and the magnet-programmed rate can vary depending on whether the battery is at the beginning or end of its life or at a time of elective replacement.

Each patient is given a card when a pacemaker is implanted that describes the manufacturer, model, and pacing parameters. The pacemaker itself also contains a radiopaque code, visible on x-ray, that identifies the unit. Pacemakers can be interrogated with a manufacturer-specific program that retrieves ECG information about the unit, which can help assess its functioning. An electrophysiologist should be consulted when a malfunction is suspected.

Two types of lead systems exist: unipolar and bipolar. Bipolar leads are considered standard unless patient-specific factors warrant the use of a unipolar lead. Unipolar programming uses the lead in the endocardium as the cathode and the pacemaker unit itself as the anode.

Because voltage in a unipolar lead is detected over a greater distance, the pacing spike is larger than with bipolar lead programming. Leads can be attached to the endocardium by active fixation (screwed into the myocardium) or passive fixation (held in place by fins). Passive fixation is associated with a greater incidence of dislodgment and perforation.¹³

Assessment of pacemaker function requires knowledge of its parameters. A pacing spike must be present on the ECG to properly evaluate the unit. If one is not present, a magnet can be placed over it and an ECG recorded. This can then be used, in combination with the clinical situation and prior ECGs, to determine the pacemaker's function.

Every pacemaker is programmed to fire after a maximum period in which no activity has been detected. This is called the *lower rate-limiting interval*, and it is the time between two consecutive paced beats. The *escape interval* is the time between a native complex and the following pacemaker spike. A slight delay beyond the lower rate-limiting interval can be programmed into the pacemaker when it senses a native QRS complex. This is an attempt to permit the heart to generate its own output and thus function in a more physiologic manner; this is called *rate hysteresis*, and it is found most often in ventricular demand pacemakers.¹⁴ Dual-chamber pacers have an interval programmed between atrial and ventricular spikes called the *AV interval*, which functions basically as the PR interval. The interval between a ventricular spike and the next atrial pacing spike is the *ventriculoatrial interval*. The AV and ventriculoatrial intervals sum to equal the lower rate-limiting interval.

Complications

Failure to Sense (Undersensing)

Undersensing occurs when the pacemaker generates output regardless of the patient's underlying rhythm (Fig. 81-5). A spike is seen at an interval earlier than the lower rate-limiting interval. Pacemaker output then competes with the patient's own intrinsic rhythm. Although ventricular pacing can present a problem when the threshold for ventricular capture has been altered (e.g., by ischemia), and atrial pacing can produce atrial fibrillation, these are rarely urgent problems.¹⁵

Specific causes of failure to sense are listed in Table 81-3. Blanking is not a true cause; rather, it is an instance of functional undersensing

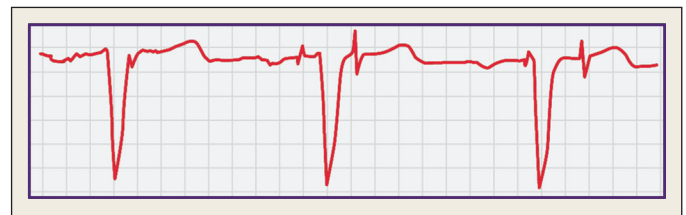


FIGURE 81-5 ■ Failure to sense. Atrial and ventricular pacing spikes are seen around the intrinsic QRS complexes. Pacemaker activity does not lead to capture.

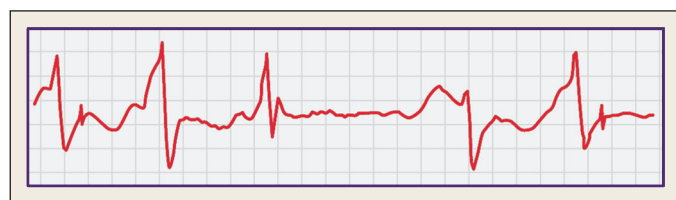
TABLE 81-2 NBG Pacemaker Code

| POSITION | I | II | III | IV | V |
|--------------|--|--|--|--|---|
| Category | Chamber paced | Chamber sensed | Response to sensing | Rate modulation or programmability | Antitachycardia functions |
| Letters used | A = atria V = ventricular D = dual (A + V) | A = atria V = ventricular D = dual (A + V) | T = triggered I = inhibited D = dual (T + I) | R = rate modulation P = simple programmable (rate or output) M = multiprogrammable O = none | P = pacing S = shock D = dual (P + S) |

Data from Bernstein AD, Camm AJ, Fletcher AD. The NASPE/BPEG generic pacemaker code for antibradyarrhythmia and adaptive rate pacing and antitachycardia devices. *Pacing Clin Electrophysiol* 1987;10:794-8.

TABLE 81-3 Causes of Pacemaker Undersensing

| CAUSE | TREATMENT |
|---|--|
| Lead fracture | Replace lead |
| Lead dislodgment | Reposition lead or increase sensitivity |
| Insulation defect in pacing lead | Replace lead |
| Magnet interrogation | Remove magnet |
| Blanking | Decrease ventricular refractory period |
| Amplitude of P wave or QRS complex too low to be sensed | Increase sensitivity |
| Myocardial fibrosis | Increase sensitivity or reposition lead |
| Myocardial perforation | Increase sensitivity or reposition lead |
| End of battery life | Replace battery |
| Acute myocardial infarction | Treat myocardial infarction |
| Electrolyte disturbance | Correct electrolytes |
| Antidysrhythmic drugs | Increase sensitivity, change drug |
| Magnetic resonance imaging | Reprogram to VOO, AOO, or DOO mode |
| Defibrillation | Place defibrillator pads as far from pacemaker unit as possible, place in anteroposterior position |
| Complexes occurring in pacemaker's refractory period | None, or use new generator with shorter refractory period |

**FIGURE 81-6** ■ Failure to pace. An unduly long interval passes after the third QRS complex before another beat occurs. The pacemaker should have fired before this intrinsic beat.

in dual-chamber pacemakers. To prevent pacemaker-induced tachycardia, a 12- to 125-millisecond period of inactivity is programmed into the ventricular component after an atrial complex. If an intrinsic QRS complex occurs during this period, it will not be sensed. Scar tissue does not conduct impulses as easily as normal myocardium does, so sensing may not occur. Most pulse generators begin asynchronous pacing at a critical point at the end of their life and will not sense intrinsic activity. Defibrillation can damage the unit; placing the defibrillator pad in an anteroposterior position may help avoid this. The unit should be observed closely after shocks are delivered.

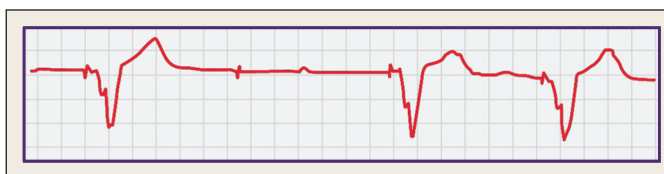
Failure to Pace (Generate Output)

This complication is noted when a pacemaker spike is not seen after the lower rate-limiting interval has been exceeded (except when hysteresis has been programmed; Fig. 81-6). Oversensing occurs when stimuli are erroneously sensed as pacemaker output. As a result, the expected proper output is inhibited; this can be continuous or intermittent. Failure to pace can be a devastating complication for a pacemaker-dependent patient. It is important to determine whether output is truly occurring or not. A 12-lead ECG should be done because spikes may be too small to be seen in a specific lead. Several causes are possible (Table 81-4).

Cross-talk is not a true malfunction of the pacemaker, but it can lead to inhibition of activity. In a dual-chamber system, the output of

TABLE 81-4 Causes of Failure to Pace

| CAUSE | TREATMENT |
|---|---|
| Lead fracture, loose connection, or insulation defect | Adjust or replace leads |
| Battery depletion | Replace battery |
| Pulse generator failure | Replace pulse generator |
| Cross-talk | Program a blanking period or safety pacing |
| Electromagnetic oversensing: | |
| Sensing P or T or U waves | Decrease sensitivity or advance tip deeper into right ventricle |
| Myopotential sensing | Decrease sensitivity or use bipolar sensing |
| Electrocautery | Decrease sensitivity or electrically isolate patient |
| Extracorporeal shock-wave lithotripsy | Decrease sensitivity or use minimal equipment necessary |
| Transcutaneous electrical nerve stimulator (TENS) | Decrease sensitivity, stop TENS unit |
| Magnetic resonance imaging | Program to DOO, VOO, or AOO mode |

**FIGURE 81-7** ■ Failure to capture. After the first QRS complex, a small pacemaker spike occurs that does not result in depolarization of the ventricles. A nonconducted P wave follows, and then a pacemaker spike with capture occurs.

one chamber is sensed as the output of the other, and no pacemaker spike is generated; this occurs more often in unipolar leads. This problem is corrected by programming a blanking period. For a brief period after the atrial output (12 to 25 milliseconds), the ventricular component is inhibited from firing. A second protection against cross-talk is to program the unit to fire depending on when in the AV interval the stimulus is detected. If it occurs immediately after the blanking period, a “safety” spike is generated because it is assumed that it is impossible to differentiate cross-talk from a native QRS complex.

Failure to Capture

This complication occurs when a pacemaker fires as expected but fails to depolarize the myocardium. A pacer spike is seen on the ECG, but no QRS complex immediately follows it (Fig. 81-7). This can be dangerous for a pacemaker-dependent patient and may require temporary pacing until the problem is fixed. Most cases are due to problems with the lead/tissue interface, although isolated problems in the leads or the myocardium can also occur (Table 81-5).^{13,16}

When a lead is placed into the myocardium, tissue fibrosis occurs over the first 4 to 6 weeks. Because scar tissue does not conduct as well as normal myocardium, the output voltage may need to be increased. Twiddler's syndrome is seen when a patient fidgets with the generator and ends up pulling the leads from their attachments to the myocardium. It is confirmed by chest x-ray. The pacemaker is replaced and fixed tightly to the underlying fascia. Perforation of the ventricle typically occurs shortly after the leads are placed and is confirmed by a chest x-ray showing the tip of the lead outside the heart. It is suggested by a change in pacing to a right bundle branch pattern, failure to

TABLE 81-5 Causes of Failure to Capture

| CAUSE | TREATMENT |
|---|---|
| Lead dislodgment from endocardial surface | Repair lead |
| Twiddler's syndrome | Fix unit to chest wall |
| Lead fracture or break in insulation | Replace lead |
| Improperly or inadequately programmed voltage | Reprogram voltage |
| Battery failure | Replace battery |
| Cardiac perforation | Reposition lead (in operating room) or increase voltage |
| Increased threshold for capture Fibrosis or scar tissue at contact site Myocardial ischemia | Increase voltage or reposition lead Treat ischemia |
| Metabolic Hyperkalemia Hypercarbia Hypoxemia Hypothyroidism | Treat abnormality |
| Drugs Beta-blockers Class Ia antidysrhythmics Verapamil Flecainide | Remove drug and replace with another |

capture, contraction of the diaphragm or intercostal muscles with pacing, or development of a pericardial friction rub. Provided the patient is not anticoagulated, the perforation is usually well tolerated.¹⁴ Echocardiography can assess for the presence of a pericardial effusion or tamponade. Repositioning of the lead is typically performed in the operating room after any coagulopathy (if present) has been reversed. An increased threshold for capture can also be caused by myocardial ischemia, metabolic abnormalities, or certain drugs. Definitive treatment involves correcting the underlying disorder.

When assessing for failure to capture, a distinction must be made between pseudofusion and fusion beats. A pseudofusion beat occurs when the pacemaker fires at the same time that an intrinsic beat occurs. The pacemaker output does not depolarize the myocardium, and instead, the pacemaker spike simply deforms the native QRS complex. It is an example of failure to capture. A fusion beat occurs when both the native complex and the pacemaker spike depolarize the myocardium, resulting in a QRS complex that is a hybrid of the two.

Other Problems

Pacemaker-mediated tachycardia, also called *endless loop* or *pacemaker reentrant tachycardia*, is a complication of dual-chamber units. A premature atrial contraction or premature ventricular contraction that travels in a retrograde manner into the atria is sensed by the atrial component of the pacemaker, which induces the ventricular component to fire. The resulting ventricular depolarization reenters the atria, and the cycle continues. An upper rate limit is programmed into the pacemaker, so the tachycardia will not exceed this rate. A tachycardia paced by atrial and ventricular spikes is seen. Application of a magnet terminates the dysrhythmia; adenosine may not reliably block it.¹⁷ A blanking period must be programmed.

Pacemaker syndrome is seen when only the ventricle is paced. Patients present with lethargy, syncope, dizziness, weakness, fatigue, palpitations, or congestive heart failure. It occurs because of an inability to raise the heart rate with exercise and because of the loss of AV synchrony. Dual chamber pacing is required to correct this.

The diagnosis of an MI in a patient with a functioning pacemaker is difficult. Criteria similar to those in patients with left bundle

BOX 81-2 Indications for Temporary Cardiac Pacing

Drug toxicity
Beta-blocker
Calcium channel blocker
Digitalis-induced dysrhythmia (when direct current cardioversion is contraindicated)
Hyperkalemia with bradycardia or asystole
Hypothermia (transcutaneous pacing only)
Symptomatic bradycardia (including hemodynamic compromise, syncope, or ventricular ectopy in response to bradycardia) not responsive to atropine
Pacemaker malfunction with symptoms
Alternating BBB (after MI)
RBBB with alternating LAFB or LPFB (after MI, not known to be old)
RBBB with LAFB or LPFB, or LBBB with first-degree heart block, not known to be old
Mobitz type II heart block
Asystole
LBBB not known to be old
Recurrent sinus pauses >3 seconds not responsive to atropine
RBBB with first-degree heart block
Possibly helpful: bifascicular block or RBBB of unknown age

BBB, bundle branch block; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block; MI, myocardial infarction; RBBB, right bundle branch block.

branch block have been proposed, but sensitivity and specificity are lower.¹⁵

Advanced Cardiac Life Support protocols are not contraindicated by the presence of a pacemaker. Defibrillator pads should be kept as far away from the pulse generator as possible to minimize any damage to the unit.

Examination by magnetic resonance imaging has been considered contraindicated because of the interaction between the strong magnetic field and the pulse generator. Increased pacing rates, decreased rates, and pacing at the magnet rate have all been seen. However, programming the pacemaker to an asynchronous mode (AOO, VOO, or DOO) and close monitoring of the patient, along with the use of lower magnetic fields, may allow safe imaging.¹⁸

TEMPORARY PACING

Temporary cardiac pacing may be required for emergent or elective reasons. In general, any patient with bradycardia causing symptoms or hemodynamic instability that is unresponsive to atropine ought to be considered for temporary pacing (Box 81-2).¹⁹ In most cases, this occurs after an acute MI,¹⁹ but certain drug poisonings may benefit from pacing,^{20,21} and some interventions may, because of underlying disease, predispose a patient to significant bradycardia.

Modes of Pacing

Several modes of temporary pacing are available. Transcutaneous pacing involves placing the pacing pads on either the chest wall and back (the usual locations) or in an anterolateral position (especially if external defibrillation may be required). The negative electrode is placed over the apex of the heart. This is the easiest mode to use, but it is uncomfortable for a conscious patient and may require analgesia or sedation.

Transvenous pacing is usually well tolerated by patients but requires a high degree of skill to correctly place the pacing electrode in the right ventricle. Therefore, the American College of Physicians and the American College of Cardiology recommend that only physicians formally trained in their use place these electrodes.²² The right internal jugular vein approach is best because of its more direct route to the heart; the left subclavian vein approach can also be used but should be avoided, if possible, because it is a preferred site for placement of a permanent pacemaker.¹⁹

Transesophageal pacing allows pacing of either the atria or the ventricles, but it is not a commonly used modality. Transthoracic pacing, in which leads are placed percutaneously into the ventricular myocardium, is also possible but is fraught with complications, including pericardial tamponade, pneumothorax, visceral injury, and coronary artery laceration.

Pacing leads placed during open heart surgery can also be used.

When establishing temporary pacing, the pacing threshold should be determined, and the pacing energy should then be set at two to three times this minimum output. Thresholds should be checked daily.

KEY POINTS

Conduction Disturbances

1. Atrioventricular (AV) node block is most often caused by medications, increased parasympathetic tone, or ischemia. Except when infarction permanently damages a portion of the conduction pathway, such blocks are usually reversible. Infranodal blocks, however, are rarely caused by physiologic abnormalities.
2. First-degree AV node block and Wenckebach block typically do not require treatment. Type II second-degree heart block and complete heart block usually do require treatment.
3. Therapy for AV block consists of atropine, adrenergic agents, digoxin immune Fab (if appropriate), and pacing.
4. Bradyarrhythmias are common after cardiac surgery and may require temporary pacing, but a decision to place a permanent pacemaker should not be made until 5 to 7 days after surgery.

Pacemakers

1. A cardiologist or electrophysiologist should be consulted when a pacemaker or cardioverter-defibrillator malfunction is suspected.

2. Placing a magnet over the pacemaker disables the sensing mechanism, causing the pacemaker to fire at its preprogrammed rate regardless of the underlying intrinsic rhythm.
3. Magnetic resonance imaging may be safe in a pacemaker patient if the unit is programmed to an asynchronous mode and the patient is watched carefully.
4. Failure to sense occurs when the pacemaker generates output regardless of the patient's underlying rhythm; this is rarely an urgent problem.
5. Failure to pace is noted when a pacemaker spike is not seen when expected (after the lower rate-limiting interval has been exceeded); this can be devastating for a pacemaker-dependent patient, and temporary pacing may be required.
6. Failure to capture occurs when a pacemaker fires as expected but fails to depolarize the myocardium. This complication may require temporary pacing.

ANNOTATED REFERENCES

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This guideline revises the indications for implantable pacemakers and cardioverter-defibrillators.

Bernstein AD, Camm AJ, Fletcher AD. The NASPE/BPEG generic pacemaker code for antibradyarrhythmia and adaptive rate pacing and anti-tachycardia devices. *Pacing Clin Electrophysiol* 1987;10:794–798.

The system for describing pacemakers is introduced and discussed in this article.

Roguin A, Schwiter J, Valhous C, et al. Magnetic resonance imaging in individuals with cardiovascular implantable electronic devices. *Europace* 2008;10:336–346.

This study reviews the evidence behind the traditional contraindication of performing magnetic resonance imaging (MRI) in patients with pacemakers and suggests that on a case-by-case basis, MRI may be performed safely. A strategy for the safe performance of an MRI in patients with pacemakers is proposed.

■ References for this chapter can be found at expertconsult.com.

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MYOCARDITIS IN THE INTENSIVE CARE UNIT

Myocarditis is defined as inflammation of the heart muscle.¹ Many different etiologic agents have been implicated in this disease, but viral infections are the most common cause. Myocarditis is also associated with autoimmune and other systemic diseases.² The clinical picture of myocarditis varies widely, from asymptomatic patients who recover without specific therapy and suffer no long-term sequelae to critically ill patients with heart failure and cardiogenic shock. There are no standardized, specific, and widely accepted criteria for making the diagnosis of myocarditis or for determining its cause in many patients.³ Last, there has been controversy regarding the most appropriate medical therapy for this condition.

On pathologic examination of myocardial biopsy specimens or at autopsy, myocarditis is usually apparent as infiltration of the myocardium with lymphocytes, macrophages, and fibroblasts, accompanied by myocyte necrosis (myocytolysis).³ It is this type of myocarditis, often termed *lymphocytic myocarditis*, that will be referred to in this chapter, unless otherwise specified. Other types of inflammatory reactions are seen less frequently in myocarditis, which involve giant cells, eosinophils, or granulomas and can be associated with specific clinical conditions.

In most patients with myocarditis, a specific cause is not found.⁴ In North America and Europe, the most common etiologic agent is presumed to be viral.¹ Coxsackie B enterovirus was considered the most common cause up to the 1990s, but human herpesvirus 6, cytomegalovirus, and parvovirus B19 have been implicated as causative agents more frequently over the past 20 years.² Hepatitis C is also a common etiology in some populations.⁵ Other viral causes include influenza, Epstein-Barr, and herpes simplex 1 and 2. Myocarditis is a common finding in patients infected with human immunodeficiency virus (HIV). However, the causative agent in these cases may be HIV or a secondary viral infection such as cytomegalovirus.^{1,6,7} Infectious illnesses such as Lyme disease, acute rheumatic fever, and diphtheria often have myocarditis as a prominent feature. In Central and South America, the most common cause of myocarditis is the protozoan *Trypanosoma cruzi*, the cause of Chagas' disease (Table 82-1). Systemic and autoimmune diseases such as systemic lupus erythematosus, polymyositis, scleroderma, sprue, Whipple's disease, and sarcoidosis can be complicated by myocarditis, and myocarditis can be a feature of the infiltrative cardiomyopathies seen in hemochromatosis or amyloidosis. Other specific forms of myocarditis include hypersensitivity or eosinophilic myocarditis, which can be caused by allergic reactions to medications including smallpox vaccination⁸ and giant cell myocarditis.⁹ Last, myocarditis can be associated with doxorubicin cardiomyopathy or with peripartum cardiomyopathy.^{10,11} (Box 82-1).

Unfortunately, clinical diagnosis of a specific viral cause of myocarditis is difficult. Antiviral antibody titers in acute and convalescent phase sera do not aid in the diagnosis, as viruses are highly prevalent in the general population and antibody levels vary over time and do not correlate well with the onset of symptoms of acute myocarditis.^{12,13} Viral cultures of tissue specimens are unreliable.⁴ The identification of viral genomes incorporated in myocyte DNA by the use of methods such as polymerase chain reaction (PCR) is highly suggestive but does not specifically prove that the virus is the cause.

PATHOGENESIS

Based on observations of human myocarditis and murine models of the disease caused by coxsackie B3, the pathogenesis of viral myocarditis can be described in three stages.^{2,14} The first stage is initiated by viral infection and replication within myocytes. Viral proteases and activation of proinflammatory cytokines initiate myocyte damage.¹⁵ The presence of this viral replication phase is difficult to detect clinically because patients may be asymptomatic during this phase or may only have nonspecific viremic symptoms. In addition, there is no rapid screening test to confirm viral infection. Parvovirus B19 may preferentially infect endothelial cells in coronary arteries, venules, and capillaries, and myocardial damage may be a result of coronary arteritis causing impairment of blood flow.¹⁶

The second stage involves host immune activation. Stimulation of cellular immunity as well as humoral responses attenuates viral proliferation and can result in recovery from the illness. However, unabated immune activation can result in activated T cells targeting myocardial antigens that cross-react with viral peptides. This reaction leads to the release of cytokines such as tumor necrosis factor, interleukin-1, and interleukin-6, resulting in further damage to myocytes and the cytoskeleton.^{1,15} Activation of CD4 cells and antibody production plays a less important pathogenetic role. This secondary immune response to viral infection may play a greater role in disease pathogenesis than the primary infection and may be genetically influenced.¹⁵ Incomplete clearing of virus or recurrent viral replication may also cause persistence of inflammation and myocardial damage. Evidence supporting these mechanisms includes the following: (1) myocardial biopsy with recombinant DNA techniques can detect viral genomes in 20% to 35% of patients; (2) tissue-specific autoantibodies have been detected in 25% to 73% of patients with evidence of myocarditis on biopsy, with antibodies directed against contractile, structural, and mitochondrial myocyte proteins; (3) inappropriate expression of the major histocompatibility complex can frequently be demonstrated on biopsy specimens¹; and (4) elevated levels of inflammatory cytokines are detected in patients with active myocarditis.

Either persistent overactivation of cellular immune activity or incomplete clearing with persistent or recurrent viral replication can lead to the third stage, which is marked by cellular apoptosis, ongoing necrosis, and fibrosis. Significant myocardial damage leads to left ventricular dilatation and remodeling, neurohormonal activation, systolic dysfunction, and manifestations of heart failure.^{15,17} These processes can then abate, with reduction in left ventricular size and improvement of left ventricular function, or can continue to progress with development of dilated cardiomyopathy, worsening ventricular function, and chronic heart failure. Chronic dilated cardiomyopathy is the major long-term sequela of acute myocarditis (Fig. 82-1).

CLINICAL PRESENTATION AND DIAGNOSIS

The incidence of myocarditis is difficult to determine, as many cases are mild with subclinical disease. Myocarditis is diagnosed on clinical grounds, as there are no specific clinical diagnostic criteria. The presentation of myocarditis varies widely. Patients can be asymptomatic,

TABLE 82-1 Causes of Myocarditis/Inflammatory Cardiomyopathy**INFECTIOUS MYOCARDITIS**

| | |
|-------------|---|
| Bacterial | <i>Staphylococcus</i> , <i>Streptococcus</i> , <i>Pneumococcus</i> , <i>Meningococcus</i> , <i>Gonococcus</i> , <i>Salmonella</i> , <i>Corynebacterium diphtheriae</i> , <i>Haemophilus influenzae</i> , <i>Mycobacterium</i> (tuberculosis), <i>Mycoplasma pneumoniae</i> , <i>Brucella</i> |
| Spirochetal | <i>Borrelia</i> (Lyme disease), <i>Leptospira</i> (Weil disease) |
| Fungal | <i>Aspergillus</i> , <i>Actinomyces</i> , <i>Blastomyces</i> , <i>Candida</i> , <i>Coccidioides</i> , <i>Cryptococcus</i> , <i>Histoplasma</i> , <i>Mucormycoses</i> , <i>Nocardia</i> , <i>Sporothrix</i> |
| Protozoal | <i>Trypanosoma cruzi</i> , <i>Toxoplasma gondii</i> , <i>Entamoeba</i> , <i>Leishmania</i> |
| Parasitic | <i>Trichinella spiralis</i> , <i>Echinococcus granulosus</i> , <i>Taenia solium</i> |
| Rickettsial | <i>Coxiella burnetii</i> (Q fever), <i>Rickettsia rickettsii</i> (Rocky Mountain spotted fever), <i>R. tsutsugamushi</i> |
| Viral | RNA viruses: coxsackieviruses A and B, echoviruses, polioviruses, influenza A and B viruses, respiratory syncytial virus, mumps virus, measles virus, rubella virus, hepatitis C virus, dengue virus, yellow fever virus, Chikungunya virus, Junin virus, Lassa fever virus, rabies virus, human immunodeficiency virus-1 DNA viruses: adenoviruses, parvovirus B19, cytomegalovirus, human herpesvirus-6, Epstein-Barr virus, varicella-zoster virus, herpes simplex virus, variola virus, vaccinia virus |

IMMUNE-MEDIATED MYOCARDITIS

| | |
|--------------|---|
| Allergens | Tetanus toxoid, vaccines, serum sickness Drugs: penicillin, cefaclor, colchicine, furosemide, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, phenylbutazone, methyl dopa, thiazide diuretics, amitriptyline |
| Alloantigens | Heart transplant rejection |
| Autoantigens | Infection-negative lymphocytic, infection-negative giant cell Associated with autoimmune or immune-oriented disorders: systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Kawasaki's disease, inflammatory bowel disease, scleroderma, polymyositis, myasthenia gravis, insulin-dependent diabetes mellitus, thyrotoxicosis, sarcoidosis, Wegener's granulomatosis, rheumatic heart disease (rheumatic fever) |

TOXIC MYOCARDITIS

| | |
|-----------------|--|
| Drugs | Amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, hemetine, interleukin-2, trastuzumab, clozapine |
| Heavy metals | Copper, iron, lead (rare, more commonly cause intramyocyte accumulation) |
| Miscellaneous | Scorpion sting, snake, and spider bites, bee and wasp stings, carbon monoxide, inhalants, phosphorus, arsenic, sodium azide |
| Hormones | Pheochromocytoma, vitamins: beriberi |
| Physical agents | Radiation, electric shock |

From Feldman A, McNamara D. Myocarditis. *N Engl J Med* 2000;343:1388-1398.

BOX 82-1 Distinct Forms of Myocarditis

| |
|---|
| Active viral |
| Postviral (lymphocytic): common form of acute myocarditis |
| Hypersensitivity or eosinophilic |
| Autoimmune |
| Infectious |
| Giant-cell myocarditis |

From Haas G: Etiology, evaluation, and management of acute myocarditis. *Cardiol Rev* 2001;9:88-95.

as myocarditis is found in 1% to 10% of autopsy specimens of young adults who had no history of cardiac illness. Myocarditis can be found at autopsy in up to 20% of cases of young, apparently healthy, adults who die suddenly and unexpectedly.^{1,4,11}

Patients ill with myocarditis present with nonspecific symptoms of dyspnea (72%), chest pain (32%), and symptoms of arrhythmia (18%).¹⁸ The presentation may be indistinguishable from acute coronary syndromes due to coronary artery disease. A viral prodrome with fever, malaise, and arthralgias may have preceded the presentation. Physical examination can show fever, tachycardia, S3 and S4 gallop sounds, and a pericardial rub if pericarditis is present. Signs of heart failure can be present, including pulmonary rales and wheezes, elevated jugular venous pressure, and peripheral edema. Murmurs of mitral regurgitation and tricuspid regurgitation may be heard. Infrequently, the presentation is fulminant and severe, with acute heart failure, pulmonary edema, and cardiogenic shock.⁴

The differential diagnosis includes acute myocardial infarction, isolated pericarditis, or chest pain from pulmonary causes, including pulmonary embolism or pneumonia. Generalized sepsis is also a consideration.

Laboratory findings can include leukocytosis, eosinophilia, and an elevated erythrocyte sedimentation rate. The cardiac biomarkers CPK, troponin T, and troponin I may be elevated, with troponin I sensitivity

reported as 34% to 53% and specificity reported as 89%.^{13,19} Rheumatologic serologic markers and HIV status should be evaluated.

The 12-lead electrocardiogram is an insensitive test for the diagnosis of myocarditis, most often showing sinus tachycardia, nonspecific ST segment depression, and T wave inversion. Patients may present with chest pain and ST segment elevation with a picture mimicking acute myocardial infarction or acute pericarditis. More severe cases can be associated with supraventricular or ventricular arrhythmias, conduction disturbances, and heart block.¹ QTc prolongation over 440 msec, QRS duration over 120 msec, and an abnormal QRS axis have been associated with a poorer prognosis.²⁰

Echocardiography is essential for diagnosing and quantitating regional or global left ventricular wall motion abnormalities, left ventricular and right ventricular size and function, and the presence of pericardial effusion and valvular regurgitation. Right ventricular involvement may be seen in 25% of patients.¹³ Fulminant myocarditis is characterized by a nondilated left ventricle with severe systolic dysfunction and increased wall thickness reflecting myocardial edema.²¹ Pericardial effusion may be present. Findings on myocardial nuclear scintigraphy are frequently abnormal, but this test is not useful in the diagnosis of myocarditis. Cardiac catheterization and coronary angiography are often necessary to exclude acute ischemia due to coronary artery disease as the cause of chest pain or acute heart failure.

Cardiac magnetic resonance imaging (CMR) with contrast enhancement is increasingly used in the diagnosis of myocarditis.^{22,23,24,25} This technique offers a noninvasive means to make this diagnosis. Diagnostic criteria include (1) focal or diffuse myocardial edema in T2-weighted images; (2) early gadolinium enhancement (EGE) on T1 imaging indicating inflammation and cell damage; and (3) late gadolinium enhancement (LGE) in subepicardial or mid-myocardial areas indicating necrosis and fibrosis. Myocardial edema may be subepicardial, transmural, or global and is not always associated with LGE. Abnormalities may be diffuse or patchy, often confined to the lateral free wall of LV or the base of the interventricular septum (Fig. 82-2). Diagnostic sensitivity is improved when all three techniques are assessed. The diagnostic accuracy of CMR is reported as 78% when 2 or 3 criteria are

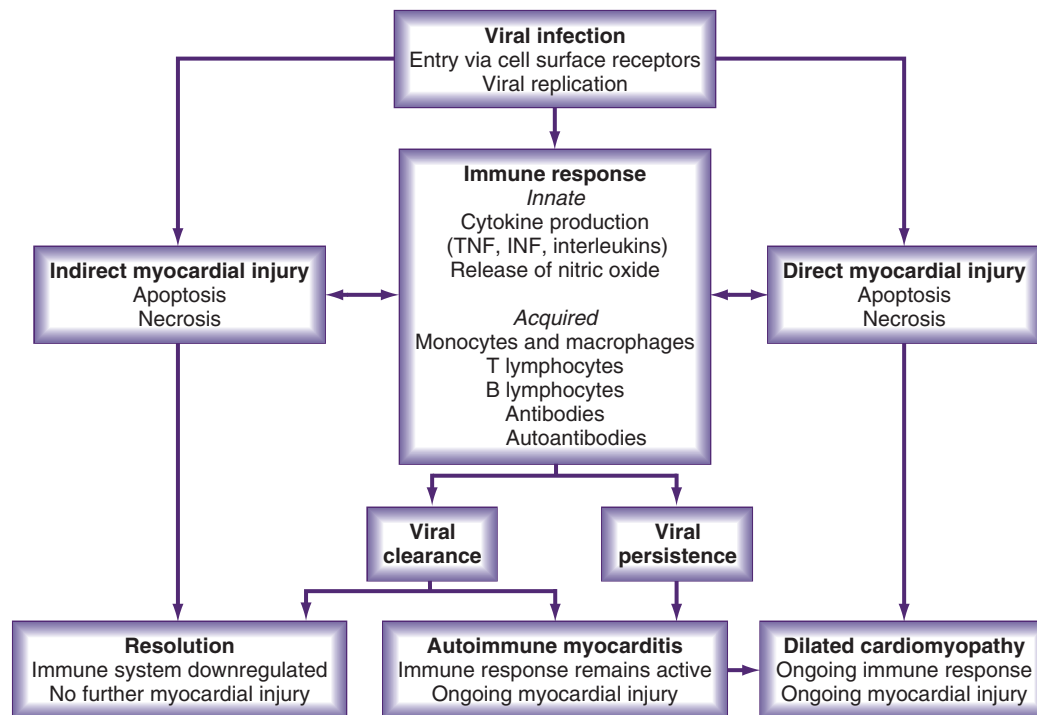


FIGURE 82-1 ■ The pathogenesis of viral myocarditis involves direct myocardial injury from viral infection as well as immune-mediated myocyte damage from cytokines, proteases, and autoantibodies. The outcome of these processes can be healing of inflammation and resolution of ongoing active myocarditis or chronic dilated cardiomyopathy. (Adapted from Blauwer LA, Cooper LT. Myocarditis. *Prog Cardiovasc Dis* 2010;52:274–88.)

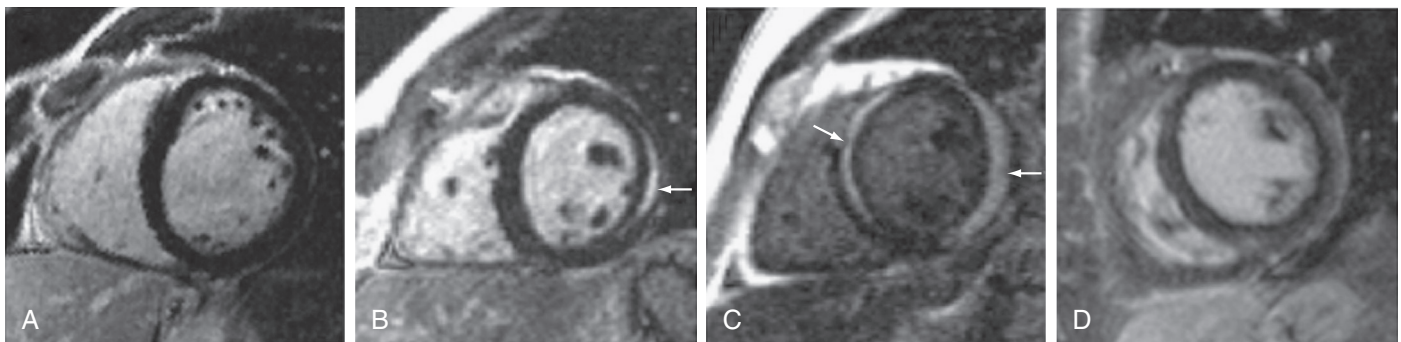


FIGURE 82-2 ■ Cardiac magnetic resonance imaging with late gadolinium enhancement: normal and abnormal findings in myocarditis. **(A)** Normal myocardium with no evidence of irreversible myocyte injury. **(B)** Regional subepicardial enhancement of the lateral wall (arrow). **(C)** Subepicardial enhancement of lateral and midwall enhancement of the septal wall (arrows). **(D)** Diffuse subepicardial enhancement. (From Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, et al. Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. *J Am Coll Cardiol* 2009;53(17):1475–87.)

present and 68% when only late gadolinium enhancement is present. CMR is more likely to be abnormal when performed more than 7 days after the onset of symptoms. CMR may also detect pericardial effusion (seen in 32%–57% of patients) and gives information regarding LV function. CMR can also be used to direct myocardial biopsy in patients with patchy uptake. The value of CMR for assessing prognosis is unknown.^{26–28}

Advantages of CMR include that it is noninvasive and low risk, has no sampling error (a problem with endomyocardial biopsy, see later discussion), and can be used serially over time to assess a patient's

course. However, CMR results may be normal in patients with milder forms of myocarditis, and it does not distinguish between viral and other etiologies of the disease. CMR is difficult to use in critically ill patients.

Endomyocardial Biopsy

Percutaneous endomyocardial biopsy (EMB) is used to aid in the diagnosis of myocarditis and is considered the definitive diagnostic technique. The Dallas criteria have been accepted as the standard for

histopathologic diagnosis, but the utility of the Dallas criteria is strongly debated (see later discussion). These criteria define *active myocarditis* as the presence of an inflammatory myocardial infiltrate (more than 5 lymphocytes per high-power field) accompanied by myocyte necrosis. *Borderline myocarditis* is defined as inflammation without myocyte necrosis. However, there is no difference in prognosis in patients with either of these biopsy results.¹⁰ Thus, lymphocyte infiltration (with or without myocyte necrosis) is the most important diagnostic criterion. A more recent pathologic definition from the World Heart Federation defined *myocarditis* as the presence on EMB of a focal or diffuse mononuclear cell infiltrate of lymphocytes and macrophages, with more than 14 cells/mm², and emphasized that immunohistochemistry to identify upregulated HLA proteins and polymerase chain reaction (PCR) to investigate viral genomes should also be performed.^{20,29,30} Viral myocarditis is considered present when there is evidence of active inflammation with a positive molecular test for virus on EMB. Autoreactive or autoimmune myocarditis is diagnosed when inflammation is present without viral markers.³¹

A positive EMB has a high positive predictive value, but there are a number of significant limitations.¹⁰ A high frequency of interobserver variation has been noted among pathologists in applying the Dallas criteria. Biopsies are not sensitive in diagnosing myocarditis, as various series have reported positive right ventricular biopsy results in only 10% to 67% of patients with myocarditis suspected on clinical grounds or with recent-onset idiopathic dilated cardiomyopathy. This variability may relate to the timing of biopsies with respect to the stage or chronicity of the patient's illness. In addition, the myocardial inflammation may not be diffuse and may be patchy or may predominantly involve the left ventricle, so random right ventricular biopsies may miss the affected myocardium.²⁹ Thus, diagnostic yields are improved by performing a biopsy earlier in a patient's clinical course, taking 3 to 6 biopsy specimens, and performing left ventricular biopsies. In addition, immunohistochemical staining for human leukocyte antigens can improve diagnostic sensitivity.^{14,32} EMB should be performed in centers with a high-volume experience, with proven safety and availability of appropriate pathologic techniques.³³ Recent reports indicate a very low rate of serious complications related to EMB in experienced centers, <0.1%.³¹ It is important to emphasize that a negative biopsy finding does not preclude the diagnosis of myocarditis.

Endomyocardial biopsy should be strongly considered in cases of suspected myocarditis when pathology results will affect management decisions. A recent AHA/ACC/ESC scientific statement offered recommendations concerning the appropriate use of EMB based on patients' clinical presentations.³⁴ EMB was deemed useful, beneficial, and effective (class I indication) in patients with acute heart failure with hemodynamic compromise, after exclusion of causes such as coronary artery disease. EMB in this setting is necessary to differentiate giant cell myocarditis and eosinophilic myocarditis, which most often present with severe heart failure or arrhythmias, from lymphocytic myocarditis, as immunosuppressive therapy is mandated in the first two conditions. A class I indication for EMB was also recommended for patients with new onset, subacute heart failure, or illness duration of 2 weeks to 3 months and in those who fail to improve with medical therapy for heart failure or demonstrate severe ventricular arrhythmia or advanced heart block. EMB should be considered if causes such as sarcoidosis or collagen vascular disease are suspected and should be performed to diagnose giant cell myocarditis or eosinophilic myocarditis.³⁵ Endomyocardial biopsy should always be performed before initiating immunosuppressive therapy (Box 82-2).

An algorithm has been proposed outlining the steps for evaluating patients suspected of having acute myocarditis (Fig. 82-3).

CLINICAL COURSE AND PROGNOSIS

The clinical course and prognosis of acute myocarditis are variable. The majority of patients diagnosed with myocarditis will improve, and those with mild symptoms most often recover without complications. Eight to 12% of young, apparently healthy adults who die suddenly

BOX 82-2 Indications for Endomyocardial Biopsy

Exclusion of potential common etiologies of dilated cardiomyopathy (familial, ischemic, alcohol, postpartum, cardiotoxic exposures) and the following:

- Subacute or acute symptoms of heart failure refractory to standard management
- Substantial worsening of ejection fraction despite optimized pharmacologic therapy
- Development of hemodynamically significant arrhythmias, particularly progressive heart block and ventricular tachycardia
- Heart failure with concurrent rash, fever, or peripheral eosinophilia
- History of collagen vascular disease such as systemic lupus erythematosus, scleroderma, or polyarteritis nodosa
- New-onset cardiomyopathy in the presence of known amyloidosis, sarcoidosis, or hemochromatosis
- Suspicion for giant cell myocarditis (young age, new subacute heart failure, or progressive arrhythmia without apparent etiology)

Adapted with permission from Wu L, Lapeyre A, Cooper L. Current role of endomyocardial biopsy in the management of dilated cardiomyopathy and myocarditis. *Mayo Clin Proc* 2001;76:1030–8.

from a cardiac cause are found to have myocarditis at autopsy, suggesting that patients even with apparently mild illness can suffer fatal arrhythmias.¹⁴ In over 50% of patients, clinically recognized myocarditis will resolve in 4 weeks. However, 25% will develop persistent abnormalities of ventricular function, and roughly 10% to 20% may develop dilated cardiomyopathy with chronic, severe heart failure.^{3,30} Fifteen to 25% of patients who present with new-onset dilated cardiomyopathy have evidence of antecedent myocarditis.³ Patients with heart failure and left ventricular dysfunction will experience spontaneous resolution of their illness within 12 months in up to 40% of cases, without long-term sequelae. Roughly one-quarter of patients with acute myocarditis and ejection fraction below 35% will improve, one-half will develop chronic cardiomyopathy and heart failure, and one-quarter will deteriorate and may be candidates for cardiac transplantation.³⁶

Examining the patient population under study and the criteria used for diagnosing myocarditis is important in any series assessing prognosis and mortality. No clinical markers reliably predict which patients with myocarditis will recover or worsen.¹⁰ In the Myocarditis Treatment Trial, the 1-year mortality rate was 20% and the 5-year mortality rate was 56% in patients with biopsy-confirmed lymphocytic myocarditis.³⁷ A series of 21 patients with active myocarditis on biopsy was analyzed for predictors of disease course. Variables assessed included baseline hemodynamics, use of ventilatory and circulatory support, and serum cardiac biomarkers. Overall, there was a 37% mortality rate (8 of 21), with death occurring at 27.6 ± 6.9 days. Factors predicting a worse prognosis included hypotension (mean 84/49 mm Hg), higher pulmonary capillary wedge pressure (mean, 24 mm Hg), and use of mechanical ventilation. Factors that were not predictive of mortality included sex, age, heart rate, cardiac index, peak CPK, and the use of intraaortic balloon counterpulsation for circulatory support.³⁸ Another trial reported 181 patients with myocarditis confirmed by EMB using the Dallas criteria, immunohistochemical staining, and PCR. LV biopsy was performed in 90% of patients. Patients were followed for an average of 59 months, and 22% died or received cardiac transplantation. Multivariate analysis concluded that functional class III and IV heart failure and a positive immunohistochemical result were the only predictors of a poor outcome, and treatment with beta-blockers was associated with better outcomes³² (Fig. 82-4). Other series have reported that LV ejection fraction less than 40% and right ventricular dysfunction also predict a poorer prognosis.¹⁴

Fulminant Myocarditis

A small percentage of patients with acute myocarditis present critically ill with acute severe heart failure and cardiogenic shock. This presentation is termed *fulminant myocarditis*. Most often these patients give

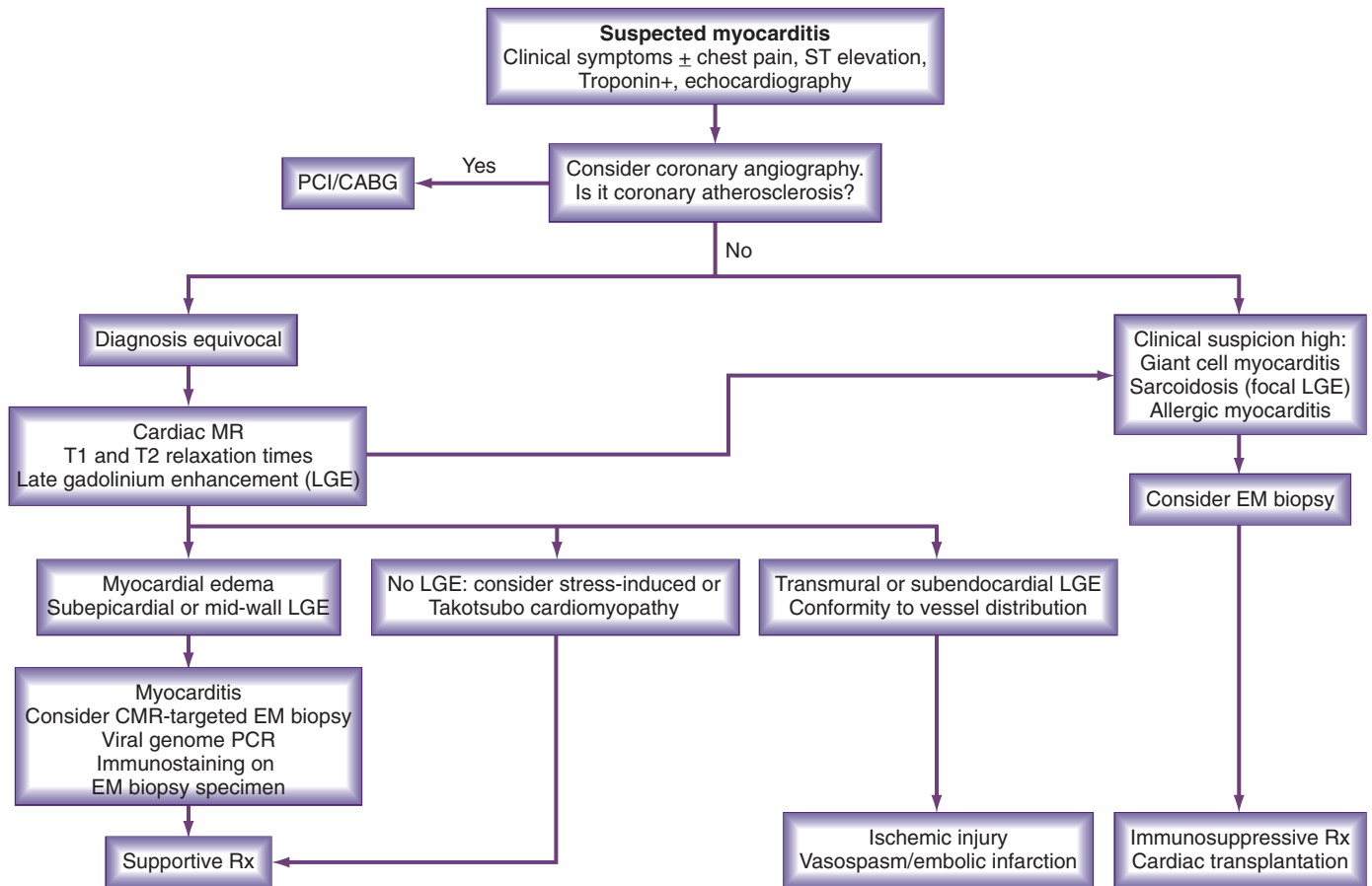


FIGURE 82-3 ■ Diagnostic algorithm for suspected acute myocarditis. (Adapted from Nelson KH, Li T, Afonso L. Diagnostic approach and role of MRI in the assessment of acute myocarditis. *Cardiol Rev* 2009;17:24–30.)

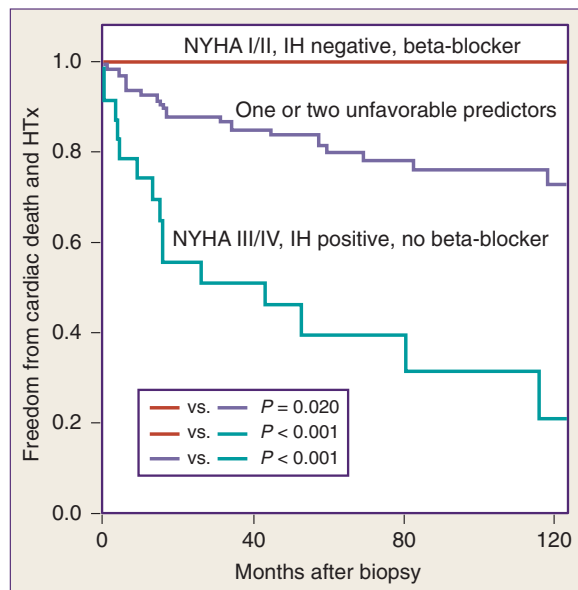


FIGURE 82-4 ■ Prognosis for patients with acute myocarditis was predicted by three factors: NYHA functional class, positive immunohistology for myocarditis at EMB, and therapy with beta-blockers. (Adapted from Kindermann I, Kindermann M, Kandolf R, et al. Predictors of outcome in patients with suspected myocarditis. *Circulation* 2008;118:639–48.)

a history of recent fever and symptoms of a viral illness during the previous several weeks, with a distinct time of onset of heart failure symptoms. This presentation can be contrasted with that of patients with myocarditis who have acute heart failure, but not cardiogenic shock, who demonstrate a less distinct time of onset of heart failure symptoms and less severe hypotension. Direct cytolysis of myocytes caused by viral infection and replication is felt to be particularly important in fulminant myocarditis. Early and extensive loss of myocytes and myocardial tissue leads to the rapid development of severe heart failure.

In a study of 147 patients presenting with heart failure due to biopsy-positive active myocarditis with ejection fraction less than 40%, 10% of patients were diagnosed with fulminant myocarditis, and 90% had acute nonfulminant myocarditis.¹⁰ The patients with fulminant myocarditis needed hemodynamic support with high-dose vasopressors or left ventricular assist devices. The acute myocarditis patients had more stable hemodynamics and did not require vasopressors or received them at low doses. Patients with fulminant myocarditis tended to be younger and had higher heart rates and lower systemic blood pressure. There was no difference between the groups in mean pulmonary capillary wedge pressure or cardiac index. With aggressive treatment, patients with fulminant myocarditis actually had better survival rates: 93% at 1 year and 93% at 11 years. Patients with acute myocarditis had an 85% 1-year survival rate and a 45% survival rate at 11 years. Patients with lower pulmonary capillary wedge pressure or higher cardiac index at presentation also had better survival. In another study of myocarditis in children, 38% of myocarditis cases were fulminant.³⁹

In summary, fulminant myocarditis has a distinct clinical course, with critical illness at presentation but with excellent long-term survival after recovery from the acute phase of illness. EMB is essential for management as immunosuppressive therapy is recommended if active inflammation is documented.¹³ Healing of myocardial injury and significant improvement of left ventricular systolic function can be expected. Therefore, an aggressive approach to therapy, including the use of ventricular assist devices or other mechanical assist devices, without resorting to early cardiac transplantation, is warranted.¹⁰

Giant Cell Myocarditis

Giant cell myocarditis is a distinct form of myocarditis, characterized by severe heart failure, life-threatening ventricular arrhythmias, and/or high-grade heart block. It has a rapidly progressive course, without significant likelihood of spontaneous resolution. On endomyocardial biopsy, infiltration with inflammatory giant cells and lymphocytes is seen. Although the pathogenesis is not clear, it is believed to be an autoimmune disorder, possibly triggered by a viral infection; it often occurs in patients with other autoimmune disorders.⁴⁰ CD4 T-lymphocytes are thought to play an important role. A total of 63 patients with biopsy-confirmed giant cell myocarditis were studied retrospectively.⁴¹ Heart failure was the presentation in 75% of cases; 14% presented with ventricular arrhythmias, and 11% presented with chest pain, an abnormal electrocardiogram, or heart block. There was an association with inflammatory bowel disease in 8% of cases. Survival was poor, with a median time of 5.5 months to death or cardiac transplantation. EMB is essential to make this diagnosis. In this uncontrolled series, immunosuppressive therapy was associated with prolonged survival: from 3 months in 30 patients not given immunosuppressive drugs and 3.8 months in patients treated with prednisone, to 11.5 months in patients given prednisone plus azathioprine and 12.6 months in patients who were given cyclosporine as part of their regimen. Other options for immunosuppressive therapy include anti-tissue necrosis factor therapy and monoclonal antibodies to CD3 cells.^{12,31} The prognosis after cardiac transplantation was also worse compared with other forms of heart disease, with a 30-day mortality rate of 15% and a 26% mortality rate during the 3.7-year posttransplant follow-up period. Twenty-six percent of patients had giant cell infiltrates seen in their transplanted heart at an average time of 3 years after transplant.

Eosinophilic Myocarditis

Eosinophilic myocarditis, also termed *hypersensitivity myocarditis*, is a rare form of myocarditis characterized by eosinophilic infiltration and degranulation on endomyocardial biopsy. The pathogenesis is thought to involve a direct role of eosinophil-mediated myocyte damage. There can be associated arteritis. This entity is distinct from eosinophilic endocarditis (Löffler's endocarditis). The clinical manifestations are not specific, aside from a high incidence of eosinophilia in peripheral blood. Patients usually present with heart failure due to left ventricular systolic dysfunction. Fever and rash may be present. Untreated, the disease is often rapidly fatal.⁸

The cause is believed to be a hypersensitivity reaction, usually to medication or rarely in association with parasitic infections. Drugs most often implicated are sulfonamides, diuretics, angiotensin-converting enzyme (ACE) inhibitors, cephalosporins, digoxin, and dobutamine. Eosinophilic myocarditis has been reported to occur weeks after smallpox vaccination, with an incidence of 1 in 16,000 vaccinated.⁴² The clinical course is unfavorable, often with rapidly worsening heart failure and sudden death due to ventricular arrhythmia. Treatment involves the discontinuation of all potentially offending medications and the use of high-dose corticosteroids with azathioprine.³¹ Excellent responses to corticosteroids, as well as some spontaneously resolving illness, have been reported.^{43,44}

Eosinophilic myocardial infiltration has been reported in 2% to 7% of myocardial biopsy specimens of patients awaiting cardiac transplantation or in the explanted heart after transplant. The cause is unclear,

but evidence implicates dobutamine therapy, sodium bisulfite used as a preservative in dobutamine solutions, and the use of left ventricular assist devices. The presence of eosinophilic myocarditis in this setting did not have an adverse effect on posttransplant survival and did not recur in the transplanted heart.^{45,46}

THERAPY

General Management of Heart Failure

The treatment of myocarditis is based on the clinical presentation. Patients with mild disease can be treated expectantly, with dietary sodium restriction and avoidance of strenuous exercise for several weeks or months.³ Animal models indicate that strenuous exercise can worsen myocarditis. Elimination of unnecessary medications is important in patients with eosinophilia.

Nonsteroidal antiinflammatory drugs should be avoided because they may worsen myocarditis.⁴ The routine use of anticoagulants for prophylaxis of systemic emboli is not recommended. Patients who present with symptoms of arrhythmia or heart failure should be hospitalized, with continuous cardiac rhythm monitoring performed for evaluation of potential life-threatening arrhythmias or conduction abnormalities. If these are diagnosed, they are treated in a similar manner as in patients with other causes of heart disease, using antiarrhythmic drugs or pacemakers. However, a period of observation is recommended to assess for improvement of cardiac function before implantation of an ICD.

Data from studies of murine models of myocarditis support the use of angiotensin-converting enzyme inhibitors, angiotensin blockers, and beta-blockers. These drugs reduce inflammation and lessen necrosis and fibrosis.^{2,3,14,26} There are convincing data in humans supporting the use of these medication as well as aldosterone antagonists in patients with dilated cardiomyopathy. Therefore, in patients with myocarditis and heart failure, the use of standard multidrug medical therapy for heart failure and left ventricular systolic dysfunction is indicated.^{3,11} These medications have been shown to improve symptoms, prolong life, and regress the adverse left ventricular remodeling in patients with dilated cardiomyopathy of various causes.^{47,48,49}

Treatment with ACE inhibitors should be initiated at low doses, with upward titration to maximally tolerated doses. Patients should be closely monitored for potential side effects, including renal insufficiency, hyperkalemia, and angioedema. Relative contraindications to the use of ACE inhibitors include renal failure, hyperkalemia, bilateral renal artery stenosis, and hepatic failure. Patients with hypotension should be treated with parenteral vasopressors or circulatory assist devices before initiation of low-dose ACE inhibitor therapy.

As described above, beta-adrenergic blockade was associated with improved survival in a multivariate analysis of patients with acute myocarditis.³² Large randomized, controlled clinical trials, which included patients with idiopathic dilated cardiomyopathy, have unequivocally shown benefit from beta-blockers in patients with left ventricular systolic dysfunction,⁵⁰⁻⁵⁴ and these agents should also be used in patients with heart failure due to myocarditis. Beta-blockers should be initiated after patients are on a stable dose of ACE inhibitors and when signs of fluid overload have resolved. Contraindications to beta-blocker therapy include bronchospastic disease or severe chronic obstructive lung disease, heart block, or significant underlying bradycardia. Hypotension should be corrected before initiating beta-blocker therapy.

Digoxin has been shown in animal models to decrease levels of cytokines, but digoxin was associated with adverse outcomes in one murine model of myocarditis. Digoxin can be useful in helping to control ventricular rates in patients with atrial fibrillation. The use of digoxin should be considered in patients with significant left ventricular systolic dysfunction, after ACE inhibitors and beta-blockers have been initiated. However, no survival benefit for digoxin has ever been shown in patients with heart failure due to dilated cardiomyopathy.⁵⁵ Contraindications to the use of digoxin include renal failure or heart block.

Last, the use of the aldosterone antagonist spironolactone has been shown to have symptomatic and survival benefits in patients with class III-IV chronic systolic heart failure.⁵⁶ In experimental models, these agents can reverse the progressive myocardial fibrosis that occurs in the remodeling process of dilated cardiomyopathy. These agents have not been studied in patients with myocarditis, but their use should be strongly considered in patients with severe left ventricular dysfunction (ejection fraction less than 35%) and symptomatic heart failure.² Contraindications to the use of aldosterone antagonists include renal insufficiency, with serum creatinine levels above 2.0 mg/dL or hyperkalemia. Serum potassium levels need to be carefully monitored during initiation and dose titration.

In critically ill patients with severe heart failure and a low cardiac index, without serious hypotension, parenteral vasodilators should be used. Intravenous nitroprusside reduces systemic vascular resistance, mean systemic arterial pressure, and pulmonary capillary wedge pressure and can improve cardiac index. It is used with invasive hemodynamic monitoring with a pulmonary artery catheter, to best gauge the appropriate dose of medication and to accurately assess response to therapy. Prolonged use of nitroprusside is associated with accumulation of the toxic metabolites. Intravenous nitroglycerin is also an effective venodilator and coronary vasodilator, with less arterial dilating property than nitroprusside. The use of nitroglycerin in cases of myocarditis has not been studied. Patients often develop tolerance to this drug.^{57,58}

Patients with severe myocarditis may develop cardiogenic shock, respiratory failure, and end-organ hypoperfusion. In these instances, treatment with inotropic agents or vasopressors is indicated. Dobutamine is a potent β_1 -agonist with fewer β_2 - and α -agonist properties. Dobutamine has favorable short-term hemodynamic effects, increasing myocardial contractility, reducing systemic vascular resistance, and reducing pulmonary capillary wedge pressure. However, dobutamine can be proarrhythmic, and patients can develop tolerance to the drug. Milrinone is another parenteral inotropic agent, which works by inhibiting phosphodiesterase. This drug leads to increased inotropy and decreased systemic vascular resistance and pulmonary capillary wedge pressure, with resultant increased stroke volume and cardiac index. Milrinone may cause hypotension. It is less proarrhythmic than dobutamine and does not induce tolerance.^{59,60} Arterial vasoconstrictors such as norepinephrine and dopamine can be used in patients with refractory hypotension and poor end-organ perfusion.

In patients with fulminant myocarditis or cardiogenic shock not responding to pharmacologic therapy, intraaortic balloon counterpulsation should be used. Mechanical ventricular assist devices (VAD) are used for patients requiring greater hemodynamic support. These devices provide physiologic cardiac output and left ventricular afterload reduction and may allow time for spontaneous improvement in left ventricular function to occur. Complications of VADs include local site infection, sepsis, thromboemboli, and device failure. Extracorporeal membrane oxygenation (ECMO) is another option for circulatory support.

In patients with severe myocarditis, mechanical circulatory support can be used to improve hemodynamics, end-organ perfusion, and coronary flow during the time necessary for spontaneous resolution of left ventricular dysfunction. Beneficial reverse remodeling may occur while patients are on mechanical support. Patients with fulminant myocarditis should be given a reasonable time to recover ventricular function before cardiac transplantation is performed.⁶¹

There are several unresolved issues regarding VAD use in patients with myocarditis. These include appropriate patient selection, timing of VAD placement, best medical therapy during VAD support, and optimal duration of VAD support. A 50-day course of VAD support in the earlier-cited study allowed identification of 50% of those patients who ultimately recovered, and a 90-day course identified 80% of patients who recovered. The optimal means of serial assessment of native heart function while on VAD support needs to be delineated, and the best weaning protocol also needs definition.

Cardiac transplantation is the final option for treating critically ill patients with myocarditis. However, these patients may have a higher

TABLE 82-2

Medical Therapy and Advanced Supportive Therapies for Heart Failure in Acute Myocarditis

| | |
|---|--|
| Heart failure with LV systolic dysfunction | Loop diuretics Beta-blockers (metoprolol succinate, carvedilol, bisoprolol) ACE-inhibitors or angiotensin receptor blockers Aldosterone blockers Digoxin |
| Severe heart failure with reduced cardiac output | Intravenous vasodilators (nitroprusside, nitroglycerin) Intravenous inotropes (milrinone, dobutamine), vasopressors (norepinephrine) |
| Cardiogenic shock not responding to medical therapy | Intraaortic balloon counterpulsation Extracorporeal membrane oxygenation (ECMO) Ventricular assist device (VAD) Cardiac transplantation |

rate of transplant rejection and a lower survival rate compared with patients transplanted for ischemic or other causes of cardiomyopathy (Table 82-2).¹¹

Immunosuppressive Therapy

Because autoimmune mechanisms are responsible for myocardial injury and the clinical manifestations of myocarditis, therapy with immunosuppressive drugs has been studied. However, given the high rate of spontaneous recovery of left ventricular function, placebo-controlled trials are essential to properly evaluate the effects of therapy. In addition, heterogeneous patient populations consisting of patients with acute myocarditis and chronic dilated cardiomyopathy have been included in immunosuppressive trials, confounding the interpretation of results.

High-dose daily prednisone therapy was used for a 3-month course in 102 patients with dilated cardiomyopathy, 59% of whom were classified as having “reactive” myocarditis on endomyocardial biopsy.⁶² The authors found a significant improvement in left ventricular ejection fraction at 3 months in treated patients with reactive myocarditis, but this improvement was not sustained at 9 months. Improvement did not occur in patients with nonreactive biopsies treated with prednisone. No significant mortality benefit from immunosuppressive treatment was noted, although this was not a prespecified primary endpoint.

The Myocarditis Treatment Trial enrolled 111 patients with a positive endomyocardial biopsy finding and left ventricular ejection fraction less than 45%, with a duration of illness of less than 2 years.³⁷ Three treatment groups were compared: daily prednisone plus azathioprine, prednisone plus cyclosporine, and placebo. Mortality was 20% at 1 year and 56% at 3 years. These investigators found no difference in ejection fraction at week 28 or week 52, no change in left ventricular size at week 28, and no difference in 1-year mortality between treated and untreated groups. Their conclusion was that these immunosuppressive strategies were not beneficial. Significant limitations of this study include a 30% dropout rate and significant interobserver variability among pathologists’ diagnoses of biopsy specimens despite using the Dallas criteria.

In view of the limitations of histopathologic diagnosis using the Dallas criteria, another group of investigators utilized immunohistologic markers of inflammation, upregulation of HLA, to diagnose active myocarditis as an indication for immunosuppressive therapy.⁶³ This criterion has the advantage of indicating that autoimmunity is playing a role in pathogenesis. Also, since HLA is distributed throughout the entire myocardium, biopsy sampling error is eliminated as a confounding variable in assessing response to therapy. In this study, 84 of 202 patients with chronic (>6 months) idiopathic dilated cardiomyopathy (ejection fraction <40%) were found to have strong expression of HLA in biopsy specimens and were randomized to receive placebo or prednisone plus azathioprine for 3 months. At 3 months’ follow-up,

a significant improvement in the prespecified secondary endpoints of left ventricular ejection fraction, left ventricular volumes, and functional capacity was seen in the treated group, and this improvement was maintained at 2 years (71.8% improvement in the treated group vs. 30.8% in the untreated group). However, there was no improvement in the prespecified composite primary endpoint of death, cardiac transplant, or hospital readmission. This study was limited by a 31% dropout rate.

In another study, patients with positive endomyocardial biopsy specimens and progressive heart failure who responded to 6 months of therapy with prednisone and azathioprine were more likely to have circulating cardiac autoantibodies and no viral genome in their myocardium as compared with nonresponders.⁶⁴ Another randomized, placebo-controlled trial of prednisone plus azathioprine was performed in 85 patients with chronic heart failure (>6-month illness) with active lymphocytic myocarditis on EMB and absence of virus genome on PCR. There was significant improvement in LV ejection fraction in the treated group (average ejection fraction increased from 26.5% to 45.6%) and no improvement in controls (average ejection fraction dropped from 27.7% to 21.3%). In addition, there was significant improvement in LV dimensions and patients' functional status in the group receiving immunosuppression. This study suggests that this therapy may have favorable effects in patients who persist with active myocardial inflammation after virus has been cleared⁶⁵ (Fig. 82-5).

Studies have suggested that in patients with heart failure and low ejection fraction, intravenous immunoglobulin (IVIg) has a pronounced antiinflammatory effect as measured by circulating levels of inflammatory markers.⁶⁶ Uncontrolled studies suggest benefit in patients with myocarditis from treatment with intravenous immunoglobulin.^{67,68} However, a placebo-controlled double-blind trial of intravenous immunoglobulin in patients with myocarditis or idiopathic dilated cardiomyopathy of less than 6 months' duration showed no significant improvement with therapy as assessed by ejection fraction or functional capacity at 6 and 12 months.⁶⁹ In this study, the average left ventricular ejection fraction improved from $25 \pm 8\%$ at baseline to $41 \pm 17\%$ at 6 months in both treated and untreated groups. One-year event-free survival rate was 91.9% in both groups, indicating a favorable prognosis. Therefore, the use of IVIg is not supported by any randomized trial.⁷⁰ Studies are ongoing evaluating the use of IVIg and antiviral therapies in patients with chronic myocarditis with persistent viral genome on EMB specimens.¹⁶ Evaluating the mechanisms of myocardial recovery during VAD support may also help direct research toward novel approaches to the treatment of myocarditis.

In summary, there is no evidence that patients with lymphocytic myocarditis or idiopathic dilated cardiomyopathy benefit from the routine use of immunosuppressive therapy. However, this treatment approach should be considered in patients with myocarditis and active inflammation seen on endomyocardial biopsy findings, those who develop early signs of severe heart failure, and those who are shown to experience progressive worsening of left ventricular function. Last, immunosuppressive therapy should be used in patients with myocarditis associated with autoimmune diseases such as SLE, eosinophilic or granulomatous forms of the disease, and in giant cell myocarditis (Box 82-3).

BOX 82-3

Indications for Immunosuppressive Therapy in Myocarditis

Inflammation present on endomyocardial biopsy and:

1. Continued severe heart failure symptoms despite good medical therapy for heart failure
2. Progressive worsening of heart failure symptoms or LV systolic function despite good medical therapy
3. Fulminant myocarditis
4. Presence of giant cell myocarditis
5. Presence of eosinophilic myocarditis
6. Presence of myocarditis in association with a systemic autoimmune disease, e.g., SLE, inflammatory bowel disease, polymyositis

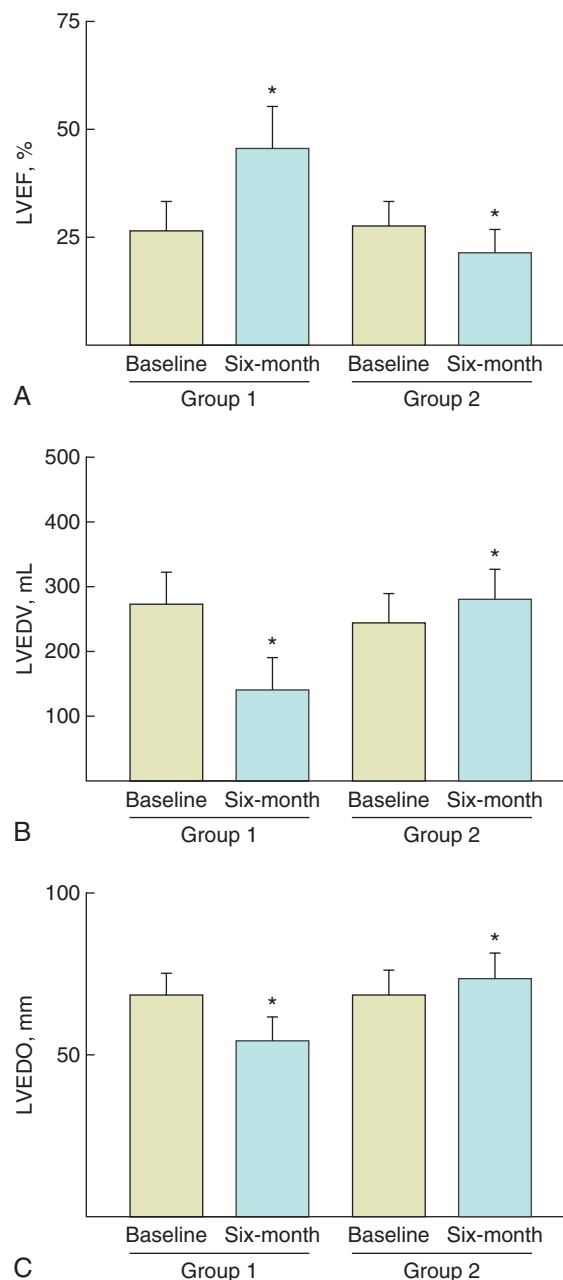


FIGURE 82-5 ■ Left ventricular function and size at baseline (clear bars) and at 6 months (dark bars) in patients with myocarditis and active inflammation and absence of viral genome on endomyocardial biopsy. Group 1 was treated with immunosuppressive therapy and group 2 with placebo. (From Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC trial. *Eur Heart J* 2009;30:1999.)

Summary

The most common cause of myocarditis is viral infection, and autoimmune mechanisms are involved in pathogenesis. Patients with myocarditis can present with acute chest pain, mimicking acute ischemic heart disease or other cardiopulmonary illnesses, or can present with heart failure due to dilated cardiomyopathy. A smaller percentage of patients present with acute heart failure due to severe left ventricular systolic dysfunction. Oral and parenteral pharmacologic therapies that are used in patients with heart failure not caused by myocarditis are

also used in these patients. Fulminant myocarditis is characterized by severe heart failure and cardiogenic shock. These patients need intensive, aggressive pharmacologic therapy and may require mechanical circulatory support. Cardiac magnetic resonance imaging is an important tool in the diagnosis of myocarditis. Endomyocardial biopsy is a safe technique used in the diagnosis of myocarditis in sicker patients to decide on immunosuppressive therapy, although it is limited by sampling error and by current histopathologic techniques for assessing disease activity. Newer immunohistologic methods may better define those patients who will respond to immunosuppressive therapy. Patients with myocarditis and progressive myocardial failure, despite conventional heart failure therapy, should be considered for immunosuppressive therapy on a case-by-case basis. Such patients should be followed with serial measures of left ventricular performance and endomyocardial biopsies.

TRANSIENT APICAL BALLOONING SYNDROME

A distinctive cardiomyopathy with acute onset, frequently precipitated by emotional or physical stress, is termed *transient apical ballooning syndrome* (TABS) due to its distinctive left ventricular wall motion abnormality. This cardiomyopathy was first described in patients in Japan in 1991.⁷¹ This syndrome has subsequently been described in the United States and Europe.^{72,73} It is characterized by the sudden onset of chest pain and/or dyspnea, ECG changes mimicking acute myocardial infarction (AMI), and mild elevation of serum myocardial biomarkers. The syndrome is precipitated by extreme emotional or physical stress in >70% of cases.⁷⁴ The characteristic left ventricular wall motion abnormality is akinesis or dyskinesis of a large area of the left ventricular apex (Figs. 82-6 and 82-7). Coronary artery stenosis is not present. This syndrome has been called TABS, stress cardiomyopathy, or takotsubo cardiomyopathy, so named because the takotsubo pot used by Japanese fishermen to trap octopus has a shape similar to the left ventricle in this condition ("short neck, round flask").⁷³⁻⁷⁶

There is a marked preponderance of elderly females affected by this condition, 86% to 100% in reported series, with a mean age of 63 to 67 years. However, many subsequent reports have described this condition in younger patients. Chest pain is the presenting symptom in 66% to 90% of patients, and 15% to 20% will present with dyspnea, pulmonary edema, or shock. The most common ECG changes seen are ST-segment elevation or marked T-wave inversions in the precordial leads. These findings are indistinguishable from acute myocardial infarction. Elevation of CK-MB and troponin is seen in the majority of patients, but the enzyme rise is typically milder than would be expected given the marked ECG and left ventricular wall motion abnormalities. Precipitators of TABS include arguments with family members, the death of loved ones, or sudden financial setbacks. Physical stresses include medical procedures such as thoracentesis or biopsy, institution of cancer chemotherapy or hemodialysis, hip fracture, and noncardiac surgeries.

Echocardiography and left ventriculography show moderate to severe left ventricular dysfunction in these patients, with characteristic hyperkinesis of inferior-basal and basal-septal segments and severe hypokinesis or dyskinesis involving mid-anteroseptal, apical, and inferior-apical wall segments. A smaller percentage of patients will demonstrate a different contraction abnormality, with akinesis involving the mid-anterior and mid-inferior walls, with normal motion or hypercontractility of the apex and basal segments. Acutely, the left ventricular ejection fraction is reduced to 20% to 40%.^{74,75} Up to 20% of patients may demonstrate a left ventricular outflow tract gradient due to basal septal hyperkinesis and transient systolic anterior motion of the anterior leaflet of the mitral valve.^{72,73,77}

Patients with TABS often present critically ill, with pulmonary edema, hypotension, and shock. Cardiogenic shock develops from marked left ventricular systolic dysfunction and decreased stroke volume. Shock can also be exacerbated by the development of a left ventricular outflow tract gradient.⁷⁸ Cardiogenic shock has been reported in 5% of patients at presentation and has occurred during the course of the illness in 6% to 46% of patients in different series.^{72,74-76,79}

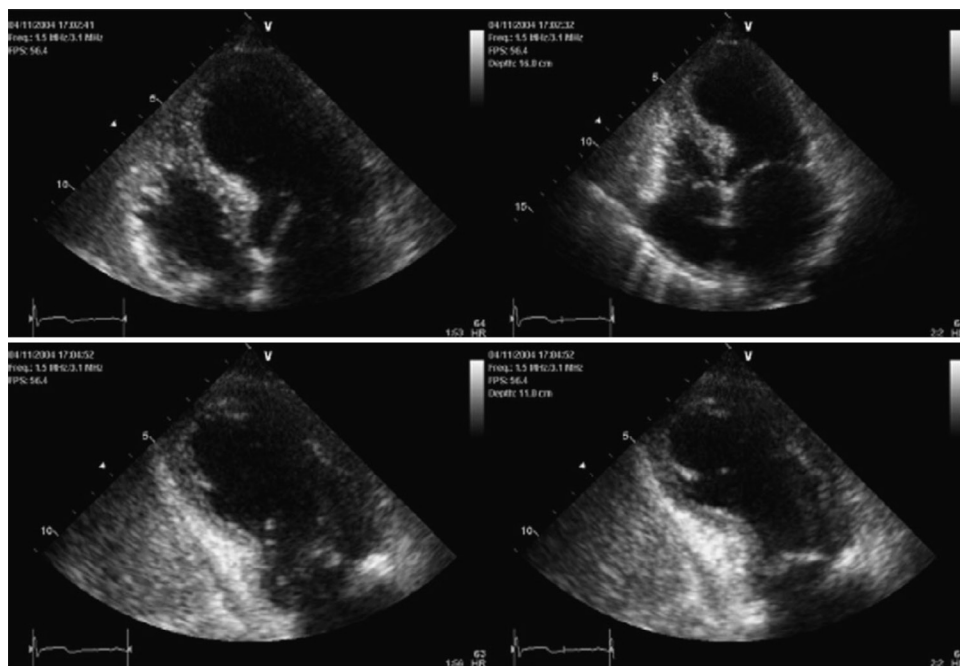


FIGURE 82-6 ■ End-diastolic and end-systolic apical four- and two-chamber echocardiographic views demonstrating the typical apical and mid-ventricular LV wall motion abnormalities of a patient with transient apical ballooning syndrome. (From Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur Heart J* 2006;27:1523–9.)

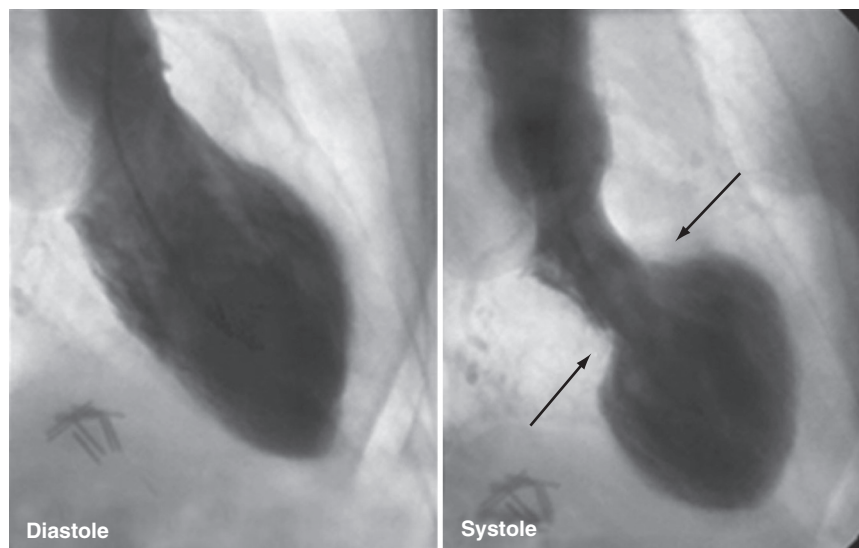


FIGURE 82-7 ■ Left ventriculogram showing typical left-ventricular wall motion abnormalities in transient apical ballooning syndrome. Arrows in systole indicate hyperkineses of basal interior and anterior segments with severe hypokinesis of remaining wall segments. (From Sharkey SW, Lesser JR, Zenovich AG, Maron MS, Lindberg J, Longe TF, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation* 2005;111:472–9.)

Suspicion of TABS and urgent diagnosis are important, as therapy and prognosis differ substantially from AMI. TABS should not be treated with thrombolytic therapy, as coronary occlusion is not involved in the pathogenesis. If cardiogenic shock develops, treatment with intraaortic balloon counterpulsation (IABP) is indicated. Inotropic therapy should be used judiciously or not at all. Dobutamine and other beta agonists may worsen cardiogenic shock by increasing hyperkinesis of the basal portion of the heart and causing or aggravating a left ventricular outflow tract gradient. Several case reports describe patients with TABS with hypotension who developed frank cardiogenic shock after initiation of inotropic therapy. Since a hyperadrenergic state is proposed to be a major pathogenic mechanism, empirical use of beta-blockers while patients are being supported with IABP has been successful. Echocardiography can be useful to guide therapy. For those with extensive wall motion abnormalities but no outflow obstruction, IABP support without beta-blockers is recommended. Administration of the alpha agonist phenylephrine can also be considered in cases with a high left ventricular outflow tract gradient, as this drug increases afterload, causing left ventricular dilatation and a decrease in mitral valve systolic anterior motion and lowering of intraventricular gradients.⁷⁷ TABS is associated with a good prognosis; therefore, aggressive therapy of hemodynamic compromise and cardiogenic shock is indicated. In almost all patients, the marked apical wall motion abnormalities begin to improve within days, and left ventricular function can be expected to recover to normal during the ensuing weeks or months. However, in a small percentage of patients, wall motion abnormalities may persist for 1 year. Follow-up in various series has shown recovery of left ventricular ejection fraction to normal in most instances. In-hospital mortality in larger series has been reported at 0% to 4%.^{72,74–76,79,80} The large majority of survivors will recover completely with normal functional status. The long-term prognosis is good. In one series, only 2 out of 72 patients had recurrence of TABS within 13 months.⁷⁴ In another series, the recurrence of TABS was calculated at 2.9% per year. Over a 4-year follow-up, long-term survival of patients who recovered from TABS was equivalent to sex- and age-matched control groups without a history of TABS.⁸⁰

The pathogenesis of TABS is unknown. Transient multivessel coronary spasm has been proposed, but this has not been demonstrated at the time of acute coronary angiography in the vast majority of patients. In most patients, the extent of left ventricular wall motion abnormality

is larger than the distribution of a single coronary artery.^{72,73} Cardiac MRI has not shown evidence of infarction or myocarditis.⁸¹ In our judgment, a hyperadrenergic state, precipitated by acute stress and causing myocardial stunning, is the most attractive hypothesis. One study documented supraphysiologic levels of serum catecholamines and stress neuropeptides in patients during the acute phase of TABS, likely due to adrenal and sympathoneuronal hyperactivity. The apex of the left ventricle may be more sensitive than other left ventricular wall segments to the deleterious effects of adrenergic hyperstimulation.⁷⁵

TABS is reported to occur in approximately 1.7% to 2.2% of admissions for acute coronary syndrome in Japan and 2% of cases of acute heart failure due to acute coronary syndrome.^{79,81} TABS may be more common than currently recognized. Correct diagnosis is more likely to be made in centers where emergency coronary angiography and primary percutaneous coronary intervention are used in the treatment of acute coronary syndrome and ST-segment elevation myocardial infarction.

In summary, TABS should be suspected in patients who present with symptoms and ECG findings consistent with acute myocardial infarction, who have a large apical wall motion abnormality seen on echocardiography or left ventriculography and whose symptoms were precipitated by severe emotional or physical stress. Diagnosis is confirmed when urgent cardiac catheterization and coronary angiography demonstrate no significant coronary artery occlusion or stenosis.

TACHYCARDIA-INDUCED CARDIOMYOPATHY

A sustained rapid heart rate can lead to the acute development of left ventricular dilation and dysfunction, with symptoms of heart failure. This is termed *tachycardia-induced cardiomyopathy* (TICMP). This can occur in otherwise normal hearts or can exacerbate heart failure in patients with preexisting cardiomyopathy. Supraventricular or ventricular arrhythmias of any type can lead to this syndrome. Arrhythmias that may be responsible for TICMP include atrial fibrillation, atrial flutter, automatic atrial tachycardia, AV node reentry tachycardia, supraventricular tachycardia involving accessory pathways, accelerated junctional tachycardia, ventricular tachycardia (from RV and LV sites), sustained rapid cardiac pacing, and even very frequent premature ventricular contractions and prolonged, sustained ventricular bigeminy.

The development of TICMP is related to the rate of the tachycardia as well as the duration of the arrhythmia and the presence of other cardiac conditions.⁸² The length of time tachycardia needs to be present to cause LV dysfunction is unknown, but sustained arrhythmia for days to weeks is likely necessary. The presence of an underlying predisposing substrate has been postulated, as not all patients with sustained tachycardia will develop cardiomyopathy.⁸³

Animal models of TICMP have been established and studied to elucidate pathophysiologic mechanisms and clinical correlates. In these models, sustained, rapid atrial or ventricular pacing leads to severe biventricular systolic and diastolic dysfunction with four-chamber dilation and to changes in LV geometry to a more spherical shape. Within 24 hours of initiating rapid pacing, there is a fall in cardiac output and blood pressure. During the first week, pulmonary artery pressure rises and there is an increase in left and right ventricular filling pressures. Neurohormonal activation occurs as typical for dilated cardiomyopathy. The cardiac output and ejection fraction fall, and the ventricular volume rises over 3 to 5 weeks. When pacing is discontinued, cardiac output improves to near normal in 48 hours, and hemodynamics are normal within 4 weeks. The ejection fraction recovers to normal in 1 to 2 weeks, although the end-diastolic volume remains high at 12 weeks, suggesting persistent remodeling. Structural cardiac changes seen include myocyte hypertrophy, apoptosis, and altered extracellular matrix. Proposed pathophysiologic mechanisms include myocardial energy depletion, ischemia, and altered myocyte handling of calcium.^{83,84,85,86}

At present, there are no data regarding the time course, mechanisms, or cellular biochemical alterations in human TICMP. TICMP can occur at any age, from infants to the elderly. TICMP has been reported to occur in fetuses with sustained supraventricular tachycardia, which resolves with correction of the arrhythmia.⁸⁴ Whether a minimal heart rate is necessary to induce cardiomyopathy is unknown. The incidence and prevalence of TICMP are also unknown. One study analyzed patients who were hospitalized for treatment of heart failure who had rapid atrial fibrillation and no prior diagnosis of cardiac illness. One-third of this group was determined to have TICMP. These patients had smaller ventricles initially and had a better long-term prognosis, with lower rehospitalization and mortality rates.⁸⁷ In other observations, patients with rapid atrial fibrillation and cardiomyopathy treated with AV node ablation also show improved cardiac function over time, indicating that the tachycardia was more important than the lack of atrioventricular synchrony in the pathophysiology of cardiomyopathy.

The diagnosis of TICMP should be suspected in any patient with impaired ventricular function in the setting of sustained SVT or VT. The diagnosis is clear when LV function before the onset of tachycardia was demonstrated to be normal and no intercurrent illness other than the arrhythmia has occurred. The diagnosis is confirmed when LV function rapidly improves with correction of the arrhythmia.

The treatment for TICMP is to rapidly restore normal heart rate. This can be done with parenteral rate-slowing medication, including beta-blockers such as esmolol or metoprolol or calcium-channel blockers such as diltiazem. Verapamil may aggravate hypotension and LV dysfunction and should be avoided. Adenosine can rapidly convert AV nodal reentry tachycardia to sinus rhythm. Intravenous digoxin can also be considered, although its onset of action is delayed. Type I drugs such as procainamide can be prescribed for SVT associated with accessory pathways. Electrical cardioversion can rapidly terminate supraventricular and ventricular tachycardia and restore sinus rhythm. In patients with atrial flutter or atrial fibrillation, reliable control of the heart rate to a range of 60 to 90 beats per minute is a reasonable alternative to conversion of the arrhythmia to sinus rhythm.

In patients with TICMP who have received appropriate arrhythmia therapy, heart failure symptoms improve rapidly. LV systolic function will generally recover to normal within 4 weeks if there is no other underlying heart disease. Cardiac rhythm monitoring for 24 to 48 hours is often necessary to ensure that heart rate is controlled during activity as well as at rest.⁸⁴ In a report of 11 patients with atrial flutter and abnormal systolic function who underwent atrial flutter ablation, ejection fraction improved from an average of 31% at baseline to 41% within 7 months of ablation. Lack of resolution of cardiomyopathy was predicted by a lower baseline ejection fraction.⁸⁸ In a series of 24 patients with TICMP, cardiomyopathy initially resolved with arrhythmia control; recurrence of arrhythmia led to repeated rapid decline in LV function and recurrent heart failure. These patients again had improvement or normalization of ejection fraction following repeated arrhythmia control within 6 months. However, 3 of the patients died suddenly and unexpectedly, emphasizing that structural and electrical abnormalities may persist on a chronic basis.⁸⁹

It is important to recognize that uncontrolled tachycardia may be responsible for causing or exacerbating left ventricular dysfunction and heart failure in many patients. Adequate control of heart rate and, at times, conversion of tachyarrhythmia to sinus rhythm can be the most important therapeutic measures to treat heart failure and initiate reverse remodeling and thus improve LV function in these patients.

KEY POINTS

1. Myocarditis is most often caused by a viral infection. Myocardial damage is mediated through activation of cellular immune processes.
2. The clinical course of myocarditis can be benign, with complete resolution, or the illness can be more severe, with the development of dilated cardiomyopathy and congestive heart failure. Fatal arrhythmia can occur.
3. The pharmacologic therapy of heart failure associated with myocarditis is similar to therapy used in other forms of dilated cardiomyopathy. Severe cases may require the use of mechanical circulatory support.
4. Fulminant myocarditis is an unusual complication with a rapidly progressive course resulting in cardiogenic shock. These cases should be managed aggressively with pharmacologic therapy and circulatory support where required, because significant improvement in left ventricular function will often occur.
5. Endomyocardial biopsy is frequently used to make the diagnosis of myocarditis and to direct therapy, although there are limitations in the interpretation of biopsy results. Newer molecular and histochemical analyses of EMB samples may assist in assessing the cause and treatment of myocarditis.
6. Immunosuppressive therapy based on the results of endomyocardial biopsy should not be used routinely in the treatment of myocarditis but should be strongly considered in patients who have severe heart failure early in the course of the illness, who have clinical characteristics of a treatable form of myocarditis, or whose condition deteriorates despite the use of conventional heart failure treatment.
7. Transient apical ballooning syndrome, or stress cardiomyopathy, is an acute, severe cardiomyopathy often precipitated by emotional or physical stress, with a presentation similar to acute myocardial infarction. The prognosis is generally good after a period of aggressive supportive care.

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These authors describe and compare the clinical course of patients with fulminant myocarditis with acute myocarditis, defining fulminant myocarditis as a distinct clinical illness.

■ References for this chapter can be found at expertconsult.com.

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ACQUIRED AND CONGENITAL HEART DISEASE IN CHILDREN

Cardiac diseases in children cover a wide range of diagnoses, from congenital to acquired and asymptomatic to life-threatening. Knowledge of the pathophysiology and clinical presentation of the most common heart diseases in children is of great importance for those involved in caring for children's health. The aim of this chapter is to highlight the physiologic and developmental aspects of cardiac disease in children and present a brief overview of acquired and congenital pathologies, focusing on common lesions and information of particular importance to intensivists. A detailed overview of all aspects is beyond the scope of this chapter, and readers are directed elsewhere for detailed coverage of pediatric cardiology,^{1,2} pediatric cardiac surgery,³ and pediatric cardiac intensive care.⁴

PHYSIOLOGY

Circulatory Changes at Birth

During the transition from intrauterine to extrauterine life, major circulatory changes occur that have important implications for the clinical care of a newborn.^{5,6} In a healthy newborn, the low-resistance placenta is eliminated from circulation at birth, resulting in an immediate increase in systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) falls when the lungs become responsible for gas exchange. In addition, the fetal channels, foramen ovale, and arterial duct become redundant and close. Failure of the transition from fetal to postnatal circulation results in altered hemodynamics, as seen in babies born with congenital heart disease (CHD) or structurally normal hearts but persistent right-to-left shunt after birth. The circulatory pattern characterized by failure of the PVR to fall is termed *persistent pulmonary hypertension of the newborn* (PPHN).⁷ PPHN is one of the two principal causes of "nonpulmonary" cyanosis in neonates, the other being cyanotic CHD.

The right ventricle (RV) and left ventricle (LV) contribute equally to fetal cardiac output. At birth, the LV becomes responsible for systemic circulation; it is characterized by its high vascular resistance. The dramatic fall in PVR at birth to 50% of the fetal level facilitates the necessary increase in pulmonary blood flow. During the first 6-8 weeks of life, PVR falls to adult values as the smooth muscle layer in the media of the pulmonary arterioles progressively thins out. The LV progressively adapts to its "high-pressure" role by rapid myocardial growth in contrast to the RV, which regresses to its "low-pressure" subpulmonary role. The presence of CHD can profoundly alter these adaptive processes (see below).

Physiology of the Neonatal Myocardium

The neonatal myocardium is functionally immature⁸ (Table 83-1). Age-dependent changes in intrinsic function and integration with maturing circulation determine its response to insults such as hypoxia and ischemia.⁹

Maturation of the myocardium in the postnatal period occurs through an increase in the number, volume, and conformation of its myocytes. The cell membrane (sarcolemma) develops a T-tubular

system, which facilitates the rapid conduction of action potential to the cell center, and the gradual uniformity of myofibril arrangement improves its contractile function. In parallel with these structural changes, myocellular metabolism matures over time. Proper contractile function of the cardiac myocyte depends on an efficient excitation-contraction process, which is activated by the binding of calcium to troponin C. In the adult heart, calcium release from the sarcoplasmic reticulum is the predominant source of calcium for troponin C activation, whereas in the neonate heart, activation relies substantially on calcium influx through the L-type calcium channels. Optimal function of the neonatal myocardium is therefore exquisitely dependent on the maintenance of normal extracellular calcium concentrations. Other elements of myocyte function are age-dependent, such as the sarcoplasmic reticulum calcium-ATPase, which is present in reduced quantities in the immature heart. This results in relatively inefficient calcium reuptake and therefore slower diastolic relaxation, which is, at least in part, responsible for the prominence of diastolic dysfunction in the failing neonatal myocardium.

Healthy infants have higher plasma concentrations of catecholamines and higher density of cardiac sympathetic innervation than older children and adults. This may partly explain the reduced ability of neonates to increase cardiac output in response to endogenous or exogenous catecholamines. Children with heart failure also have higher plasma catecholamine concentrations¹⁰ but reduced beta adrenergic receptor densities than age-matched controls.¹¹ The effects of this are similar to those seen with exogenous agonist-induced desensitization. Children with severe heart failure show evidence of uncoupling of beta1 adrenergic receptors from the enzyme adenylyl cyclase¹¹ and other maladaptive responses, which result in a reduced response to receptor agonists. In addition to heart failure, chronic hypoxia as seen in cyanotic CHD induces activation of the sympathetic nervous system with resultant adrenergic receptor desensitization. Developmental aspects of myocardial support have been reviewed.¹²

Congestive Heart Failure

Although the basic pathophysiologic mechanisms of heart failure are age-independent, the presentation and management of heart failure change with age. The overwhelming cause of heart failure in the first year of life is CHD, usually with an intracardiac left-to-right shunt or a ventricular obstructive lesion (Table 83-2). By contrast, the primary abnormality in adult heart failure is usually LV dysfunction. Heart failure in adults is often gradual in onset, whereas the limited functional reserve in neonates leads to rapid decompensation and an emergent presentation.

The clinical findings² in an infant are listed in Box 83-1. A prominent sign of cardiac failure in infancy is difficulty in feeding secondary to an increased respiratory rate and effort. This equates to exertional dyspnea in an older child or adult. This results in failure to thrive and leads to the classic "wizened" appearance. Although hepatomegaly is a common sign of heart failure in infants (resulting from an increase in total circulating volume and hepatic venous congestion), peripheral edema, ascites, and pericardial or pleural effusions are much less commonly seen in infants than in adults. One relatively common feature of severe heart failure in infancy is the occurrence of compression of the bronchial tree, particularly the left main stem or lower lobe

TABLE 83-1 Characteristics of the Neonatal Ventricle

| COMPARISON TO MATURE VENTRICLE | |
|--------------------------------|---|
| Contractility | Contractility of the neonatal ventricle is reduced. |
| Compliance | Neonatal ventricle inherently noncompliant. |
| Augmentation cardiac output | Little stroke volume reserve due to low compliance. Therefore cardiac output is highly heart rate dependent in neonates. |
| Afterload | Neonatal ventricle tolerates poorly increased afterload. |
| Energy substrate | Lactate primary substrate of neonatal ventricle under aerobic conditions. Glucose metabolized under anaerobic conditions. By 1-2 years changeover to primary “adult” substrate, free fatty acids. |

TABLE 83-2 Common Causes of Heart Failure in Childhood

| NEONATE <2 WEEKS OF AGE | NEONATE >2 WEEKS OF AGE, INFANT | OLDER CHILD |
|---|--|---|
| CONGENITAL HEART DISEASE Left-Sided Obstructive Lesions <ul style="list-style-type: none"> Critical Aortic Stenosis Aortic Coarctation Hypoplastic Left Heart Syndrome ARRHYTHMIAS Incessant Supraventricular Tachycardia “CONGENITAL” MYOCARDITIS SEVERE VENTRICULAR DYSFUNCTION DUE TO BIRTH ASPHYXIA, SEPSIS, OR SEVERE METABOLIC DISORDERS | CONGENITAL HEART DISEASE Left-to-Right Shunt Lesions <ul style="list-style-type: none"> Ventricular Septal Defect Atrioventricular Septal Defect Truncus Arteriosus Total Anomalous Pulmonary Venous Connection | CONGENITAL HEART DISEASE Any Lesion <ul style="list-style-type: none"> Following Surgery Late Deterioration of Ventricle in Palliated Circulations ACQUIRED HEART DISEASE Cardiomyopathies (Idiopathic or Specific) Myocarditis Rheumatic Fever Infective Endocarditis Arrhythmias Severe Anemia Nutritional Deficiencies |

BOX 83-1 Clinical Features of Heart Failure in Infants

| |
|--|
| Respiratory signs <ul style="list-style-type: none"> Initially tachypnea Dyspnea manifesting as poor feeding Later signs: retractions, intercostal recession, nasal flaring Pulmonary wheeze/rales |
| Tachycardia—little variability even at rest |
| Gallop rhythm |
| Hepatomegaly |
| Cardiomegaly |
| Poor peripheral perfusion—in severe failure “ashen” appearance |

bronchus as a result of extrinsic compression by an enlarged left atrium (LA) or pulmonary artery (PA). This can cause airway obstruction and associated lobar collapse or localized hyperinflation as a result of distal air trapping. Long-standing extrinsic compression may rarely cause tracheobronchomalacia, resulting in long-term respiratory difficulties even after the resolution of heart failure.

Cyanosis

Cyanosis is the visible manifestation of greater than 5 g/dL of reduced deoxygenated hemoglobin in cutaneous blood vessels and is a prominent feature in many types of CHD. *Peripheral cyanosis* results from high oxygen extraction ratios across the tissue vascular bed, reflecting low tissue blood flow, or a high tissue oxygen demand. *Central cyanosis* results from the desaturation of arterial blood, which may be due to pulmonary disease or the right-to-left shunting of deoxygenated systemic venous blood in association with a congenital heart defect. The “pulmonary” and “cardiac” causes of central cyanosis can usually be differentiated by allowing the child to breathe 100% oxygen (“hyperoxic test”), which results in a substantial improvement in oxygen saturation in case of cyanosis of pulmonary origin, while having little effect on a child with cyanosis due to a right-to-left shunt.¹³ During the administration of 100% oxygen an arterial oxygen tension (PaO₂) above 160 mm Hg is highly suggestive of a noncardiac diagnosis, and a PaO₂ greater than 250 mm Hg excludes it. Occasionally, *differential cyanosis* is seen, where one or both upper limbs are normally saturated and the lower limbs cyanosed. This is caused by deoxygenated blood traversing the arterial duct to enter the aorta distal to the origin of one or both subclavian arteries and supply the lower limbs, while oxygenated blood from the LV predominantly supplies the upper limbs.

Chronic hypoxemia induces twin physiologic responses of erythropoiesis, resulting in polycythemia and an increase in blood volume as a compensatory attempt to maintain oxygen carrying capacity. However, as hemoglobin concentrations rise, blood viscosity increases and ultimately results in sluggish flow in peripheral circulation, cellular aggregation, and occurrence of thrombotic lesions. Polycythemic patients are at a high risk of thrombotic complications in situations of increased fluid loss (e.g., intercurrent diarrheal illness) or inadequate fluid intake (e.g., preoperative fasting). In addition, most children with chronic cyanosis develop finger clubbing as a result of an increased number of capillaries laid down in the vascular beds of the fingers and toes. Rare, but important, complications of severe cyanosis arise primarily from hypoxemia and polycythemia and include cerebral and pulmonary thrombosis and cerebral abscess.

Pulmonary Vasculature and Pulmonary Hypertension¹⁴

The pulmonary vascular bed is of central importance to the manifestation of CHD from the first hours of life. As previously described, PVR falls dramatically at birth and reaches adult values by approximately 2 months of age. In infants with congenital heart lesions where intracardiac communication occurs between systemic and pulmonary circulations such as a ventricular septal defect (VSD), the fall in PVR encourages flow into the low-resistance pulmonary vascular bed, and a left-to-right shunt develops. The increased flow and subsequent shear stress induce progressive structural changes in the pulmonary arteries and arterioles. Initially, these changes consist of accelerated extension of muscle to the distal “nonmuscular” pulmonary arteries and medial muscular hypertrophy in the proximal muscular arteries. Later changes involve gradual hypertrophy of the arterial intima with the deposition of collagen and elastin, leading to gradual luminal obstruction and eventual occlusion. Associated with this is the development of plexiform lesions, the histologic hallmark of pulmonary vascular disease. Mild pulmonary vascular changes are of little significance to cardiac intensivists; however, children with more extensive medial muscular hypertrophy of the pulmonary arteries are at a risk of labile pulmonary pressure, leading to pulmonary hypertension (PHT) in the postoperative period (see below). The extent of pulmonary pressure changes—that is, hypertension—frequently determines the feasibility of surgical options. Children with established fixed high PVR are not suitable for undergoing corrective surgery, as the surgical separation of the two circulations in the face of fixed high PVR will result in immediate RV failure. Smaller elevations in PVR determine operability in the single ventricle “Fontan” circulation (see Complex Single Ventricle

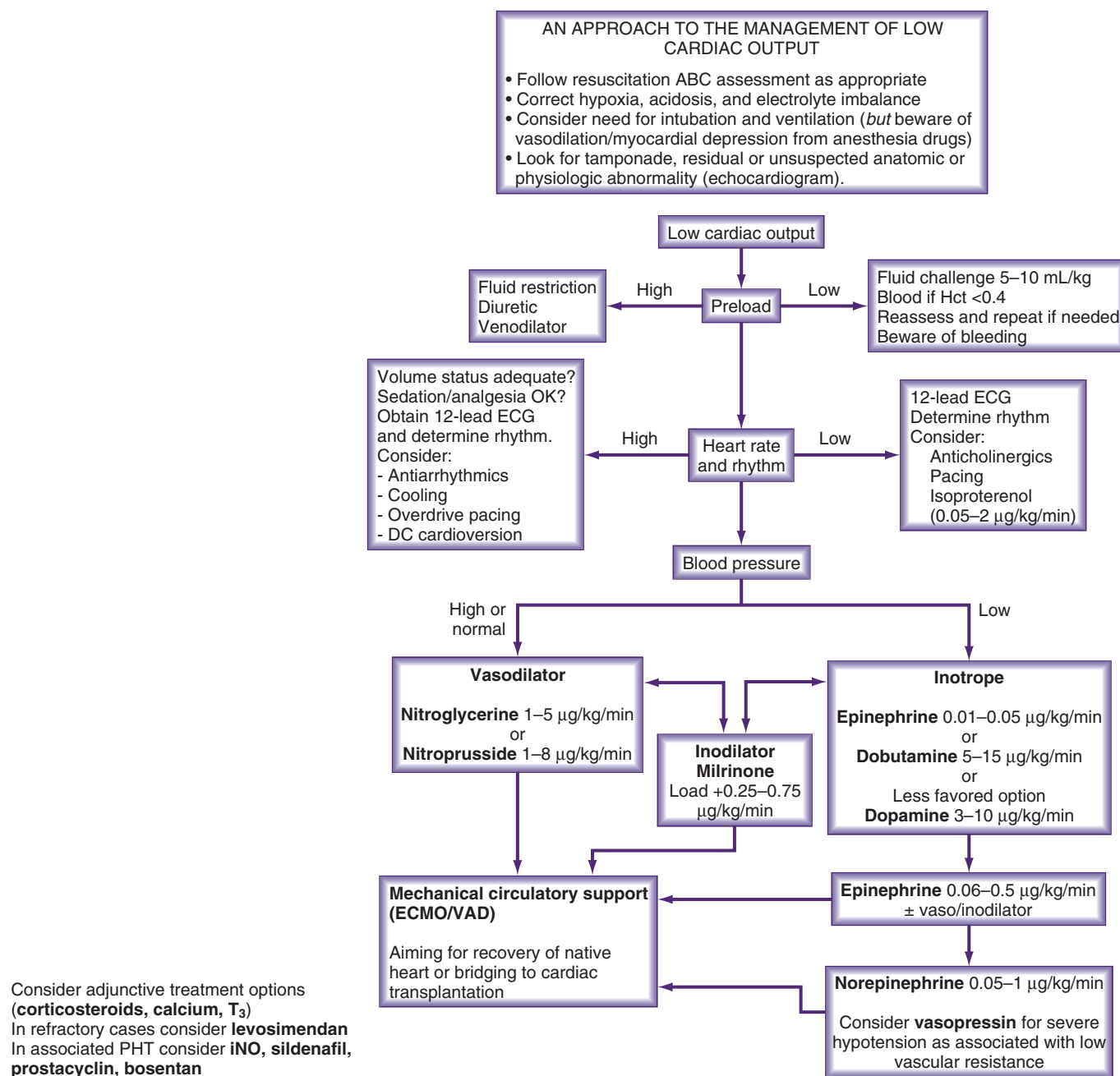


FIGURE 83-1 ■ Management of low cardiac output in children.

Circulations). The calculation of PVR and the response to varying vasodilators can be achieved following a pulmonary reversibility study in a cardiac catheter laboratory.^{15,16}

■ CIRCULATORY SUPPORT IN CHILDREN

Children presenting with circulatory failure must initially be assessed and managed according to standard resuscitation algorithms¹⁷ (Fig. 83-1). These require that an adequate oxygenation and circulating volume be achieved. If cardiac output remains low, cardiovascular drug therapy is usually indicated. Developmental differences noted above serve to emphasize the need to adopt age-appropriate pharmacologic strategies when supporting the failing myocardium of neonates and infants.¹⁸⁻²⁰ If the cardiac output remains low despite the application of such measures, mechanical circulatory support should be considered.

Pharmacologic Support¹²

Beta Adrenergic Agonists

Clinical and experimental studies have demonstrated marked age-related differences in the hemodynamic response to inotropic therapy. Although some of the observed differences may be accounted for by differences in drug pharmacokinetics, the variable maturation of the sympathetic nervous system, its receptors, and the cardiac myocytes mitigate against the recommendation of specific dose ranges for the use of catecholamines in neonates and children.^{12,21}

In clinical practice, the use of adrenergic agonists in children is in a titrating manner, which is similar to that in adult practice. When systolic ventricular function is impaired, low-dose epinephrine is commonly used as the first-line inotrope, although dobutamine and dopamine still have their advocates. Dopamine was formerly

preeminent but is now less favored as a result of its noncardiac adverse effects.²² Additional agents should be administered according to the assessment of response judged clinically and from available hemodynamic monitoring. Higher dose epinephrine, norepinephrine, or an alternative class of vasoconstrictors such as vasopressin (see below) can be used in refractory circulatory failure, particularly if vasodilatation is present, which occurs occasionally after cardiopulmonary bypass (CPB) in children. Isoproterenol is a nonspecific beta adrenergic agonist whose principal cardiovascular effects are vasodilatation and increasing the heart rate. The drug is rarely used in intensive care except as a chronotropic agent when the heart rate is critically low and cardiac pacing is not yet established. Caution is needed when higher dose catecholamine support is used in neonates, as these can induce a rise in ventricular end-diastolic pressure in a ventricle that is already developmentally noncompliant. Catecholamine-induced myocardial necrosis has been identified in neonatal animal models.^{23,24} All adrenergic agonists should be administered cautiously at higher doses as they may have deleterious effects on the failing myocardium, increasing heart rate, and SVR, resulting in increased myocardial oxygen consumption.

Phosphodiesterase III Inhibitors

Phosphodiesterase (PDE) III inhibitors have emerged as important agents in the management of neonates and children with cardiac failure due to both inotropic and vasodilator properties. The cardiovascular actions of the clinically available PDEIII inhibitors—e.g., amrinone, milrinone,²⁵ and enoximone—are similar, although milrinone is the most commonly used drug in children. By inhibiting the breakdown of cyclic adenosine monophosphate (cAMP), intracellular calcium accumulation is promoted, thus augmenting the contractile state of the myocyte. In addition, calcium reuptake, a cAMP-dependent process, is augmented, which may enhance diastolic relaxation, a particularly important aspect of neonatal cardiac function. In a multicenter randomized controlled study of neonates and young children following cardiac surgery, the prophylactic administration of milrinone resulted in a lower incidence of low cardiac output.²⁶ Clinical studies in infants and children have demonstrated a synergistic effect when beta1 agonists and PDE III inhibitors such as amrinone, milrinone, or enoximone are coadministered and that this effect may be greater in neonates than in adults. In clinical use, the prominent vasodilating action of PDE III inhibitors is a useful property given the usual low cardiac output associated with rising SVR and PVR, which has been well documented in young patients following cardiac surgery.²⁷ Milrinone is widely used in the initial management of low cardiac output syndrome associated with elevated SVR following heart surgery in children.²⁸

Vasopressin

The arginine-vasopressin hormone is an alternative to alpha adrenergic vasoconstrictors in the management of refractory hypotension associated with vasodilation in sepsis or following CPB, a situation where endogenous vasopressin might be deficient.²⁹⁻³¹ Vasopressin acts directly at vasopressin V1 receptors on vascular smooth muscle without direct effects on the myocardium or cardiac conduction system.

Systemic Vasodilators

This drug class is useful in situations where lowering SVR will reduce LV afterload and improve cardiac output (Table 83-3). This is particularly important in neonates where the elevation of SVR is poorly tolerated by the immature neonatal myocardium. Vasodilators are also employed in the management of systemic hypertension following the repair of aortic coarctation or other left-sided obstructive lesions. Vasodilators have variable effects on preload through concomitant venodilatation, the manifestations of which are dependent on the position that the resultant end-diastolic pressure occupies on the ventricular function curve. If preload reduction brings the resultant end-diastolic pressure to the preplateau sloping portion of the

ventricular function curve, stroke volume can only be maintained or augmented if the preload is optimized by appropriate fluid administration. Directly placed left atrial pressure monitoring lines are commonly used to determine systemic ventricular loading conditions in neonates. Systemic vasodilators should be used with extreme caution in patients with systemic hypotension and LV outflow tract (LVOT) obstruction since they are at risk of severe systemic hypotension and myocardial ischemia.

In children, sodium nitroprusside is frequently the systemic vasodilator of choice because of its powerful arteriolar dilating properties and short half-life, which render it both effective and highly titratable. Nitroglycerine is an alternative short-acting drug, which acts as an arteriolar dilator at higher doses, but is an effective venodilator at lower doses. Phenoxybenzamine, a long-acting alpha adrenergic blocker, is used in some centers in children undergoing surgery for CHD.^{32,33}

Beyond the acute phase of therapy and when enteral drugs can be reliably administered, angiotensin-converting enzyme (ACE) inhibitors such as captopril and enalapril are used.³⁴ They have peripheral vascular and neurohormonal effects as well as direct effects on the myocardium through the activation of intracellular signaling pathways involved in the growth and apoptosis of cardiac myocytes and fibroblasts. Studies in adults have established that ACE inhibitors improve survival and symptoms in heart failure due, in part, to favorable effects on cardiac remodeling. Evidence for the use of ACE inhibitors in children is much less clear. Acute hemodynamic benefits have been demonstrated in children with heart failure caused by left-to-right shunts or mitral/aortic insufficiency and systolic dysfunction of the systemic ventricle. Prolonged treatment with ACE inhibitors has been shown to be effective in reducing not only LV volume overload but also LV hypertrophy in the hearts of growing children with chronic LV volume overload.^{35,36} However, a multicenter randomized controlled trial of ACE inhibitors and placebo showed no difference on somatic growth, ventricular function, or severity of heart failure with enalapril administration to infants with a single ventricle during the first year of life.³⁷ Children with heart disease secondary to muscle disease—that is, Duchenne cardiomyopathy (CM)—may benefit from ACE inhibitors as it seems to delay the progression of heart disease.³⁸ ACE inhibitors should be avoided in patients with left heart obstruction.

Digoxin

Digoxin may have weak inotropic actions through its inhibitory effect on Na/K ATPase and may also have peripheral effects that attenuate the actions of the neurohormonal system. Several studies in adults have shown that digoxin improves symptoms in heart failure.³⁹ Although no studies have shown survival improvement,^{39,40} there is a resurgence of interest in defining the role of digoxin in the management of heart failure. Digoxin is widely used to treat heart failure in children, although as in adults, there are insufficient data that support or refute its use.²⁰ It has been recommended as an alternative drug for symptomatic heart failure and low ejection fraction with careful serum level monitoring, especially when combined with carvedilol or amiodarone and in patients at risk of renal dysfunction.⁴¹

Diuretics

The use of diuretics is ubiquitous in the treatment of children with heart failure,²⁰ with the main goal of improving symptoms of pulmonary congestion. There are no pediatric studies showing that diuretic therapy in heart failure reduces morbidity or mortality, although fluid overload following cardiac surgery has been suggested to be associated with poor outcomes.⁴²⁻⁴⁴ Furosemide is the most widely used diuretic in pediatric cardiac care.⁴⁵ While intravenous bolus administration of furosemide is preferred to oral administration in acute situations, studies have shown that continuous infusion leads to a smoother control of fluid and electrolyte shifts than intermittent IV bolus administration.⁴⁵ Potassium-sparing diuretics such as spironolactone are also widely used adjunct to therapy with furosemide, particularly in

TABLE 83-3 Vasoactive Agents in Children

| ADRENERGIC AGONISTS | | | | | | |
|----------------------------|---|---|----------------|---------------|----------|---|
| | INTRAVENOUS DOSE RANGE | ALPHA 1 | BETA 1 | BETA 2 | DOPA | COMMENTS |
| DOPAMINE | 1-5 µg/kg/min 5-15 µg/kg/min | 0 0/++ | +/++ ++ | | ++ ++ | Beta-mediated inotropic effects at lower doses. Alpha-mediated vasoconstriction at higher doses |
| DOBUTAMINE | 2-15 µg/kg/min | 0 | +/+++ | 0/++ | 0 | |
| EPINEPHRINE | 0.01-0.1 µg/kg/min 0.2-0.5 µg/kg/min | 0/++ ++/+++ | ++/+++ ++++ | ++/+++ +++ | 0 0 | Beta-2 effect prominent at lower doses. Alpha constrictor effects at higher doses |
| NOREPINEPHRINE | 0.05-0.5 µg/kg/min | ++/++++ | + | 0 | 0 | Increases SVR. Reserved for treatment of severe hypotension associated with vasodilatation |
| ISOPROTERENOL | 0.02-0.4 µg/kg/min | 0 | ++++ | ++++ | 0 | Prominent chronotropic activity. Beta-2 effects cause vasodilatation |
| OTHER CARDIOVASCULAR DRUGS | | | | | | |
| | DOSAGE | EFFECTS | | | | |
| Amrinone | Neonates: 4 mg/kg over 15 minutes, then 3-5 µg/kg/min IV >4 weeks age: 1-3 mg/kg over 30 minutes, then 5-15 µg/kg/min IV | Cardiac: Mild nonadrenergic inotropic and lusitropic effects Vascular: Systemic and pulmonary vasodilator | | | | |
| Milrinone | All ages: 50-75 µg/kg over 20 minutes Maintenance: 0.25-0.75 µg/kg/min IV | May cause thrombocytopenia Reduce amrinone dose in slow acetylators Reduce milrinone dose in renal failure Duration of effect, 3-7 days | | | | |
| Levosimendan | 0.05-0.2 µg/kg/min IV for 24 hours | | | | | |
| DIGOXIN | Initial dose: 15 µg/kg, then 5 µg/kg after 6 hours Thereafter 5 µg/kg 12 hourly. Slow IV or oral. | Delays AV conduction, used in management of supraventricular tachycardia Mild inotropic properties. May provide symptomatic relief in congestive heart failure Bradycardia, supraventricular or ventricular dysrhythmias in overdose Aim for plasma level 0.8-2.0 ng/mL Dose adjustment required in renal failure | | | | |
| ESMOLOL | Short-term management of SVT and perioperative hypertension 5-200 µg/kg/min IV | Bradycardia Hypotension Bronchospasm | | | | |
| NITROPRUSSIDE | 0.5-8 µg/kg/min IV Direct blood pressure monitoring required | Systemic and pulmonary vasodilatation Systemic hypotension prominent Cyanide toxicity <ul style="list-style-type: none"> • Metabolic acidosis earliest sign • Monitor thiocyanate levels when used >48 hours or in renal failure | | | | |
| CAPTAPRIL | Oral administration: 0.05 mg/kg as a test dose, then incremental increases to 0.4 mg/kg (occasionally up to 1.0 mg/kg), titrated to effect (systemic blood pressure). 8 hourly dosing. | Systemic vasodilatation/hypotension Small increase in plasma potassium levels | | | | |
| NITROGLYCERIN | 0.2-8 µg/kg/min IV Direct blood pressure monitoring required | Systemic and pulmonary vasodilatation | | | | |
| PROPRANOLOL | Relief of RV spasmodic RV outflow obstruction in the emergency management of hypercyanotic spells in tetralogy of Fallot 0.05-0.1 mg/kg IV stat Systemic hypertension 2-6 mg/kg in 4-6 divided doses | Bradycardia Hypotension Bronchospasm Lethargy | | | | |

long-term therapy. Although dopamine has a natriuretic effect, there is no evidence to support the use of dopamine for prevention or treatment of renal impairment.

Beta-Blockers

Although beta-blockers have an established role in the management of heart failure in adults, evidence of benefits in children with heart failure is limited and based on small studies.^{34,46-49} A recent publication has suggested that the benefit of adding beta-blockers to ACE inhibitors is minimal.⁵⁰ While it might be reasonable to extrapolate adult survival advantages to older children and adolescents with heart failure, extreme caution should be exercised in seeking to apply such therapy in younger children and neonates, as there may be differences among age groups regarding genetics, pharmacology, and underlying

causes of heart failure.⁵¹ Furthermore, beta-blockers should always be introduced with extreme caution in patients with heart failure. Beta-blockers have an established role in children in the management of hypertension and ventricular outflow tract obstruction such as that which occurs in tetralogy of Fallot.

Levosimendan

Levosimendan offers a new therapeutic adjunct in the management of patients with severe ventricular dysfunction by enhancing cardiac contractility and vasodilatation without affecting intracellular free calcium.⁵² The drug acts by enhancing the sensitivity of cardiac myofilaments to calcium. Levosimendan is a prodrug acting mainly through its active metabolite, which has a long elimination half-life with effects lasting for up to 7 to 9 days after a single dose, a sharp

contrast to intravenous catechol-based inotropes with extremely short half-lives. The myocardial effects of levosimendan show improvement not only in systolic function but also in improved diastolic function, which is significantly impaired in those with severe heart failure. One of the problems in understanding the clinical utility of levosimendan has been to quantify the magnitude of its lusitropic effects, separating it from inotropic and chronotropic effects. Jorgensen et al.⁵³ published a study of the use of levosimendan in a carefully monitored group of adult patients with aortic valve disease. They demonstrated unequivocally that levosimendan exerts a direct positive lusitropic effect, shortening isovolemic relaxation time and improving LV filling.

There is increasing interest in the use of levosimendan in children.⁵⁴⁻⁵⁶ A randomized double-blind controlled clinical trial of levosimendan administration following pediatric cardiac surgery showed it to be at least as effective as milrinone, with the levosimendan group having significantly lower myocardial oxygen demand.⁵⁷ Some authors have suggested using levosimendan on a rotating inotrope therapy for children with decompensated heart failure.⁵⁸ More substantial clinical trials are still needed to support the use of levosimendan as a routine inotrope after cardiac surgery and in heart failure.

Thyroid Hormone

Thyroid hormones (triiodothyronine-T3 and thyroxine-T4) play an important role in the regulation of heart metabolism,⁵⁹ upregulation of beta adrenoceptors, and increasing cardiac myocyte contractility.⁶⁰ Critical illness can be associated with inappropriately normal or suppressed TSH levels, despite low T3 levels, the so-called nonthyroidal illness or sick euthyroid syndrome. This can occur in children after CPB,⁶¹⁻⁶³ and its importance is disputed, although clinical studies have shown that T3 supplementation can produce elevation in the heart rate without a concomitant decrease in systemic blood pressure⁶⁴ and may enhance cardiac function reserve in infants after CPB. In a double-blind placebo-controlled trial of T3 supplementation in children <2 years of age undergoing CPB, although some indices of cardiac function assessed by echocardiography were judged to be better in the T3 group, no significant differences were found in the clinical endpoint of time to extubation in the entire study population.⁶⁵ Further age-stratified analysis showed reduced time to extubation and lower inotropic score among infants younger than 5 months in the T3 group.⁶⁶ Further studies are needed before T3 can be recommended in critically ill children without abnormal thyroid function.

Insulin

The use of tight glycemic control (TGC) to improve outcomes in critical illness remains controversial.⁶⁷ Pediatric randomized controlled trials of TGC that included children following pediatric cardiac surgery, although supportive of the intervention in general pediatric critical care population,^{68,69} have failed to provide evidence for the use of TGC in children following cardiac surgery.^{69,70} A secondary analysis by Agus et al. suggests that TGC in children >60 days of life lowers the risk of infection.⁷¹ The use of TGC after pediatric cardiac surgery is not currently recommended.

Steroids

Steroids are used in the perioperative management of patients undergoing cardiac surgery in some centers, either in association with CPB (pre- or intraoperatively) or postoperatively in relative adrenal insufficiency. CPB is associated with systemic inflammatory response syndrome, and therefore steroids have been prophylactically administered with the aim of preventing or minimizing it.^{72,73} However, the results of pediatric studies of preoperative steroids are open to wide interpretation, and its benefits have been questioned.⁷⁴⁻⁷⁸ Similar to critical illness-related adrenal insufficiency, patients who have undergone CPB may develop absolute or relative adrenal insufficiency, which may precipitate or evolve to low cardiac output syndrome following cardiac surgery. For this reason, steroids have been used in patients with hypotension and signs of adrenal insufficiency post cardiac surgery.⁷⁹

Pulmonary Vasodilators and Other Strategies to Prevent and Treat PHT¹⁴

Oxygen alone is a potent pulmonary vasodilator, with both higher alveolar oxygen concentrations and higher pulmonary arteriolar oxygen saturations lowering PVR. Lung volume also affects PVR, being raised at both low and very high lung volumes. Avoiding atelectasis, alveolar hypoxia, and pulmonary arteriolar hypoxia are simple initial strategies to minimize PVR and PA pressure.

Elevation of PVR, as seen in all children following CPB²⁷ with reactive postoperative pulmonary hypertensive episodes, typically occurs following correction of left-to-right shunt lesions or in those with preoperative pulmonary venous hypertension.⁸⁰ Additional perioperative risk factors for pulmonary hypertensive spells with associated systemic hypotension include long CPB duration and late presentation for surgery. In the current era, early corrective surgery has dramatically reduced the number of infants in whom PHT is a major perioperative issue. Postoperative PHT is still seen in neonates and infants with obstructed total anomalous pulmonary venous drainage, truncus arteriosus, and mitral valve replacement for congenital mitral stenosis. Children with mild to moderate PHT with or without RV dysfunction may also benefit from pulmonary vasodilatation such as following cardiac transplantation⁸¹ and in Fontan circulations,⁸² where low PVR is necessary. General measures directed to the prevention and treatment of PHT should be considered before deploying specific pulmonary vasodilators (Table 83-4). In patients at a high risk of PHT following cardiac surgery, LV filling can be maintained by right-to-left shunting through a small surgically created atrial septal defect (ASD). A right-to-left shunt acts as a safety gradient valve, while tolerating some systemic desaturation, to maintain LV filling and hence cardiac output.

Historically, most IV drugs used to treat PHT had nonselective effects, dilating both the pulmonary and systemic vascular beds, and these include tolazoline, prostaglandin E1, prostacyclin, and nitrodilators. Prostacyclin is a short-acting vasodilator that acts via increasing the levels of the intracellular messenger cAMP and has been widely used in the treatment of primary PHT in children.⁸³ The pulmonary effects of such nonselective agents are frequently limited by their nonspecific action, leading to clinically important systemic hypotension. In contrast, nitrates, sodium nitroprusside, and nitric oxide act via the activation of guanylate cyclase and hence increase cellular levels of cyclic guanosine monophosphate, which is then inactivated by PDE 5.

Nitric oxide is an endogenous endothelial-derived vasodilator and a gas at room temperature. If added to inhaled gas mixtures in children

TABLE 83-4

Strategies to Prevent and Treat Pulmonary Hypertension

| STRATEGY | COMMENT |
|------------------------------------|---|
| Anatomic investigation | Rule out residual or undiagnosed anatomic abnormalities |
| Permit right-to-left decompression | Deliberate residual ASD acts as "pop off" in at-risk situations |
| Analgesia/sedation | Facilitate ventilation. Minimize sympathetic influences |
| Avoid acidosis | Respiratory and metabolic acidosis raises PVR |
| Maintain oxygenation | Normal/high alveolar and mixed venous PO ₂ lowers PVR |
| Optimize hematocrit | Ensures optimal oxygen delivery and higher mixed venous PO ₂ |
| Optimize cardiac output | Ensures optimal oxygen delivery and higher mixed venous PO ₂ |
| Pulmonary vasodilators | Selectively reduce PVR |

with reactive PHT, it induces selective pulmonary vasodilatation.⁸⁴ It is distributed to ventilated alveoli, from where it diffuses into the adjacent pulmonary arteriolar smooth muscle. Inhaled nitric oxide (iNO) has been shown in randomized controlled trials to be an effective and a safe therapy in PPHN. Although the evidence for outcome benefit is drawn mainly from one randomized controlled study,⁸⁵ there is a substantial body of evidence to show that iNO is effective in pediatric cardiac patients including those with acute postoperative PHT following congenital heart surgery^{86,87} and following pediatric heart transplantation. iNO can be used in the preoperative assessment of patients with PHT.^{16,88} A recent metaanalysis of randomized and quasi-randomized controlled trials comparing iNO with placebo or conventional management of PHT in children with CHD after surgery has shown no benefit of iNO in terms of mortality, number of PHT crises, and hemodynamic changes; however, the limited number of studies included and potential biases impede solid conclusions, with the need for further well-designed trials.⁸⁹

Other selective pulmonary vasodilators investigated for use in children include inhaled prostacyclin,^{90,91} the PDE 5 inhibitor sildenafil,⁹²⁻⁹⁵ and bosentan, an endothelin 1 receptor blocker.⁹⁶⁻⁹⁸ Inhaled prostacyclin (iloprost) may be useful for the management of PPHN and children with CHD undergoing cardiac surgery,⁹⁹ but beyond small case series, consistent clinical trials are needed to advocate inhaled prostacyclin administration. The type 5 PDE inhibitor sildenafil is increasingly used in the clinical management of PHT in children. Bosentan seems to have favorable effects in children with PHT and in PPHN,^{100,101} although strong evidence is still lacking.

Mechanical Circulatory Support

Mechanical circulatory support may be lifesaving in cases of severe circulatory failure.¹⁰² The aim of mechanical circulatory support is to provide optimal systemic blood flow; facilitate decompression and “rest” for the heart, thereby facilitating its recovery; or as a bridge to cardiac transplantation. Extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs) are the two available forms of delivering mechanical circulatory support in children. ECMO is a mature technology that has been used to support over 25,000 neonates with respiratory failure in whom survival rates to hospital discharge of 75% are expected.¹⁰³ Its use in this setting is supported by randomized controlled trials that demonstrate good short- and medium-term outcomes.¹⁰⁴ ECMO has subsequently been used to provide temporary circulatory support in children with intractable circulatory failure (see Chapter 91). The main advantages of ECMO are its ability to provide biventricular support, additional respiratory support, and its ease of emergency initiation; however, its use is limited to days or weeks.¹⁰² VAD usage in children has been facilitated with the development of smaller devices, and VADs have the advantage of use for weeks or months, which is ideal for bridging to transplant in donor-poor environments. Single-center series¹⁰⁵ and collaborative registry figures of ECMO¹⁰³ or VADs for acute postcardiac surgery indications report similar figures of survival to hospital discharge (~40%), in children who were assumed to not survive without mechanical support. Short- and long-term follow-up and outcome rates of ECMO survivors vary among different reports, which should be further explored in future studies.¹⁰⁶ Rapid ECMO deployment has been reported as an effective intervention for the management of cardiac arrest in a pediatric cardiac ICU and cardiac catheter laboratory.¹⁰⁷ Hospital survival figures for CPR-ECMO seem encouraging, with an estimated survival rate of over 40%,¹⁰⁸ but there are weak and controversial data of long-term neurodevelopmental follow-up.¹⁰⁸⁻¹¹⁰

ACQUIRED HEART DISEASE

Cardiomyopathies

The two most common causes of heart failure in children are CHD and CM. CM is a primary or secondary myocardial disease of either known

KEY POINTS

1. The immature myocardium has little functional reserve, tolerating both increased preload and afterload poorly.
2. Cardiac output in neonates is critically dependent on heart rate.
3. A hyperoxic test will usually differentiate cyanosis resulting from intracardiac shunting of deoxygenated blood and that due to intrapulmonary ventilation-perfusion mismatch.
4. Manipulation of the pulmonary circulation, directed to PVR, and the function of the subpulmonary (“right”) ventricle are pivotal in the understanding and, in turn, managing of the divert setting of congenital heart lesions.
5. Systemic vasodilators play a prominent role in balancing “shunted” circulations and in managing heart failure in children.

or unknown cause associated with cardiovascular dysfunction, and it occurs in children and adults of all ages (see Chapter 82). According to its pathophysiology, CM is classified as dilated, hypertrophic, restrictive, or arrhythmogenic ventricular CM. LV myocardium non-compaction has also been recognized as congenital CM.

Nugent et al. reported the incidence of pediatric CM in a 10-year population-based study in Australian children as 1.24 cases per 100,000 children younger than 10 years of age,¹¹¹ a finding remarkably similar to a recently reported U.S. study.¹¹² Of 314 cases of CM reported by Nugent et al., 184/314 (59%) were dilated CM, 80 (25%) were hypertrophic CM, 8 (2.5%) were restrictive CM, and 42 (13%) unclassified, of which 29 (69%) exhibited LV noncompaction. In this study, 20% of CMs were classified as familial, and in 8.9%, specific mitochondrial or metabolic disease etiologically linked to CM was identified. Of the children in Nugent et al.’s study who underwent myocardial biopsy, 40.3% had histologic evidence of lymphocytic myocarditis according to the Dallas criteria,¹¹³ which contrasts with an incidence of lymphocytic myocarditis in studies in adults of only 10%.¹¹⁴

Presentation

Most children with CM present with signs and symptoms of heart failure, including dyspnea, upper abdominal discomfort, nausea, and vomiting. Abdominal symptoms are often misdiagnosed as indicative of gastroenteritis, although an astute clinician will note the absence of diarrhea. It is presumed that these abdominal symptoms result from hepatic congestion and gut edema as a result of right heart failure or ischemia from splanchnic vasoconstriction. In acute-onset dilated CM, a history of an antecedent flu-like illness is strongly suggestive of a diagnosis of myocarditis. Some children with myocarditis follow a fulminant course typified by the rapid onset of cardiogenic shock.^{115,116} In some cases, CM may present with arrhythmia, especially in LV noncompaction and arrhythmogenic CM cases.

According to the type of CM, a chest X-ray in those with acutely presenting CM shows various degrees of cardiomegaly and pulmonary venous congestion, which are usually more prominent in dilated CM. An echocardiogram is possibly the most useful diagnostic tool, usually able to differentiate the CM type and provide short- and long-term follow-up. In dilated CM, echocardiography will reveal left atrial and ventricular dilatation and impaired systolic and diastolic function and often mitral or tricuspid regurgitation. ECG features are mostly non-specific and may include signs of atrial enlargement, ventricular hypertrophy, ST and T wave changes, and arrhythmias. The presence of Q waves suggests an anomalous origin of the left coronary artery from PA (ALCAPA). If ALCAPA cannot be unequivocally excluded by echocardiography, coronary angiography or CT angiography should be performed.

As CM results from a variety of acquired or inherited disorders, the differentiation of secondary (and possibly treatable causes) from the primary form of the disease is of greatest importance. Vitamin deficiency, viral and bacterial infections, autoimmune disorders, and genetic and metabolic causes should therefore be investigated. Endomyocardial biopsies can be obtained to assist in the diagnosis of myocarditis and other specific myocardial diseases.

Prognosis

Recent studies have reported 5-year survival rates in childhood CM of between 64% and 84%, although the impact of cardiac transplantation on survival rates is not clear in all studies. In contrast to myocarditis, sudden death is uncommon in children with other forms of dilated CM but may be the initial presentation in arrhythmogenic and LV noncompaction CM. Children with CM who fail to respond to conservative treatment and especially those with ongoing requirement for intravenous inotropic support, ventilatory support, or mechanical circulatory support and children with recurrent arrhythmias are candidates for early cardiac transplantation.¹¹⁷ Late recovery of ventricular function is, however, possible.¹¹⁸ The prognosis for CM due to myocarditis in children appears to differ from that in adults, with survival of up to 80% among children who reach the hospital alive.^{119,120} Many children who survive the acute phase recover normal cardiac function in marked contrast to adults, with mortality rates of 20% at 1 year and increasing to 56% at 5 years.¹¹⁴

ICU Management of Decompensated CM

In children presenting with acute heart failure, hypotension, or cardiogenic shock, beta adrenergic agonists may improve systolic ventricular function, especially for those with dilated CM and myocarditis. However, according to the clinical status and dose administered, the inotropic and chronotropic effects of beta adrenergic agonists can increase the diastolic dysfunction further, which is usually seen in patients with hypertrophic CM. In this type of CM, excessive tachycardia is poorly tolerated by the hypertrophied ventricle, and perhaps cautious introduction of beta-blockers at an early stage could be considered as this facilitates diastolic filling. PDE III inhibitors such as milrinone have hemodynamic benefits in acute heart failure (either dilated or hypertrophic CM), improving both systolic and diastolic dysfunction. There are relatively insufficient data to support the use of pure systemic vasodilators in the ICU management of acute heart failure in children. Beta-blockers such as metoprolol and carvedilol may be of benefit in chronic heart failure,^{34,46,47} but they should be avoided in hemodynamically unstable children as should ACE inhibitors. Children with pulmonary venous congestion and pulmonary edema will benefit from diuretics. However, in decompensated hypertrophic CM, adequate ventricular filling is required, and therefore, diuretics should be cautiously administered to avoid hypovolemia.

Nasal or mask continuous positive airway pressure has been shown to result in symptomatic improvement by the unloading of respiratory muscles and lowering of LV afterload as a consequence of raising the intrathoracic pressure.¹²¹ Children with severe heart failure have a high SVR and no ventricular reserve. Great care is therefore needed if sedative agents are administered to facilitate tracheal intubation or ICU procedures. Agents with the fewest effects on the cardiovascular system should be chosen, and an allowance should be made for slow circulatory times when titrating sedative doses.

Anticoagulation may be considered in children with severe cardiac dysfunction. In cases where acute myocarditis is suspected, intravenous immunoglobulin is commonly used, despite the lack of strong evidence to support or refute this practice. Until treatable deficiencies can be ruled out as a cause of CM from the evidence of normal pretreatment blood levels, high-dose vitamin D, carnitine, and coenzyme Q10 should be administered.

The use of mechanical circulatory support with ECMO or VADs can be lifesaving in children with myocarditis or CM who develop

cardiogenic shock.^{122,123} Among neonates and children who require ECMO due to cardiac failure, those with underlying CM and myocarditis have better survival rates than those with other causes of cardiac failure.¹⁰³ A high proportion of children who receive mechanical support for fulminant myocarditis will recover ventricular function. Those who do not recover may be bridged to cardiac transplantation. Clearly, survival with a recovered native ventricle is a better outcome for a child than survival via cardiac transplantation. A multicenter series¹²⁰ documented a median time to return of ventricular function of 9 days in those who survived without transplantation. The absolute time limits for the recovery of native ventricular function have not been established, although pragmatic decisions on whether to proceed to cardiac transplantation should probably be made if cardiac recovery has not occurred after 10 to 14 days of support.¹²⁴

KEY POINTS

1. Mechanical circulatory support is effective in bridging many children with severe heart failure to recovery or cardiac transplantation
2. In the era of mechanical circulatory support, acute fulminant myocarditis in children should be regarded as a recoverable condition.

CONGENITAL HEART DISEASE

CHD, classified as moderate or severe, is detected in approximately 6/1000 live births, of whom between 2.5 and 3 will require expert cardiologic care soon after birth. The presence of extracardiac anomalies in children with CHD is associated with poorer outcomes. Syndromes associated with cardiovascular involvement are of particular significance to pediatric intensivists who must coordinate the cardiac and extracardiac aspects of care.¹²⁵ Trisomy 21 (Down syndrome) is associated with a high incidence of CHD—in particular, atrioventricular septal defects (AVSDs). Deletion of the q11 region of chromosome 22 is associated with a spectrum of cardiac (conotruncal defects, e.g., truncus arteriosus, tetralogy of Fallot) and extracardiac abnormalities.¹²⁶ Of the latter, thymic aplasia places infants at risk of impaired cellular immunity and hypocalcemia secondary to hypoparathyroidism.

Many classifications of congenital heart lesions have been proposed. While a sequential approach to the description of cardiac anatomy is most frequently employed by pediatric cardiologists, a broader physiologic approach is more useful to intensivists.

Lesions with Predominant Left-to-Right Shunt

VSD is the archetypal lesion associated with left-to-right shunting of blood. ASDs, AVSDs, patent ductus arteriosus (PDA), and truncus arteriosus are also lesions with left-to-right shunt. Ventricular output will follow the path of least resistance, resulting in blood shunting across the defect and into the lungs as PVR is lower than SVR. The magnitude of the shunt, usually expressed as the ratio of pulmonary blood flow to systemic blood flow ($Q_p:Q_s$), depends on the size of the defect and the level of PVR. If the defect has a small diameter, it offers resistance at its level, limiting flow from the left-to-right chambers and maintaining a pressure gradient between them. Larger diameter defects are unrestrictive, with no pressure gradient between right and left chambers, and in this situation, flow is solely dependent on the ratio of PVR to SVR—the lower the PVR, the greater will be the shunt and pulmonary blood flow.

Small restrictive defects rarely result in symptoms in infancy, typically presenting when a cardiac murmur is detected as an incidental finding. Infants with larger unrestrictive defects gradually develop congestive cardiac failure due to the increase in pulmonary blood flow, which occurs as PVR falls in the first weeks of life.¹²⁷ Thus, the

consequences of a moderate or large unrestrictive defect are increased pulmonary blood flow (high Qp : Qs) and extra volume work demanded of the LV. The volume overload of the LV results in LV enlargement and failure. If large left-to-right shunts are left untreated, PVR gradually rises. Although the initial rise is the result of pulmonary arteriolar muscular hypertrophy, which is reversible, irreversible pulmonary vascular obstructive disease¹²⁸ eventually ensues, resulting in PA pressure and vascular resistance that exceeds that of the systemic circulation and leads to shunt reversal (right-to-left) and cyanosis (Eisenmenger syndrome). For this reason, steps must be taken in all children with congenital heart lesions and raised pulmonary blood flow to correct the lesion or protect the lungs by either a corrective procedure or a palliative procedure such as PA banding before severe pulmonary vascular changes develop. With the exception of isolated atrial septal defects, most L-R shunt lesions that require surgical intervention present in the first year of life with heart failure and are associated with development of PHT. The principal lesions are described below.

Ventricular Septal Defect

Anatomy. VSD can occur in any part of the interventricular septum and is classified by location,^{129,130} the most common being perimembranous VSD. It may be present in isolation or in association with other cardiac anomalies.

Pathophysiology. Left-to-right shunting at the ventricular level is determined by the defect size and PVR and leads to increased pulmonary blood flow, LA dilatation, and LV volume overload.

Many small VSDs close spontaneously,¹³¹ but if closure does not occur or if the defect is unrestrictive infants will fail to thrive and develop congestive heart failure as PVR falls in early infancy. Untreated VSD leads to PHT and eventual progression to fixed pulmonary vascular obstructive disease and ultimately Eisenmenger syndrome. Patients with a fixed high PVR are not suitable for VSD closure since the RV will not tolerate the excessive afterload of the hypertensive pulmonary vascular bed.

VSD Closure. Most VSDs are repaired as a primary surgical procedure,¹³² with closure performed with a sutured patch during CPB. Alternatively some defects may be closed with an occlusion device at cardiac catheterization.¹³³ Occasionally, PA banding is undertaken to reduce pulmonary blood flow and protect the pulmonary vascular bed in neonates in whom primary repair is high risk or if the complete repair is not possible. This may be the case with complex and multiple defects or in very small premature babies. However, these conservative strategies are questioned by some surgeons.^{134,135}

Postoperative Management. Most children undergoing elective VSD closure progress rapidly to extubation. Patients with severe cardiac failure or high PA pressures preoperatively benefit from a more cautious approach in the early postoperative period as do those with complex associated lesions. Low cardiac output or pulmonary edema may be noted in the early postoperative period as a consequence of generalized myocardial hypocontractility or due to a residual VSD (unusual with the advent of intraoperative transesophageal echocardiography). PHT is relatively rare in the current era of “early” primary repair of VSD. However, late presenting cases may have PHT, and life-threatening pulmonary hypertensive “crises” can occur in the postoperative period. Surgically placed PA catheters greatly assist in the early detection and management of such episodes.¹³⁶ Junctional ectopic tachycardia (JET)^{137,138} and complete heart block are generic risks of surgery in the vicinity of the ventricular septum. Complete heart block may be transient, but if AV synchrony has not returned by 7 to 10 days, a permanent pacing system is required.¹³⁹

Atrial Septal Defect

Anatomy. Anatomically, interatrial communications^{129,140} are of four types and can occur in isolation or in association with other CHD. An ostium secundum defect is the most common form of ASD and is centrally located in the atrial septum (fossa ovalis). An ostium primum-type defect is part of the AVSD spectrum (see below). A sinus

venosus defect occurs close to the RA-superior vena cava or RA-inferior vena cava junction and is commonly associated with partial anomalous pulmonary venous drainage. A coronary sinus defect describes a type of ASD in which the wall between the LA and coronary sinus is absent, allowing left atrial blood to reach the RA via the coronary sinus.

Pathophysiology. Left-to-right shunting of blood at the atrial level leads to RA and RV dilatation with increased pulmonary blood flow. Congestive heart failure occurs in up to 5% of children with ASD in the first year of life. Small ASDs are likely to close spontaneously in the first 2 years of life. PHT in association with ASD is relatively rare in childhood with an incidence of 13% in unoperated children <10 years of age, although patients may progress to irreversible PHT if defects are not closed.¹⁴¹ Occasionally infants or young children with primary PHT, pulmonary hypoplasia, or similar conditions present with apparently symptomatic ASD with right-to-left shunting. In these situations, the ASD is beneficial, decompressing the right heart, with symptoms being a consequence of PHT rather than simply the presence of an ASD. Atrial arrhythmias may occur in adulthood in some cases left untreated.

ASD Closure. Centrally located secundum ASD is frequently closed by placement of an ASD closure device through cardiac catheter.^{142,143} Occasionally, surgery is required in association with immediate or long-term complications of ASD device closure.¹⁴⁴ Large defects and nonsecundum defects are closed surgically with direct suture or patch and using CPB. Defects are typically closed if a child becomes symptomatic or electively between 3 and 5 years of age, as the likelihood of spontaneous closure is low after this age. There is essentially no mortality risk associated with closure of an isolated ASD and good long-term morbidity-free survival is expected.¹⁴⁵

Postprocedure Management. The vast majority of elective ASD closures progress rapidly to extubation post procedure (within hours). Specific postoperative problems seen following ASD closure include **sinoatrial node dysfunction**, which manifests as an inappropriate chronotropic response or as atrial or junctional arrhythmias. The problem is caused either by direct trauma to the sinoatrial node or interruption to its blood supply during surgery. **Postpericardiotomy syndrome** manifests as fever, malaise, lymphocytosis, nausea, vomiting, or abdominal pain in the weeks following surgery. The symptoms are caused by a sterile inflammatory process, which can cause pericardial fluid to accumulate to the point at which pericardial tamponade is manifest. A history of recent cardiac surgery with symptoms as above should raise the suspicion of the syndrome and of potential tamponade, particularly if cardiomegaly is present on chest x-ray. **PHT** is relatively rare in children after ASD repair—a previously undiagnosed ASD presenting in adulthood is more likely to be associated with PHT. **Venous obstruction** of pulmonary veins or vena cava may occur in association with repair of sinus venosus defects. **LV dysfunction** with transiently elevated LA pressure and pulmonary edema is occasionally seen after ASD closure in older patients due to chronic RV overload and decreased LV compliance.

Atrioventriculoseptal Defect

Anatomy. AVSD¹⁴⁶ results from failure of the lower part of the atrial septum to fuse with the upper part of the ventricular septum. The hallmark of all AVSDs is the presence of a common atrioventricular (AV) junction and common AV valve with 2 bridging (anterior and posterior) and 3 smaller leaflets. The common AV valve has varying degrees of competence. There are three potential components of this defect, an ostium primum ASD, a VSD, and an abnormal formation of the AV valves. The condition presents as partial AVSDs and complete AVSDs. Partial AVSDs, sometimes referred to as *primum* ASDs, present with an ASD and cleft AV valve with fused anterior and posterior bridging leaflets, creating separate right and left orifices (tricuspid and mitral valve). A complete AVSD has a VSD in addition and the bridging leaflets are not fused; thus, a common orifice is present. According to common AV valve commitment in relation to ventricles, AVSDs can be classified as balanced when equally committed to both ventricles or unbalanced if it favors one of

the ventricles, in which case hypoplasia of the opposite ventricle may occur. AVSD spectrum lesions commonly occur in children with Down syndrome.

Pathophysiology. Partial defects behave like a secundum ASD, with left-to-right shunt at the atrial level causing RA and RV volume overload. Associated incompetence of the left AV valve may lead to significant regurgitation and worsening symptoms. In complete defects, left-to-right shunting of blood at the ventricular level leads to congestive heart failure by about 2 months of age. PHT and pulmonary vascular obliterative diseases occur if repair is not undertaken by 6 to 9 months age (earlier in infants with Down syndrome).

Surgery. Partial defects are usually repaired electively between 1 and 5 years, whereas complete defects are usually repaired between 3 and 6 months to avoid severe pulmonary hypertensive complications.¹⁴⁶ Unbalanced AVSDs may undergo single ventricle palliation if associated with hypoplasia of one ventricle.

Postoperative Management. Problems seen after AVSD surgery include PHT,¹⁴⁷ although this is uncommon in the current era of early surgical repair. Residual lesions such as residual left AV valve regurgitation or residual VSD will slow postoperative recovery and require prompt diagnosis and aggressive management including reoperation if necessary. Afterload reduction with sodium nitroprusside or milrinone is useful if mild AV valve regurgitation is present following repair. If residual valve incompetence persists or increases, the operation should be revised. Elevated LA pressure following AVSD repair can occur for reasons including the presence of residual left AV valve regurgitation, left AV valve stenosis, LVOT obstruction, residual VSD, and left ventricular myocardial dysfunction. The precise cause of elevated LA pressure must be diagnosed and appropriate management instituted. Patients undergoing AVSD repair are also at risk of developing JET and complete heart block postoperatively.

Patent Ductus Arteriosus (PDA)

Anatomy. The ductus arteriosus is a vascular communication necessary in the fetal circulation between the junction of the main and left PA and the lesser curvature of the aorta (proximal descending aorta), which normally closes within 2 weeks of birth. Persistent patency occurs as an isolated defect in premature neonates and in association with other congenital heart lesions. The occurrence of PDA in premature neonates results from the low constrictor response of the immature duct to oxygen.

Pathophysiology. The key pathophysiologic abnormality in PDA, as in VSD, is left-to-right shunting leading to increased pulmonary blood flow, PHT and LV volume overload.¹⁴⁸ Neonates with this condition usually present with congestive heart failure, apneas, or respiratory problems. In term infants and older children, isolated PDA may present incidentally or with the onset of cardiac failure or problems with recurrent pulmonary infections. PHT progressing to pulmonary vascular obstructive disease can occur within the first year of life, the rate of onset of symptoms depending on the size of the duct.

Management. Indomethacin or ibuprofen are used to induce closure of PDA in premature neonates, acting through inhibition of the vasodilatory prostaglandin production, with success in about 70% cases.¹⁴⁹ Transcatheter catheter occlusion can be effective in suitable cases, with a low incidence of associated complications.¹⁵⁰ Surgical ligation or division is required in very small babies and in older children with large or tortuous ducts in whom occlusion devices cannot be safely deployed. Surgical closure is carried out via a lateral thoracotomy or as a video-assisted thoracoscopic procedure.¹⁵¹

Postoperative Management. The principal complications of conservative treatment of PDA with indomethacin or ibuprofen in preterm neonates are failure to induce closure and renal failure.¹⁴⁹ Surgical approaches may be complicated by occlusion failure and complications of thoracotomy including infection and hemorrhage. Adjacent structures including the thoracic duct, phrenic nerve, and recurrent laryngeal nerve may be damaged during surgery. Complications following transcatheter closure include residual shunt, embolization of closure device, and hemolysis.

Truncus Arteriosus

Anatomy. Truncus is caused by the failure of the common arterial trunk to divide into the aorta and PA. A single arterial vessel originates from both ventricles overriding the ventricular septum and supplying the coronary, pulmonary, and systemic circulations. Anatomic variations depend on the respective origins of the right and left PA branches from the main PA (type I), posterior (type II), or lateral (type III) aspects of the common arterial trunk or the aorta (type IV). A VSD lies immediately below a single ventriculoarterial truncal valve, which is commonly dysplastic, leading to stenosis or regurgitation. Coronary artery abnormalities are common and may lead to difficulties when conducting surgical repair. Ten to fifteen percent of the cases have associated hypoplasia, coarctation, or interruption of the aortic arch, and a small proportion of patients have stenosis or hypoplasia of the pulmonary arteries. Right aortic arch may also be present.

Aortopulmonary window is a rare lesion in which an abnormal vascular communication exists between the ascending aorta and the main PA. Like truncus arteriosus, this lesion is associated with the 22q11 chromosomal deletion^{152,153} (see later discussion).

Pathophysiology. The RV and LV are pressure and volume overloaded, particularly if truncal valve stenosis or regurgitation is present. Runoff into the pulmonary circulation due to low PVR and into the ventricles due to truncal valve regurgitation leads to a low diastolic pressure, which in the presence of high ventricular end-diastolic pressures may exacerbate myocardial ischemia. Pulmonary blood flow depends on PVR and the presence or absence of stenoses in the proximal PAs. Most commonly pulmonary overcirculation and congestive heart failure result as PVR falls in the first weeks of life. The defect is commonly associated with the 22q11 chromosomal deletion (Di George syndrome, Sphrintzen's syndrome). The important clinical manifestations associated with these include scanty or absent T cells and the consequent risk of graft versus host reactions if transfused with viable leukocytes. Irradiation of all blood products is recommended unless normal T-cell status is confirmed.

Surgery.^{154,155} The pulmonary arteries are removed from the arterial trunk, leaving a vessel that becomes the neo-aorta. A valved conduit is then placed from the RV to the pulmonary arteries, and the VSD is closed. Mortality risk is less than 10% if the truncal valve is functionally normal, no other lesions are present, and the child is of an acceptable weight. Higher mortality is seen when truncal valve replacement is required. Long-term results are encouraging although the valved conduit will require upsizing during childhood.¹⁵⁶

Postoperative Management. Specific postoperative problems associated with repair of truncus include PHT and low cardiac output. Inotropic support is required routinely, and delayed sternal closure may be employed to prevent tissue tamponade in the early postoperative period. Intensivists must be aware of the possibility of right-to-left shunting as surgeons may leave a smaller interatrial communication to decompress the RV. Failure to appreciate this mechanism may lead to an inappropriate focus on pulmonary causes of cyanosis. Right bundle branch block is common after truncus repair due to the surgical right ventriculotomy. Heart block and atrial or junctional arrhythmias are also seen. There is some evidence that children with 22q11 microdeletions have more postoperative complications than children undergoing identical surgery without deletions.

Left Heart Obstruction

Obstruction to the exit of blood from the LV can occur at subvalvular, valvular, or supra-valvular levels or more distally in the aortic arch. Babies with severe obstruction of the aortic valve or arch present in the neonatal period with either heart failure or cardiogenic shock. Aortic coarctation, aortic interruption, and critical aortic stenosis (AS) are associated with a duct-dependent systemic circulation and typically present in the first few days of life as the arterial duct closes. Less severe obstruction may be detected later as an incidental finding (murmur) or with the gradual onset of signs and symptoms including those of LV

failure. Chronic obstruction to LVOT causes LV hypertrophy, and while systolic function may initially be well preserved, reduced diastolic compliance may occur early in the clinical course. If the obstruction is unrelieved, the subendocardial region becomes ischemic and endocardial fibrosis occurs. Papillary muscle ischemia may also occur and results in acquired mitral valve regurgitation.

Valvular Aortic Stenosis

Anatomy. AS at valve level is the most common form of AS and may be associated with other left heart abnormalities (e.g., supravulvar AS, mitral valve anomalies, aortic coarctation), aortic insufficiency, and endocardial fibroelastosis. In neonatal aortic stenosis,¹⁵⁷ the LV and other left-sided structures may be hypoplastic.

Pathophysiology. Neonates with clinically apparent valvular AS present with acute left ventricular failure or shock. Systemic perfusion may be maintained by right-to-left shunting of blood across a PDA with consequent systemic desaturation and the risk of reduced systemic perfusion if the ductus closes spontaneously. The LV exhibits poor performance in both diastole and systole, and as a consequence there is high LA pressure. Pulmonary edema is a prominent clinical feature. End organ ischemic damage including renal failure and necrotizing enterocolitis are frequently seen as a consequence of poor systemic perfusion. Less severe AS typically presents later in infancy or childhood with exercise-induced syncope, chest pain, or sudden death. In these patients, concentric LV hypertrophy induced by chronic pressure overload is usually seen.

Surgery. A number of treatment options are available, with the choice of procedure dependent on age, clinical status of the child at presentation, associated anomalies, and anatomic complexity. The simplest procedure, percutaneous balloon valvotomy, is appropriate in patients with mild to moderate stenosis and favorable aortic valve anatomy.¹⁵⁸ Open aortic valve surgery is an alternative to balloon valvuloplasty and may be favored if additional procedures—for example, duct ligation—are required. If the native aortic valve cannot be salvaged or reconstructed, surgical choices include replacement of the aortic valve with a homograft or valved conduit or placement of the patient's own pulmonary valve into the aortic position with associated pulmonary homograft autograft (the Ross procedure).^{159–161} A variant of the Ross procedure, the Ross-Konno procedure, is indicated for complex LVOT obstruction in which in addition to the Ross operation, annular enlargement or aortoventriculoplasty is undertaken.¹⁶²

Postoperative Management. Most neonates presenting in heart failure or shock who undergo urgent procedures remain critically ill postoperatively and require ongoing multiorgan support.¹⁶³ If low cardiac output persists following repair, residual AS or regurgitation must be excluded. Inotropic and vasodilator support of the failing myocardium should be guided by serial hemodynamic and echocardiographic evaluations. Relief of AS in older children may be associated with systemic hypertension secondary to the unrestrained force of contraction of the hypertrophied LV. Children undergoing prosthetic valve replacement require long-term anticoagulation therapy.¹⁵⁹

Subvalvular Aortic Stenosis

Anatomy. Subvalvular AS¹⁶⁴ is seen in various forms including a fibrous diaphragm-like ring with a central orifice; a fibromuscular tunnel, frequently associated with hypoplasia of ascending aorta and LV anomalies; or simply as dynamic obstruction due to hypertrophy of the LVOT. Subvalvular AS presents in neonates in association with other lesions including malalignment-type VSD, double-outlet RV, and aortic or aortic valvular lesions or as an isolated lesion in childhood.

Pathophysiology. Similar to valvular AS, pressure overload in LV leads to hypertrophy with resultant raised pressure overload.

Surgery. The choice of surgical procedure depends on the anatomic substrate. Membranous subvalvular AS requires simple resection. The tunnel form may be suitable for resection or require a more extensive Konno or Ross-Konno-type procedure. Finally, the hypertrophic form of subvalvular AS requires a Ross-Konno operation with resection of LV myocardium.^{159,162} Some children with a small-diameter

aortic valve and endocardial fibroelastosis of the LV with poor function may not be suitable for biventricular repair and are palliated by creation of cavopulmonary circulations.

Postoperative Management. The perioperative course is usually uneventful after resection of membranous subvalvular AS although later recurrence is common. Following surgery for tunnel and hypertrophic forms of subvalvular AS, the recovery pathway is determined by the age of the child, the nature and complexity of surgery performed, and most critical of all, the size and function of the LV. Specific postoperative problems include **residual LVOT stenosis, mitral regurgitation, VSD with L-R shunt, and left bundle branch block or complete heart block** secondary to resection of left ventricular myocardium.

Supravulvar Aortic Stenosis

Anatomy. Supravulvar AS may be a localized or diffuse narrowing above the sinotubular junction. The stenosis is occasionally associated with a hypoplastic ascending aorta, and there may be compromise to coronary filling. It can occur in isolation and in association with Williams syndrome (supravulvar AS, RV outflow tract–RVOT obstruction, peripheral pulmonary stenosis, renal artery stenosis).^{165,166}

Pathophysiology. Similar to valvular AS, pressure overload in the LV leads to hypertrophy, with resultant raised pressure overload. In addition, coronary arteries fill under high pressure and may become tortuous and dysplastic.

Surgery. Patch angioplasty is performed in most cases. There is a significant risk of postprocedural coronary ischemia as coronary perfusion pressure is acutely lowered when the supraaortic obstruction is released.

Postoperative Management. The postoperative course is usually uneventful. Specific postoperative problems include **residual aortic or LVOT stenosis** leading to cardiac failure and **coronary ischemia**, which occurs if the repair has disturbed the coronary arteries or if LV hypertension and LV subendocardial ischemia persist. Care should be taken to avoid excessive systemic vasodilatation or hypotension, which might lead to coronary ischemia.

Aortic Coarctation

Anatomy. Aortic coarctation is a constriction of the thoracic aorta in the region of the left subclavian artery where the ligamentum arteriosum originates. The complexity of the lesion varies from a discrete narrowing to more extensive aortic arch hypoplasia extending back to the proximal aortic arch.¹⁶⁷ Coarctation commonly coexists with VSD¹⁶⁸ and can also be associated with other left-sided lesions including aortic and mitral valve stenosis.

Pathophysiology. In the neonatal presentation of aortic coarctation, a normal circulation is maintained until ductal tissue contracts, at which point distal aortic flow is severely reduced, leading to a clinical presentation of heart failure or shock and characteristic loss of lower limb pulses.¹⁶⁹ Prostaglandin E1 or E2 infusion should be started as soon as the diagnosis of a duct-dependent lesion is suspected in order to reopen or maintain patency of the ductus arteriosus. Following initial resuscitation, urinary output and resolution of metabolic acidosis are early indicators of successful reperfusion of the distal aorta. Early surgical repair is indicated.

Beyond the early neonatal period, aortic coarctation presents as progressive onset of cardiac failure or as an incidental finding (murmur, upper limb hypertension, absent weak femoral pulses) later in childhood. Thoracic aortic collaterals develop and may be noted as rib notching on a plain chest x-ray.

Surgery. In the neonatal period, surgical resection of the narrowed aortic segment and associated ductal tissue is followed by either direct anastomosis or repair with a subclavian flap or similar angioplasty without CPB.¹⁷⁰ If aortic arch hypoplasia is more extensive a homograft or prosthetic tube graft may be incorporated in the repair and CPB may be required.¹⁷¹ Neonatal coarctation associated with VSD can be palliated by resection of the coarctation and banding of the PA to restrict pulmonary blood flow, with delayed VSD repair, especially in the context of high PVR. Alternatively, both lesions can be corrected

in the neonatal period.¹⁶⁸ The mortality rate for repair of neonatal coarctation is low. Kanter et al. reported 91% survival in a series that included both isolated and complex coarctation.¹⁷² In older children, mortality is <1%, although paraplegia secondary to interruption of spinal cord perfusion remains a concern.

Balloon angioplasty with or without endovascular stent placement is frequently used to alleviate recurrent aortic coarctation and is increasingly being used with apparent success, to address native coarctation particularly in older patients but is not favored in symptomatic neonates.^{170,173}

Postoperative Management. Specific postoperative problems include **systemic hypertension**, which is thought to be due to multiple factors including altered baroreceptor and adrenal catecholamine and renin-angiotensin axes.^{174,175} Persistent hypertension is less common following neonatal repair, and when present it usually responds to short-term vasodilator therapy.^{174,176} Additional beta adrenergic blockade (esmolol,¹⁷⁷ propranolol, or labetalol) may be required, particularly with late presenting coarctation, but should be used with caution if ventricular function is impaired. Some children have persistent hypertension following repair¹⁷⁸ and require long-term antihypertensive therapy. **Postcoarctectomy syndrome**¹⁷⁹ occurs in older patients and is thought to be the result of restoration of higher pressure pulsatile flow to the mesenteric arterial tree and presents as abdominal distention, abdominal pain, ascites, or occasionally, enteric infarction. The condition is best managed by avoiding enteral feeding for 24 hours following repair and aggressive treatment of systemic hypertension. The necessity of aortic clamping during surgical repair interrupts distal aortic flow and may result in spinal cord ischemia (rare in neonates, 0.4% incidence in older patients) or renal ischemia. Intensivists must seek positive confirmation of lower limb movement and adequate renal function in the early postoperative period. In neonates low cardiac output may persist due to preexisting ventricular dysfunction, although residual coarctation should be excluded. Structures near the aortic arch prone to surgical injury include the thoracic duct, recurrent laryngeal nerve, and phrenic nerve, leading to postoperative chylothorax, stridor, or hemidiaphragm paralysis.

Interrupted Aortic Arch (IAA)

Anatomy. In this condition, the aortic arch is either atretic or interrupted, creating either complete disruption or luminal obstruction (without external interruption). It is classified according to the location of the interruption along the aortic arch, which may be distal to the left subclavian artery (type A), between the left common carotid and left subclavian arteries (type B), or between the brachiocephalic trunk and left common carotid arteries (type C). A PDA is necessary to maintain perfusion of the distal aortic arch, closure of which leads to emergent presentation. A VSD and obstruction of the LVOT commonly coexist. The more common form of interrupted aortic arch, type B, is associated with the 22q11 chromosomal deletion^{152,153} (see above).

Pathophysiology. Interrupted aortic arch can be regarded as a severe form of aortic coarctation, with duct-dependent distal aortic perfusion, and requires similar initial management.¹⁶⁹

Surgery. Surgical reconstruction of the aortic arch and closure of the associated VSD are usually undertaken under CPB in the neonatal period.

Specific postoperative problems seen after repair of interrupted aortic arch include PHT, residual aortic arch obstruction, and residual VSD. There is a risk of transfusion-associated graft-versus-host disease and hypocalcemia in children with type B interrupted aortic arch associated with 22q11 deletion and Di George phenotype.¹⁸⁰

Cyanotic Lesions

Tetralogy of Fallot (TOF)

Anatomy. Tetralogy of Fallot¹⁸¹ was initially described in the 19th century as an association of four anatomic findings: VSD, subpulmonary stenosis, aortic override of the ventricular septum, and right ventricular hypertrophy. The four lesions are actually the result of just one central

problem, anterior and superior malalignment of the infundibular septum with respect to the muscular septum, which creates an obstruction in the RVOT and leads to the four features seen. Coronary artery abnormalities may also be present, and a right-sided aortic arch is seen in approximately 20% of cases. Children presenting with TOF should be investigated for a 22q11 microdeletion (see previous discussion).

Pathophysiology. Preoperative physiology depends mainly on the degree of RVOT obstruction. Patients with minimal RVOT obstruction have unrestricted pulmonary blood flow with left-to-right shunt through the VSD. Conversely patients with severe obstruction will be cyanosed with saturations in the 70% to 80% range preoperatively as a result of right-to-left shunting across the VSD. RVOT obstruction is often dynamic and may cause profound cyanosis (hypercyanotic spells), which requires treatment aimed at alleviating the dynamic RVOT obstruction and maintaining right heart output. Treatment of such episodes requires oxygen, sedation, and volume expansion. The knee-chest or over-shoulder positions compress the liver and increase RV filling. If such maneuvers fail, beta blockade (propranolol 0.1 mg/kg) or vasoconstriction (e.g., phenylephrine 5–20 µg/kg IV, max 500 µg per dose) may be required or, as a last resort, preoperative ECMO support.

Surgery. The timing and type of surgical intervention in TOF is controversial.^{182,183} Complete repair is usually undertaken in the first year of life with VSD closure, RVOT obstruction relief, and pulmonary valvotomy. However, some centers adopt a two-stage approach with initial placement of a modified systemic-to-pulmonary arterial (Blalock-Taussig) shunt to secure pulmonary blood flow in cyanotic neonates with complete repair being undertaken after a few months. Surgical repair of the RVOT obstruction can be complex if major coronary abnormalities are present, especially with the anterior descending branch originating from the right coronary artery and running over the RVOT.

Specific Postoperative Problems. Residual VSD is poorly tolerated after TOF repair and requires early surgical closure. Moderate degrees of residual RVOT obstruction may be well tolerated in the early postoperative period, but severe residual obstruction demands early reinvestigation and reoperation with placement of a larger RVOT patch or valved RV-PA conduit. All patients with a right ventricular incision develop right bundle branch block. JET is poorly tolerated after Fallot repair.¹⁸⁴ Low cardiac output due to RV dysfunction is relatively common and should be suspected if the child is hypotensive and tachycardic and has a raised CVP and hepatomegaly. The problem is predominantly one of poor RV compliance, often referred to as *RV restriction*¹⁸⁵ and typically resolves in 3 to 5 days. Until recovery occurs, the heart should be supported by optimizing RV filling and ensuring AV synchrony. Negative pressure ventilation has been shown to improve cardiac output where RV restriction exists.^{17,186}

Pulmonary Atresia with Intact Ventricular Septum¹⁸⁷

Anatomy. In this condition, there is complete obstruction to the RVOT, along with a variable degree of hypoplasia of the RV and tricuspid valve, which may also be incompetent. Pulmonary blood flow occurs via a PDA. Coronary artery sinusoids or fistulae are often found in severe pulmonary atresia with intact ventricular septum and a small RV. Ten percent of cases will have a right ventricular-dependent coronary circulation, where coronary sinusoids/fistulae are associated with proximal stenosis, and perfusion of areas of myocardium is dependent on flow via the RV. In some patients, the pulmonary arterial supply is abnormal, with segments of the lungs being supplied solely or partially ("dual supply") from systemic collateral vessels termed *major aortopulmonary collateral arteries* (MAPCA).¹⁸⁸ Children presenting with this condition should be investigated for a 22q11 micro-deletion (see previous discussion).

Pathophysiology. Preoperatively, there is complete mixing of systemic and pulmonary venous return in a duct-dependent circulation. The RV may be very hypertensive since there is no path for egress of blood. Some blood may pass via coronary sinusoids, if present, or back through a regurgitant tricuspid valve.

Surgery. The goal of treatment is to provide a secure source of pulmonary blood flow balanced to systemic flow and to permit the RV to develop to its maximal potential, always aiming for a two-ventricle repair where possible.^{188,189} Interventional procedures are needed in all cases in the fetal¹⁹⁰ or neonatal period^{191,192} because of duct dependency. Subsequent strategies are chosen according to individual anatomic findings.

In severe forms of the condition (severe RV hypoplasia + coronary fistulae) a two-ventricle repair will never be possible and a palliative approach is adopted. Initial palliation secures pulmonary blood flow with systemic-to-pulmonary artery shunts (30%-40% PA/IVS), with the ultimate aim being a single-ventricle Fontan circulation (see later discussion). In contrast, babies with a normal-sized RV may be suitable for RVOT reconstruction in the neonatal period, therefore avoiding shunting and ending up with early anatomic correction (10% of cases). An intermediate group of patients, the majority of cases of PA/IVS, need initial palliation with decompression of the RV by radiofrequency perforation of the atretic pulmonary valve or outflow tract patch, and often require a systemic-to-pulmonary artery shunt. They progress to either a single, "one-and-a-half"¹⁹³ or biventricular repair depending on subsequent development of the RV and PA. Fetal cardiac valvuloplasty may have a role in the management of this condition in the future.¹⁹⁰

Specific Postoperative Problems. These include low cardiac output due to excessive runoff through the shunt, myocardial ischemia due to decompressed coronary fistulae, or low systemic diastolic pressure due to excessive shunt runoff.¹⁹⁴

Transposition of the Great Arteries (TGA)

Anatomy. In TGA,^{195,196} which accounts for 5%-7% of all CHD, the great vessels are transposed so that the aorta arises from the anatomic RV and the PA from the LV, so-called ventriculoarterial discordance. It is also called complete TGA or D-TGA, which refers to the aorta being positioned right and anteriorly to the PA. The condition occurs with a VSD in approximately 40% of cases. Other commonly associated lesions include coarctation (10%), LVOT obstruction (5%), and coronary abnormalities (33%). Congenitally corrected TGA is a different and rare pathology in which both atrioventricular and ventriculoarterial discordances are present, with the aorta positioned left to the PA (also called L-TGA).

Pathophysiology. The predominant finding in TGA is cyanosis due to parallel rather than serial function of the pulmonary and systemic circulations, with the greatest proportion of the output of a ventricle being recirculated to that ventricle. Survival is therefore dependent on the presence of mixing between the two circulations (Fig. 83-2). The presence of either a PDA or VSD alone or in combination without an atrial communication does not ensure adequate mixing of the two circulations. If the diagnosis is suspected in a neonate, an infusion of prostaglandin E1 or E2 should be established to maintain ductal patency, and following echocardiographic confirmation of the diagnosis, a balloon atrial septostomy is sometimes necessary to enlarge the foramen ovale and secure mixing at the atrial level, particularly if the foramen ovale is restrictive, leading to high pulmonary venous pressures. Saturations typically increase from very low levels (<50%) to 65%-85% following these interventions, and it is then usually possible to discontinue the prostaglandin infusion.

Surgery. The preferred surgical option in the current era is the arterial switch (Jatene) operation,¹⁹⁵⁻¹⁹⁸ although long-term results following Senning operations also appear to be acceptable.¹⁹⁹ The switch operation is usually performed within the first 2 weeks of life, beyond which the LV (functioning as a low-pressure subpulmonary or right ventricle since birth) is less able to cope with systemic pressures.²⁰⁰ Babies with a large VSD have equal ventricular pressures, and repair can be delayed a little longer, although in practice most surgeons repair TGA with VSD within the first month of life. The operation consists of transection of the aorta and PA with reconstruction of the vessels in their anatomic position, which necessitates transfer of the coronary arteries from the aorta (neo-PA) to the PA (neo-aorta).

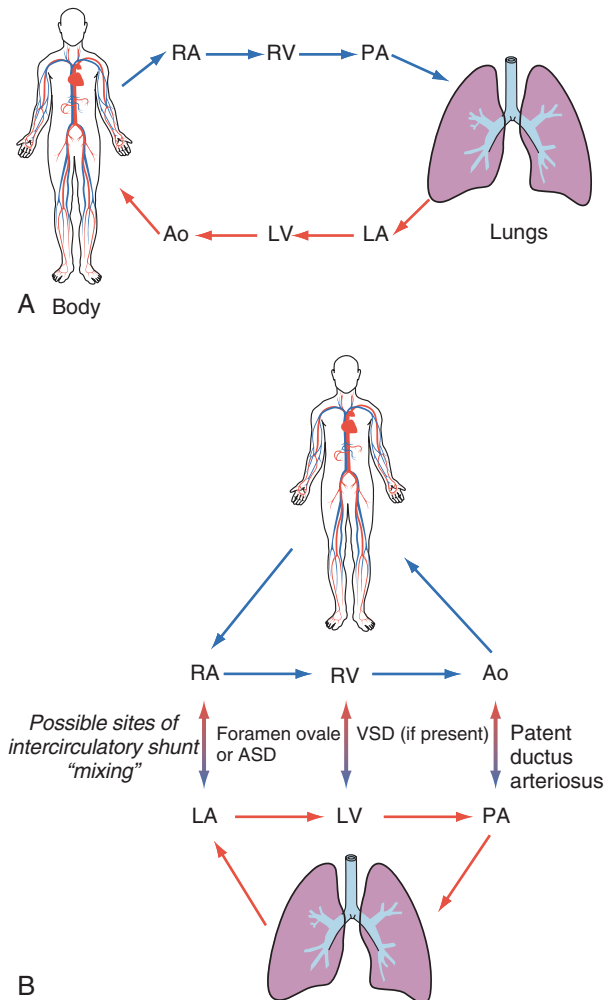


FIGURE 83-2 ■ **A**, Normal series circulatory arrangement. **B**, Parallel circulation of transposition of the great vessels.

Specific Postoperative Problems After the Arterial Switch Operation. Left ventricular dysfunction is common in babies during the first 12 hours following the arterial switch operation.²⁷ It may be a sign of coronary insufficiency²⁰¹ or of acute dysfunction secondary to an unprepared/involved LV, or simply nonspecific post-CPB low cardiac output. In the absence of ECG or echocardiographic evidence of regional coronary ischemia, low cardiac output is managed conservatively. The postoperative LV of neonates is poorly compliant. Therefore rapid volume infusion should be avoided as LV distention and ischemia may result. Preload should be augmented gradually, titrating volume infused against measured left atrial pressure.

Alternative Surgical Techniques. Atrial switch operations (the Senning and Mustard procedures) are alternatives to the arterial switch operation and may be chosen in infants presenting beyond the early neonatal period in whom a one-stage arterial switch is not possible due to deconditioning of the LV. In atrial switch operations, blood is diverted by an atrial baffle to establish a series circulation leaving the RV as the systemic ventricle. It is believed that the burden of late complications such as RV failure is greater after atrial switch procedures. An alternative strategy for late-presenting transposition is a two-stage repair with initial banding of the PA to condition the LV with switch once the ventricle is conditioned.²⁰²

Postoperative Care. Atrial switch procedures are usually performed outside the neonatal age group and, compared to arterial switch patients, have a relatively uneventful postoperative course.

Atrial volumes and compliance are reduced by the procedure such that postoperatively left and right atrial pressures must be maintained at higher than normal levels to maintain ventricular filling. Slow heart rates and arrhythmias are poorly tolerated.

Complex Single-Ventricle Circulations

Some defects are such that they can never be corrected to provide two functioning ventricles.^{203,204} These complex arrangements include any heart in which one ventricle is hypoplastic such that it would be incapable of supporting either the pulmonary or systemic circulation independently. Examples of such situations include tricuspid atresia or double-inlet LV. In these examples the RV has failed to develop adequately and is connected to a dominant LV via a VSD. Flow to the circulation supplied by the rudimentary ventricle originates from the dominant chamber and is dependent on an adequate VSD. Children with this type of anatomy will always have two ventricles, even if one is hypoplastic, but physiologically they behave as if the heart consists of only a single ventricle.

Complex single-ventricle hearts can be palliated with a series of interventions leading to creation of a Fontan circulation in which the systemic and pulmonary circulations are completely separated.²⁰⁵ Initially adequate intracardiac communications are established to ensure both systemic and pulmonary venous return have unobstructed access to the dominant ventricle that supplies both systemic and pulmonary blood flow. If necessary, pulmonary flow is augmented by the use of a systemic-to-PA shunt or RV-to-PA conduit. Systemic and pulmonary blood flow is assured at the expense of mixing of pulmonary and systemic venous returns, with consequent cyanosis and volume loading of the single ventricle.

Subsequently, if hemodynamic conditions are favorable, the Fontan circulation is established, usually in two-staged procedures. Initially a bidirectional cavopulmonary (Glenn operation) or a “hemi-Fontan” anastomosis is created in which the SVC is connected to the proximal right PA. This has the benefit of reducing the volume load placed on the systemic ventricle by previously placed systemic-pulmonary shunt. Finally, venous return from the IVC is also directed to the pulmonary circulation. This is achieved by forming a lateral tunnel²⁰⁶ or the use of a synthetic extracardiac conduit²⁰⁷ to channel blood from the IVC to the inferior aspect of the right PA, completing the total cavopulmonary connection or Fontan circulation.

In the Fontan circulation, there is no “subpulmonary” ventricle, all ventricular tissue having been incorporated in the single ventricle that receives pulmonary venous return and ejects into the systemic circulation. This establishes a form of series circulation and results in normal systemic oxygenation and equality of pulmonary and systemic blood flow. Pulmonary blood flow in the Fontan circulation is driven by the transpulmonary hydrostatic gradient and is only viable if PVR and systemic ventricular end-diastolic pressures (pulmonary venous pressures) are low. Good systemic ventricular function and low PVR are crucial determinants of operability. Patients with Fontan circulation tolerate factors that impede systemic venous return very poorly, such as dehydration, pneumothorax, pericardial effusion, positive pressure ventilation¹²¹, raised PVR, or compromised ventricular or respiratory²⁰⁸ function. Perioperative use of ACE inhibitors²⁰⁹ has been shown to reduce the severity and duration of pleural drainage,²¹⁰ a common problem caused by high postoperative systemic venous pressures. A communication, or fenestration, between the systemic venous pathway and pulmonary venous atrium may be created in patients thought to be at higher risk of complications such as effusions or perioperative low cardiac output as a result of relatively high PVR.

Long-term follow-up studies have demonstrated that systemic ventricular function remains abnormal after Fontan procedures.²¹¹ Ultimately, the Fontan circulation may fail and cardiac transplantation be considered.

Hypoplastic left heart syndrome (HLHS) is a term encompassing a range of hypoplastic abnormalities of the left-sided cardiac structures and connections including the ascending aorta.²¹² The condition is

usually palliated in three stages, although some authorities prefer to offer cardiac transplantation without prior palliative surgery.²¹³ The first-stage procedure secures systemic and pulmonary blood flow with either a Norwood procedure or similar or a hybrid procedure.^{214,215} The Norwood approach consists of reconstruction of the aortic arch and the establishment of pulmonary blood flow via a central systemic-to-pulmonary artery shunt. Some advocate replacing the systemic-to-pulmonary artery shunt of the classical Norwood with an RV-to-PA conduit, which may be easier to manage postoperatively as there is potentially less diastolic runoff, with less risk of coronary ischemia, than occurs across the central shunt of the classical Norwood operation.²¹² In a large randomized trial comparing modified Blalock-Taussig shunt to RV-PA conduit shunt in infants with hypoplastic left heart syndrome or related single right ventricle anomalies who underwent Norwood procedure, those in the RV-to-PA conduit group had higher transplantation-free survival at 12 months.²¹⁶ However, patients on the RV-to-PA conduit group experienced more complications and unexpected cardiovascular interventions.

Balancing the pulmonary and systemic circulations in the immediate postoperative period can be challenging. Interventions such as sudden hyperventilation or increases in oxygen concentration that lower PVR should be avoided. Strategies to manage the postoperative Norwood patient include the use of long-acting vasodilators such as phenoxybenzamine^{32,33} and close monitoring of cerebral oxygenation, venous oxygen saturation, and plasma lactate. ACE inhibitors are subsequently introduced, and very close interstage monitoring may be undertaken in an attempt to minimize interstage morbidity and mortality.

Following the first-stage procedure, a bidirectional cavopulmonary anastomosis is undertaken typically between 2 and 6 months of age, and finally a completion to a Fontan circulation follows at 18 to 24 months of age. Fetal diagnosis facilitates early and appropriate management and may contribute to improved outcomes in HLHS,²¹⁷ although there is known to be significant risk of poor neurodevelopmental status in survivors of neonatal HLHS interventions.²¹⁸

Pulmonary Vein Abnormalities

Anomalous Pulmonary Venous Connection

Anatomy. Pulmonary veins drain anomalously into a systemic venous structure and subsequently to the RA rather than directly into the LA. The condition may affect all pulmonary veins (total anomalous pulmonary venous connection, TAPVC) or fewer, typically one vein (partial anomalous pulmonary venous connection). In *supracardiac* TAPVC (45% of cases) the pulmonary veins drain via a vertical vein to the innominate vein or connect directly into the SVC. In *intracardiac* TAPVC (25% of cases) the venous confluence drains via the coronary sinus into the RA, and in *infracardiac* TAPVC (25% of cases), the veins drain into the IVC or portal veins. Mixed forms also exist (5% cases).²¹⁹ TAPVC is associated with an obligate ASD to allow mixing of systemic and pulmonary venous return to access the LV and systemic circulation.

Pathophysiology. In the case of TAPVC, two patterns emerge depending on presence of obstruction to the pulmonary venous return. Obstruction of the pulmonary venous pathway is common (especially in the infracardiac type) and causes pulmonary venous hypertension and edema, reflex PA vasoconstriction, and subsequent right heart failure. If obstruction is not present, the main pathophysiologic effects result from complete mixing of systemic and pulmonary venous blood in the right heart with RV volume overload and failure. Partial anomalous venous connection has similar pathophysiology to that of ASD, with RA and RV dilatation and pulmonary overflow.

Surgery. The pulmonary veins are anastomosed or baffled into the LA. In the current era, the expected operative mortality is less than 5%, although higher risks are reported in complex cases with associated lesions.²²⁰ Babies presenting with life-threatening obstruction must undergo emergency surgery or a short period of preoperative stabilization with ECMO followed by surgery.

Specific Postoperative Problems. PHT, which may, on occasion, be severe or even life threatening, is common in infants following surgery for obstructed anomalous pulmonary veins.¹⁴⁷ If high PA pressure occurs postoperatively, it is essential to rule out residual pulmonary vein obstruction. Late restenosis is seen in up to 10% cases and carries a poor prognosis, often related to a progressive fibrotic process occluding the lumen of the pulmonary veins.²²¹

Other Lesions

Vascular Rings and Slings

Vascular rings and slings²²² result from abnormal branching or positioning of the great vessels, which in turn, result in encirclement or compression of the trachea and/or the esophagus. They are seen in isolation or in association with intracardiac defects.

Anatomy. Three common types occur either in isolation or in association with other cardiac lesions including right aortic arch, tetralogy of Fallot, and AVSDs.

- Double aortic arch

This results from failure of the embryonic regression of one of the arches. The right arch, which is commonly dominant and usually larger, passes posterior to the esophagus and trachea to connect to the left-sided descending thoracic aorta, forming a vascular ring. The left arch is commonly smaller and may exhibit varying degrees of hypoplasia, coarctation, or true atresia. The carotid and subclavian arteries originate from both arches. Sometimes a PDA or ligamentum arteriosum forms a true ring around the trachea.

- Right aortic arch with aberrant left subclavian artery

In this condition, the left subclavian has its origin from the ascending aorta and courses to the left behind the esophagus with the vascular ring completed by the ligamentum arteriosum.

- PA sling

The left PA arises from the right PA and passes to the left by passing behind the trachea. The trachea is squeezed between the aorta and the left PA, and a true ring may be formed by a PDA or ligamentum arteriosum.

Pathophysiology. Vascular rings have the potential to compress both trachea and esophagus. PA slings usually cause chronic tracheal compression, which eventually results in destruction of the tracheal skeleton with resultant tracheal stenosis in 50% of cases.

Surgery.^{223,224} Vascular rings are usually approached via a lateral thoracotomy (usually left). The left arch or ligamentum is divided to release the ring, and the descending aorta is dissected away from the esophagus. To correct PA sling, the anomalous left PA is transected and rerouted anteriorly and reanastomosed to the central PA.

Postoperative Care. This is usually uneventful. Extubation at the end of anesthesia or early in the ICU course is expected. **Tracheomalacia** may persist or present postoperatively, especially after PA sling surgery, and may require long periods of respiratory support postoperatively via a tracheostomy.

Anomalous Left Coronary Artery from the Pulmonary Artery

Anatomy. ALCAPA usually occurs as an isolated lesion in which the left coronary artery arises from the PA rather than the aorta.

Pathophysiology. Symptoms develop gradually as PVR falls during early infancy. There is progressive onset of myocardial ischemia as left coronary flow falls in parallel with the fall in PA pressure. The myocardium is initially well perfused by desaturated PA blood, but as coronary flow falls, severe left ventricular ischemia and dysfunction occur.

Surgery. Surgical intervention is necessary to reconnect the left coronary with the aorta, and this can be achieved either by creating a tunnel from the left coronary orifice to the aorta²²⁵ (the Takeuchi operation) or by directly reimplanting the coronary artery.²²⁶

Postoperative Care. The principal perioperative problem in infants with symptomatic ALCAPA is management of low cardiac output. Beta adrenergic agonists, PDE III inhibitors such as milrinone,²⁶ and occasionally mechanical circulatory support may be required.

SPECIFIC ISSUES FOR INTENSIVISTS

Surgical Control of Pulmonary Blood Flow-PA Banding

PA banding is a surgical procedure in which a constriction is created in the main PA with the physical effect of limiting pulmonary blood flow. The aim is to protect the lungs from excessive blood flow, thus maintaining a balance between the systemic and pulmonary circulations, and to prevent the onset of PHT in some complex anomalies unsuitable for early anatomic repair.²²⁷ PA banding is primarily a palliative procedure and usually a stepping stone to a later definitive or more complex repair. It is performed without CPB through either a left thoracotomy or median sternotomy.

Physiology

The reduction of pulmonary blood flow by a PA band limits volume loading of the systemic or single ventricle. Arterial saturations may be 75% to 85% following effective banding, with pressure gradient typically in the range of 40 mm Hg to 60 mm Hg in a neonate. However, arterial saturations above 90% may be reached where complete mixing occurs.

Specific Management Issues

Very low oxygen postoperative saturations ($\text{SaO}_2 < 70\%$) may indicate restricted pulmonary blood flow by tight banding, although low cardiac output with consequent low mixed venous saturations may also be a factor. Urgent echo evaluation of the band gradient²²⁸ and exclusion of other causes of hypoxemia should be undertaken. If hypoxemia persists, and particularly if significant metabolic acidosis develops, urgent relief or removal of the band may be indicated.

High oxygen saturations in excess of 90% should alert the possibility of PA band being too loose and ineffective in controlling pulmonary blood flow. Signs of congestive cardiac failure may be noted and require medical treatment (diuretics) or further surgical interventions (rebanding or lesion correction).

Delayed Sternal Closure

Complex cardiac surgery involving CPB can result in edema of the myocardium and other mediastinal tissues. Sternal closure at the end of the surgical procedure may cause cardiac compression (tissue tamponade), which decreases ventricular compliance and leads to reduced cardiac output and elevated pulmonary venous pressures.^{229,230}

In such a situation, it is not uncommon for the child to return to the ICU with an open chest and to defer the sternal closure in the unit once the hemodynamic situation has improved. Transient deteriorations at delayed closure are usually self-limiting and tolerated; however, hypotension, oliguria, rising plasma lactate, or falling venous saturations suggest suboptimal cardiac output reserve and closure will not be tolerated.²³¹ Although temporal delay in sternal closure may be essential in some cases, it has to be balanced with the possibility of associated increased risk of surgical site infection.²³²

Infective Endocarditis

Children with CHD are at higher risk of developing infective endocarditis, especially those with cyanotic diseases.²³³ While prophylactic antibiotic treatment prior to noncardiac procedures is no longer recommended in children and young people with native heart valve disease,²³⁴ prophylaxis is still recommended prior to dental procedures for patients with a previous episode of infective endocarditis, prosthetic valves, cardiac transplant recipients who develop valve dysfunction, and patients with certain CHD, such as cyanotic CHD not fully repaired (including shunts and conduits), any CHD fully repaired using surgical or catheter-placed prosthetic material or device for 6 months after procedure, and any CHD fully repaired that

present residual defect adjacent to or at the site of prosthetic patch or device. Intensivists should aim to minimize the risk of catheter-related blood-stream infection complications by employing best practice guidelines with care bundles to include surveillance of central venous catheters.²³⁵

Thrombosis and Prophylaxis

Children with CHD are at risk of thrombosis, which may contribute to higher morbidity and mortality, especially in those with cyanotic CHD and shunt-dependent circulation. Recommendations for thrombosis prevention and treatment in children have been recently reviewed, with special consideration given to CHD and surgical procedures such as systemic-to-pulmonary shunts, cavopulmonary anastomosis, and valve replacement.^{236,237}

Of additional importance to intensivists is central venous catheter—associated thrombosis in children with CHD as it may adversely affect surgical plan and outcome ultimately. Central venous catheters should be avoided or removed as soon as no longer needed in these patients. Low-dose heparin may be considered for patients who present with additional thrombosis risk factors and those planned for total cavopulmonary anastomosis.²³⁷ Prompt catheter removal and systemic anticoagulation should be considered for documented catheter-associated thrombosis after weighing the risk of embolization.

Chylothorax

The incidence of chylothorax following cardiac surgery in children is around 3%, with higher figures according to procedure's complexity and in cavopulmonary anastomosis.^{238,239} Morbidities associated with chylothorax include respiratory failure, venous thrombosis, immunosuppression, and malnutrition. Patients receiving normal fat containing feeds will present with opaque, milky pleural drainage. Diagnosis is confirmed by fluid analysis, which shows triglyceride content >1.1 mmol/L (if on fat containing feed) and white cell count >1000 cells per mm^3 with lymphocytes $>80\%$.²⁴⁰ Initial management is based on feeding strategies that include medium-chain triglycerides—only enteral feed, low-fat modular diet with intravenous lipid administration, or total parenteral nutrition. Surgical drainage is frequently required for respiratory distress or failure to wean from ventilatory support. Further management with octreotide infusion may be an option in selected cases, and surgical treatment may be required if medical management is unsuccessful.^{238,241} Depletion of plasma proteins including clotting factors and immunoglobulins may occur if high losses are not controlled and may warrant replacement.

Sepsis and Infection

Common hospital-acquired infections after cardiac surgery include superficial surgical site infection, catheter-related bloodstream infection, and ventilator-associated pneumonia. Rare but important are deep soft tissue infections such as cellulitis, sternal osteomyelitis, and mediastinitis. Care bundles in association with aseptic technique practices and antibiotic prophylaxis can reduce the incidence of procedure-related and hospital-acquired infection. For surgery and interventions, antibiotic prophylaxis is recommended prior to skin incision. Choice of antibiotic should cover known common gram-positive and gram-negative organisms, according to local guidelines

and known patterns of bacterial resistance. Short-duration therapy—that is, less than 48 hours—should be aimed for surgical prophylaxis as prolonged administration does not seem to reduce further surgical site infection and is associated with acquired antimicrobial resistance.²⁴² Should infection or sepsis be suspected or confirmed, antimicrobial therapy has to be based on local epidemiology and ideally with microbiologist consultation. Optimal therapy includes adequate dosing with close monitoring of serum levels where available and treatment review guided by microbiology and antibiogram results along with clinical progress.

Rhythm Disturbance After Cardiac Surgery

Children undergoing cardiac surgery may present with rhythm disturbance perioperatively, a situation that can contribute to increased morbidity and require urgent treatment.²⁴³ Dysrhythmias can develop following direct surgical damage or stimulation of the cardiac conduction system, or secondary to systemic conditions such as electrolyte imbalance, high core temperature, hypoxia, circulating catecholamine, or low cardiac output state. Although a variety of arrhythmias can occur after cardiac surgery, they are often related to the proximity of surgical site to cardiac conduction system (see specific lesions). Treatment of associated conditions such as electrolyte abnormalities and hemodynamic instability, antiarrhythmic drugs, and temporary pacing may be needed. Complete heart block may be transient, but if AV synchrony has not returned by 7 to 10 days after surgery, a permanent pacing system is required.¹³⁹

Necrotizing Enterocolitis

Neonates with CHD are at risk of developing necrotizing enterocolitis, especially those presenting with left heart obstruction and single-ventricle physiology. Additional risk factors are prematurity, hemodynamic instability, infection, and enteral nutrition, notably with formula.²⁴⁴ Neonates with NEC classically present a triad of abdominal distention, gastrointestinal bleeding, and pneumatosis intestinalis. In severe cases intestinal perforation and/or septic shock is seen. Initial management includes nil per os and gastric decompression, hemodynamic stabilization, and triple antibiotics with close monitoring and case review at least 6 to 12 hourly. Further surgical management may be required if advanced injury or perforation exists.

KEY POINTS

1. Appropriate intensive care management of the congenital heart patient must be based on a sound understanding of the anatomy and pathophysiology of the child's circulation.
2. Issues relating to the management of intracardiac shunts, cyanosis, and the management of the pulmonary circulation and right ventricle are of great importance in managing children with CHD.
3. Specialist advice should be sought early if children with known or suspected heart disease are admitted to nonspecialist pediatric or adult facilities.

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ETIOLOGY AND CLASSIFICATION OF PERICARDIAL DISEASE

The spectrum of pericardial diseases consists of congenital defects, pericarditis (dry, effusive, effusive-constrictive, or constrictive), neoplasms, and cysts. The etiologic classification comprises infectious pericarditis, pericarditis in systemic autoimmune diseases, type 2 (auto) immune process, postmyocardial infarction syndrome, and autoreactive (chronic) pericarditis.¹⁻³

PERICARDIAL SYNDROMES

Congenital Defects of the Pericardium

Congenital defects of the pericardium are found in 1 in 10,000 autopsies. Pericardial absence can be partial left (70%), partial right (17%), or total bilateral (rare). Additional congenital abnormalities occur in approximately 30% of patients.⁴ Most patients with total pericardial absence are asymptomatic. Homolateral cardiac displacement and augmented heart mobility impose an increased risk for traumatic aortic dissection.⁵ Partial left-side defects can be complicated by herniation and strangulation of the heart through the defect (causing chest pain, shortness of breath, syncope, or sudden death). Surgical pericardioplasty (Dacron, Gore-Tex, or bovine pericardium) is indicated for imminent strangulation.⁶

Acute Pericarditis

Acute pericarditis is dry, fibrinous, or effusive, independent of its etiology. The major symptoms are retrosternal or left precordial chest pain (which radiates to the trapezius ridge, can be pleuritic or simulate ischemia, and varies with posture) and shortness of breath. A prodrome of fever, malaise, and myalgia is common, but elderly patients may not be febrile. A pericardial friction rub can be transient and monophasic, biphasic, or triphasic. A pleural effusion may be present. The heart rate is usually rapid and regular. Echocardiography is essential to detect effusion and concomitant heart or paracardial disease (Table 84-1).⁷⁻¹⁹

Hospitalization and symptomatic treatment are warranted. Nonsteroidal antiinflammatory drugs (NSAIDs) are the mainstay. Indomethacin should be avoided in elderly patients owing to its effect on reducing flow in the coronaries. Ibuprofen (300 to 800 mg tid) is preferred for its rare side effects, favorable impact on coronary blood flow, and large dose range.⁷ Colchicine 0.5 mg at least twice daily for 3 months added to aspirin or another NSAID reduced the recurrence rate impressively in the COPE trial,²⁰ even at the first episode of pericarditis or even as monotherapy in “idiopathic” effusions. Colchicine is well tolerated, with fewer side effects than NSAIDs. Systemic corticosteroids should be restricted to connective tissue diseases and autoreactive or uremic pericarditis. Intrapericardial steroid application, as long-acting crystalloid triamcinolone, is effective for autoreactive effusions and avoids systemic side effects.²

Chronic Pericarditis

Chronic (>3 months) pericarditis includes effusive (inflammatory or hydropericardium in heart failure), adhesive, and constrictive forms.⁷

Symptoms (chest pain, palpitations, and fatigue) are usually mild and related to the degree of cardiac compression and pericardial inflammation. The detection of curable causes (e.g., tuberculosis, toxoplasmosis, myxedema, or viral, autoimmune, and systemic diseases) allows successful specific therapy. Symptomatic treatment and pericardiocentesis should be applied, if indicated. For recurrences, the etiology should be investigated intensely, and if no specific therapy is effective, balloon pericardiotomy or pericardiectomy may be considered.^{21,22}

Recurrent Pericarditis

The term *recurrent pericarditis* encompasses (1) the intermittent type (symptom-free intervals without therapy) and (2) the incessant type (discontinuation of antiinflammatory therapy precipitates a relapse). Massive pericardial effusion, overt tamponade, or constriction is rare. Symptomatic management relies on exercise restriction and regimens used for acute pericarditis. Colchicine may be effective when NSAIDs and corticosteroids fail to prevent relapses.^{20,23-25} It should be considered the first-choice treatment for recurrent pericarditis according to the CORE trial.²³ Corticosteroids should be used only in patients with a poor general condition or in frequent crises.⁷ A common mistake could be to use a dose too low to be effective or to taper the dose too rapidly. The recommended regimen is prednisone 1 to 1.5 mg/kg for at least 1 month. If patients do not respond adequately, azathioprine (75 to 100 mg/day) or cyclophosphamide can be added.²⁶

Corticosteroids should be tapered over a 3-month period. Toward the end of the taper, introduce antiinflammatory treatment with colchicine (0.5 mg bid or tid) or an NSAID. Renewed treatment should continue for 3 to 6 months. Recently, it has been demonstrated in “idiopathic” pericarditis that previous corticosteroid treatment was a risk factor for recurrence or chronicity. Therefore, corticosteroids should be administered after the definite exclusion of viral or bacterial infection of the pericardium. Pericardiectomy is indicated only for frequent and highly symptomatic recurrences resistant to medical treatment.²⁷

Pericardial Effusion and Cardiac Tamponade

Pericardial effusion may appear as transudate (hydropericardium), exudate, pyopericardium, or hemopericardium. Large effusions are common with neoplastic, tuberculous, cholesterol, and uremic pericarditis, as well as with myxedema and parasitoses.²⁸ Loculated effusions are more common when scarring has supervened (e.g., postsurgical, posttraumatic, or purulent pericarditis). Effusions that develop slowly can be remarkably asymptomatic, whereas rapidly accumulating smaller effusions can present as tamponade. Cardiac tamponade is the decompensated phase of cardiac compression caused by effusion accumulation, leading to increased intrapericardial pressure. Heart sounds are distant. Orthopnea, cough, and dysphagia, occasionally with episodes of unconsciousness, can be observed. Insidiously developing tamponade may present as signs of its complications (renal failure, abdominal plethora, shock liver, worsening of glaucoma,²⁹ and mesenteric ischemia). Tamponade without two or more inflammatory signs (typical pain, pericardial friction rub, fever, or diffuse ST segment elevation) is usually associated with a malignant effusion (likelihood ratio, 2.9).³⁰

TABLE 84-1

Diagnostic Pathway and Sequence of Performance in Acute Pericarditis

| DIAGNOSTIC MEASURE | CHARACTERISTIC FINDINGS |
|--------------------|--|
| OBLIGATORY | |
| Auscultation | Pericardial rub (monophasic, biphasic, or triphasic) |
| ECG* | <i>Stage I:</i> anterior and inferior concave ST segment elevation. PR segment deviations opposite to P wave polarity <i>Early stage II:</i> all ST junctions return to the baseline. PR segments deviated <i>Late stage II:</i> T waves progressively flatten and invert <i>Stage III:</i> generalized T-wave inversions in most or all leads <i>Stage IV:</i> ECG returns to prepericarditis state |
| Echocardiography | Effusion types B to D (Horowitz) Signs of tamponade |
| Blood analyses | Erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, leukocytes (inflammation markers) Troponin I, [†] CK-MB (markers of myocardial involvement) |
| Chest radiograph | Ranging from normal to “water bottle” shape of the heart shadow Performed primarily to reveal pulmonary or mediastinal pathology |

MANDATORY IN TAMPONADE, OPTIONAL IN LARGE/RECURRENT EFFUSIONS OR IF PREVIOUS TESTS INCONCLUSIVE IN SMALL EFFUSIONS

| | |
|-----------------------------|--|
| Pericardiocentesis/drainage | Polymerase chain reaction and histochemistry for etiopathogenetic classification of infection or neoplasia |
|-----------------------------|--|

OPTIONAL OR IF PREVIOUS TESTS INCONCLUSIVE

| | |
|--|--|
| CT | Effusions, pericardium, and epicardium |
| MRI | Effusions, pericardium, and epicardium |
| Pericardioscopy, pericardial/epicardial biopsy | Establishing the specific etiology |

*Typical lead involvement: I, II, aVL, aVF, and V3-V6. The ST segment is always depressed in aVR, frequently in V1, and occasionally in V2. Stage IV may not occur, and there are permanent T-wave inversions and flattenings. If an ECG is first recorded in stage III, pericarditis cannot be differentiated by ECG from diffuse myocardial injury, “biventricular strain,” or myocarditis. ECG in early repolarization is very similar to stage I. Unlike stage I, this ECG does not acutely evolve, and J-point elevations are usually accompanied by a slur, oscillation, or notch at the end of the QRS just before and including the J point (best seen with tall R and T waves—large in an early repolarization pattern). Pericarditis is likely if, in lead V6, the J point is greater than 25% of the height of the T-wave apex (using the PR segment as a baseline).

[†]A rise in cardiac muscle troponin I (cTnI) was detected in 38/118 patients (32.2%), more frequently in younger, male patients, with ST segment elevation and pericardial effusion at presentation. An increase beyond 1.5 ng/mL was rare (7.6%) and associated with CK-MB elevation. cTnI increase was not a negative prognostic marker for the incidence of recurrences, constrictive pericarditis, cardiac tamponade, or residual left ventricular dysfunction.

Data from references 2, 3, and 7 to 19.

CK-MB, creatine kinase-MB; CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging.

Electrocardiography demonstrates low QRS and T wave voltages, PR-segment depression (Fig. 84-1), ST segment/T wave changes, bundle branch block, and electrical alternans (rarely seen in the absence of tamponade).⁷ Microvoltage and electrical alternans are reversible after the drainage of the effusion and resolution of the inflammatory process.¹⁹ In chest radiography, large effusions are depicted as globular cardiomegaly with sharp margins (“water bottle” silhouette) (Fig. 84-2).¹² The size of effusions noted during echocardiography can be graded as (1) small (echo-free space in diastole <10 mm), (2) moderate (10 to 20 mm) (Fig. 84-3), (3) large (≥20 mm), or (4) very large (≥20 mm and compression of the heart). In large pericardial effusions, the heart may move freely within the pericardial

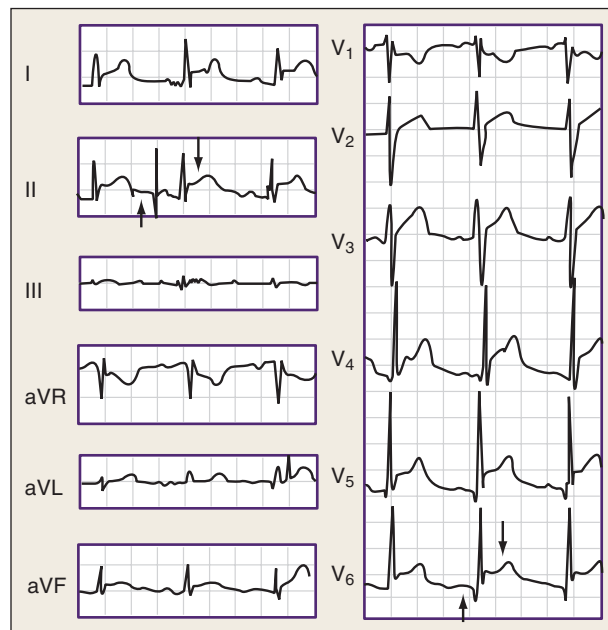


FIGURE 84-1 ■ Typical electrocardiographic changes in acute pericarditis: PR depression (small arrow) and concave ST-segment elevation (large arrow).

cavity (“swinging heart”), inducing pseudoprolapse and pseudosystolic anterior motion of the mitral valve, paradoxical motion of the interventricular septum, and midsystolic aortic valve closure (Table 84-2).³¹⁻⁴¹ Up to one-third of patients with an asymptomatic large pericardial chronic effusion develop unexpected cardiac tamponade.²¹ Triggers for tamponade include hypovolemia, paroxysmal tachyarrhythmia, and intercurrent acute pericarditis.

Constrictive Pericarditis

Constrictive pericarditis is a rare, but severely disabling, consequence of chronic inflammation of the pericardium, leading to impaired filling of the ventricles and reduced ventricular function. Until recently, increased pericardial thickness has been considered an essential diagnostic feature of constrictive pericarditis. However, in a large surgical series from the Mayo Clinic, constriction was present in 18% of patients with normal pericardial thickness.⁴² Tuberculosis, mediastinal irradiation, and previous surgical procedures are frequent.⁴³ Constrictive pericarditis may rarely develop only in the epicardial layer in patients with a previously removed parietal pericardium.⁴⁴ Transient constrictive pericarditis is an uncommon, but important, entity because pericardiectomy is not indicated in these patients.⁴⁵

Patients complain of fatigue, peripheral edema, breathlessness, and abdominal swelling, which may be aggravated by a protein-losing enteropathy. In decompensated patients, venous congestion, hepatomegaly, pleural effusions, and ascites may occur. Hemodynamic impairment can be additionally aggravated by systolic dysfunction due to myocardial fibrosis or atrophy. Differential diagnosis has to include acute dilatation of the heart, pulmonary embolism, right ventricular infarction, pleural effusion, chronic obstructive lung disease,⁴⁶ and restrictive cardiomyopathy. The best way to distinguish constrictive pericarditis from restrictive cardiomyopathy is by Doppler and/or tissue Doppler echocardiographic analysis of respiratory changes with or without changes in preload.⁴⁷ However, physical findings, an electrocardiogram (ECG), chest radiography (see Fig. 84-2, right), computed tomography (CT) (Fig. 84-4, left), magnetic resonance imaging (MRI) (see Fig. 84-4, right), hemodynamics, and endomyocardial biopsy may be helpful as well.⁷

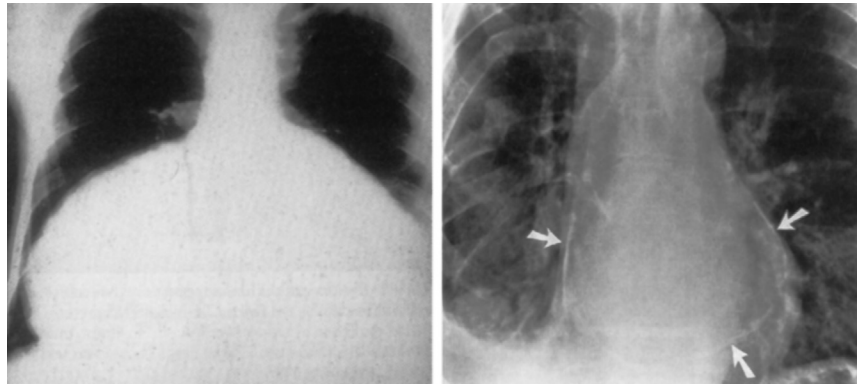


FIGURE 84-2 ■ Chest radiographs in a patient with a very large pericardial effusion—“water bottle” sign (*left*)—and in a patient with constrictive pericarditis and pericardial calcifications (*white arrows, right*).

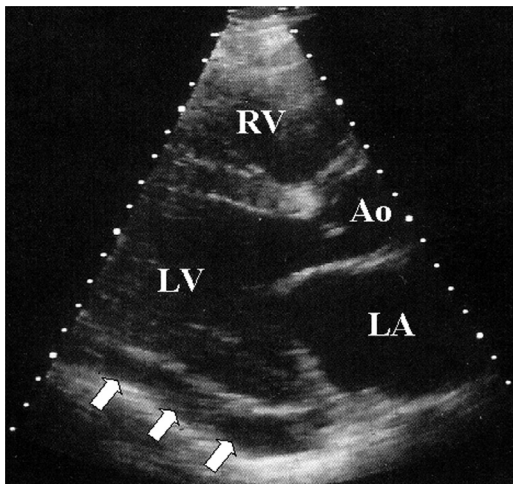


FIGURE 84-3 ■ Echocardiographic findings in a small to moderate pericardial effusion (*white arrows*). Long-axis parasternal view. Ao, aortic root; LA, left atrium; LV, left ventricle; RV, right ventricle.

Pericardiectomy is the only treatment for permanent constriction. The indications are based on clinical symptoms, echocardiographic findings, CT/MRI, and heart catheterization. A primary installation of cardiopulmonary bypass (CPB) is not recommended, as diffuse bleeding can occur following systemic heparinization. Pericardiectomy for constrictive pericarditis has a mortality rate of 6% to 12%,⁴⁸⁻⁵¹ and complete normalization of cardiac hemodynamics is reported in only 60% of patients.^{48,50} Major complications include acute perioperative cardiac insufficiency and ventricular wall rupture.⁵² Cardiac mortality and morbidity with pericardiectomy are mainly caused by the presence of myocardial atrophy or myocardial fibrosis that was not recognized before surgery.⁴³ The exclusion of patients with extensive myocardial fibrosis and/or atrophy has reduced the mortality rate of pericardiectomy to 5%. Postoperative low cardiac output⁵² should be treated by fluid substitution and catecholamines, high doses of digitalis, and intraaortic balloon pump, in the most severe cases. If indications for surgery are established early, long-term survival after pericardiectomy corresponds to that of the general population.^{49,50} However, if severe clinical symptoms are present for a longer period before surgery, even complete pericardiectomy may not achieve total restitution.

Pericardial Cysts

Congenital pericardial cysts are uncommon; they may be unilocular or multilocular, with a diameter ranging from 1 to 5 cm.⁵³ Inflammatory cysts comprise pseudocysts, as well as encapsulated and loculated pericardial effusions, caused by rheumatic pericarditis, bacterial infection (particularly tuberculosis), trauma, and cardiac surgery. Most patients are asymptomatic, and cysts are detected incidentally on chest radiographs as an oval, homogeneous radiodense lesion, usually at the right cardiophrenic angle.⁵⁴ However, patients can also present with chest discomfort, dyspnea, cough, or palpitations, owing to compression of the heart. Echocardiography is useful, but additional imaging by CT (density readings) or MRI is often needed.⁵⁵ Treatment of congenital and inflammatory cysts involves percutaneous aspiration and ethanol sclerosis.^{56,57} If this is not feasible, video-assisted thoracotomy or surgical resection may be necessary. Echinococcal cysts usually originate from ruptured hydatid cysts in the liver and lungs. Their surgical excision is not recommended; percutaneous aspiration and instillation of ethanol or silver nitrate after pretreatment with albendazole (800 mg/day for 4 weeks) is recommended instead.⁵⁷

SPECIFIC FORMS OF PERICARDITIS

Viral Pericarditis

Viral pericarditis is the most common infection of the pericardium. Inflammatory abnormalities are due to direct viral attack, the immune response (antiviral or anticardiac), or both.^{3,58} Early viral replication in pericardial and epimyocardial tissue elicits cellular and humoral immune responses against the virus and/or cardiac tissue. Deposits of immunoglobulin (Ig)M, IgG, and occasionally IgA can be found in the pericardium and myocardium for years.⁵⁸ Various viruses can cause pericarditis, including enteroviruses, echoviruses, adenoviruses, cytomegaloviruses, Epstein-Barr virus, herpes simplex, herpes humanus 6 (HHV6), influenzaviruses, parvovirus B19 (PVB19), hepatitis C, and human immunodeficiency virus (HIV). In the past few years, PVB19 and HHV6 have been increasing and entero-, echo-, and adenoviruses have been decreasing as causes; these trends have also been observed in myocarditis. Attacks of enteroviral pericarditis follow the seasonal epidemics of coxsackievirus A and B and echovirus infections.⁵⁹ Cytomegalovirus (CMV) pericarditis has an increased incidence in immunocompromised and HIV-infected hosts.⁶⁰ Infectious mononucleosis may also present as pericarditis.

Diagnosing viral pericarditis is not possible without evaluating pericardial effusion and/or pericardial/epicardial tissue, preferably by polymerase chain reaction (PCR) or in situ hybridization. A four-fold

TABLE 84-2 Diagnosis of Cardiac Tamponade

| | |
|---------------------------------------|---|
| Clinical presentation | Elevated systemic venous pressure,* hypotension, [†] pulsus paradoxus, [‡] tachycardia, [§] dyspnea, or tachypnea with clear lungs |
| Precipitating factors | Drugs (cyclosporine, anticoagulants, thrombolytics), recent cardiac surgery, indwelling instrumentation, blunt chest trauma, malignancies, connective tissue disease, renal failure, septicemia [†] |
| ECG | Can be normal or nonspecifically changed (ST-T wave), electrical alternans (QRS, rarely T), bradycardia (end stage), electromechanical dissociation (agonal phase) |
| Chest radiograph | Enlarged cardiac silhouette with clear lungs |
| M-mode/two-dimensional echocardiogram | Diastolic collapse of the anterior RV free wall, [†] RA collapse, LA and rarely LV collapse, increased LV diastolic wall thickness "pseudohypertrophy," IVC dilatation (no collapse in inspiration), "swinging heart" |
| Doppler | Tricuspid flow increases and mitral flow decreases during inspiration (reverse in expiration) Systolic and diastolic flows are reduced in systemic veins in expiration and reverse flow with atrial contraction is increased |
| M-mode color Doppler | Large respiratory fluctuations in mitral/tricuspid flows |
| Cardiac catheterization | Confirmation of the diagnosis and quantification of the hemodynamic compromise RA pressure is elevated (preserved systolic \times descent and absent or diminished diastolic γ descent) Intrapericardial pressure is also elevated and virtually identical to RA pressure (both pressures fall in inspiration) RV mid-diastolic pressure is elevated and equal to the RA and pericardial pressures (no dip-and-plateau configuration) Pulmonary artery diastolic pressure is slightly elevated and may correspond to the RV pressure Pulmonary capillary wedge pressure is also elevated and nearly equal to intrapericardial and right atrial pressure LV systolic and aortic pressures may be normal or reduced Documenting that pericardial aspiration is followed by hemodynamic improvement** Detection of coexisting hemodynamic abnormalities (LV failure, constriction, pulmonary hypertension) Detection of associated cardiovascular diseases (cardiomyopathy, coronary artery disease) |
| RV/LV angiography | Atrial collapse and small hyperactive ventricular chambers |
| Coronary angiography | Coronary compression in diastole |

*Jugular venous distention is less notable in hypovolemic patients or in "surgical tamponade." An inspiratory increase or lack of fall of pressure in the neck veins (Kussmaul sign), when verified by tamponade or after pericardial drainage, indicates effusive-constrictive disease.

[†]Heart rate is usually greater than 100 beats per minute but may be lower in patients with hypothyroidism or uremia.

[‡]Pulsus paradoxus is defined as a drop in systolic blood pressure greater than 10 mm Hg during inspiration, while diastolic blood pressure remains unchanged. It is easily detected by simply feeling the pulse, which diminishes significantly during inspiration. Clinically significant pulsus paradoxus is apparent when the patient is breathing normally. When this sign is present only in deep inspiration, it should be interpreted with caution. The magnitude of pulsus paradoxus is evaluated by sphygmomanometry. If pulsus paradoxus is present, the first Korotkoff sound is not heard equally well throughout the respiratory cycle but only during expiration at a given blood pressure. The blood pressure cuff is, therefore, inflated above the patient's systolic pressure. Then it is slowly deflated, while the clinician observes the phase of respiration. During deflation, the first Korotkoff sound is intermittent. Correlation with the patient's respiratory cycle identifies a point at which the sound is audible during expiration but disappears when the patient breathes in. As the cuff pressure drops further, another point is reached when the first blood pressure sound is audible throughout the respiratory cycle. The difference in systolic pressure between these two points is the clinical measure of pulsus paradoxus. Pulsus paradoxus is absent in tamponade complicating an atrial septal defect and in patients with significant aortic regurgitation.

[§]Occasional patients are hypertensive, especially if they have preexisting hypertension.

[†]Febrile tamponade may be misdiagnosed as septic shock.

[†]Right ventricular collapse can be absent in elevated right ventricular pressure and right ventricular hypertrophy or in right ventricular infarction.

**If after drainage of the pericardial effusion, the intrapericardial pressure does not fall below atrial pressure, effusive-constrictive disease should be considered.

IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Data from references 31 to 41.

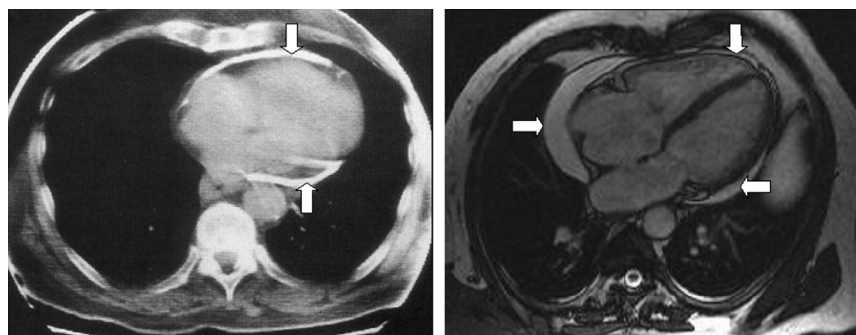


FIGURE 84-4 ■ **Computed tomography findings in constrictive pericarditis (left).** White vertical arrows are depicting thickened pericardium and pericardial calcification. The magnetic resonance imaging results of a patient with effusive-constrictive pericarditis are shown in the right image. Horizontal arrows show a loculated pericardial effusion, and the vertical arrow shows thickened pericardium.

rise in serum antibody levels is suggestive, but not diagnostic, of viral pericarditis.

Treatment of viral pericarditis is directed toward resolving symptoms (see [Acute Pericarditis](#)), preventing complications, and eradicating the virus. In patients with chronic or recurrent symptomatic pericardial effusion and confirmed viral infection, the following specific treatments are under investigation⁶¹:

1. CMV pericarditis: hyperimmune globulin once per day 4 mL/kg on days 0, 4, and 8 and 2 mL/kg on days 12 and 16
2. Coxsackievirus B pericarditis: interferon alfa or interferon beta 2.5×10^6 IU/m² subcutaneously three times per week
3. Adenovirus, PVB19, and HHV6 perimyocarditis: immunoglobulin treatment with 20 g or more intravenously on days 1 and 3 for 6 to 8 hours, which may be repeated and combined with gancyclovir to become effective for virus elimination

Pericardial manifestations of HIV infection can be due to infective, noninfective, and neoplastic (Kaposi's sarcoma and/or lymphoma) diseases. Infective (myo)pericarditis results from local HIV infection and/or from other viral, bacterial (e.g., *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycobacterium avium*, *M. tuberculosis*), and fungal coinfections (*Cryptococcus neoformans*).⁶² In progressive disease, the incidence of echocardiographically detected pericardial effusion may be up to 40%.⁶³ Cardiac tamponade is rare.⁶⁴ During treatment with retroviral compounds, lipodystrophy can develop (best demonstrated by MRI), with intense paracardial fat deposition leading to heart failure. Treatment is generally symptomatic, whereas in large effusions and cardiac tamponade, pericardiocentesis is necessary. The use of corticosteroid therapy is contraindicated except in patients with secondary tuberculous pericarditis, as an adjunct to tuberculostatic treatment.⁶⁵

Bacterial Pericarditis

Purulent pericarditis in adults is rare but always fatal if not treated.⁶⁶⁻⁶⁹ The mortality rate in treated patients is 40%, mostly due to cardiac tamponade, toxicity, and constriction. It is usually a complication of an infection originating elsewhere in the body, arising by contiguous spread or hematogenous dissemination.⁷⁰ Predisposing conditions are pericardial effusion, immunosuppression, chronic diseases (e.g., alcohol abuse, rheumatoid arthritis), cardiac surgery, and chest trauma. The disease appears as an acute, fulminant infectious illness of short duration. Percutaneous pericardiocentesis must be promptly performed, and the obtained pericardial fluid should undergo Gram staining, acid-fast staining, and fungal staining, followed by cultures of the pericardial and body fluids. Rinsing of the pericardial cavity, combined with effective systemic antibiotic therapy, is mandatory (antistaphylococcal antibiotic plus aminoglycoside, followed by tailored antibiotic therapy according to the pericardial fluid and blood culture results).⁶⁷ Intrapericardial instillation of antibiotics (e.g., gentamicin) is useful but not sufficient. Frequent irrigation of the pericardial cavity with urokinase or streptokinase using large catheters may liquefy the purulent exudate,^{68,69} but open surgical drainage through a subxiphoid pericardiectomy is preferable.⁶⁶ Pericardiectomy is required in patients with dense adhesions, a loculated and thick purulent effusion, recurrence of tamponade, persistent infection, and progression to constriction.⁶⁷ Surgical mortality is up to 8%.

Tuberculous Pericarditis

In the past decade, tuberculous pericarditis in developed countries has been primarily seen in immunocompromised patients, such as those with acquired immunodeficiency syndrome (AIDS).⁷¹ The mortality rate in untreated effusive tuberculous pericarditis approaches 85%. Pericardial constriction occurs in 30% to 50% of patients.^{72,73}

The clinical presentation is variable: acute pericarditis with or without effusion; cardiac tamponade; silent, often large pericardial effusion with a relapsing course; toxic symptoms with persistent fever; acute constrictive pericarditis; subacute constriction; effusive-

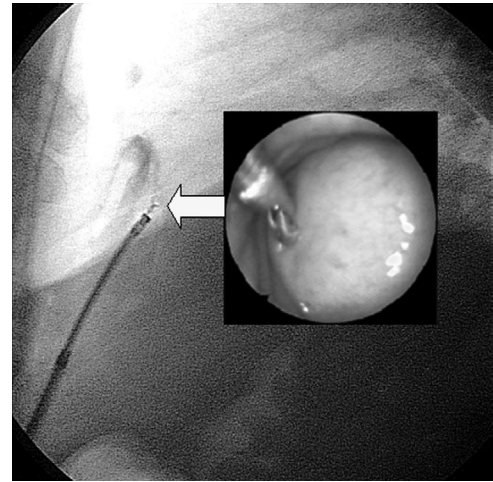


FIGURE 84-5 ■ Flexible percutaneous pericardioscopy and epicardial biopsy (arrow).

constrictive or chronic constrictive pericarditis; and pericardial calcifications.^{3,74} The diagnosis is made by identification of *M. tuberculosis* in the pericardial fluid or tissue and/or the presence of caseous granulomas in the pericardium.⁷¹ Importantly, PCR can identify the DNA of *M. tuberculosis* rapidly from only 1 μ L of pericardial fluid.^{75,76} Increased adenosine deaminase activity and interferon gamma concentration in pericardial effusion are also diagnostic, with a high sensitivity and specificity. Both pericardioscopy and pericardial biopsy have also improved the diagnostic accuracy for tuberculous pericarditis (Fig. 84-5).¹⁵ Pericardial biopsy enables rapid diagnosis with better sensitivity than pericardiocentesis (100% vs. 33%).

Pericarditis in a patient with proven extracardiac tuberculosis is strongly suggestive of a tuberculous etiology (several sputum cultures should be taken).⁷⁷ The tuberculin skin test may be falsely negative in 25% to 33% of tests⁷² and falsely positive in 30% to 40% of patients.⁷¹ The more accurate enzyme-linked immunospot test detects T cells specific for *M. tuberculosis* antigen.⁷⁸ Perimyocardial tuberculous involvement is also associated with high serum titers of antimyolemmal and antimyosin antibodies.⁷⁹ The diagnostic yield of pericardiocentesis in tuberculous pericarditis ranges from 30% to 76% according to methods used for analyzing pericardial effusions.^{72,75} Pericardial fluid demonstrates high specific gravity, high protein levels, and a high white blood cell count (from 0.7 to 54×10^9 /L).⁷¹

Various antituberculous drug combinations of different durations (6, 9, or 12 months) have been used.^{71,72,77,80-83} Prevention of constriction in chronic pericardial effusion of undetermined etiology by “ex iuvantibus” antitubercular treatment was not successful.⁸⁰ The use of corticosteroids remains controversial.^{77,81-84} A meta-analysis of patients with effusive and constrictive tuberculous pericarditis^{82,83} suggested that tuberculostatic treatment combined with corticosteroids might be associated with fewer deaths and less frequent need for pericardiocentesis or pericardiectomy.^{77,85} If given, prednisone should be administered in relatively high doses (1 to 2 mg/kg/day) because rifampicin induces its liver metabolism.⁷ This dose is maintained for 5 to 7 days and progressively reduced in 6 to 8 weeks. If constriction develops despite combination therapy, pericardiectomy is indicated.

Pericarditis in Renal Failure

Renal failure is a common cause of pericardial disease, producing large pericardial effusions in up to 20% of patients.⁸⁶ Two forms have been described:

1. Uremic pericarditis: this occurs in 6% to 10% of patients with advanced renal failure (acute or chronic) before dialysis has

been instituted or shortly thereafter.⁸⁷ It results from inflammation of the visceral and parietal pericardium and correlates with the degree of azotemia (blood urea nitrogen > 60 mg/dL).

2. Dialysis-associated pericarditis: this occurs in up to 13% of patients on maintenance hemodialysis⁸⁸ and occasionally with chronic peritoneal dialysis. It is due to inadequate dialysis and/or fluid overload.⁸⁹ Pathologic examination of the pericardium shows adhesions between the thickened pericardial membranes ("bread and butter" appearance). The clinical features may include transient pericardial rubs, fever, and pleuritic chest pain, but many patients are asymptomatic. Because of autonomic impairment in uremic patients, the heart rate may remain slow (60-80 beats/min) during tamponade, despite fever and hypotension. Anemia, due to induced resistance to erythropoietin, may worsen the clinical picture.⁹⁰ The ECG may not show the typical diffuse ST segment/T wave elevations observed with other causes of acute pericarditis, owing to a lack of myocardial inflammation.⁹¹ If the ECG is typical of acute pericarditis, intercurrent infection must be suspected.

Most patients with uremic pericarditis respond rapidly to hemodialysis or peritoneal dialysis with resolution of chest pain and the pericardial effusion. To avoid hemopericardium, heparin-free hemodialysis should be used. Hypokalemia and hypophosphatemia should be prevented by supplementing the dialysis solution when appropriate.⁹² Intensified dialysis usually leads to resolution of the pericarditis within 1 to 2 weeks.⁹³ Peritoneal dialysis, which does not require heparinization, may be therapeutic in pericarditis resistant to hemodialysis or if heparin-free hemodialysis cannot be performed. NSAIDs and systemic corticosteroids have limited success when intensive dialysis is ineffective.⁹⁴ Cardiac tamponade and large chronic effusions resistant to dialysis must be treated with pericardiocentesis. Large, nonresolving symptomatic effusions should be treated with intrapericardial instillation of corticosteroids after pericardiocentesis or subxiphoid pericardiectomy (triamcinolone hexacetonide 50 mg every 6 hours for 2-3 days).^{88,94} Pericardiectomy is indicated only in severely symptomatic patients refractory to other treatment owing to its potential morbidity and mortality. After renal transplantation, pericarditis has also been reported in 2.4% of patients.⁹⁵ Uremia or infection (CMV) may be the causes.

Autoreactive Pericarditis and Pericarditis in Systemic Autoimmune Diseases

The diagnosis of autoreactive pericarditis is established using the following criteria²:

1. Pericardial fluid containing increased number of lymphocytes, as well as mononuclear cells greater than 5000/mm³ (autoreactive lymphocytic) or antibodies (e.g., antisarcolemmal) against heart muscle tissue (autoreactive antibody mediated)
2. Inflammation in epicardial/endomyocardial biopsy samples of more than 14 cells/mm²
3. Exclusion of active viral infection both in the pericardial effusion and endomyocardial/epimyocardial biopsy samples (no virus isolation, no IgM-titer against cardiotropic viruses in the pericardial effusion, and PCR negative for major cardiotropic viruses)
4. Tuberculosis, *Borrelia burgdorferi*, *Chlamydia pneumoniae*, and other bacterial infections excluded by PCR and/or cultures
5. Neoplastic infiltration absent in the pericardial effusion and biopsy samples
6. Exclusion of systemic metabolic disorders and uremia

For autoreactive pericarditis, intrapericardial treatment with triamcinolone is effective, with rare side effects.

Pericarditis occurs in many systemic autoimmune diseases: rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, polymyositis/dermatomyositis, mixed connective tissue disease, seronegative spondyloarthropathies, systemic and hypersensitivity vasculitides, Behçet's syndrome, Wegener's granulomatosis, and

sarcoidosis.⁷ Intensified treatment of the underlying disease and symptomatic management are indicated.

The Postcardiac Injury Syndrome: Postpericardiectomy Syndrome

Postcardiac injury syndrome develops within days to months after cardiac injury, pericardial injury, or both.^{7,96,97} It resembles postmyocardial infarction syndrome, with both conditions appearing to be variants of a common immunopathologic process. Pericardial effusion also occurs after orthotopic heart transplantation (21% of patients). It is more frequent in patients receiving aminocaproic acid during the operation.⁹⁸ Cardiac tamponade after open heart surgery is more common after valve surgery than after coronary artery bypass grafting and may be related to the preoperative use of anticoagulants.⁹⁹

Warfarin administration in patients with early postoperative pericardial effusion imposes the greatest risk, particularly in those who did not undergo pericardiocentesis and drainage of the effusion.¹⁰⁰ Symptomatic treatment is generally the same as in acute pericarditis (NSAIDs or colchicine for several weeks or months¹⁰¹), but this has been questioned recently.¹⁰² In patients undergoing cardiac surgery, perioperative use of colchicine compared with placebo reduced the incidence of postpericardiectomy syndrome but with an increased rate of gastrointestinal adverse effects.¹⁰³ Long-term (3 to 6 months) oral corticosteroids, or preferably pericardiocentesis and intrapericardial instillation of triamcinolone (300 mg/m²), are therapeutic options in refractory forms. Redo surgery is rarely needed.

Postinfarction Pericarditis

Two forms of postinfarction pericarditis can be distinguished: an "early" form (pericarditis episternocardiaca) and a "delayed" form (Dressler's syndrome).¹⁰⁴ Episternocardiaca pericarditis, caused by direct exudation, occurs in 5% to 20% of transmural myocardial infarctions but is rarely discovered clinically. Dressler's syndrome occurs from 1 week to several months after myocardial infarction and has symptoms and manifestations similar to those of postcardiac injury syndrome. It does not require a transmural infarction,¹⁰⁵ and it can also appear as an extension of episternocardiaca pericarditis. Its incidence is 0.5% to 5%¹⁰⁶ and is lower still in patients treated with thrombolytics (<0.5%)¹⁰⁷ but more frequent in cases of pericardial bleeding after antithrombotic treatment.^{104,108} Of note, ECG changes are often overshadowed by myocardial infarction changes. Stage one ECG changes are uncommon and suggest "early" postmyocardial infarction syndrome, whereas failure to evolve or "resurrection" of previously inverted T waves strongly suggests myocardial infarction pericarditis.^{109,110} Postinfarction pericardial effusion greater than 10 mm is most frequently associated with hemopericardium, and two-thirds of these patients may develop tamponade/free wall rupture.¹¹¹ Urgent surgical treatment is lifesaving. If immediate surgery is not available or contraindicated, pericardiocentesis and intrapericardial fibrin glue instillation could be an alternative in subacute tamponade.^{111,112} Ibuprofen, which increases coronary flow, is the agent of choice.¹¹³ Aspirin, up to 650 mg every 4 hours for 2 to 5 days, has also been successfully applied. Corticosteroids can be used for refractory symptoms but may delay healing after the infarction.⁷

Traumatic Pericardial Effusion and Hemopericardium in Aortic Dissection

Direct pericardial injury can be induced by accidents or iatrogenic wounds.¹¹⁴⁻¹¹⁷ Iatrogenic tamponade occurs most frequently in percutaneous mitral valvuloplasty, during or after transeptal puncture, particularly if no biplane catheterization laboratory is available and a small left atrium is present. Whereas puncture of the interatrial septum is asymptomatic, passage through the free wall induces immediate chest pain. If high-pressure-containing structures are punctured, rapid deterioration occurs. However, if only the atrial wall is perforated, tamponade may be delayed for 4 to 6 hours. Rescue

pericardiocentesis is successful in 95% to 100% of cases, with less than 1% mortality.¹¹⁸

Transection of the coronary artery and acute or subacute cardiac tamponade occur very rarely during percutaneous coronary interventions.^{119,120} A breakthrough in the treatment of coronary perforation has been the development of membrane-covered graft stents.^{121,122}

During right ventricular endomyocardial biopsy, the catheter may pass through the myocardium, particularly when the bioprobe has not been opened before reaching the endocardial border or has been directed toward the right ventricular free wall instead of toward the septum. Frank cardiac perforations are accompanied by sudden bradycardia and hypotension.¹²³ Perforation rates of 0.3% to 5% have been reported, leading to tamponade and circulatory collapse in less than half of cases.¹²³⁻¹²⁵ The incidence of pericardial hemorrhage with left ventricular endomyocardial biopsy is lower (0.1%-3.3%). Severe complications, leading to procedure-related mortality, were reported in only 0.05% of more than 6000 cases in a worldwide survey¹²⁴ and in none of the 2537 patients at our center.¹²⁵

Pacemaker leads penetrating the right ventricle or epicardial electrodes may cause pericarditis with tamponade, adhesions, or constriction.¹²⁶⁻¹²⁹ A right bundle branch block instead of the usual left bundle branch block is a clue that this has occurred.

Blunt chest trauma is a major risk of motor vehicle accidents. The deceleration force can lead to myocardial contusion with intrapericardial hemorrhage, cardiac rupture, pericardial rupture, or herniation. Transesophageal echocardiography or immediate CT should be performed.^{130,131} Pericardial laceration and partial extrusion of the heart into the mediastinum and pleural space may also occur after injury.¹¹⁵

In dissection of the ascending aorta, pericardial effusion can be found in 17% to 45% of patients and 48% of autopsy cases.¹³⁰ In a clinical series of aortic dissection, pericardial tamponade was found by CT,¹³¹ MRI,¹³² or echocardiography¹³³ in 17% to 33% of patients with type I dissection, 18% to 45% with type II dissection, and 6% with type III dissection.¹³¹ Pericardiocentesis is contraindicated, owing to the risk of intensified bleeding and extension of the dissection.^{134,135} Surgery should be performed immediately.

Neoplastic Pericarditis

Primary tumors of the pericardium are 40 times less common than metastatic ones.⁷ Mesothelioma, the most common primary tumor, is almost always incurable. The most common secondary malignant tumors are lung cancer, breast cancer, malignant melanoma, lymphoma, and leukemia. Effusions may be small or large with imminent tamponade (frequent recurrences) or constriction. Tamponade may even be the initial sign of malignant disease.¹³⁶ With small effusions, most patients are asymptomatic. The onset of dyspnea, cough, chest pain, tachycardia, and jugular venous distention is observed when the volume of fluid exceeds 500 mL. Pulsus paradoxus, hypotension, cardiogenic shock, and paradoxical movement of the jugular venous pulse are important signs of cardiac tamponade. The diagnosis is based on confirmation by cytology or biopsy of malignant infiltration within the pericardium. Of note, in almost two-thirds of patients with documented malignancy, pericardial effusion is caused by nonmalignant diseases (e.g., radiation pericarditis, opportunistic infections).^{137,138} The chest radiograph, CT, and MRI may reveal mediastinal widening, a hilar mass, or pleural effusion.⁷ The analysis of pericardial fluid and pericardial or epicardial biopsy is essential for the confirmation of malignant pericardial disease.

Cardiac tamponade is an absolute indication for pericardiocentesis. In suspected neoplastic pericardial effusion without tamponade, systemic antineoplastic treatment as baseline therapy can prevent recurrences in up to 67% of cases.¹³⁶ However, pericardial drainage is recommended in all patients with large effusions because of the high recurrence rate (40%-70%).¹¹⁰⁻¹⁴⁶ Prevention of recurrences may be achieved by intrapericardial instillation of sclerosing agents, cytotoxic agents, or immunomodulators. Intrapericardial treatment tailored to the type of the tumor indicates that administration of cisplatin is

effective in secondary lung cancer, and intrapericardial instillation of thiotepa appears to be highly effective in breast cancer pericardial metastases.¹⁴⁷⁻¹⁵² No patient in these studies showed signs of constrictive pericarditis. Tetracyclines as sclerosing agents also control malignant pericardial effusions in around 85% of cases, but side effects and complications are quite frequent: fever (19%), chest pain (20%), and atrial arrhythmias (10%).^{136,145,146} Although intrapericardial administration of radionuclides has yielded very good results, it is not widely accepted because of the logistic problems connected with radioactivity.¹⁵³ Radiation therapy is very effective (93%) in controlling malignant pericardial effusions in patients with radiosensitive tumors, such as lymphoma and leukemia. However, radiotherapy of the heart itself can cause myocarditis and pericarditis.¹³⁶

RARE FORMS OF PERICARDIAL DISEASE

Fungal pericarditis occurs mainly in immunocompromised patients or in the course of endemic, acquired fungal infections.¹⁵⁴ It is due to endemic (*Histoplasma*, *Coccidioides*) or opportunistic fungi (*Candida*, *Aspergillus*, *Blastomyces*) and semifungi (*Nocardia*, *Actinomyces*).¹⁵⁵⁻¹⁵⁷ Diagnosis is obtained by staining and culturing pericardial fluid or tissue. Antifungal antibodies in serum are also helpful in establishing the diagnosis.³ Treatment with fluconazole, ketoconazole, itraconazole, amphotericin B, liposomal amphotericin B, or amphotericin B lipid complex is indicated. NSAIDs can support the treatment with antifungal drugs. Patients with histoplasmosis pericarditis do not need antifungal therapy but respond to NSAIDs given for 2 to 12 weeks. Sulfonamides are the drugs of choice for nocardiosis. A combination of three antibiotics, including penicillin, should be given for actinomycosis. Pericardiocentesis or surgical treatment is indicated for hemodynamic impairment. Pericardiectomy is indicated in fungal constrictive pericarditis.

Radiation pericarditis may begin during exposure (very rare) or months to years later, with a latency of up to 15 to 20 years. Its occurrence is influenced by the applied source, dose, fractionation, duration, radiation-exposed volume, form of mantle field therapy, and age of the patient.¹⁵⁸ The effusion may be serous or hemorrhagic, later on with fibrinous adhesions or constriction; it is typically without tissue calcification. The symptoms may be masked by the underlying disease or chemotherapy. Imaging should start with echocardiography, followed by cardiac CT or MRI, if necessary. Pericarditis without tamponade may be treated conservatively, but effusions respond favorably to intrapericardial triamcinolone instillation. Pericardiocentesis and fluid analysis can rule out neoplastic progression to the pericardium.¹⁵⁹ Pericardial constriction occurs in up to 20% of patients, requiring pericardiectomy. Operative mortality is high (21%) and postoperative 5-year survival is poor (1%), mostly because of myocardial fibrosis.¹⁶⁰

Chylopericardium refers to a communication between the pericardium and thoracic duct. It may be the result of trauma, congenital anomalies, complications of open-heart surgery,¹⁶¹ mediastinal lymphangiomas, lymphangiomatous hamartomas, lymphangiectasis, and obstruction or anomalies of the thoracic duct.¹⁶² Infection, tamponade, or constriction may aggravate the prognosis.¹⁶³ The pericardial fluid is sterile, odorless, and opalescent, with a milky white appearance and the microscopic finding of fat droplets. The chylous nature of the fluid is confirmed by its alkaline reaction, specific gravity between 1010 and 1021, Sudan III stain for fat, and high concentrations of triglycerides (5 to 50 g/L) and protein (22 to 60 g/L).^{164,165} Enhanced CT, alone or combined with lymphography, can identify not only the location of the thoracic duct but also its lymphatic connection to the pericardium.^{166,167}

Treatment depends on the etiology and amount of chylous accumulation.¹⁶⁸ Chylopericardium after thoracic or cardiac operations is preferably treated by pericardiocentesis and diet (medium-chain triglycerides).^{169,170} If further production of chylous effusion continues, surgical treatment is mandatory. When conservative treatment and pericardiocentesis fail, creation of a pericardioperitoneal window is a reasonable option.^{171,172} Alternatively, when the course of the thoracic

duct is precisely identified, its ligation and resection just above the diaphragm is the most effective treatment.¹⁷³

Drug- and toxin-related pericarditis, tamponade, adhesions, fibrosis, or constriction may be induced by several drugs.^{7,174} Mechanisms include drug-induced lupus reactions, idiosyncrasy, “serum sickness,” foreign substance reactions, and immunopathy. Management is based on discontinuation of the causative agent and symptomatic treatment.

Pericardial effusion in hypothyroidism occurs in 5% to 30% of patients.⁷ Fluid accumulates slowly, and tamponade occurs rarely. In some cases, cholesterol pericarditis may be observed. The diagnosis is based on serum levels of thyroxine and thyroid-stimulating hormone. Bradycardia, low QRS voltage and T-wave inversion or flattening on the ECG, cardiomegaly on a chest radiograph, and pericardial effusion on echocardiography, as well as a history of radiation-induced thyroid dysfunction, myopathy, ascites, pleural effusion, and uveal edema, may be observed.¹⁷⁵⁻¹⁷⁹ Therapy with thyroid hormone decreases the pericardial effusion.

Pericardial effusion and constriction in pregnancy may manifest as a minimal to moderate, clinically silent hydropericardium by the third trimester. Cardiac compression is rare.¹⁸⁰ ECG changes of acute pericarditis in pregnancy should be distinguished from the slight ST segment depression and T wave changes seen in normal pregnancy.^{180,181} Occult constriction becomes manifest in pregnancy because of the increased blood volume.¹⁸¹ Most pericardial disorders are managed as in nonpregnant women.^{182,183} However, caution is necessary because high-dose aspirin may prematurely close the ductus arteriosus, and colchicine is contraindicated in pregnancy. Pericardiotomy and pericardiectomy can be safely performed if necessary and do not impose a risk for subsequent pregnancies.^{183,184}

Fetal pericardial fluid can be detected by echocardiography after 20 weeks' gestation and is normally 2 mm or less in depth. A greater amount of fluid should raise questions about the possibility of Rh disease (hydrops fetalis), neoplasia, hypoalbuminemia, immunopathy, or maternally transmitted mycoplasmal or other infections.¹⁸⁵

KEY POINTS

1. The diagnosis of acute pericarditis is based on clinical presentation (chest pain, pericardial friction rub) and typical four-stage ECG changes. For etiologic diagnosis, pericardiocentesis, pericardioscopy, and pericardial/epicardial biopsy may be necessary.
2. Echocardiography is essential in all patients with pericarditis to detect pericardial effusion and determine its physiologic significance, as well as to check for signs of constriction, concomitant heart disease, or paracardial pathology.
3. A large proportion of patients usually classified as having “idiopathic” pericarditis actually have viral and autoreactive pericarditis. The diagnosis of viral pericarditis is not possible without the evaluation of pericardial effusion and/or pericardial/epicardial tissue, preferably by polymerase chain reaction (PCR) or in situ hybridization.
4. PCR identification of *Mycobacterium tuberculosis*, high adenosine deaminase activity, and interferon gamma concentration in pericardial effusion are diagnostic with a high sensitivity and specificity for tuberculous pericarditis.
5. Pericardiocentesis is indicated for cardiac tamponade; for a high suspicion of purulent, tuberculous, or neoplastic pericarditis; or in patients with a very large effusion without signs of tamponade (>20 mm in echocardiography in diastole). Electrical alternans and pulsus paradoxus are clinically important signs of the advanced stages of cardiac tamponade and indicate the need for prompt pericardial drainage.
6. Aortic dissection is a major contraindication to pericardiocentesis. Relative contraindications include uncorrected coagulopathy; anticoagulant therapy; thrombocytopenia less than 50,000/mm³; and small, posterior, and loculated effusions.
7. In cardiac wounds, postinfarction myocardial rupture, or dissecting aortic hematoma, emergency cardiac surgery is lifesaving. Loculated effusions may require open surgery or thoracoscopic drainage.
8. Postinfarction pericardial effusions larger than 10 mm in diastole are frequently associated with cardiac rupture. Urgent surgical treatment is indicated.
9. Intrapericardial instillation of antineoplastic (e.g., cisplatin, thiopeta) and/or sclerosing agents (e.g., gentamycin) can prevent recurrences of neoplastic pericardial effusions. Intrapericardial instillation of triamcinolone is highly effective in preventing recurrences in patients with autoreactive pericardial effusion and avoids the adverse effects of systemic corticosteroid therapy.
10. Pericardiectomy is the only treatment for permanent constrictive pericarditis. However, surgery should not be performed too early to avoid operating on patients with transient constriction. Even more important is not to perform surgery too late or in patients with myocardial fibrosis and/or atrophy. If indications for surgery are established early enough, long-term survival after pericardiectomy corresponds to that of the general population.

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In the critical care setting, there are two distinct presentations of valvular heart disease: acute valve dysfunction resulting in acute heart failure and chronic valve disease with decompensation due to increased metabolic demands (Table 85-1).¹ Valve regurgitation is the most common type of acute valve dysfunction. Valve stenosis, with rare exceptions, is a chronic, slowly progressive disease. However, in patients with asymptomatic chronic valve stenosis, acute deterioration can occur if there is a superimposed hemodynamic burden. For example, patients with previously asymptomatic mitral stenosis may present with pulmonary edema in the setting of a systemic infection. Another example is an elderly adult with asymptomatic aortic stenosis who presents with cardiogenic shock in the setting of acute gastrointestinal bleeding. Prosthetic valve dysfunction, particularly mechanical valve thrombosis, can also present emergently.

The key concepts in the management of a critically ill patient with valvular heart disease are the use of echocardiography to provide an accurate diagnosis of disease severity and the appropriate use of invasive hemodynamic monitoring to optimize loading conditions. Handheld echocardiography may provide clues to the presence of valve disease but does not replace the need for a complete diagnostic study when this diagnosis is suspected. With acute valve regurgitation or prosthetic valve thrombosis, urgent surgical intervention can be life-saving. In critically ill patients who are poor surgical candidates, novel percutaneous valve interventions may be useful.

■ MITRAL REGURGITATION

Etiology

Mitral regurgitation may be caused by disease or the distortion of any component of the mitral valve apparatus—the mitral annulus, leaflets, chordae, and papillary muscles—as well as by alterations in left ventricular (LV) geometry or systolic function (Fig. 85-1).² Primary causes of chronic mitral regurgitation include myxomatous valve leaflets (mitral valve prolapse) and rheumatic disease. Chronic secondary mitral regurgitation may be due to dilated cardiomyopathy or coronary artery disease with regional or global LV dysfunction. The management of mitral regurgitation frequently differs between primary and secondary causes, making the identification of the correct etiology essential during evaluation.

Acute mitral regurgitation may also be due to the involvement of the valve leaflets or the left ventricle. Patients with myxomatous mitral valve disease may develop acute regurgitation due to spontaneous chordal rupture.³ Bacterial endocarditis results in acute mitral regurgitation due to the destruction of valve tissue, often with leaflet perforation. Moderate to severe mitral regurgitation due to papillary muscle involvement or regional myocardial dysfunction complicates 12% of acute myocardial infarctions and is associated with an increased risk of heart failure or death.⁴

Clinical Presentation

Although patients with chronic mitral regurgitation may be asymptomatic for many years, the regurgitant lesions impose a volume load on the left ventricle because an increased total stroke volume is needed to maintain a normal forward cardiac output. LV volume overload

results in progressive LV dilation and may lead to an irreversible decline in ventricular contractility, even in the absence of clinical symptoms. The evaluation of ventricular contractility is problematic in patients with mitral regurgitation, given that the measures of ventricular performance are affected by preload and afterload.⁵ However, based on outcomes after mitral valve surgery, the empiric parameters of ventricular end-systolic dimension and ejection fraction can be used to optimize the timing of surgical intervention. Thus, patients with moderate to severe chronic regurgitation undergo periodic echocardiography, with valve repair or replacement recommended when the end-systolic dimension is ≥ 40 mm and the ejection fraction is $\leq 60\%$.⁶

Chronic mitral regurgitation is usually well tolerated even when there is a superimposed hemodynamic load such as systemic infection, pregnancy, or trauma. However, mitral regurgitant severity may acutely worsen by at least two mechanisms. An increase in afterload, for example, with a hypertensive crisis, may increase regurgitant severity due to an increased driving pressure from the left ventricle to the left atrium. An alteration in the LV geometry, for example, with ventricular dilation due to decompensated heart failure, may change the orientation of the papillary muscles such that leaflet closure is impaired, resulting in a larger regurgitant orifice area.⁷ In this situation, a vicious cycle may ensue where LV dilation worsens mitral regurgitant severity, which increases LV dilation.

Acute mitral regurgitation presents with acute pulmonary edema and is a surgical emergency (Figs. 85-2 and 85-3). Mitral chordal rupture results in the acute presentation of heart failure, often in patients unaware of the diagnosis of mitral valve prolapse. Patients with mitral valve perforation due to endocarditis present with pulmonary edema superimposed on the signs and symptoms of endocarditis. Papillary muscle rupture or dysfunction after myocardial infarction (MI) usually presents several days after acute MI; in some cases, the initial presentation is of acute pulmonary edema, with the MI being clinically silent.

Diagnosis

A high level of clinical suspicion is needed to make a diagnosis of acute mitral regurgitation (Table 85-2). Acute pulmonary edema often obscures the signs and symptoms of the underlying disease process. The classical finding is a holosystolic murmur at the apex, radiating to the axilla. Although there is some correlation between murmur loudness and regurgitant severity with chronic regurgitation, the murmur may be soft with acute severe mitral regurgitation. In patients with severe mitral regurgitation after MI, a murmur cannot be appreciated in up to 50% of patients.

Thus, in patients presenting with acute pulmonary edema or cardiogenic shock, prompt echocardiography is essential. Transthoracic images are often diagnostic, allowing the identification of the etiology of valve dysfunction, quantitation of regurgitant severity, estimation of pulmonary pressures, and measurement of ventricular size and systolic function. If transthoracic images are nondiagnostic, transesophageal echocardiography (TEE) can be performed at the bedside in the intensive care unit (ICU). TEE provides excellent images of valve anatomy and the Doppler evaluation of valve function.

Other diagnostic tests are based on the clinical presentation. Multiple blood cultures should be obtained in febrile patients with systemic

TABLE 85-1 Causes of Acute Valve Dysfunction

| | |
|-------------------------|---|
| Mitral regurgitation | Myxomatous disease with flail leaflet Spontaneous chordal rupture Endocarditis Acute myocardial infarction Papillary muscle rupture Regional wall motion abnormality LV dilation and systolic dysfunction |
| Aortic regurgitation | Endocarditis Spontaneous rupture of a congenital fenestration Aortic dissection |
| Tricuspid regurgitation | Endocarditis Penetrating chest trauma Blunt chest wall trauma Iatrogenic pacemaker lead trauma |
| Prosthetic valves | Endocarditis Valve thrombosis Paravalvular dehiscence Leaflet tear |

TABLE 85-2 Diagnostic Approach to Acute Valve Dysfunction

| | |
|----------------------------------|---|
| Physical examination | Unreliable Consider valve dysfunction in all patients with pulmonary edema |
| Echocardiography (transthoracic) | Accurate diagnosis of etiology of disease Quantitation of severity of stenosis or regurgitation Measurement of ventricular ejection fraction Estimation of pulmonary pressures |
| Transesophageal echocardiography | Sensitive for detection of valvular vegetations Detection of paravalvular abscess Essential for prosthetic mitral valve dysfunction Useful for prosthetic aortic valve dysfunction |
| Right heart catheterization | Not reliable for the diagnosis of valve disease May be helpful for optimizing loading conditions |
| Chest computed tomography | Sensitive and specific for diagnosis of aortic dissection |
| Angiography | Used when coronary angiography is needed |

or pulmonary edema to exclude the possibility of endocarditis. In patients with an abnormal electrocardiogram (ECG), chest pain, or a history of coronary artery disease, coronary angiography may be needed.

In patients with acute pulmonary edema or cardiogenic shock after MI, the differential diagnosis includes acute mitral regurgitation, a ventricular septal defect, or a contained rupture of the ventricular free wall. All these possibilities can be diagnosed by echocardiography in an experienced center.

When imaging is nondiagnostic or discrepant with clinical findings, invasive hemodynamic monitoring with a Swan-Ganz catheter for the measurement of pulmonary pressure and cardiac output may

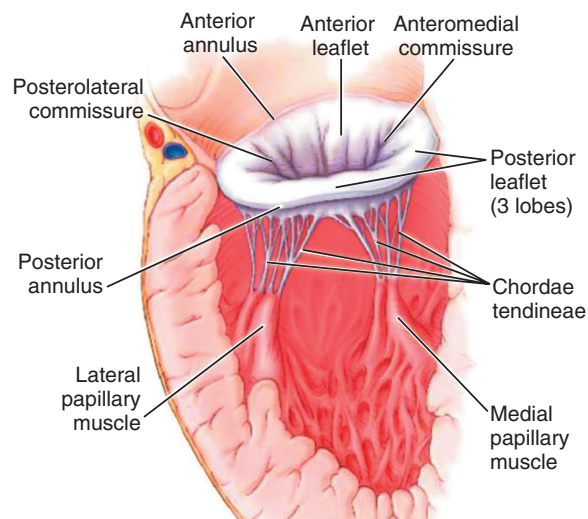


FIGURE 85-1 ■ Mitral valve anatomy: mitral annulus, anterior and posterior leaflets, chordae tendineae, and papillary muscles. Mitral regurgitation may be due to a disease that primarily affects the valve leaflets (e.g., mitral valve prolapse, rheumatic mitral valve disease) or may result from alterations in the function or structure of the left ventricle, such as those induced by ischemic disease or dilated cardiomyopathy. (From Otto CM. Clinical practice. Evaluation and management of chronic mitral regurgitation. *N Engl J Med* 2001;345:740–746.)

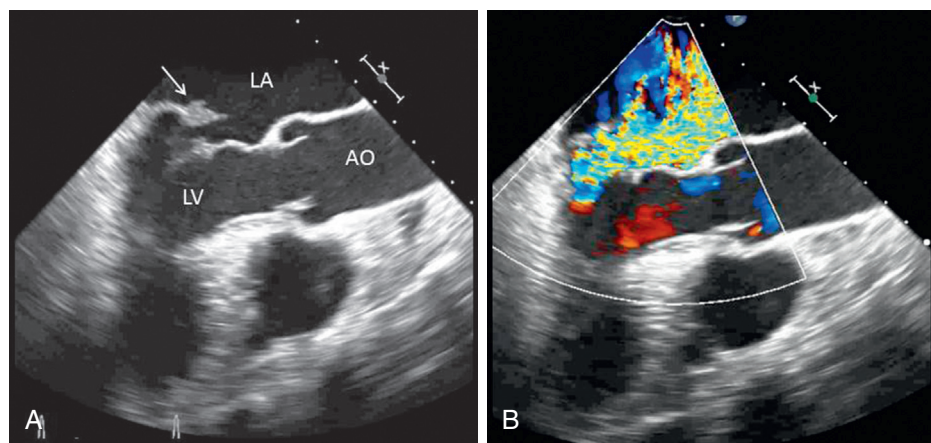


FIGURE 85-2 ■ Two-dimensional transesophageal echocardiogram (A) in a 72-year-old male with known mitral valve prolapse; ruptured chordae resulted in flail of the mitral posterior leaflet (arrow) and acute worsening of symptoms. Color Doppler (B) shows severe eccentric mitral regurgitation with a mosaic pattern through the noncoapting mitral valve. AO, aorta; LA, left atrium; LV, left ventricle.

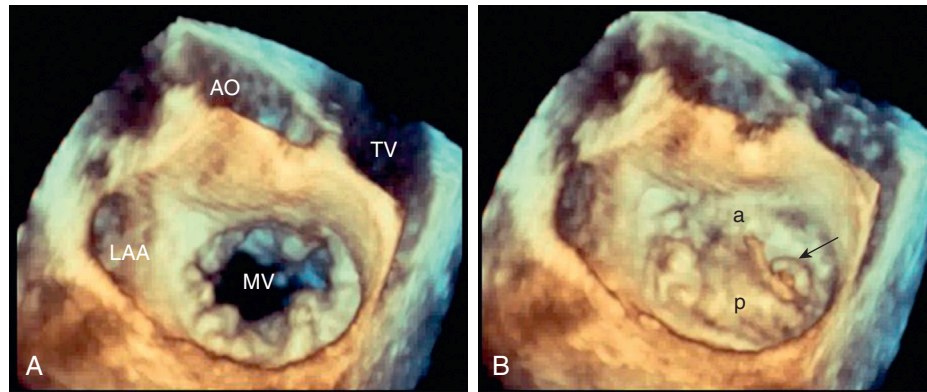


FIGURE 85-3 ■ Three-dimensional (3D) echocardiography of the same patient as in Fig. 85-2 in both diastole (**A**) and systole (**B**). 3D imaging provided a “surgeon’s view,” allowing instant viewing of the mitral valve en-face to assist operative planning for potential repair. In systole, the posterior leaflet (p) can be seen to prolapse above the anterior (a) leaflet, and ruptured chordae with flail segments can be seen (white arrow). AO, aorta; LAA, left atrial appendage; MV, mitral valve; TV, tricuspid valve.

BOX 85-1

Therapeutic Approach to Acute Valve Dysfunction

1. Accurate diagnosis with echocardiography; differentiates acute valve dysfunction from acute decompensation with chronic valve disease
2. Treat the underlying disease process associated with decompensation (endocarditis, acute myocardial infarction, anemia, etc.).
3. Optimize loading conditions using diuretics, vasodilators, and other agents with invasive hemodynamic monitoring.
4. Consult the cardiac surgery team as soon as the diagnosis is made.
5. Intraaortic balloon pump for acute mitral regurgitation.
6. Consider surgical or percutaneous intervention.

be considered in patients with suspected acute mitral regurgitation. At the time of placement, oxygen saturations in the right atrium, right ventricle, and pulmonary artery should be measured. A ventricular septal defect results in a “step-up” in oxygen saturation between the right atrium and ventricle secondary to oxygenated blood from the left ventricle entering the right ventricle. The pulmonary artery balloon-occluded (wedge) pressure tracing should be examined for the presence of a giant “v-wave,” which supports the diagnosis of acute mitral regurgitation but is not always present.

Management

In patients with chronic mitral regurgitation and heart failure, management is directed at treating the process leading to decompensation and optimizing loading conditions (Box 85-1). For example, in a patient with a systemic infection, treating the infection, controlling fever and tachycardia, and invasive monitoring to optimize preload and afterload are utilized. Medical therapy typically includes afterload reduction with nitroprusside or other vasodilators and preload reduction with diuretics.^{8,9} The goal is to support the patient through the period of decompensation. Typically, hemodynamics returns to the baseline-compensated state after the acute illness.

In contrast, acute severe mitral regurgitation is a surgical emergency. Mortality is extremely high without the restoration of valve competence; even with prompt valve surgery, the 30-day mortality is 23%.¹⁰ Medical stabilization should occur concurrently with consultation by a cardiac surgeon. Acutely, the placement of an intraaortic balloon pump (IABP) provides optimal afterload reduction while improving diastolic coronary blood flow.

The timing and risk of surgical intervention depend on the etiology of acute mitral regurgitation. Spontaneous chordal rupture can usually be treated early with mitral valve repair. Compared to valve replacement, mitral valve repair is associated with a lower operative mortality, improved preservation of LV function, and better long-term survival. In addition, the risks of a prosthetic valve and anticoagulation are avoided.

The timing of surgery for endocarditis depends on the disease course in that individual, but most centers now advocate early surgical intervention in patients with heart failure or severe valve regurgitation to prevent progressive valve damage and paravalvular abscess formation.^{11,12} In a large prospective multicenter study, early surgery was associated with a lower mortality than medical therapy (12% versus 21%).¹³ Valve repair is preferred but may not be possible, depending on the extent of tissue destruction. Early surgery is particularly beneficial in patients with paravalvular complications or systemic embolization.¹⁴

In patients with acute ischemic mitral regurgitation, treatment depends on the exact etiology of valve dysfunction.¹⁵ In patients with acute mitral regurgitation due to a regional wall-motion abnormality, myocardial function and mitral regurgitation may improve after percutaneous revascularization.¹⁶ In these patients, the use of an IABP and medical therapy may be advantageous during the acute episode, with weaning of therapy as myocardial function improves.

Mitral regurgitation due to partial or complete papillary muscle rupture requires surgical intervention. Although the risk of surgery is high, with an operative mortality rate of about 50%, the outcome is worse with medical therapy, with a mortality of 75% at 24 hours and 95% within 2 weeks after complete papillary muscle rupture.¹⁷ With the use of echocardiography, partial papillary muscle rupture can be recognized; prognosis in these patients depends on the extent of myocardial damage and severity of mitral regurgitation.¹⁸ With partial papillary muscle rupture, some surgeons prefer to stabilize the patient and delay surgery for 6 to 8 weeks after MI to avoid operating on the necrotic myocardial tissue. However, many patients cannot be stabilized, so acute intervention must be considered. Again, valve repair is preferred, but myocardial necrosis may necessitate valve replacement. Risk factors of surgery include older age, female gender, and poor LV systolic function.

In some patients, the risk of surgical intervention may be so high, such that it is futile. Less invasive transcatheter mitral valve repair may be an option in these situations (Table 85-3). MitraClip, the most widely used device, reduces mitral regurgitation by approximating the

TABLE 85-3 Catheter-Based Techniques for Valve Interventions

| | |
|-------------------|---|
| Commonly accepted | Mitral balloon valvotomy for rheumatic mitral stenosis Edge-to-edge mitral valve repair with MitraClip Aortic balloon valvuloplasty Transcatheter aortic valve replacement Transcatheter pulmonary valve replacement in congenital heart disease. |
| Investigational | Transcatheter mitral valve implantation Transcatheter mitral annuloplasty repair techniques Paravalvular leak closures Transcatheter valve placement within surgical bioprosthetic valve ("valve-in-valve") |

two leaflets of the mitral valve. MitraClip is currently recommended for the treatment of chronic primary mitral regurgitation in inoperable symptomatic patients.¹⁹ Its selective use in acute ischemic mitral regurgitation has been successful.²⁰

AORTIC REGURGITATION

Etiology

Chronic aortic regurgitation is most often due to a congenital bicuspid valve, rheumatic valve disease, or aortic root dilation. There are numerous causes of aortic root dilation, including hypertension, cystic medial necrosis, Marfan syndrome, and a bicuspid aortic valve.²¹ The most common causes of acute aortic regurgitation are endocarditis, rupture of a congenital fenestration, blunt trauma, and acute aortic dissection.¹ Endocarditis results in aortic regurgitation by the destruction of the valve leaflet tissue, with a high percentage of cases also having paravalvular abscess formation. Aortic dissection results in acute aortic regurgitation either due to the enlargement of the aortic annulus or extension of dissection into the valve region, resulting in a flail aortic valve leaflet.

Clinical Presentation

The acute backflow of blood from the aorta to the left ventricle in diastole results in an acute elevation in LV end-diastolic pressure, with consequent pulmonary edema. Because there is no time for compensatory LV dilation, forward cardiac output falls abruptly owing to the regurgitant flow across the valve in diastole, so patients with acute aortic regurgitation may also be in cardiogenic shock. Decreased coronary perfusion pressure results in diffuse subendocardial ischemia, further impairing ventricular function.

Diagnosis

The clinical diagnosis of acute aortic regurgitation differs markedly from that of chronic aortic regurgitation (Fig. 85-4). In contrast to the high-pitched diastolic decrescendo murmur of chronic aortic regurgitation, there is a "to-and-fro" murmur across the aortic valve that many clinicians fail to recognize as an indication of aortic regurgitation. The pulse pressure is narrow due to the low forward stroke volume, and peripheral signs of aortic regurgitation are not seen. As with acute mitral regurgitation, physical examination findings are often subtle, so a high index of suspicion and prompt echocardiography are needed to make this diagnosis.

Acute aortic regurgitation should be considered in patients with signs or symptoms of endocarditis, with a personal or family history of aortic root disease, and with a presentation consistent with acute aortic dissection.²²

Echocardiography allows the imaging of the aortic valve and root and determination of the severity of aortic regurgitation based on a

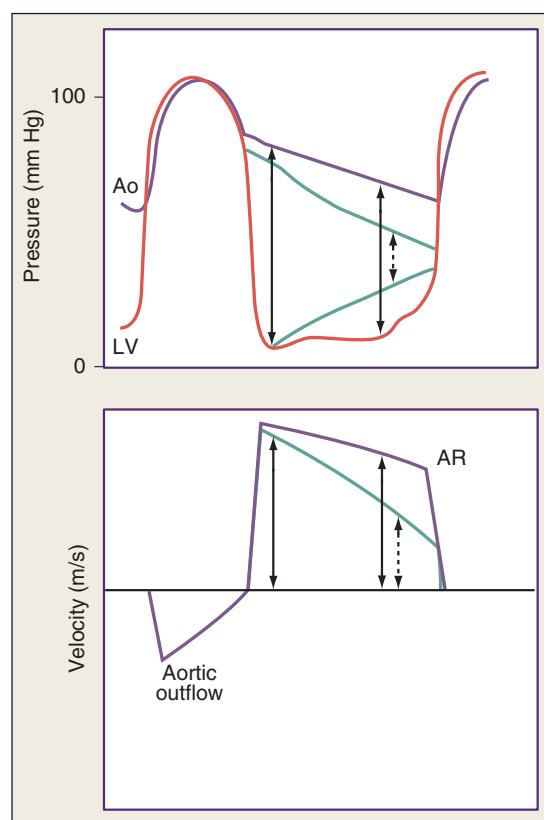


FIGURE 85-4 ■ Left ventricular (LV) and central aortic (Ao) pressures and corresponding Doppler velocity curves are shown for chronic (purple lines) and acute (green lines) aortic regurgitation. The shape of velocity curve is related to the instantaneous pressure differences across the valve over the cardiac cycle, as stated in the Bernoulli equation. With acute aortic regurgitation (AR), aortic pressures fall more rapidly and ventricular diastolic pressure rises more rapidly, resulting in a steeper deceleration slope on the Doppler curve. (From Otto CM. Textbook of clinical echocardiography. 5th ed. Philadelphia: Saunders; 2013, p. 316.)

combination of two-dimensional (2D) imaging and pulsed, continuous-wave, and color Doppler modalities (Figs. 85-5 and 85-6).²³ The continuous-wave Doppler curve shows a steep diastolic slope corresponding to the rapid equalization of diastolic pressure in the aorta and left ventricle. With severe acute regurgitation, there is no pressure gradient at end diastole, so cuff diastolic blood pressure is equal to LV end-diastolic pressure. Echocardiography also allows the accurate assessment of LV size and systolic function. When the differential diagnosis includes aortic dissection, transthoracic echocardiography is inadequate to exclude this possibility. Instead, TEE or computed tomography (CT) images should be obtained.

Management

Acute aortic regurgitation is a surgical emergency.¹ Preoperative management is supportive, with ventilatory support and invasive hemodynamic monitoring. While the diagnosis is being made, therapy may include the use of diuretics, inotropic agents, and nitroprusside or other vasodilators in an attempt to stabilize hemodynamics.^{1,9} However, an IABP is contraindicated, as inflation of the balloon in the descending thoracic aorta in diastole will increase the amount of backflow across the aortic valve.

If acute aortic regurgitation is due to aortic dissection, acute surgical intervention is needed. The surgical approach may be the

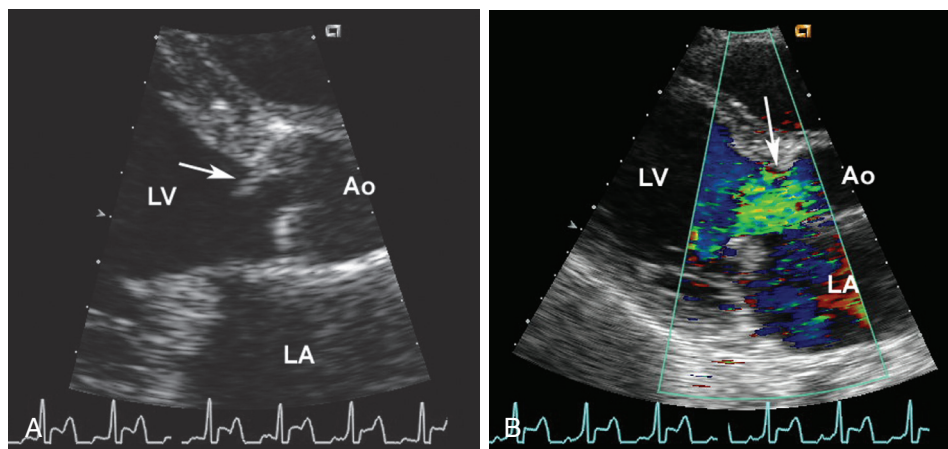


FIGURE 85-5 ■ Endocarditis resulting in acute severe aortic regurgitation. In a long-axis view of the aortic valve (**A**), a flail aortic valve leaflet is seen (arrow), with the leaflet (arrow) prolapsing into the left ventricular (LV) outflow tract in diastole. Color-flow Doppler imaging (**B**) in the same view shows a broad jet of diastolic flow filling the outflow tract, consistent with severe regurgitation. Ao, aorta; LA, left atrium; LV, left ventricle.

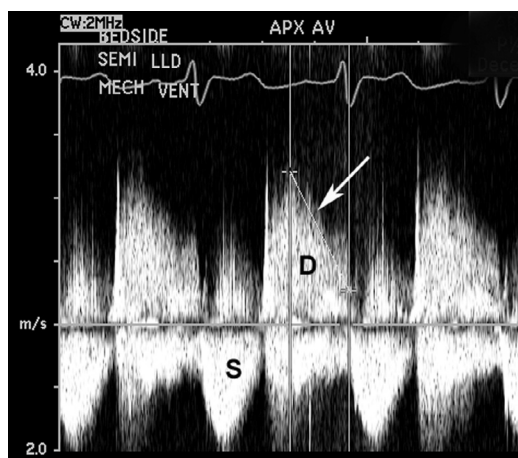


FIGURE 85-6 ■ Same patient as Fig. 85-5. Continuous-wave Doppler recording of flow across the aortic valve shows an increased antegrade velocity in systole (S) consistent with a high transaortic stroke volume. In diastole (D), a dense signal of retrograde flow is seen, with a steep deceleration slope (arrow) consistent with rapid equalization of pressures between the aorta and left ventricle in diastole from acute regurgitation.

replacement of the ascending aorta and valve with a combined prosthetic valve and fabric tube. When the valve leaflets are normal, some centers will preserve the native valve by the resuspension of the leaflets in the prosthetic conduit (called the *David procedure*). Beta blockers should be avoided when acute aortic regurgitation complicates an aortic dissection. A reduction in heart rate leads to increased diastolic retrograde filling of the left ventricle, raising LV end-diastolic pressures and compromising hemodynamics.

When acute aortic regurgitation is due to endocarditis, surgical options include a mechanical valve, a heterograft tissue valve such as a porcine aortic valve or bovine pericardial valve, or a cryopreserved homograft aorta valve. Rarely, the patient may undergo valve repair if there is a simple perforation with adjacent normal leaflet tissue.

■ MITRAL STENOSIS

Etiology and Clinical Presentation

Mitral stenosis is almost always due to rheumatic disease, with only rare cases of calcific mitral stenosis seen in the elderly. Rheumatic mitral stenosis is a slowly progressive disease with an insidious decline in exercise tolerance and symptom onset over many years.²⁴ However, in an asymptomatic patient with compensated moderate or severe mitral stenosis, acute decompensation can occur in the setting of increased systemic hemodynamic demands. Because mitral stenosis is more common in women (80% of cases) and occurs during the reproductive years, the most common emergency presentation of mitral stenosis is a pregnant woman with heart failure. Many of these patients are unaware of the underlying valve disease and are initially diagnosed during pregnancy. The clinical presentation may also be due to or exacerbated by the onset of atrial fibrillation.

A large atrial myxoma may mimic the clinical presentation of mitral stenosis, presenting with acute hemodynamic compromise due to the obstruction of the mitral valve orifice by the tumor mass.

Diagnosis

The apical diastolic rumble and opening snap of mitral stenosis is challenging to appreciate even in a quiet room with optimal patient positioning and is frequently inaudible in the ICU setting. However, the diagnosis is easily made by transthoracic echocardiography, with the mitral leaflet showing the characteristic findings of rheumatic disease: commissural fusion, chordal shortening and fusion, and restriction of the diastolic opening of the leaflets (Fig. 85-7).²⁵ The mitral valve area can be quantitated by 2D or three-dimensional planimetry or the Doppler pressure half-time method, with severe stenosis defined as a valve area of less than 1.5 cm² (Fig. 85-8). Transthoracic echocardiography also provides information on LV size and systolic function, left atrial size, pulmonary pressure, and any associated valve lesions. If evaluation for left atrial thrombus is needed, TTE has a sensitivity of only 60% compared to that of nearly 100% of the transesophageal approach.

Management

Most patients with mitral stenosis and acute decompensation can be managed conservatively with the treatment of the superimposed

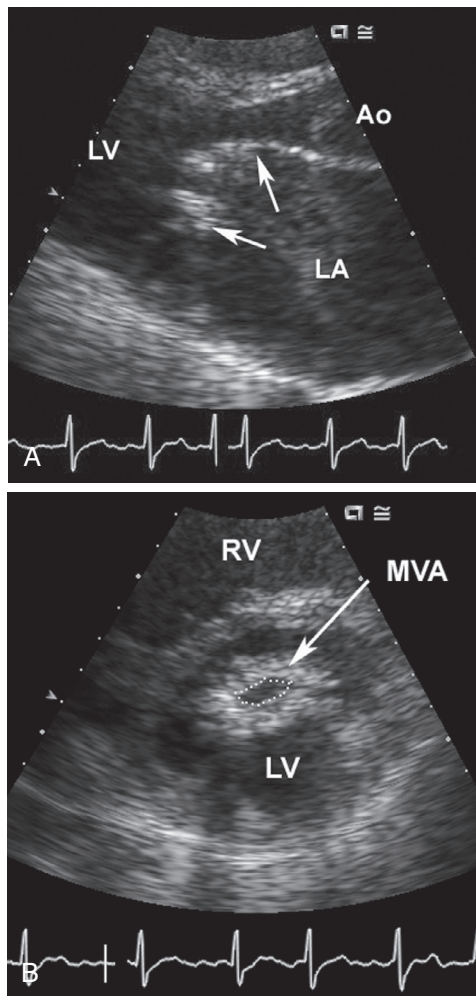


FIGURE 85-7 ■ In a patient with mitral stenosis, the long-axis view (A) demonstrates the classic findings of the diastolic doming of leaflets (arrows) due to commissural fusion, with thickening predominantly at the leaflet tips. In the short-axis view (B), the restricted mitral orifice with fusion of the commissures is visualized, providing accurate measurement of the valve area by direct planimetry. In this case, the valve area of 0.7 cm^2 indicates severe valve obstruction. Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

illness.⁹ Efforts should be directed toward decreasing overall metabolic demand and increasing oxygen delivery by controlling fever, maintaining a normal hemoglobin level, and providing supplemental oxygen. If atrial fibrillation is present, rate control is essential, preferably with conversion back to sinus rhythm. Even when sinus rhythm is present, beta blockers may improve ventricular diastolic filling by prolonging the duration of diastole as the heart rate is decreased.²⁶ Invasive hemodynamic monitoring and ventilatory support may be needed when severe heart failure is present.

In patients who do not respond to conservative therapy, emergency intervention should be considered. The optimal intervention is percutaneous balloon mitral valvotomy (PBMV), which typically results in an increase in mitral valve area to more than 1.5 cm^2 (Fig. 85-9).^{27,28} PBMV can be safely performed even during pregnancy.²⁹⁻³¹ Patients with a left atrial thrombus, coexisting moderate to severe mitral regurgitation, or heavily calcified and deformed mitral valves are not candidates for PBMV; in these patients, surgical mitral valve replacement may be needed.

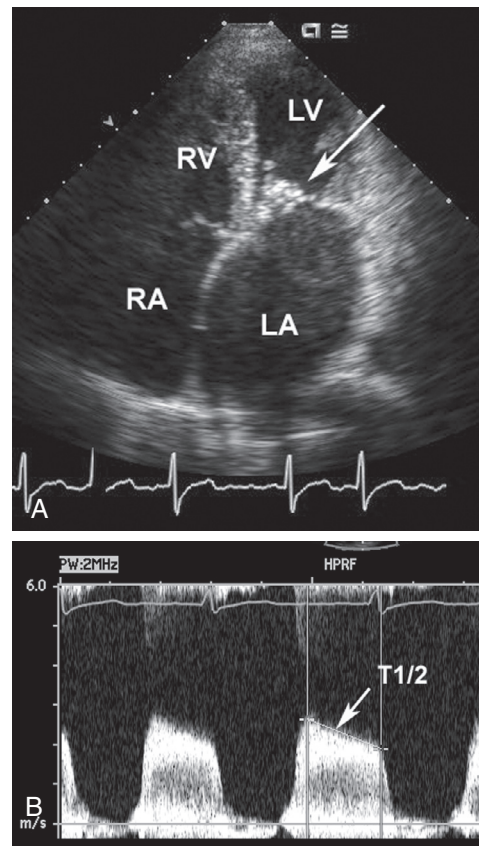


FIGURE 85-8 ■ Same patient as Fig. 85-7. The apical four-chamber view (A) shows severe left atrial enlargement due to mitral obstruction, with thickened valve leaflets (arrow). Haziness in the left atrium is due to the stasis of blood flow, with spontaneous contrast on echocardiography. (B) Continuous-wave Doppler recording of flow across mitral valve shows increased velocity corresponding to transvalvular pressure gradient. Pressure half-time (T1/2) can be used to accurately calculate mitral valve area (0.7 cm^2).

■ AORTIC STENOSIS

Etiology and Clinical Presentation

Valvular aortic stenosis in adults is most often due to the calcification of a normal trileaflet or congenital bicuspid valve (Fig. 85-10A). Rheumatic aortic stenosis is less common and is invariably accompanied by mitral valve involvement. In younger adults, congenital aortic stenosis may be encountered; some of these patients have restenosis after prior commissurotomy in childhood.

Like mitral stenosis, aortic valve stenosis is a chronic, slowly progressive disease that presents acutely only in patients who have not been receiving regular medical care.³²⁻³⁴ As in mitral stenosis, acute decompensation may occur with a superimposed systemic condition. Young women with congenital aortic stenosis may present with angina or heart failure during pregnancy. In older adults, asymptomatic patients with moderate to severe valve obstruction may present with heart failure in the setting of pneumonia, anemia, or other conditions with increased metabolic demands.

Diagnosis

Classic physical examination findings for aortic stenosis include a delayed and decreased carotid upstroke, a narrow pulse pressure, a single second heart sound (S_2), and a systolic ejection murmur at the

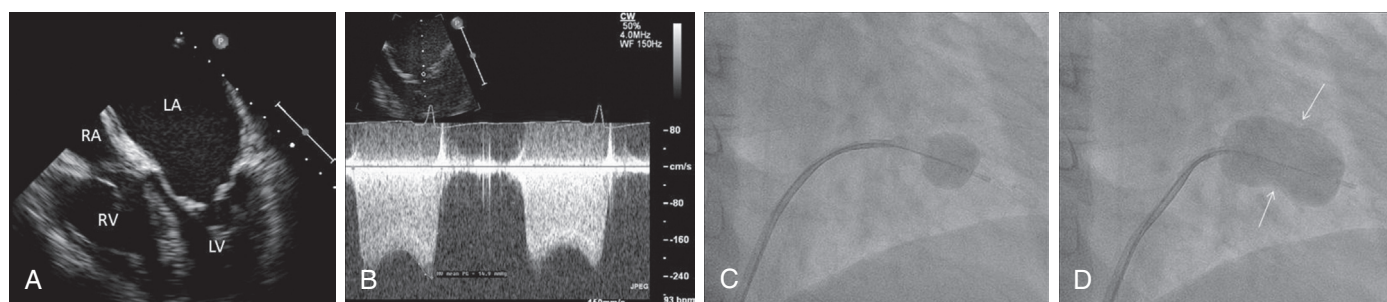


FIGURE 85-9 ■ This 48-year-old female underwent percutaneous balloon mitral valvotomy (PBMV) due to severe symptomatic rheumatic mitral stenosis and acute pulmonary edema. The transesophageal echocardiogram four-chamber view demonstrates restricted diastolic mitral valve opening with hockey-stick deformation and severely enlarged left atrium (**A**). Continuous wave Doppler prior to PBMV measures a severely elevated mean gradient of 15 mm Hg (**B**). Fluoroscopic images show the use of an Inoue balloon distally inflated across the mitral valve via a transseptal catheter (**C**). The initial distal inflation stabilizes the position of the balloon, allowing for full inflation to split the mitral valve commissures, a waist (white arrows) in the balloon is seen from the resistance of the mitral valve (**D**). Successful PBMV reduced the mean gradient to 6 mm Hg and relieved the patient's symptoms. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

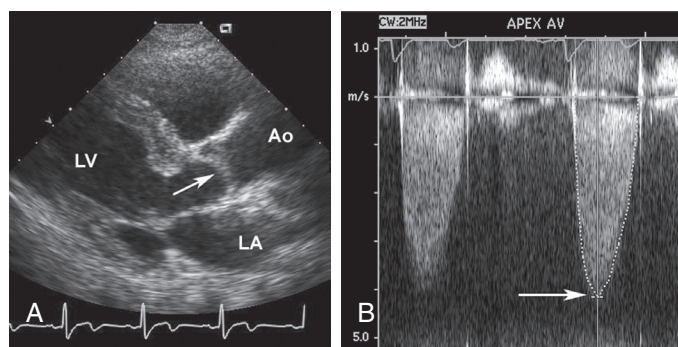


FIGURE 85-10 ■ **A**, In this 26-year-old pregnant woman with a loud systolic murmur, the long-axis view shows doming of the aortic valve in systole (arrow). Short-axis images confirmed a unicuspid aortic valve. **B**, Continuous-wave Doppler examination of the aortic valve demonstrates a high-velocity signal consistent with severe aortic stenosis. The maximum velocity of 4.2 m/sec corresponds to a maximum transaortic pressure gradient of 69 mm Hg and a mean gradient of 41 mm Hg. Valve area, calculated by the continuity equation, was 0.8 cm². Ao, aorta; LA, left atrium; LV, left ventricle.

aortic region that radiates to the carotids. However, while a grade 4 murmur (palpable thrill) with a single S₂ and diminished carotids is specific for severe stenosis, these findings are very insensitive for the diagnosis.³⁵ In particular, when a patient is decompensated, the murmur may be soft, and carotid upstrokes may be altered by coexisting vascular disease or loading conditions.

Echocardiography provides the reliable evaluation of aortic stenosis severity based on the maximum velocity through the narrowed orifice and valve area, calculated with the continuity equation (Fig. 85-10B). Disease severity is a continuum, and velocities may be relatively low despite severe stenosis when stroke volume is reduced. In general, stenosis can be graded as severe (valve area < 1.0 cm² or jet velocity > 4 m/sec), moderate (valve area, 1.0–1.5 cm² or jet velocity, 3–4 m/sec), or mild (valve area > 1.5 cm² or jet velocity < 3 m/sec). Echocardiography also allows the evaluation of ventricular systolic and diastolic function and any associated valve disease.²³

Management

As with mitral stenosis, most patients with decompensated aortic stenosis can be managed conservatively by (1) treating the underlying disease process that led to decompensation and (2) restoring the patient's normal loading conditions. However, in patients who have denied symptoms or have not been receiving medical care, the first presentation of severe aortic stenosis may be syncope or pulmonary edema. In these patients, aortic stenosis is the cause of decompensation, as evidenced by very severe valve obstruction, often with a low ejection fraction. Treatment is urgent aortic valve replacement. The cautious use of nitroprusside may improve hemodynamics prior to valve replacement in severe decompensated aortic stenosis, if the mean arterial pressure is above 60 mm Hg,^{36,37} and some patients can be managed by careful diuresis. However, in unstable patients who are surgical candidates, it is more prudent to proceed promptly to valve replacement. For prohibitive and high-risk surgical patients, transcatheter aortic valve implantation can be performed in experienced centers.^{38,39} If aortic valve replacement is temporarily contraindicated, primarily due to an active infection, balloon aortic valvuloplasty can be used.⁴⁰

RIGHT-SIDED VALVE DISEASE

Pulmonic valve disease is almost always congenital in origin, with a chronic disease course. Tricuspid valve stenosis is rare and usually accompanies rheumatic mitral valve disease. Tricuspid valve endocarditis often results in acute severe regurgitation; pulmonic valve endocarditis is rare. Cases of acute traumatic disruption of the tricuspid valve with blunt chest trauma have been described, although myocardial contusion or thoracic aorta disruption is more common.^{41,42} Acute severe tricuspid regurgitation results in a low forward cardiac output and signs of an elevated right atrial pressure.

PROSTHETIC VALVES

Mechanical Valves

Prosthetic mechanical heart valves are very durable, with complications most often due to valve thrombosis or paravalvular regurgitation.⁴³ Valve thrombosis occurs in the setting of inadequate anticoagulation and may result in functional valve stenosis if movement of the valve occluder is restricted or valve regurgitation if the clot

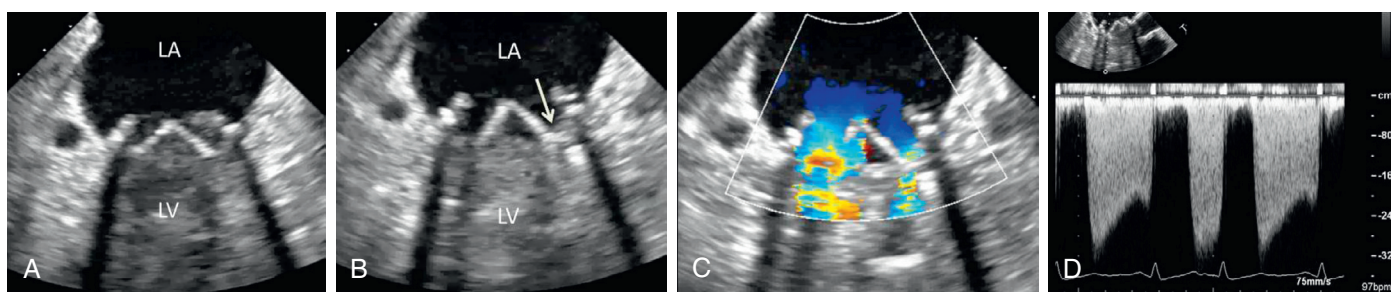


FIGURE 85-11 ■ Transesophageal echocardiogram of a thrombosed bileaflet mechanical mitral valve in a 43-year-old female who stopped anticoagulation for a dental procedure with inadequate bridging. In systole (**A**), the bright occluder can be seen in a closed position, causing reverberation artifact into the left ventricle (LV). During diastole (**B**), there is a minimal opening of the occluder (*white arrow*) from the acute thrombus. Color-flow Doppler (**C**) shows flow primarily through only one side of the valve, while there is only a very narrow jet at the site of the stuck leaflet. Continuous-wave Doppler (**D**) estimated a severely elevated mean gradient of 24 mm Hg, and the patient required emergent surgical valve replacement with a bioprosthesis.

prevents full closure of the valve. The clinical presentation of valve thrombosis is similar to that of native valve stenosis or regurgitation. Echocardiography provides key information on the presence and severity of valve dysfunction.⁴⁴ TEE is especially important with mitral prosthetic valves (**Fig. 85-11**); the valve itself blocks ultrasound penetration from a transthoracic approach.

The treatment of prosthetic valve thrombosis is controversial. When only a small thrombus and mild hemodynamic compromise are present, conservative therapy with full-dose intravenous anticoagulation for several days may be adequate. With severe hemodynamic compromise, surgical intervention with repeat valve replacement may be necessary, although operative mortality is reported to be high, ranging from 17% to 40%.⁶ Systemic thrombolytic therapy can restore valve function in about 80% of patients but is associated with death in 20%, systemic embolism due to fragmentation of the valve thrombosis in 16%, and the need for emergency surgery in 20%.⁶ The duration of thrombolytic therapy is based on the resolution of the Doppler echocardiographic evidence of the resolution of thrombus and valve dysfunction. Current guidelines recommend emergency operation for left-sided valve thrombosis and severe symptoms or a large clot burden, except in patients with an excessively high surgical risk. Fibrinolytic therapy is reasonable for right-sided valve thrombosis, left-sided thrombosis with mild symptoms of recent onset or a small clot burden, and patients who are not surgical candidates.^{6,45,46}

Paravalvular regurgitation early after valve replacement may be related to suture dehiscence at a site of annular calcification. Paravalvular regurgitation may be associated with hemolytic anemia, which can be treated conservatively if mild but may require reoperation if severe recurrent anemia is present. The new onset of paravalvular regurgitation should prompt careful evaluation for endocarditis (see Chapter 86). Paravalvular regurgitation has been successfully treated with the percutaneous techniques in high-risk surgical candidates with refractory heart failure and hemolytic anemia (**Fig. 85-12**).⁴⁷

Tissue Valves

Tissue valves are subject to the degeneration of the leaflets, with superimposed calcification that may result in stenosis or regurgitation. Usually, this is a slowly progressive process with presentation 10 to 15 years after valve implantation.⁴⁸ As with native valve disease, acute

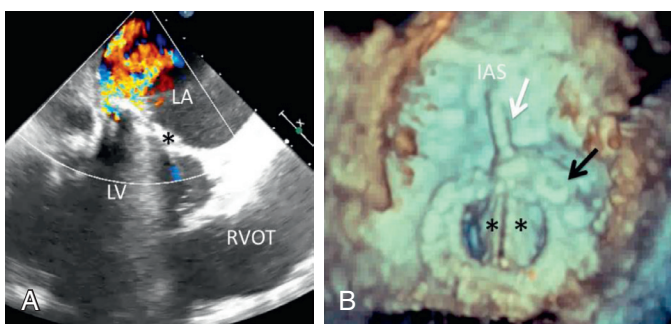


FIGURE 85-12 ■ Severe paravalvular leak in a 72-year-old male with a history of multiple mitral valve (MV) replacements due to previous endocarditis presenting with symptomatic heart failure and hemolytic anemia. Two-dimensional transesophageal color Doppler (**A**) shows eccentric regurgitation around the closed prosthetic MV occluder (*) during systole. Three-dimensional echocardiography (**B**) assists with paravalvular closure of the defect using an Amplatzer plug (*black arrow*). A second plug is required in this case and can be seen being deployed via a transseptal catheter (*white arrow*) during diastole with an open MV occluder. IAS, interatrial septum; LA, left atrium; LV, left ventricle; RVOT, right ventricular outflow tract.

decompensation may occur in patients with chronic prosthetic valve dysfunction if there is a superimposed hemodynamic stress.

Acute regurgitation of a tissue valve can result from endocarditis or a leaflet tear due to tissue degeneration. Tears in the valve leaflet typically occur adjacent to an area of calcification secondary to the increased stress on the normal leaflet tissue. As with mechanical valves, both transthoracic and transesophageal imaging are needed for the full evaluation of suspected prosthetic tissue valve dysfunction. Treatment is similar to that for native valves, with medical stabilization followed by surgery for repeat valve replacement. However, many patients are at a very high surgical risk due to advanced age, comorbidities, and repeated sternotomy; in these patients, investigational transcatheter techniques for “valve-in-valve” replacement may be performed at experienced centers.⁴⁹

KEY POINTS

Acute Mitral Regurgitation

1. Causes include endocarditis, mitral prolapse, and acute myocardial infarction
2. Presents with pulmonary edema
3. Murmur may be soft or absent.
4. Prompt echocardiography is essential.
5. Pulmonary wedge v-wave is not always seen.
6. Intraaortic balloon pump improves hemodynamics.
7. Definitive treatment is mitral valve surgery, but transcatheter approaches may be considered in selected patients.

Acute Aortic Regurgitation

1. Causes include endocarditis and aortic dissection
2. Diastolic murmur may be soft.
3. Prompt echocardiography is essential.
4. Treatment is emergency aortic valve replacement surgery.

Mitral Stenosis

1. Rheumatic mitral stenosis typically occurs in young women.
2. May present during pregnancy
3. Echocardiography is diagnostic.

4. Acute decompensation can be treated medically.
5. Percutaneous balloon mitral commissurotomy is the optimal intervention.

Aortic Stenosis

1. Aortic stenosis is common in the elderly.
2. Decompensation occurs with increased hemodynamic demand.
3. Physical examination shows a systolic murmur.
4. Echocardiography is diagnostic.
5. Conservative management for decompensation is appropriate.
6. Severe symptomatic disease requires surgical or transcatheter aortic valve replacement.

Prosthetic Valves

1. Mechanical valves are at a risk of valve thrombosis.
2. Management of prosthetic valve thrombosis is controversial.
3. Tissue valves undergo degeneration 10 to 15 years after implantation.
4. Presentation and management of acute regurgitation is similar to native valve disease.

ANNOTATED REFERENCES

Stout KK, Verrier ED. Acute valvular regurgitation. *Circulation* 2009;119:3232-41.

Detailed summary of the literature on acute valve regurgitation, clinical presentation, diagnostic approach, and management. Surgical considerations in the decision for valve repair versus replacement are reviewed. References to earlier publications can be found here.

Prendergast BD, Tornos P. Surgery for infective endocarditis: who and when? *Circulation* 2010;121:1141-52.

Review paper that summarizes the literature on the timing of surgery for infective endocarditis and provides a practical approach for patient management.

Lalani T, Cabell CH, Benjamin DK, et al. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis: use of propensity score and instrumental variable methods to adjust for treatment-selection bias. *Circulation* 2010;121:1005-13.

In this prospective study of 1552 patients with native valve endocarditis, the 46% who underwent early surgery were compared to the 54% who were treated medically. Overall survival was significantly better with early surgery, with an estimated absolute risk reduction of 11%. Propensity score sub-

group analysis identified patients most likely to benefit from early surgery as those with paravalvular complications, systemic embolization, infection with Staphylococcus aureus, and stroke.

Chandrasekhar Y, Westaby S, Narula J. Mitral stenosis. *Lancet* 2009;374:1271-83.

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Sun JC, Davidson MJ, Lamy A, Eikelboom JW. Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. *Lancet* 2009;374:565-76.

This review of antithrombotic therapy for prosthetic valves covers preventive anticoagulation and management of thrombotic complications. For obstructive valve thrombosis, the authors recommend thrombolytic therapy and echocardiographic monitoring, with surgery reserved for patients with contraindications to thrombolysis or those who do not respond to thrombolytic therapy. Smaller (<5 mm) nonobstructive thrombi can usually be managed with standard anticoagulation alone.

■ References for this chapter can be found at expertconsult.com.

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Infectious endocarditis is associated with a myriad of complications, both cardiac and extracardiac, that may require intensive care unit (ICU) admission. Local progression of the infection causes destruction of valve cusps or leaflets and chordae and may extend to peri- and paravalvular structures. Hemodynamic deterioration leads to secondary organ failure. Finally, embolization of infected tissues may damage vital organs and cause peripheral abscesses. Intensivists are often confronted with complex treatment decisions, such as the indication for and timing of cardiac surgery and the management of hemodynamic and neurologic complications. Therefore, treatment of patients with complicated infectious endocarditis requires close cooperation between intensivists, infectious disease specialists, cardiologists, and cardiac surgeons. This chapter focuses on the changing epidemiology and progress made during the past 2 decades in the diagnosis and management of complicated infectious endocarditis.

■ PATHOPHYSIOLOGY

Infectious endocarditis is a microbial infection of the endocardial surface of the heart. The process is initiated by bloodborne microorganisms that adhere directly to the endothelium or by nonbacterial thrombotic endocarditis. The most important factors facilitating nonbacterial thrombotic endocarditis are organic valvular lesions, with associated perturbation of blood flow, and prosthetic valves. Circulating microorganisms can adhere to microscopic lesions, which explains why some patients with infectious endocarditis have no previously known valvular abnormality.¹

In simple infectious endocarditis, infection is limited to the valve cusps or leaflets and chordae and consists of vegetations (Fig. 86-1) that are formed by pathogens, platelets, fibrin, and inflammatory cells. In advanced infectious endocarditis, deep tissue invasion results in the destruction or invasion of valvular and perivalvular structures. The infection may spread as cellulitis, with the formation of an abscess or pseudoaneurysm that can rupture into another heart chamber or even the pericardium.

In prosthetic valve endocarditis (PVE), lesions may differ according to the type of prosthesis. With biological prostheses or homografts, the infection may be limited to the cusps, whereas with mechanical prostheses, involvement of the sewing ring and valve annulus is the rule. Bacterial adherence to the prosthesis results from a complex relationship among the biomaterial, plasma proteins (e.g., fibronectin, laminin, thrombospondin, fibrinogen), and bacterial adhesion proteins. Staphylococci express numerous surface factors: clumping factors A and B, which promote bacterial adhesion to fibrinogen and fibrin, and fibronectin-binding proteins A and B, which permit adhesion to fibronectin.² In addition, once staphylococci have escaped the microbicidal effects of platelet peptides, they can bind to the platelet surface by a series of pathogenetic steps including direct binding to the platelet surface, upregulation of platelet surface receptors for fibrinogen, and interaction between specific bacterial proteins and platelet surface receptors. Surface charge modifications are associated with increased in vitro resistance profiles of *Staphylococcus aureus* to a number of endogenous cationic antimicrobial peptides, such as α -defensins.^{3,4}

■ INCIDENCE AND CLASSIFICATION

The incidence of infective endocarditis ranges from 3 to 10 episodes/100,000 person-years, varying from one country to another.

This may reflect methodological differences between surveys rather than true variations.⁵ The overall annual incidence of infectious endocarditis in Europe and the United States is between 15 and 60 cases per million. In a study conducted in France, the crude annual incidence of infectious endocarditis was 30 (95% confidence interval [CI], 27 to 33) per million inhabitants.¹ Infectious endocarditis can be classified into three groups that differ markedly in terms of incidence, clinical presentation, microbiological features, and outcome: left-sided native valve, right-sided native valve, and PVE.

Left-sided native valve infectious endocarditis traditionally occurs in patients with underlying heart disease, but it may also affect patients with no known valvular disease, especially when endocarditis is caused by highly virulent bacteria such as *S. aureus* or *Streptococcus pneumoniae*. Most infections are community acquired, but nosocomial cases are becoming more common.

Right-sided native valve infectious endocarditis is usually associated with intravenous (IV) drug use and still accounts for 10% of all infectious endocarditis episodes.⁶ Nosocomial cases are frequently a consequence of catheter-related infections. In most cases of pacemaker and implantable cardioverter-defibrillator infectious endocarditis, vegetations are located only on leads, but tricuspid valve involvement may also occur.⁷

Prosthetic valve endocarditis occurs in 1% to 6% of patients with a valve prosthesis, with an incidence of 0.3% to 1.2% per patient-year.⁴ It accounted for 21% of the 2781 patients with definite infective endocarditis in the International Collaboration on Endocarditis–Prospective Cohort Study⁶ (ICE-PCS). Early PVE is classically defined as occurring within 1 year of surgery and late PVE as occurring beyond 1 year because of significant differences between the microbiological profiles observed before (usually nosocomial origin) and after this time point (predominance of community-acquired pathogens).⁸ However, a recent large prospective multicenter international registry found that 37% of all PVE was associated with nosocomial infections or nonnosocomial healthcare-associated infections in outpatients with extensive healthcare contact.⁹

■ DEMOGRAPHICS AND ETIOLOGIC PROFILES

Classic and Changing Patient Characteristics

The demographic characteristics of patients who develop infectious endocarditis have changed over the past few decades. Today, patients tend to be older, and their underlying diseases have changed.^{10,11} In ICE-PCS, 38% of all definite infectious endocarditis occurred in patients older than 65 years.¹¹ In developing countries, rheumatic heart disease remains the most frequent underlying cardiac condition predisposing patients to infectious endocarditis. In contrast, nonrheumatic heart abnormalities, including mitral valve prolapse, aortic valve calcification, aortic bicuspid valve, and hypertrophic obstructive cardiomyopathy, are the main risk factors in the United States and Western Europe. For patients with mitral valve prolapse, risk factors include mitral regurgitation and thickened mitral leaflets. However, results of a 1-year survey of infectious endocarditis in France showed a significantly lower incidence of known underlying heart disease between 1991 and 1999. Nowadays, congenital heart diseases are rarely involved, except bicuspid aortic valve. Other conditions, including diabetes mellitus, long-term hemodialysis, and immunosuppression,

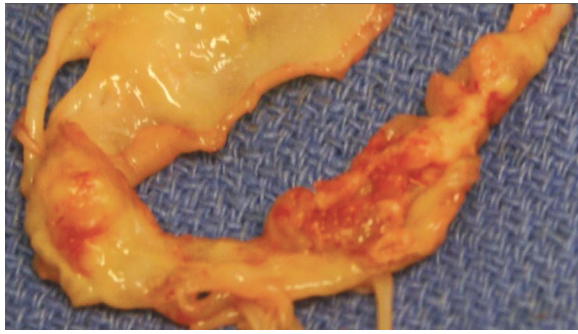


FIGURE 86-1 ■ Vegetations on a native mitral valve in a patient with streptococcal endocarditis.

are associated with a higher incidence of infectious endocarditis. At Duke University Medical Center, rates of hemodialysis dependence and immunosuppression among 329 patients with infectious endocarditis rose significantly between 1993 and 1999.¹² Moreover, a recent study showed that more than one-third of cases of native valve endocarditis in non-injection drug users involve contact with healthcare. Such episodes of endocarditis may be nosocomial if they occur in a patient hospitalized for more than 48 hours before the onset of signs or symptoms consistent with infective endocarditis. A higher proportion of nonnosocomial healthcare-associated endocarditis is now observed in patients with extensive out-of-hospital contact with healthcare interventions or systems (e.g., wound care, receipt of hemodialysis or IV chemotherapy, residence in a nursing home or long-term care facility).¹³

Causative Organisms

Overall Distribution

Most Frequently Isolated Pathogens. Streptococci are traditionally the most common causative agent of infectious endocarditis, but the results of the ICE-PCS showed that streptococci had fallen to second place behind staphylococci as the leading cause.⁶ However, this apparent temporal shift from predominantly streptococcal to predominantly staphylococcal infective endocarditis may be partly due to recruitment/referral bias in specialized centers, since this trend is not evident in population-based epidemiologic surveys of infective endocarditis.¹⁴ *Streptococcus* species (mainly *Streptococcus mitis*, *Streptococcus sanguis*, and *Streptococcus mutans*), which abound in the mouth and nasopharynx, are associated with dental procedures and diseases. Poor dental hygiene and minor or unrecognized periodontal disease may be the source of *Streptococcus viridans* infectious endocarditis. *Streptococcus gallolyticus* (previously *S. bovis*) may be involved in valve infections of dental or buccal origin. In addition, the association of *S. gallolyticus* with carcinoma or other lesions of the colon (e.g., diverticulitis, polyps) is well known. Beta-hemolytic streptococci (groups A, B, C, and G) and *Streptococcus milleri* are isolated from 6% of patients with infectious endocarditis,¹ with the predominant species being group B. The majority of nonpregnant patients with group B streptococcal infectious endocarditis have an underlying condition, such as diabetes mellitus, breast cancer, decubitus ulcer, or cirrhosis.¹⁵

Enterococci, mainly *Enterococcus faecalis* and *Enterococcus faecium*, account for only 10% of cases of infectious endocarditis.⁶ These pathogens affect older patients, as demonstrated by a description of 93 episodes of enterococcal infectious endocarditis occurring in patients with a mean age of 74 years.¹⁶ The portals of entry are the gastrointestinal and urogenital tracts through a lesion or a procedure (e.g., injection sclerotherapy of esophageal varices, transurethral prostate resection, urethral dilatation) resulting in transient bacteremia, in which case the infection is healthcare associated.

Staphylococcus aureus is now implicated in approximately 30% of all cases of left-sided native valve infectious endocarditis⁶ and in 23%

of PVE.⁹ It is the most common cause of healthcare-associated infections.¹⁵ *S. aureus* is also the causative agent in most acute infections, with about half of patients having no previously known heart disease. A clinically identifiable focus of infection (e.g., carbuncle, cellulitis, bursitis, ulcer, burn, osteomyelitis) may be present. However, in 50% to 60% of cases, no obvious portal of entry is detected, although the skin is probably the source in many of them. The relationship between *S. aureus* nasal carriage and infection has been established in specific subsets of patients, especially in IV drug users and patients with diabetes mellitus or on hemodialysis.¹² Methicillin-resistant strains are isolated in healthcare-associated endocarditis, although rare cases of community-acquired methicillin-resistant endocarditis have been reported.

Coagulase-negative staphylococci (CoNS), in a recent international study, were found to cause 16% of 537 cases of definite noninjecting drug use-associated PVE. Nearly 50% of patients with CoNS PVE presented between 60 days and 365 days after valve implantation. Methicillin resistance was present in 68% of CoNS strains.¹⁷ CoNS are also a well-documented, albeit rather rare, cause of native valve infective endocarditis. Most patients have documented valvular abnormalities, especially mitral valve prolapse. A substantial subset of CoNS infective endocarditis has been identified as being due to *Staphylococcus lugdunensis*, which causes destructive cardiac lesions; its differentiation from other CoNS species in the laboratory may be difficult.

Overall, staphylococci, streptococci, and enterococci account for more than 80% of microorganisms responsible for infective endocarditis.

Infrequent Pathogens: Enterobacteriaceae and HACEK Group.

Despite the high frequency of Enterobacteriaceae bacteremia leading to severe sepsis or septic shock, infectious endocarditis caused by these pathogens is extremely uncommon, probably because gram-negative bacilli adhere less avidly to the endothelium than do gram-positive cocci. Most cases of native valve infective endocarditis develop in patients with severe comorbidities, including cirrhosis or immunosuppression.¹⁸ Gram-negative bacilli are usually encountered in early and late PVE, but they account for only 2% of cases. Bacteria of the HACEK group (fastidious organisms) originate from the oropharyngeal or urogenital flora and include *Haemophilus aphrophilus* or *paraphrophilus* (H), *Actinobacillus actinomycetemcomitans* (A), *Cardiobacterium hominis* (C), *Eikenella corrodens* (E), and *Kingella* species (K). These HACEK pathogens are implicated in 2% of cases of infectious endocarditis on either native or prosthetic valves.⁶

Streptococcus pneumoniae infectious endocarditis occurs more commonly in alcoholics, but other patients, such as those with diabetes, malignancy, or chronic obstructive pulmonary disease, may be affected as well. Approximately 65% to 80% of patients have no known predisposing cardiopathy. The primary infection focus is the lungs, and meningitis is present in 40% to 60% of cases.¹⁹

Fungi are a rare cause of infective endocarditis, being isolated in 2% of all cases but in 4% of those patients with prosthetic valve infection. Although injection drug use was traditionally an important risk factor, a recent study showed that patients with *Candida* infective endocarditis were more likely to have a prosthetic valve, short-term indwelling catheters, and healthcare-associated infections.²⁰ Other fungi, such as *Aspergillus* spp., are even less frequently encountered. Fungi are frequently responsible for mural endocarditis.

Patients with Negative Blood Cultures. Five main points should be emphasized: (1) *Abiotrophia* spp. (previously classified as nutritionally variant streptococci) are the main cause of culture-negative infective endocarditis in patients who have recently received antibiotics. (2) Only 5% to 7% of patients who have not recently taken antibiotics have negative blood cultures. Polymerase chain reaction (PCR; of samples from blood, excised vegetation, or systemic emboli) can be used to identify the causative organism, such as *Bartonella* spp., *Tropheryma whippelii*, or *Coxiella burnetii*, as well as streptococci or other pathogens not isolated from blood cultures.²¹ (3) Serologic tests are useful to diagnose infectious endocarditis caused by those organisms or by *Brucella* and *Legionella* species. (4) HACEK organisms may

TABLE 86-1 Causative Agents of Left-Sided Native Valve Infectious Endocarditis

| MICROORGANISMS | ICE-PCS ⁶ (2781 PATIENTS), NUMBER (%) | BICHAT–CLAUDE BERNARD ICUs ²² (120 PATIENTS), NUMBER* (%) |
|---------------------------------|--|---|
| Streptococci | 810 (29) | 42 (35) |
| <i>Staphylococcus aureus</i> | 869 (31) | 48 (40) |
| Enterococci | 283 (10) | 4 (3) |
| CoNS | 304 (11) | 2 (1) |
| <i>Streptococcus pneumoniae</i> | NR | 5 (4) |
| HACEK | 44 (2) | NR |
| Fungi | 45 (2) | 4 (3) |
| Other | 121 (4) | 9 (7) |
| Negative blood cultures | 277 (10) | 10 (8) |

*The number of microorganisms exceeds the number of patients because some cases were polymicrobial.

CoNS, coagulase-negative staphylococci; HACEK, *Haemophilus aphrophilus* or *paraphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; ICU, intensive care unit; ICE-PCS, International Collaboration on Endocarditis–Prospective Cohort Study; NR, not reported.

require prolonged incubation and subculturing. (5) *Candida* (but not *Aspergillus*) spp. are usually isolated from routine blood cultures, but in some cases, fungi are recovered only from excised vegetations or peripheral emboli.

Specific Microbiological Characteristics of Infectious Endocarditis in ICU Patients

The microbiological characteristics of infectious endocarditis in patients who require ICU admission differ from those in the overall population. Analysis of a large series of infectious endocarditis patients hospitalized in two medical ICUs in a Parisian teaching hospital between 1994 and 2001 showed that *S. aureus* was the leading pathogen responsible for left-sided native valve and PVE²² (Table 86-1). Those figures were confirmed by an Austrian study of 33 ICU patients with infectious endocarditis: *S. aureus* was isolated from 36% of patients, versus 15% *S. viridans* and 12% enterococci.²³ In a French multicenter study, *S. aureus* accounted for 46% of 198 critically ill patients with definite endocarditis according to Duke criteria (see later discussion).²⁴ Clearly these findings are largely explained by *S. aureus* causing valve destruction, septic shock, and emboli to vital organs, such as the brain.

CLINICAL CHARACTERISTICS AND DIAGNOSIS

In 1994, a new set of diagnostic criteria, known as the *Duke criteria*, were proposed for the diagnosis of infectious endocarditis. It included two major and six minor criteria. Modifications of these criteria were proposed in 2000 to take into account transesophageal echocardiography findings and to consider all *S. aureus* bacteremias and positive Q fever serology as major criteria.²⁵

Clinical Characteristics

In ICU patients, the clinical presentation of infectious endocarditis often includes extracardiac manifestations or findings associated with cardiac complications. Patients are generally referred to the ICU for cardiogenic or septic shock, pulmonary edema caused by valvular or prosthetic dysfunction, neurologic events, acute renal failure, or respiratory failure in the setting of pulmonary emboli complicating right-sided infectious endocarditis. Two salient features, usually

associated with high-grade fever, strongly suggest the diagnosis of infectious endocarditis: (1) a heart murmur (most commonly preexisting) or a prosthetic valve and (2) petechiae on the skin (especially the extremities; Fig. 86-2) and conjunctivae. A typical ICU candidate has an acute febrile and toxic illness with a heart murmur, petechiae, and meningeal signs. Cerebrospinal fluid examination reveals pleocytosis and gram-positive cocci. Blood cultures yield *S. aureus*, and echocardiography confirms left-sided infectious endocarditis. In patients with catheter-related bacteremia, the diagnosis of infective endocarditis may be suggested by persistent positive blood cultures 3 to 5 days after the onset of antimicrobial treatment and removal of the catheter.

Echocardiography

Echocardiography has the following objectives: (1) to detect vegetations and determine their size, (2) to diagnose paravalvular extension of the infection, (3) to evaluate myocardial function, (4) to detect pericardial effusion, and (5) if cardiac surgery is being considered, to measure the valve ring to choose the appropriate prosthetic valve for replacement. Transthoracic echocardiography is rapidly obtained and noninvasive, but its overall sensitivity is only 40% to 65%. False-negative results are obtained when the examination is inadequate (especially in patients with obesity or chronic obstructive pulmonary disease) or when vegetations are less than 5 mm. Transesophageal echocardiography associated with color Doppler techniques is more invasive, but its sensitivity for detecting vegetations is 90% to 100%.⁵ Transesophageal echocardiography is particularly useful in patients with suspected valve perforation or extension of perivalvular infectious endocarditis and in those with PVE. Its sensitivity and specificity for the detection of cardiac abscess are 80% and 95%, respectively. This technique is necessary for all patients undergoing valve surgery and may be repeated at close intervals to help the physician decide when to operate. However, transesophageal echocardiography should be used cautiously in nonintubated critically ill patients with respiratory failure. Follow-up echocardiography to monitor complications and response to treatment is mandatory.⁵

COMPLICATIONS

Cardiac complications and hemodynamic failure, central nervous system (CNS) complications, and acute renal failure are the leading causes of ICU admission for patients with infectious endocarditis. Other complications are not addressed in detail.

Cardiac Complications and Hemodynamic Failure

Congestive heart failure (CHF) is usually caused by infection-induced valvular damage or prosthesis dysfunction. CHF is observed in 50% to 60% of cases overall and is more frequently associated with aortic disease than with mitral disease. CHF caused by aortic failure may require urgent valve replacement. Perivalvular extension of infectious endocarditis is frequently associated with CHF, and spread into the septum may lead to heart block. Erosion of a mycotic aneurysm of the sinus of Valsalva can cause hemopericardium and tamponade or can create fistulas to the right or left ventricle. Myocardial infarction due to coronary artery embolization is a rare event. Hemodynamic failure can also be caused by septic shock, especially during the bacteremic phase of *S. aureus* infectious endocarditis.²² All these complications may require the administration of positive inotropes or vasoconstrictors and the use of mechanical ventilation before valve replacement.

Neurologic Complications

CNS complications of infectious endocarditis occur frequently. They may be the first or predominant manifestation of the disease and can



FIGURE 86-2 ■ Typical purpuric lesions in a patient with *Staphylococcus aureus* mitral valve endocarditis.

arise through several mechanisms. CNS complications are a leading cause of death due to infectious endocarditis, and their specific management may be complex.

Frequency, Microbiology, and Timing

In most series, CNS involvement during the course of infectious endocarditis occurs in 20% to 40% of cases. Among 1329 episodes of infectious endocarditis from seven series described between 1985 and 1993, 437 (33%) were accompanied by CNS manifestations.²⁶ In a Finnish teaching hospital, 55 of 218 infectious endocarditis (25%) episodes were associated with neurologic complications.²⁷ However, two other studies reported lower rates: in France, strokes occurred in 17% of 264 infectious endocarditis cases caused by staphylococci or streptococci,¹ and in the United States, among 513 episodes of complicated, left-sided, native valve infectious endocarditis, focal neurologic signs or altered mental status were observed in 18% and 16% of cases, respectively.¹⁰ Experience from the large, contemporary ICE-PCS reported a similar (17%) incidence of strokes.⁶ The use of sensitive methods of detection, such as magnetic resonance imaging (MRI), indicates that silent cerebral complications are frequent. Among 60 patients who experienced episodes of left-sided infective endocarditis, 35% had a symptomatic neurologic event, while silent cerebral complications were detected in another 30%.²⁸ In a recently published study involving 127 patients with definite endocarditis who underwent systematic MRI, cerebral lesions were detected in 106 patients, most being asymptomatic.²⁹ Not surprisingly, the incidence of symptomatic neurologic complications is much higher in the subset of patients with infective endocarditis requiring admission to the ICU. A multicenter study showed a 55% incidence of symptomatic neurologic events among 198 critically ill patients with left-sided endocarditis.²⁴ Neurologic complications are a hallmark of left-sided abnormalities of either native or prosthetic valves. When neurologic complication rates were assessed as a function of the causative agent, the frequency of CNS involvement was two to three times higher with *S. aureus* than with other pathogens.²⁷

Most neurologic complications are already evident at the time of hospitalization or develop within a few days. The probability of developing these complications decreases rapidly once antimicrobial therapy has been started. In the ICE-PCS, the crude incidence of stroke in patients receiving appropriate antimicrobial therapy was 4.82/1000 patient-days in the first week of therapy and fell to 1.71/1000 patient-days in the second week. This rate continued to decline with further

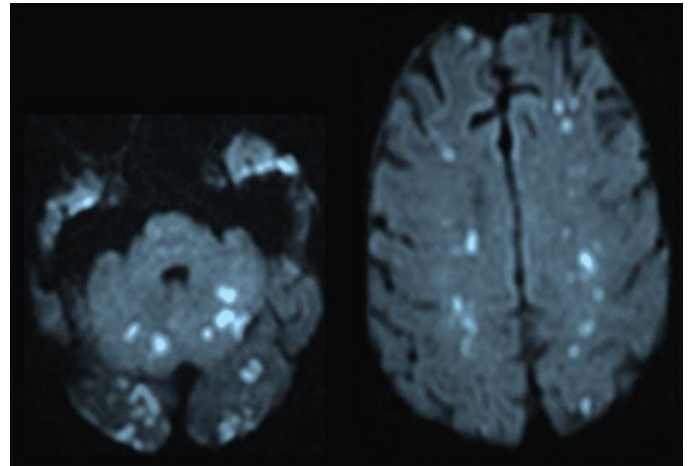


FIGURE 86-3 ■ T2-weighted magnetic resonance imaging sequence performed at the acute phase of aortic valve *Staphylococcus aureus* endocarditis, showing multiple ischemic cerebral lesions.

therapy.³⁰ Moreover, recurrent neurologic events, although possible even late, are uncommon.

Pathogenesis and Distribution

Neurologic complications of infectious endocarditis can arise through various mechanisms, but the major mechanism is cerebral embolization. Cerebral emboli (Fig. 86-3) result from dislodgment or fragmentation of cardiac vegetations, followed by vessel occlusion; this results in various degrees of ischemia and infarction, depending on the vessels and collateral blood flow. Occlusion of cerebral arteries, with either stroke or transient ischemic attack, accounts for 40% to 50% of CNS complications of infectious endocarditis.²⁶⁻²⁷ Cerebral hemorrhage may be the consequence of different mechanisms, each of which accounts for one-third of bleeding complications: rupture of an intracranial aneurysm; septic erosion of the arterial wall, without a well-delineated aneurysm (acute necrotizing arteritis); or hemorrhagic transformation of ischemic brain infarcts, especially in anticoagulated patients. Overall, intracranial hemorrhage represents 10% of CNS complications. Brain hemorrhage is more frequent during the bacteremic phase of *S. aureus* infectious endocarditis and is more likely with severe thrombocytopenia and anticoagulant therapy.²² A case-control study using diffusion-weighted MRI (Fig. 86-4) reported that cerebral microbleeds were observed in 57% of patients with infective endocarditis, compared to 15% of control subjects.³¹ Meningitis, occurring in 5% to 40% of patients with CNS manifestations of infectious endocarditis, can be the consequence of a wide variety of mechanisms. The cerebrospinal fluid may be purulent with positive cultures, clear with moderate pleocytosis, or hemorrhagic. Brain abscesses associated with infectious endocarditis are uncommon; they account for less than 5% of CNS events, but the rate depends on the imaging technique used. In addition, many small abscesses or areas of cerebritis resolve with antibiotics alone. Finally, *toxic encephalopathy*, defined as mental changes or stupor without focal neurologic manifestations and without computed tomography (CT) abnormalities, is often included among the CNS complications of infectious endocarditis. Obviously this manifestation can have different causes, such as subtle cerebral lesions, or it may be present in the setting of severe sepsis.²⁴

Specific Management

Infectious endocarditis occurring in patients receiving anticoagulant therapy poses a difficult problem. In the absence of CNS complications or in patients with nonhemorrhagic neurologic lesions, warfarin should be discontinued and replaced by heparin. However, in the presence of brain hemorrhage, anticoagulant therapy should be

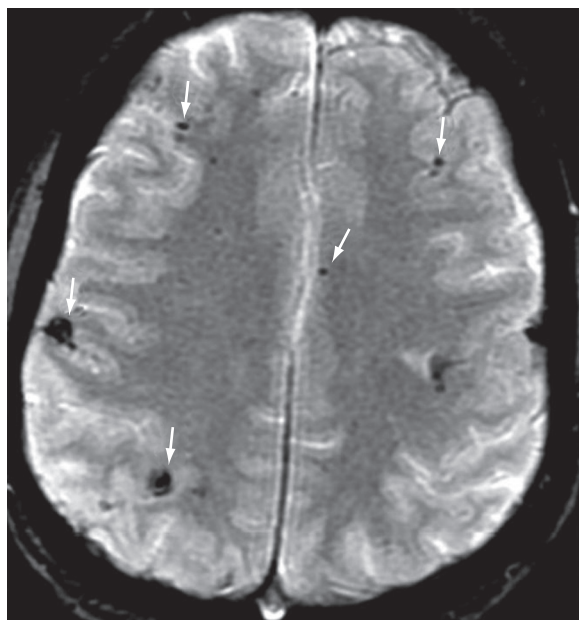


FIGURE 86-4 ■ T2-weighted magnetic resonance imaging sequence performed at the acute phase of definite mitral valve *Staphylococcus aureus* endocarditis, showing multiple cerebral microbleeds (arrows).

temporarily discontinued. CT scanning is essential for the diagnosis and management of CNS events associated with infectious endocarditis. In addition, it may be the only technique available for unstable ICU patients, especially those receiving mechanical ventilation. CT may show intracranial bleeding, ischemic lesions, or a pattern consistent with cerebral abscess. MRI is more sensitive for most lesions and should be performed in hemodynamically stable patients because it can modify clinical management.²⁹ Although conventional four-vessel angiography remains the gold standard for the evaluation of mycotic aneurysms, magnetic resonance angiography is a promising technique. In the absence of randomized trials, which are difficult (if not impossible) to organize, the respective roles of medical, endovascular, and neurosurgical treatment of intracranial aneurysms are not easily assessable. Endovascular treatment (coil embolization) seems to be a reliable and safe technique that should be considered when cerebral mycotic aneurysms are diagnosed.³²

Acute Renal Failure

Acute renal failure occurs in up to 40% of complicated infectious endocarditis cases necessitating ICU admission^{2,23} and may result from several mechanisms. It is often the consequence of cardiogenic or septic shock (with or without multiorgan failure), leading to acute tubular necrosis. Drugs, such as the combination of a glycopeptide and an aminoglycoside, and the use of iodine contrast medium for radiologic investigations may cause further deterioration of renal function. In some patients with streptococcal or staphylococcal infectious endocarditis, acute renal failure is caused by severe glomerulonephritis. Acute renal failure may require the initiation of dialysis.

Other Complications

Systemic embolism can involve many organs, such as the spleen and kidneys; rarely, the liver or the iliac, mesenteric, or peripheral arteries are involved. Splenic abscesses are caused mainly by *S. aureus* or *S. viridans*. Abdominal CT is the best procedure to detect splenic abscesses, which may require percutaneous drainage or splenectomy. Pulmonary emboli, the hallmark of right-sided endocarditis, may be

responsible for respiratory failure or even acute respiratory distress syndrome, especially in IV drug users with *S. aureus* infectious endocarditis.

MEDICAL AND SURGICAL TREATMENT

In the absence of large prospective randomized studies, which present a considerable challenge, the overall strategy for infectious endocarditis treatment is derived mainly from retrospective series, clinical judgment, and expert recommendations.

Antibiotic Treatment

Certain general principles underlie the current guidelines^{5,33} for infectious endocarditis treatment. In cases of streptococcal infectious endocarditis, determination of the minimal inhibitory concentration of penicillin is necessary to choose the best regimen. Parenteral antibiotics are recommended over oral drugs because of the importance of sustained antibacterial activity, which requires high dosages (e.g., 150 to 200 mg/kg of amoxicillin for streptococcal infectious endocarditis). However, oral antibiotics may be considered for right-sided *S. aureus* infectious endocarditis after a few days of parenteral antibiotics if IV administration is not possible because of poor venous access. In that case, the combination of a fluoroquinolone and rifampin is an acceptable regimen. Many experts recommend using a combination of agents with activities against the cell wall (β -lactams or glycopeptides) plus an aminoglycoside (gentamicin) for most cases of infectious endocarditis, especially complicated cases, such as those occurring in ICU patients. Gentamicin can be administered in one or two daily doses, except for infective endocarditis due to enterococci, for which two doses are recommended. The use and duration of aminoglycosides depend on the pathogen and, for streptococci, their susceptibility to penicillin G and the presence of a prosthesis (Table 86-2). Although a shorter course of aminoglycosides has been proposed for enterococcal infectious endocarditis,¹⁶ no controlled study has confirmed the safety of this strategy. For staphylococcal infectious endocarditis, a triple regimen including rifampin is recommended,³⁴ especially for patients with PVE. Short-term therapy (15 days) was shown to be effective in selected cases of uncomplicated *S. aureus* right-sided infectious endocarditis or left-sided native valve infectious endocarditis due to highly susceptible streptococci. However, most current recommendations emphasize prolonged antibiotic administration (4–6 weeks or even 8 weeks) for *S. aureus* PVE. The results of repeat valve cultures, but not positive gram staining or positive PCR, should be taken into account to decide how long to continue antimicrobial therapy after valve replacement.⁵

The role of new molecules in the treatment of infective endocarditis remains to be evaluated. Daptomycin is a bactericidal lipopeptide that can be used in methicillin-resistant *S. aureus*³⁵ and vancomycin-resistant enterococci infective endocarditis.³⁶

Surgical Management

In recent series,^{6,9} 48% to 50% of patients (up to 75% in specialized medical-surgical centers) undergo valve replacement during the acute phase of infectious endocarditis before the completion of antibiotic treatment.

Indications for and Timing of Cardiac Surgery

Absolute indications are CHF caused by valvular insufficiency, prosthesis obstruction or dehiscence, periannular abscess, or *S. aureus* or fungal PVE. These microorganisms cannot be eradicated without removal of the prosthesis. The development of CHF in the setting of infectious endocarditis generally requires cardiac valve replacement regardless of the number of days on antibiotics. Emergency cardiac surgery is recommended for the following situations: (1) aortic or mitral infective endocarditis with severe acute regurgitation or valve obstruction, causing refractory pulmonary edema or cardiogenic

TABLE 86-2

Antibiotic Treatment of Complicated Infectious Endocarditis as a Function of Valve Type, Pathogen, and Susceptibility

| MICROORGANISM | NATIVE-VALVE INFECTIOUS ENDOCARDITIS | PROSTHETIC-VALVE ENDOCARDITIS |
|---|---|---|
| Penicillin-susceptible streptococci (MIC < 0.125 mg/L) | Penicillin G, amoxicillin, or ceftriaxone for 4 wk* | Penicillin G or amoxicillin for 6 wk + gentamicin for 2 wk* |
| Relatively penicillin-resistant streptococci (MIC ≥ 0.125-2 mg/L) | Penicillin G or amoxicillin for 4 wk + gentamicin for 2 wk* | Penicillin G or amoxicillin for 4-6 wk + gentamicin for 4 wk* |
| Streptococci with penicillin G MIC > 2 mg/L, enterococci, and <i>Abiotrophia</i> spp. | Penicillin G or amoxicillin for 4-6 wk + gentamicin for 4 wk* | Penicillin G or amoxicillin for 6 wk + gentamicin for 6 wk* |
| MSSA | Nafcillin or oxacillin for 4-6 wk + gentamicin for 3-5 days† | Nafcillin or oxacillin + rifampin for ≥6 wk + gentamicin for 2 wk† |
| MRSA | Vancomycin + rifampin for 4-6 wk + gentamicin for 3-5 days | Vancomycin + rifampin for ≥6 wk + gentamicin for 2 wk |
| HACEK organisms | Ceftriaxone or cefotaxime for 4 wk | Ceftriaxone or cefotaxime for 6 wk |
| Enterobacteriaceae | Ceftriaxone or cefotaxime for 4 wk + gentamicin or amikacin for 1 wk‡ | Ceftriaxone or cefotaxime for 6 wk + gentamicin or amikacin for 2 wk‡ |
| <i>Bartonella</i> spp. | Ceftriaxone or doxycycline for 6 wk + gentamicin for 2-3 wk | Ceftriaxone or doxycycline for 6 wk + gentamicin for 2-3 wk |
| <i>Coxiella burnetii</i> | Doxycycline or ofloxacin + hydroxychloroquine for ≥18 mo | Doxycycline or ofloxacin + hydroxychloroquine for ≥18 mo |
| <i>Candida</i> spp. | LF AmB with or without 5-FC or AmB with or without 5-FC or an echinocandin for 2 wk, then fluconazole for susceptible organism in stable patient with negative blood culture results for 4 wk | LF AmB with or without 5-FC or AmB with or without 5-FC or an echinocandin for 2 wk, then fluconazole for susceptible organism in stable patient with negative blood culture results for 4 wk. Lifelong suppressive therapy for prosthetic valve endocarditis is recommended if valve cannot be replaced. |

*Vancomycin or teicoplanin therapy is indicated for patients who are allergic to β -lactam antibiotics. Optimal antimicrobial therapy is not available for high-level aminoglycoside-resistant and vancomycin-resistant enterococci. Eradicating these pathogens requires consultation with an infectious disease specialist or a microbiologist.

†A first-generation cephalosporin is indicated for patients who are allergic to penicillin, except those with immediate-type hypersensitivity reactions to β -lactam antibiotics, who should be treated with a glycopeptide.

‡The results of susceptibility tests might indicate the need to adapt the initial regimen.

5-FC, 5-fluorocytosine; HACEK, *Haemophilus aphrophilus* or *paraphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; LF AmB, lipid formulation of amphotericin B; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

shock and (2) aortic or mitral infective endocarditis with a fistula into a cardiac chamber or pericardium, causing pulmonary edema or shock.⁵

Relative indications requiring case-by-case evaluation are persistent bacteremia beyond 7 days despite appropriate antibiotic therapy, non-*S. aureus* PVE, and difficult-to-treat organisms, such as *C. burnetii*, *Bartonella* spp., multiresistant enterococci, or *P. aeruginosa*, especially in patients with PVE.

With regard to other potential indications, contraindications, and timing of valve replacement, the following factors should be emphasized. (1) Although the risk of systemic embolization is higher in patients with large vegetations on the mitral valve, vegetation characteristics alone rarely justify valve surgery. The decreasing risk of emboli with time, especially after the first week of effective antibiotic therapy, should be considered when deciding whether to operate.³⁰ (2) In patients with neurologic complications, a conservative approach is to delay cardiac surgery for 2 or 3 weeks after an embolic event and for at least 1 month after cerebral bleeding. However, in the case of CHF, the valve can be replaced within 7 days or less after an embolic infarct, especially when the infarct is of limited size and the patient's good mental status prevails.⁵ (3) In that case, there is a high probability of complete neurologic recovery.³⁷ True contraindications to valve surgery are rare and include uncontrolled septic shock, unhealed sternal wound infection, and severe coagulation disorders.

Coronary angiography is recommended for patients older than 40 years and those with at least one risk factor for coronary artery disease, except when emergency surgery is needed.⁵

Surgical Technique

Surgery includes complete removal of all infected and necrotic tissue, followed by valve reconstruction. In selected cases, good results have

been achieved with conservative mitral valve valvuloplasty. In most patients, valve replacement with a mechanical or biological prosthesis or a homograft is necessary. The use of cryopreserved homografts has been suggested to reduce the risk of persistent or recurrent infection. However, mechanical prostheses and xenografts compare favorably, with improved durability.³⁸

OUTCOME AND PROGNOSTIC FACTORS

The overall in-hospital mortality was 18% in the large, contemporary ICE-PCS.⁶ This figure included all types of infectious endocarditis, however, and warrants refinement according to the different categories of disease. Another recent cohort of 513 patients with complicated left-sided native valve infectious endocarditis had a 6-month mortality rate of 26%.¹⁰ Two studies found mortality rates for PVE of 33% and 22%, respectively.^{9,36} In the ICE-PCS, healthcare-associated native valve endocarditis was associated with higher in-hospital mortality (25%) compared to community-acquired endocarditis (13%).¹³ Survival of ICU patients with infective endocarditis is lower. Among 228 patients with infectious endocarditis referred to the two ICUs in our hospital, the in-hospital mortality rate was 45%.²² It was 42% in a multicenter study involving 198 critically ill patients with infective endocarditis.²⁴

Prognostic factors for survival have been studied by several authors. In most cases, these reflect the site of infectious endocarditis (see earlier discussion), comorbidities, causative agent, and types of complications. CHF, septic shock, neurologic events, *S. aureus* PVE, increasing age, and paravalvular complications are associated with in-hospital mortality in most studies.^{6,10,13,23,24} The hemodynamic status of the patient at the time of valve replacement is the main determinant of perioperative mortality, with a poorer prognosis for patients with

pulmonary edema or impaired left ventricular function.^{3,7} Neurologic events markedly increase the risk of death, which can reach 50% in patients with altered mental status.¹⁰ Among microorganisms, *S. aureus* is associated with higher mortality rates than streptococci for left-sided native valve endocarditis and PVE.^{13,25,26} Finally, mounting evidence shows that for both complicated left-sided native valve infectious endocarditis and *S. aureus* PVE, valve replacement during active endocarditis combined with medical therapy is associated with a better outcome than medical treatment alone.^{6,12,13,39,40} The reoperation rate, mainly for prosthesis dehiscence or new infectious endocarditis, is 2% to 3% per year, and the 5-year survival rate is approximately 80% to 90% for native valve infectious endocarditis and 60% for PVE. A

scoring system taking into account mental status, comorbidity, CHF, microbiology, and use of surgical treatment in left-sided native valve infectious endocarditis was recently published.⁴¹

CONCLUSION

Despite advances in both diagnosis and treatment, infectious endocarditis still carries high morbidity and mortality rates, especially for patients requiring ICU admission. Improvement of outcomes requires a multidisciplinary approach to optimize medical treatment and decision making concerning valve surgery.

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Hypertension is a common problem, and population data suggest its incidence is increasing globally. One billion individuals worldwide now have hypertension.¹ Nearly one in three U.S. adults have hypertension. Compared to two-thirds in the past decade, currently half of these individuals don't have their blood pressure under control. One-third of those in whom it is not controlled are unaware of their diagnosis.^{2,3} The exact risk of hypertensive crisis is not clear, but most authors estimate it to be less than 1%. The incidence may have decreased with widespread use of antihypertensive therapy.^{4,5}

Hypertensive emergency is defined as an elevated blood pressure associated with evidence of acute end-organ damage. With acute damage to vital organs such as the kidney, heart, and brain, there is a significant risk of morbidity in hours without therapeutic intervention. Both the absolute level of blood pressure and the time course of the elevation determine the development of an emergency. In general with hypertensive emergency, the diastolic blood pressure is above 120 mm Hg. However, in children, gravid females, and previously normotensive individuals, hypertensive emergencies may occur with relatively minor increases in blood pressure. It is very important to identify this syndrome early to prevent end-organ damage and institute appropriate therapy as soon as the diagnosis is made. Malignant hypertension is a specific syndrome in which a markedly elevated blood pressure is associated with hypertensive neuroretinopathy.

Individuals with *hypertensive urgency* have an elevated blood pressure (systolic blood pressure often > 180 and diastolic pressure often > 115 mm Hg) without evidence of acute end-organ damage. Hypertensive urgency may be associated with chronic, stable complications such as stable angina, previous myocardial infarction, chronic congestive heart failure, chronic renal failure, previous transient ischemic attacks, or previous cerebrovascular accident with no threat of an acute insult. The focus of this chapter is on both types of hypertensive crises, with the emphasis on hypertensive emergency.

PATHOPHYSIOLOGY OF HYPERTENSIVE EMERGENCY

The precise pathophysiology of hypertensive emergency is unknown. An abrupt increase in blood pressure is one of the initiating events in the transition from simple hypertension or normotension to hypertensive emergency. The product of cardiac output and peripheral vascular resistance determines blood pressure. The initial blood pressure increase is likely secondary to an increase in vascular resistance. Considerable evidence suggests that mechanical stress in the arteriolar wall leads to disruption of endothelial integrity.⁶ With disruption of vascular integrity, diffuse microvascular lesions develop.^{7,8} Fibrinoid necrosis of the arterioles is seen in vulnerable organs and is considered the histologic hallmark of hypertensive emergency.^{7,8} It is unclear whether hypertension alone causes the development to hypertensive emergency or whether other factors are necessary. For example, increases in peripheral vascular resistance result in part from activation of the renin-angiotensin-aldosterone system. Evidence suggests angiotensin II may directly injure the vascular wall by activation of genes for proinflammatory cytokines (e.g., interleukin 6) and also of nuclear factor κ B.^{9,10} Other vascular-toxic influences may contribute to increased peripheral vascular resistance, including hyperviscosity, immunologic factors, and other hormones including catecholamines, vasopressin, and endothelin.¹¹⁻¹³ The end result of these changes is a

significant increase in peripheral vascular resistance, with ischemia of heart, brain, and kidneys.

In considering hypertensive emergencies and their treatment, the impact of blood pressure on cerebrovascular physiology is important. For example, hypertensive encephalopathy is a distinct clinical syndrome that occurs when rapidly rising central perfusion pressures exceed the ability of the central nervous system (CNS) to autoregulate. *Autoregulation* of cerebral blood flow (CBF) refers to the ability of the brain to maintain a constant CBF as the cerebral perfusion pressure (CPP) varies between 60 to 150 mm Hg. In the setting of chronic hypertension, the range of autoregulation is increased to a range of 80 to 160 mm Hg. Autoregulation of CBF is a function of CPP (derived from the mean arterial pressure [MAP] minus the venous pressure) and cerebral vascular resistance (CVR), according to the following equation:

$$CBF = CPP / CVR$$

Under normal physiologic conditions, the backflow in the cerebral venous system or venous pressure is near zero, and the arterial pressure determines the CPP. With acute brain injury, as seen with subarachnoid hemorrhage, stroke, and intracranial hemorrhage, the ability of the brain to autoregulate and maintain CBF is impaired. Inability to autoregulate CBF is also seen in hypertensive emergency when the MAP is greater than 140 mm Hg.

DIAGNOSIS OF HYPERTENSIVE EMERGENCIES

Medical History, Physical Examination, and Laboratory Evaluation

From 40% to 50% of hypertensive emergencies arise in patients with preexisting hypertension without identifiable secondary causes.^{14,15} Essential hypertension is the underlying disorder in the majority of African American individuals.¹⁶⁻¹⁸ In contrast, from 50% to 60% of white patients with malignant hypertension have an identifiable cause (Box 87-1). Renovascular hypertension secondary to either fibromuscular dysplasia or atherosclerosis is not uncommon. Hypertensive emergency can occur in individuals with no hypertensive history, as in preeclampsia, pheochromocytoma, drug withdrawal, and acute glomerulonephritis. A medication history, including over-the-counter medications and illegal drug use, should be ascertained from every patient. Malignant hypertension is a unique clinical and pathologic syndrome where increases in blood pressure and target-organ damage are caused by changes in the vasculature characterized by fibrinoid necrosis and a proliferative endarteritis. Risk factors associated with the development of malignant hypertension include age between 30 and 50 years,¹⁹ male gender,⁶ African American background,¹⁵ and smoking (increases the risk by 2.5- to 5-fold).²¹

The clinical presentation of hypertensive emergency may include headache that is generally located occipitally or anteriorly, with a steady quality. Other symptoms include visual complaints (scotoma, diplopia, hemianopsia, blindness), neurologic symptoms (focal deficits, stroke, transient ischemic attacks, seizures, confusion, somnolence), ischemic chest pain, renal symptoms (nocturia, polyuria, hematuria), back pain (aortic aneurysm), and gastrointestinal complaints (nausea,

BOX 87-1 Syndromes of Hypertensive Crisis

Malignant hypertension
 Nonmalignant hypertension with target-organ disorders
 Patient requiring emergency surgery with poorly controlled hypertension
 Hyperviscosity syndrome
 Postoperative patient
 Renal transplant patient: acute rejection, transplant renal artery stenosis
 Quadriplegic patient with autonomic hyperreflexia
 Severe burns
 Acute aortic dissection
 Intracranial hemorrhage, ischemic stroke, or subarachnoid hemorrhage
 Hypertensive encephalopathy
 Myocardial ischemia/acute left ventricular failure
 Preeclampsia/eclampsia
 Antiphospholipid antibody syndrome
 Acute renal failure
 Scleroderma renal crisis
 Chronic glomerulonephritis
 Reflux nephropathy
 Analgesic nephropathy
 Acute glomerulonephritis
 Radiation nephritis
 Ask-Upmark kidney
 Chronic lead intoxication
 Renovascular hypertension
 Fibromuscular dysplasia
 Atherosclerosis
 Endocrine hypertension
 Congenital adrenal hyperplasia
 Pheochromocytoma
 Oral contraceptives
 Aldosteronism
 Cushing's disease/syndrome
 Systemic vasculitis
 Atheroembolic renal crisis
 Drugs
 Oral contraceptives
 Nonsteroidal antiinflammatory agents
 Atropine
 Corticosteroids
 Sympathomimetics
 Erythropoietin
 Lead intoxication
 Cyclosporine
 Catecholamine excess states
 Pheochromocytoma
 MAO/tyramine interaction
 Antihypertensive withdrawal
 Cocaine intoxication, sympathomimetic overdose

vomiting). Weight loss occurs as the high levels of circulating renin and angiotensin induce a diuresis.²² These patients often present with intravascular volume depletion, which has strong implications for treatment.

The blood pressure is measured in both arms with the patient lying and standing. Pathologic processes such as atherosclerosis, Monckeberg's medial calcification, and metastatic calcification as experienced in end-stage renal disease (ESRD), cause stiffening of the vascular wall, which can prevent vessel compression by external compression with a blood pressure cuff. This results in an artificial and at times extreme increase in the systolic and diastolic blood pressure, or "pseudohypertension." Clues to pseudohypertension include a markedly elevated blood pressure in an individual without evidence of end-organ damage. The diagnosis is suggested by a palpable radial artery despite proximal compression with a sphygmomanometer (Osler's maneuver).²³

A dilated funduscopic examination should be performed on all individuals. Arteriolar thickening reflects chronic hypertension and is manifested by increased light reflex, vascular tortuosity, and arteriovenous nicking where the arterioles cross the venules. These changes have

BOX 87-2 Differential Diagnosis of Hypertensive Encephalopathy

Cerebral infarction
 Subarachnoid hemorrhage
 Intracerebral hemorrhage
 Subdural or epidural hematoma
 Brain tumor or other mass lesion
 Seizure disorder
 Central nervous system vasculitis
 Encephalitis/meningitis
 Drug ingestion
 Drug withdrawal

no prognostic significance with regard to hypertensive emergency. However, as hypertension increases in severity, there are additional findings caused by the breakdown of the blood-retina barrier, leading to retinal hemorrhage and leakage of lipids, causing hard exudates or cotton-wool spots as a result of nerve ischemia and swelling of the optic nerve with papilledema.²⁴

A complete cardiovascular examination should include a careful evaluation for evidence of left ventricular hypertrophy and heart failure and peripheral pulse examination for absence or delay suggestive of aortic dissection. Examination of the abdomen should include evaluation for enlarged kidneys as seen with polycystic kidney disease as well as for evidence of aortic aneurysm. Last, a careful neurologic examination should be done to rule out any evidence of a cerebral vascular accident. Alterations in mental status may indicate a stroke or hypertensive encephalopathy. The initial laboratory evaluation should include a serum sodium, chloride, potassium, bicarbonate, creatinine and blood urea nitrogen, complete blood count (with a peripheral smear to identify schistocytes), prothrombin time, activated partial thromboplastin time, serum and urine toxicology screen, pregnancy test when appropriate, an electrocardiogram, and a urinalysis. Evidence of intravascular hemolysis is common and may make it difficult to differentiate hypertensive emergency from primary vasculitis with secondary hypertension.^{25,26} The renin-angiotensin-aldosterone axis is markedly activated, as evidenced by hypokalemia and metabolic alkalosis.^{4,27} The blood urea nitrogen and creatinine are often elevated. The urinalysis may show small amounts of proteinuria as well as hematuria with occasional erythrocyte casts.⁶ Marked increases in proteinuria suggest a primary glomerular process such as glomerulonephritis as the etiology of the elevated blood pressure.

If hypertensive encephalopathy is suspected, magnetic resonance imaging (MRI) of the brain should be performed. Edema seen posteriorly, particularly in the parieto-occipital regions (a finding called *posterior leukoencephalopathy*) and rarely in the brainstem are the manifestations of hypertensive encephalopathy.^{28,29} It is important to consider and eliminate other conditions with a similar clinical presentation (Box 87-2). Several important diagnostic considerations help exclude other causes of altered mental status: (1) symptoms of generalized brain dysfunction tend to develop over time (12-24 hours) with hypertensive encephalopathy, as compared with acutely in ischemic stroke or cerebral hemorrhage; (2) focal neurologic findings are unusual with hypertensive encephalopathy unless there is an associated bleed; (3) papilledema is almost always noted with hypertensive encephalopathy and if absent should raise suspicion of another etiology; and (4) in comparison with an acute CNS bleed, mental status with hypertensive encephalopathy improves within 24 to 48 hours of treatment.

TREATMENT OF HYPERTENSIVE EMERGENCY

Patients with hypertensive emergency are best treated parenterally with intensive care monitoring by arterial cannulation or automated blood pressure cuff measurement. In general, the need to lower the blood

pressure and the rate at which this should occur is dictated by the clinical setting. Excessive falls in pressure should be avoided, given the potential for resulting in renal, cerebral, and coronary ischemia.

In most but not all settings, blood pressure can be reduced acutely by 20% to 25% within minutes to hours.⁴ Although the autoregulatory range of CBF is reset upward in chronic hypertension, the lower limit of the autoregulation remains approximately 25% below the resting MAP in patients with both normotension and chronic hypertension.³⁰ When the arterial blood pressure falls below this lower limit, CBF progressively decreases and symptoms of low CBF, including nausea, yawning, hyperventilation, clamminess, and syncope, develop. To protect cerebral function, after an initial reduction of blood pressure by 20% within the first hour, blood pressure is further reduced over the next 2 to 6 hours to the 160/110 range as long as the patient remains stable.⁴ Assuming continued stability, the blood pressure may then be decreased to 140/90 mm Hg over the next 24 to 48 hours.⁴ With these decreases in blood pressure, CBF autoregulation is usually maintained. There are several clinical settings where additional issues and alternative approaches to reducing blood pressure should be considered. In ischemic stroke, immediate reduction of blood pressure is usually not indicated except when the blood pressure is over 220/120 or the patient requires thrombolytic therapy. Recent data indicate that acute blood pressure reduction is of no benefit (CATIS trial) or even harmful (SCAST trial).^{31,32} In intracerebral hemorrhage, acute lowering of systolic blood pressure to 140 mm Hg is recommended based on weak evidence. Results of the recent INTERACT2 study support this recommendation.³³ In acute aortic dissection, if the patient tolerates, a rapid blood pressure reduction in 15 to 30 minutes to a systolic blood pressure under 100 mm Hg is clinically warranted. Finally, in previously normotensive subjects with abrupt increases in BP and those with active unstable angina or congestive heart failure with pulmonary edema,

Exceptions to rapid blood pressure reduction may include older patients with carotid stenosis, since these individuals are particularly susceptible to CNS hypoperfusion. Significant reduction of blood pressure in the setting of ischemic stroke may not be beneficial (discussed later). Overall, blood pressure management in patients with stroke or intracranial bleeding is controversial, since the loss of CBF autoregulation and the presence of brain edema require high systemic pressures to provide adequate cerebral perfusion.

SPECIFIC TREATMENT RECOMMENDATIONS FOR HYPERTENSIVE EMERGENCY BASED ON ETIOLOGY

General Comments on Medications Used to Treat Hypertensive Emergency

The classes of parenteral antihypertensive agents available to treat hypertensive emergency include direct vasodilators (sodium nitroprusside, nitroglycerin), α - and β -adrenergic blockers (labetalol), α -adrenergic blockade (phenolamine), angiotensin-converting enzyme (ACE) inhibitors (enalaprilat), calcium channel blockers (nicardipine and clevidipine), and dopamine agonists (fenoldopam). Some of the advantages and disadvantages of these medications are detailed in Table 87-1. There is no consensus on the most effective antihypertensive medications in the setting of a CNS insult and no large randomized trials demonstrating the superiority of a given agent. Rather, the choice of antihypertensive therapy should be individualized to the patient and clinical setting. Most authors now caution against the use of nitroprusside in the setting of increases in intracranial pressure (ICP). Vasodilators increase blood volume and therefore have the potential to increase the ICP. Animal and human studies in the setting of a normal ICP show no effect of nitroprusside on ICP.²⁵⁻²⁷ However, in studies on animals and humans with preexisting increased ICP, nitroprusside further increased the ICP, likely reflecting vasodilatation on the background of decreased cranial compliance.³⁴⁻³⁸ When sodium nitroprusside is

contraindicated, other treatment options include labetalol and nicardipine. Fenoldopam, which is an agonist of the vasodilator dopamine-1 receptor, shares with nitroprusside a rapid onset and short duration of action. In addition, in contrast to nitroprusside, fenoldopam increases renal blood flow, induces natriuresis, and produces no toxic metabolites.³⁹⁻⁴³

Malignant Hypertension

As noted above, malignant hypertension is specific syndrome characterized by markedly elevated pressures in conjunction with hypertensive neuroretinopathy. Funduscopic examination often reveals flame-shaped hemorrhages, cotton-wool spots, or papilledema. Malignant hypertension is also associated with nephropathy, encephalopathy, microangiopathic hemolytic anemia, and cardiac ischemia. Untreated malignant hypertension is a rapidly fatal disorder, with a mortality of more than 90% within 1 year, as reported in a classic series by Kincaid-Smith.⁷ In this series, deaths were due to renal failure (19%), congestive heart failure (13%), renal failure plus congestive heart failure (48%), stroke (20%), and myocardial infarction (1%).

Aggressive therapy to prevent progressive ischemic injury in malignant hypertension is critical. Nitroprusside had been the preferred agent; however, due to the concerns related to increased ICP, cyanide toxicity in the setting of anemia or liver disease, thiocyanate toxicity in the setting of renal failure, and the availability of the newer agents, its utility has decreased over the years. A number of parenteral agents including fenoldopam and nicardipine have been used as successful alternatives to nitroprusside. If nitroprusside is used, thiocyanate levels should be monitored and the duration of therapy kept to less than 72 hours whenever possible. Fenoldopam has no toxic metabolites and may protect renal function.³⁹⁻⁴³ Premature discontinuation of parenteral therapy may cause rebound hypertension. Oral therapy is usually started after the pressure has been stabilized on parenteral therapy, and the latter is then slowly weaned.

Renal failure is common with malignant hypertension, and, in a vicious cycle, the renal failure exacerbates the hypertension. Aggressive treatment can arrest and reverse renal damage. Since the arteriolopathy of malignant hypertension includes fixed anatomic lesions, initial lowering of blood pressure may worsen renal function. Dialysis may be required in patients presenting with a creatinine greater than 4.5 mg/dL.⁴⁴ In the majority of patients, renal function begins to improve after 2 weeks of therapy. Of the patients who require dialysis, 50% will regain sufficient function to discontinue dialysis.⁴⁵ Recovery of renal function is predicted when the combined length of both kidneys is 20.2 cm or more but is felt to be unlikely when the length is 14.2 or less.⁴⁶ The mean time to recovery is approximately 2 to 3 months, but recovery after up to 26 months has been reported.⁴⁷ In patients with malignant hypertension secondary to glomerulonephritis, eventual deterioration to ESRD may occur despite blood pressure control.⁴⁸ In contrast, renal function tends to remain well preserved in patients without underlying glomerulonephritis if the blood pressure is well controlled.

Hypertensive Encephalopathy

In hypertensive encephalopathy, the MAP exceeds the limits of autoregulation, and brain edema develops from extravasation of plasma proteins. If hypertensive encephalopathy is untreated, coma and death may follow.⁴⁹ The challenge of hypertensive encephalopathy is appropriate lowering of blood pressure in the setting of CNS ischemia and edema. The hallmark of hypertensive encephalopathy is improvement within 12 to 24 hours of adequate blood pressure reduction. The MAP should be cautiously reduced by no more than 15% over 2 to 3 hours. Neurologic complications have been reported from reductions in MAP of 40% or more.⁵⁰

Hypertensive encephalopathy is one of the medical conditions believed to cause reversible posterior leukoencephalopathy, a condition that results from reversible vasogenic subcortical edema without

TABLE 87-1 Treatment of Hypertensive Crisis: Intravenous Medications

| DRUG NAME AND MECHANISM OF ACTION | INDICATIONS/ADVANTAGES/DOSE | DISADVANTAGES/ADVERSE EFFECTS/METABOLISM CAUTIONS |
|---|--|--|
| SODIUM NITROPRUSSIDE Nitric oxide compound; vasodilation of arteriolar and venous smooth muscle Increases cardiac output by decreasing afterload | Useful in most hypertensive emergencies Onset of action immediate, duration of action 1-2 min Dose: 0.25 µg/kg/min Maximum dose: 8-10 µg/kg/min | Contraindicated in high-output cardiac failure, congenital optic atrophy. Anemia and liver disease at risk of cyanide toxicity: acidosis, tachycardia, change in mental status, almond smell on breath. Risk of thiocyanate toxicity with renal disease: psychosis, hyperreflexia, seizure, tinnitus. Cautious use with increased intracranial pressure. Do not use maximum dose for more than 10 minutes. Crosses the placenta. |
| NITROGLYCERIN Directly interacts with nitrate receptors on vascular smooth muscle Primarily dilates venous bed Decreases preload | Use with symptoms of cardiac ischemia, perioperative hypertension in cardiac surgery Initial dose: 5 µg/min Maximum dose: 100 µg/min | Contraindicated in angle-closure glaucoma, increased intracranial pressure. Blood pressure decreased secondary to decreased preload, cardiac output—avoid when cerebral or renal perfusion compromised. Caution with right ventricular infarct. |
| LABETALOL β- and α-Adrenergic blockade α:β-Blocking ratio is 1:7 | Onset of action 2-5 min, duration 3-6 hours Bolus 20 mg, then 20-80 mg every 10 min for maximum dose 300 mg Infuse at 0.5-2 mg/min | Avoid in bronchospasm, bradycardia, congestive heart failure, greater than first-degree heart block, second/third trimester pregnancy. Use caution with hepatic dysfunction, inhalational anesthetics (myocardial depression). Enters breast milk. |
| ESMOLOL Cardioselective β1-adrenergic blocking agent | Use with aortic dissection Use during intubation, intraoperative, and postoperative hypertension Onset of action 60 seconds, duration 10-20 min 200-500 µg/kg/min for 4 min, then infuse 50-300 µg/kg/min | See labetalol. Not dependent on renal or hepatic function for metabolism (metabolized by hydrolysis in red blood cells). |
| FENOLDOPAM Postsynaptic dopamine-1 agonist; decreases peripheral vascular resistance; 10 times more potent than dopamine as vasodilator | May be advantageous in kidney disease, increases renal blood flow, increases sodium excretion, no toxic metabolites Initial dose: 0.1 µg/kg/min, with titration every 15 min No bolus | Contraindicated in glaucoma (may increase intraocular pressure) or allergy to sulfites; hypotension, especially with concurrent β-blocker. Check serum potassium every 6 hours. Concurrent acetaminophen may significantly increase blood levels. Dose-related tachycardia. |
| HYDRALAZINE Primarily dilates arteriolar vasculature | Primarily used in pregnancy/eclampsia Dose: 10 mg every 20-130 min; maximum dose 20 mg Decreases blood pressure in 10-20 min Duration of action 2-4 h | Reflex tachycardia; give β-blocker concurrently. May exacerbate angina. Half-life 3 hours, affects blood pressure for 100 hours. Depends on hepatic acetylation for inactivation. |
| PHEHTOLAMINE α-Adrenergic blockade | Used primarily to treat hypertension from excessive catecholamine excess (e.g., pheochromocytoma) Dose: 5-15 mg Onset of action 1-2 min, duration 3-10 min | β-blockade is generally added to control tachycardia or arrhythmias. As in all catecholamine excess states, β-blockers should never be given first, as the loss of β-adrenergically mediated vasodilatation will leave α-adrenergically mediated vasoconstriction unopposed and result in increased pressure. |
| NICARDIPINE Dihydropyridine calcium channel blocker; inhibits transmembrane influx of calcium ions into cardiac and smooth muscle | Onset of action 10-20 min, duration 1-4 h Initial dose: 5 mg/h to maximum of 15 mg/h | Avoid with congestive heart failure, cardiac ischemia. Adverse effects include tachycardia, flushing, headache. |
| CLEVIDIPINE Short-acting dihydropyridine calcium channel antagonist ¹⁰¹ | Initial dose: 1 mg/h; can be increased to 21 mg/h | Reduces blood pressure without affecting cardiac filling pressures or causing reflex tachycardia |
| ENALAPRILAT Angiotensin-converting enzyme inhibitor | Onset of action 15-20 min, duration 12-24 h Dose: 1.25-5 mg every 6 h | Response not predictable, with high renin states may see acute hypotension. Hyperkalemia in setting of reduced glomerular filtration rate. Avoid in pregnancy. |
| TRIMETHAPHAN Nondepolarizing ganglionic blocking agent; competes with acetylcholine for postsynaptic receptors | Used in aortic dissection Dose: 0.5-5 mg/min | Does not increase cardiac output. No inotropic cardiac effect. Disadvantages include parasympathetic blockade, resulting in paralytic ileus and bladder atony and development of tachyphylaxis after 24-96 hours of use. |

infarction.^{28,29} This syndrome is characterized by headache, decreased alertness, changes in behavior including confusion and diminished speech, seizures, and alterations in visual perceptions. It is rapidly reversible with lowering of the blood pressure.^{28,29} An MRI examination shows characteristic findings including white matter edema in the posterior cerebral hemispheres.²⁸

There is a growing literature supporting a shared pathologic process between hypertensive encephalopathy and eclampsia. Both clinical

syndromes have the same clinical features and imaging findings. Eclampsia during pregnancy, as well as postpartum eclampsia, has also been associated with reversible posterior leukoencephalopathy.^{28,29}

In previously normotensive patients, including those with eclampsia, blood pressure should be normalized. If the mental status worsens with treatment, the pressure should be allowed to increase until neurologic symptoms resolve and then be reduced to within the normal range over several days to allow restoration of autoregulation.

Ischemic Cerebral Infarction

When the CPP decreases below the level of autoregulation, ischemia develops. In response, there may be a marked elevation in arterial blood pressure to maintain perfusion, which tends to spontaneously return to baseline 24 to 48 hours after the acute event. Thus, treatment of acutely increased blood pressure may not be required. Following ischemic cerebrovascular accident, it is also important to consider other causes that may contribute to an increase in blood pressure, including a full bladder, nausea, pain, preexisting hypertension, hypoxia, or increased ICP. Often times, simply calming the patient, treating pain, and relieving a full bladder may reduce the blood pressure.

Data from animal studies show that in the area surrounding the ischemic infarct, there are “neurons at risk” that rely on collateral circulation to maintain perfusion.⁵¹ These neurons are nonfunctional but not dead, a phenomenon referred to as *ischemic penumbra*, and they can potentially be rescued by reperfusion.⁵² The degree to which this occurs in humans is not known. In addition, in acute stroke, autoregulation is impaired, and CBF is therefore not preserved in a predictable manner. As a result of these changes, acute reductions in blood pressure could potentially increase the area of infarct, resulting in severe clinical consequences.

Comprehensive guidelines for the treatment of stroke recommend that patients determined to be candidates for administration of intravenous recombinant tissue plasminogen activator, the blood pressure must be reduced if the systolic blood pressure is >185 mm Hg or the diastolic blood pressure is >110 mm Hg, and the patient must be carefully monitored before, during, and after administration of this compound. Thrombolytic therapy is contraindicated if the blood pressure is >185/100 mm Hg.⁵³

Questions remain as to how to manage individuals with ischemic stroke who are not candidates for thrombolysis. There are no good data from randomized controlled trials to guide blood pressure management. A prospective observational study analyzing the impact of blood pressure lowering in the setting of ischemic stroke in 1092 patients suggested an improved outcome at 3 months with modest reductions in systolic blood pressure between 10 and 27 mm Hg. However, the authors noted that the benefit of blood pressure reduction waned with age. If the systolic pressure was lowered by more than 27 mm Hg, the odds ratio for a poor outcome at 3 months increased more than 5-fold at age 70 to 76 years, nearly 10-fold for 76 to 80 years, and nearly 15-fold in patients older than 80 years.⁵⁴ Moreover, recently published randomized controlled studies, where patients were enrolled as long as 30 to 48 hours after stroke onset, do not show any significant difference in mortality and functional outcome with aggressive hypertension treatment.^{31,32} In the absence of any definitive data, the current recommendation is that if there is no indication for acute lowering of the blood pressure (e.g., acute ischemic damage to vital organs such as cardiac ischemia or aortic dissection), then the threshold for treatment should be a systolic blood pressure over 220 mm Hg or a diastolic blood pressure over 120 mm Hg, with the aim to lower the blood pressure 15% to 25% over the first 24 hours in the acute phase of ischemic stroke.⁵³

Subarachnoid Hemorrhage

Approximately 10% of cerebrovascular accidents are due to subarachnoid hemorrhage, which remains a devastating entity with a mortality rate of 50% to 60% at 30 days and a 50% dependency rate in survivors.⁵⁵ Subarachnoid hemorrhage increases ICP and decreases cerebral perfusion, causing global ischemia. Complications include an intracerebral hemorrhage or the development of hydrocephalus. Management of these patients is significantly different from those with ischemic stroke. In contrast to ischemia, intracranial bleeding induces intense vasospasm in neighboring vessels 4 to 12 days after the initial bleed, increasing the risk for significant cerebral ischemia. The mental status evaluation may be used to guide therapy, with an intact mental status implying adequate cerebral perfusion.

Markedly elevated pressures increase the risk of rebleeding. The goal is a 20% to 25% reduction in blood pressure over 6 to 12 hours, but not to less than 160 to 180/100 mm Hg.⁵⁶ Labetalol or nicardipine are the preferred agents, as they have no significant adverse effects on ICP or CPP.⁴ There are clinical data to show that treatment with oral nimodipine within 4 days of the acute event decreases vasospasm and cerebral ischemia.⁵¹ Nimodipine may also directly protect against ischemic damage to nerve cells by blocking calcium uptake into cells.

Intracerebral Hemorrhage

Intracerebral hemorrhage accounts for 10% to 20% of all strokes.⁵⁷ Hypertension is a major risk factor; 75% of affected individuals have preexisting hypertension.⁵⁸ Although patients with intracerebral hemorrhage may present with nausea, vomiting, change in mental status, hypertension, headache, and a focal neurologic examination, the definitive diagnosis must be made by neuroimaging. Unlike ischemic stroke, where blood pressure generally returns to normal within 24 to 48 hours, in intracerebral hemorrhage, the most rapid decline in blood pressure occurs in the first 24 hours, but it may remain elevated for 7 to 10 days.⁵² The hematoma compresses normal tissue, creating an area of ischemia, increasing ICP and further decreasing CPP. Autoregulation is altered, making cerebral perfusion critically dependent on systemic blood pressure.⁵⁹

There is no clear consensus on the appropriate treatment of hypertension in the setting of acute intracranial hemorrhage. The decision to treat or not treat blood pressure should be made based on individual considerations including baseline blood pressure, etiology of hemorrhage, age, and elevated ICP. The central issue is whether aggressive lowering of blood pressure reduces the risk of intracerebral bleeding without disrupting blood flow to collateral areas. Some argue that decreasing blood pressure lowers the risk of hemorrhage extension, edema, and associated systemic complications, particularly when systolic blood pressure exceeds 200 mm Hg, a level associated with hematoma growth in some studies.⁵⁷⁻⁵⁹ A retrospective analysis of 76 patients with intracerebral hemorrhage and hypertension showed that maximum systolic blood pressure was significantly associated with hematoma enlargement, particularly if the systolic blood pressure was ≥ 160 mm Hg.⁶⁰ Others argue that not treating hypertension allows continued perfusion of areas at risk from low blood flow.⁵⁹ It was previously believed that rebleeding was rare in the first 24 hours. More recent data suggest that it is more common than thought, occurring in up to a third of affected individuals.^{58,61} The greatest risk is in the first few hours after the initial insult.^{61,62} An increased risk of bleed is associated with an initial large irregular bleed,⁶³ coagulopathy, liver disease,⁶⁴ and a low platelet count.⁶⁴ There is consensus on the following issues. (1) Aggressive lowering of blood pressure using intravenous medication and blood pressure monitoring every 5 minutes should be considered when the systolic blood pressure is over 200 mm Hg or the MAP is over 150 mm Hg. (2) In the setting of suspected intracranial hypertension, ICP should be monitored and consideration given to aggressive lowering of the blood pressure with continuous or intermittent intravenous medication when the systolic blood pressure is over 180 mm Hg or the MAP is over 130 mm Hg, keeping the CPP above 60 to 80 mm Hg. The recent randomized controlled trial INTERACT2 supports the safety of this approach. In this study, half of 2839 patients received intensive treatment to lower their blood pressure to a target systolic level of <140 mm Hg within 1 hour. While there was no significant reduction in death, patients assigned to intensive treatment had improved functional outcomes at 3 months.³³ (3) If there is no suspected elevation of the ICP and the systolic blood pressure is >180 or MAP >130, consider lowering to a target blood pressure of 160/90 mm Hg or an MAP of 110 mm Hg.

There is no consensus on the agent of choice. Concern revolves around the impact of different antihypertensives on ICP. Common to all agents is a decrease in MAP and a decrease in CPP. Vasodilating agents may increase CBF and in the setting of decreased cranial compliance may potentially increase ICP, further decreasing CPP.^{37,59} The

combination of decreased cerebral compliance, decreased CBF, and altered autoregulation—as occurs in chronic hypertension—makes the administration of any antihypertensive agent potentially dangerous. No large randomized studies are available to guide therapy. Combination α - and β -blockers are recommended when antihypertensive treatment is indicated in intracerebral hemorrhage. Risks of this therapy include worsening of bradycardia associated with the Cushing response. However, in the setting of normal cranial compliance and an increased ICP, vasodilators are probably safe. Because of the very high levels of circulating catecholamines with an intracerebral bleed, β -blockade is added when vasodilator therapy alone is ineffective.

Head Trauma

Head trauma complications include skull fractures, epidural hematomas, subdural hematomas, intracerebral hematomas, and diffuse axonal damage. With trauma, there is often edema. Acute increases in ICP are initially prevented by flow of blood and CSF from the cranial vault. However, with increasing edema, ICP eventually increases. In most trauma centers, ICP monitoring has become the standard of care.⁶⁵ Anywhere from 31% to 61% of patients with a closed head injury may have defective autoregulation.⁶⁶ If autoregulation is intact, increasing the MAP will cause vasoconstriction and produce no change in ICP. With altered autoregulation, increasing the MAP may cause vasodilatation, increasing blood volume and leading to edema and increased ICP. The goal is to maintain a minimum CPP of 70 mm Hg and an MAP above 90 mm Hg. If an antihypertensive agent is needed, a major consideration is its impact on ICP. A combination α - and β -blockers or nicardipine may be preferred when there is decreased intracranial compliance and increased ICP.^{67,68} In the absence of intracranial hypertension, vasodilators may be preferred.

Aortic Dissection

Aortic dissection begins with a tear in the intima of the aorta that is propagated by the aortic pulse wave. Myocardial contractility, heart rate, and blood pressure contribute to the aortic pulse wave. There are two types of aortic dissections, type A and type B. Type A dissections are often associated with a tear in the intima of the proximal aorta next to a coronary artery and may extend to the aortic arch.⁶⁹ Type B dissections occur in the descending aortic arch and usually begin with an intimal tear next to the subclavian artery.⁷⁰ Risk factors for dissection include advanced atherosclerosis, Marfan syndrome, Ehlers-Danlos syndrome, and coarctation of the aorta.⁷¹ Symptoms occur as the expanding hematoma causes pressure on the vasculature. This may cause myocardial infarction, stroke, spinal cord or bowel infarction, and acute renal failure. Kidney ischemia may develop, leading to refractory hypertension.⁷² Dissection to the aortic root can precipitate acute aortic insufficiency, and rupture of the ascending aorta leads to hemopericardium and tamponade.⁷³

Both types of dissections may present with severe, often tearing pain in the chest, back, or abdomen, accompanied by diaphoresis, nausea, or vomiting. Dissection is often but not always associated with hypertension.⁷⁴ Discrepancies in peripheral pulses may be observed. Chest pain is reportedly present in only half of individuals with type B dissections.⁷⁵ The diagnosis may be confirmed with CT or MRI. Multiplane transesophageal echocardiography is also used. Type A dissections usually require surgery to prevent the catastrophic consequences of great-vessel occlusion, aortic insufficiency, or tamponade. Type B dissections may usually be treated medically^{76,77} unless there is rupture, in which case open or endovascular repair is indicated. A recent meta-analysis suggested that endovascular repair may be preferred.⁷⁶

Treatment for both type A and type B dissections is initiated based on clinical suspicion alone, given the high mortality associated with this entity. The first goal of treatment is to decrease myocardial contractility and heart rate with a β -blocking agent. Esmolol has advantages in the acute setting due to its short half-life and ability to titrate to effect. Next, the blood pressure is reduced to the lowest tolerable level

until pain is relieved. Relief of pain suggests arrest of ongoing aortic dissection. The most widely used agent is nitroprusside, titrated to a systolic pressure of 100 to 120 mm Hg or to as low as 70 to 80 mm Hg. Prior treatment with β -blockade prevents reflex cardiac stimulation and a potential increase in the aortic pulse wave seen with nitroprusside. Heart rate must be maintained between 60 and 80 beats per minutes. Even normotensive individuals should be treated with antihypertensive medications to keep the heart rate and shear forces low.

Pulmonary Edema

Many patients who present with pulmonary edema have long-standing antecedent hypertension with concentric left ventricular hypertrophy and well-preserved systolic contraction.^{78,79} They develop acute diastolic dysfunction in response to abrupt increases in cardiac afterload due to increased systemic blood pressure.⁸⁰ With poor diastolic relaxation, the left ventricle requires markedly elevated filling pressures, leading to pulmonary venous hypertension and edema. The therapeutic goal is to decrease afterload, improve diastolic relaxation, and decrease pulmonary pressure. Vasodilators are the agents of choice, as they improve diastolic relaxation and lower pulmonary venous pressure.⁸¹ A β -blocker may also be used. Nitroprusside is often used because it reduces preload and afterload, improving left ventricular function and reducing myocardial oxygen demand. Modest decreases in pressure improve symptoms markedly. In less emergent settings, ACE inhibitors or calcium channel antagonists have been shown to improve diastolic function and cause regression of concentric ventricular hypertrophy.⁸²

In patients with left ventricular failure secondary to poor systolic function, vasodilators are the agents of choice. Nitroglycerin is preferred with cardiac ischemia. Nitroprusside may be used in patients refractory to nitrites. Whereas nitroglycerin dilates intercoronary collateral vessels more than small resistance arterioles and improves perfusion of ischemic myocardium, nitroprusside dilates resistance arterioles predominantly, thereby resulting in a potential steal of blood flow away from ischemic areas. Diuretics are used to reduce left ventricular end-diastolic volume.

In the setting of acute myocardial infarction, acute catecholamine release and sympathetic outflow contribute to hypertension. The hypertension usually resolves in a few hours with sedation and pain control alone. Diastolic blood pressures over 100 mm Hg should be treated with nitroglycerin. The pressure is rapidly, but cautiously, reduced to near-normotensive levels; overshoot hypotension can worsen coronary perfusion. Therapy can usually be stopped within 24 hours. There is considerable evidence that the early use of β -blocking agents may reduce ultimate infarct size independent of blood pressure control.⁸³

Perioperative Hypertension

Perioperative hypertension is a major risk factor for the development of postoperative hypertension.⁸⁴ Whenever possible, it is preferred to postpone elective surgery until the blood pressure has been well controlled over days to weeks. However, when waiting is not an option, lowering the blood pressure to below 180/110 prior to noncardiac surgery is recommended.⁸⁴ In patients with chronic hypertension on adequate treatment, oral medications should be taken the morning of surgery. Adequate blood pressure control reduces the risk of bleeding from suture lines, premature graft closure, and ischemic damage to organs at risk.

Induction of anesthesia and surgical stimuli increase sympathetic activity, causing elevated blood pressure both intra- and postoperatively. This response may be exaggerated in uncontrolled hypertension, with decreased use of deep anesthesia and absence of prolonged sedation. As anesthesia continues, there is generally a fall in blood pressure. Rapid and wide fluctuations in blood pressure leading to intraoperative hypotension, stroke, myocardial ischemia, or acute renal failure are more common in individuals with a hypertensive history.

Patients taking hypertensive therapy prior to surgery should continue treatment after surgery, changing to an equivalent intravenous medication if they are unable to take oral medications. If patients have been on a β -blocker or clonidine, this medication should be continued postoperatively to prevent rebound hypertension. Effective pain control and avoidance of hypoxia may be sufficient to treat the hypertension. If intravenous medication is necessary, nitroglycerin is preferred for the post-coronary bypass patient. Fenoldopam, with its impact on increasing renal blood flow, is also recommended, especially in clinical settings where renal ischemia is a risk. Clevidipine has been gaining popularity in this setting because of its rapid onset and short duration of action with limited effect on cardiac preload and output. However, there is limited experience with this drug, and cost is an issue.⁸⁵

Catecholamine-Associated Hypertension

Hypertensive emergency related to excess catecholamine secretion can result from the ingestion of sympathomimetic agents such as cocaine, amphetamines, phencyclidine, phenylpropanolamine (diet pills), decongestants such as ephedrine and pseudoephedrine, and other agents including atropine, ergot alkaloids, and tricyclic antidepressants. It may also be caused by tyramine ingestion in conjunction with monoamine oxidase (MAO) inhibitor therapy, autonomic dysfunction, withdrawal from certain antihypertensive medications, and pheochromocytoma (Box 87-3). Critically elevated pressures can result and cause myocardial infarction, aortic dissection, and stroke.

Pheochromocytoma is a very rare cause of hypertension.⁸⁶ Excess catecholamine secretion by the tumor results in a sustained elevation of blood pressure in the majority of cases, while peripheral catecholamine uptake and storage lead to paroxysmal symptoms when the catecholamines are released in response to stimuli. Symptoms of pheochromocytoma include headache, palpitations, hypertension, anxiety, abdominal pain, and diaphoresis. Patients may present with orthostatic changes in blood pressure, a clue to the diagnosis.⁸⁷ For the patient with hypertensive emergency, the treatment of choice is the short-acting parenteral α -antagonist, phentolamine. Following blood pressure reduction, β -blockade is generally added to control tachycardia or arrhythmias. As in all catecholamine excess states, β -blockers should not be used as initial therapy. Loss of β -adrenergically mediated vasodilatation leaves α -adrenergically mediated vasoconstriction unopposed and results in increased pressure. An oral regimen of the nonselective α -antagonist, phenoxybenzamine, can be used in less critical situations. Labetalol has been effective in treating hypertension related to pheochromocytoma in selected patients. However, as its β -blockade exceeds its α -blocking effect, severe hypertension has been reported.⁸⁸

Gestational Hypertension/Preeclampsia/Eclampsia

Gestational hypertension is defined as a systolic blood pressure of at least 140 mm Hg and a diastolic blood pressure of at least 90 mm Hg on two separate blood pressure measurements done 6 hours apart. It occurs after 20 weeks of pregnancy in patients known to previously be normotensive.⁸⁹ Up to 50% of these women develop preeclampsia if gestational hypertension develops before 30 weeks of gestation. *Preeclampsia* is defined as gestational hypertension with 300 mg or more

of protein on a 24-hour urine (urine dipstick 1+). A 24-hour urine is necessary because dipstick urine protein correlates poorly with 24-hour urine protein in gestational hypertension.⁹⁰ Preeclampsia should also be suspected in patients with hypertension developing after 20 weeks' gestation and associated with nausea, vomiting, cerebral symptoms, abnormal liver function tests, and thrombocytopenia, even in the absence of proteinuria. Preeclampsia develops in 5% of all pregnancies and occurs twice as often in primigravida versus multigravida women.⁹¹ Preeclampsia also appears in women with a history of multiple pregnancies but with a new partner.⁹¹ In the setting of molar pregnancy, it is seen in up to 70% of individuals.⁹² During normal pregnancy, blood pressure is initially decreased and then slowly rises toward the normal range during the third trimester. In preeclampsia, intravascular volume is low despite peripheral edema, and the renin-angiotensin system is activated. Progression to seizures defines eclampsia and may occur with diastolic pressures of as low as 100 mm Hg. Clinical treatment includes bed rest and parenteral magnesium.

With regard to hypertensive treatment in pregnancy, the optimal blood pressure has not been defined. The goal is to prolong the pregnancy until the fetus can be delivered. In the case of mild preeclampsia, there are no large studies to guide therapy.⁹¹ With more severe preeclampsia, treatment is given to prevent cerebral hemorrhage. The recommendation is to initiate antihypertensive therapy when the systolic blood pressure is above 160 mm Hg or the diastolic blood pressure is above 110 mm Hg. Intravenous labetalol and hydralazine have long been considered first-line medications to keep the systolic blood pressure 140 to 155 mm Hg and the diastolic blood pressure 90 to 105 mm Hg.⁹¹ However, hydralazine use can be associated with severe hypotension and maternal and fetal complications.⁹³ A recent meta-analysis reported good blood pressure control with the use of oral nifedipine. Fewer doses were required and less time needed to achieve control, and the adverse effect profile was similar to intravenous labetalol.⁹⁴ In an updated opinion, the American College of Obstetricians and Gynecologists Committee adds oral nifedipine as a first-line therapy.⁹⁵ Concern for neuromuscular blockade and severe hypotension with the contemporaneous use of nifedipine and magnesium sulfate were not substantiated in a large retrospective review.⁹⁶ However, because both drugs are calcium antagonists, careful monitoring is advisable. Nitroprusside should be avoided because of the risk of cyanide toxicity in the fetus. ACE inhibitors should also be avoided because of their potential impact on the fetal kidney.

Other Hypertensive Situations

The renal crisis of scleroderma is an aggressive form of malignant hypertension in which proliferative endarteritis precedes hypertension. Ischemic-induced activation of the renin-angiotensin system causes the hypertension. The incidence of this condition among patients with scleroderma ranges from 8% to 13%, and it is more common among blacks.⁹⁷ Progression to ESRD occurs in 1 to 2 months without treatment. Aggressive pressure control with ACE inhibitors leads to a long-term survival of about 50% to 70%.⁹⁸

Hypertension is a feature of both primary and secondary antiphospholipid antibody syndromes, occurring in up to 93% of patients.⁹⁹ Malignant hypertension occurs in this syndrome secondary to both microvasculopathy and emboli to the renal artery. Antihypertensive treatment is similar to that for malignant hypertension. Successful treatment outcomes have been reported with anticoagulation.⁹⁹

One-fourth of patients with extensive second- or third-degree burns develop severe hypertension in the first few days, likely due to high levels of circulating catecholamines and renin. Nitroprusside or phentolamine (in countries where it is still available) are other treatments.

Patients with transverse spinal cord lesions at the T6 level or higher, including patients with Guillain-Barré syndrome, have dysreflexia in which noxious stimuli in dermatomes below the level of lesion trigger a massive sympathetic discharge. This leads to severe hypertension, bradycardia, diaphoresis, and headache. In 90% of patients, distention

BOX 87-3 Tyramine-Containing Foods

| | |
|---------------|-------------------|
| Chianti wine | Fermented sausage |
| Chicken liver | Bananas |
| Soy sauce | Canned figs |
| Yeast | Coffee |
| Avocados | Certain beers |

of the bladder or bowel causes the dysreflexia, and prompt decompression leads to resolution of hypertension.¹⁰⁰ Drugs that have been used successfully in treating this condition include nitroprusside, phentolamine, and labetalol.

HYPERTENSIVE URGENCY

Hypertensive urgency refers to patients in whom blood pressure is severely elevated, but based on detailed history, physical examination, and laboratory evaluation, there is no evidence of acute end-organ damage related to the current episode of hypertension, although there may be evidence of previous hypertension-induced end-organ damage. Although long-term control of blood pressure in this setting can prevent complications due to stroke, myocardial infarction, or congestive heart failure, there is no evidence that acute reduction of blood pressure results in any improvement in short- or long-term prognosis. Unfortunately, the term *urgency* is a misnomer and has led to overly aggressive management of many patients. Aggressive treatment with intravenous drugs or even oral agents, such as clonidine or nifedipine, to rapidly lower blood pressure can lead to cumulative effects causing hypotension, sometimes following discharge from the emergency room. A more appropriate clinical term to describe this condition is severe uncomplicated hypertension, because there is no need for urgent reduction of blood pressure as would be required in patients with true hypertensive emergencies (Box 87-4).

BOX 87-4 Severe Uncomplicated Hypertension

SEVERE HYPERTENSION (DIASTOLIC >115 mm Hg) IN ASSOCIATION WITH ONE OR MORE OF THE FOLLOWING

Chronic renal failure
Chronic congestive heart failure
Stable angina
Previous myocardial infarction
Transient ischemic attacks
Previous cerebrovascular accident

The treatment of choice is gradual pressure reduction over a few days in the outpatient setting. The choice of antihypertensive agent is based on ease of administration and side-effect profile rather than on rapid blood pressure reductions. Frequently, restarting a previously effective regimen is all that is necessary. It is critically important to follow these patients over the next 24 to 48 hours to ensure the blood pressure is appropriately reduced. While medicolegal issues may pressure physicians into loading these patients with medication to observe on-the-spot control of their blood pressure, this practice has been questioned as having no clear rational scientific basis.

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■ PATHOPHYSIOLOGY OF SHOCK

Circulatory shock represents a final common pathway of cardiovascular failure. Septic shock is the most common cause of shock followed by cardiogenic and hypovolemic shock.¹ Mortality remains high, particularly for patients with septic and cardiogenic shock, where it ranges from 40% to 60%, respectively.^{2,3} From a physiologic perspective, circulatory shock is defined as a syndrome in which blood flow is inadequate to meet cellular metabolic requirements.⁴ Clinically, shock is manifested by organ hypoperfusion, which is most evident in the skin and peripheries, kidneys, and brain. The principal signs of circulatory shock are as follows: cool, clammy, and cyanotic extremities; decreased pulses; oliguria with a urine output <0.5 mL/kg per hour; and confusion, disorientation, and obtundation.

Mechanisms Underlying Impaired Cardiovascular Performance

The development of shock is related to alterations in the components of the circulatory system that regulate cardiovascular performance. The first component is intravascular volume, which regulates mean circulatory pressures and venous return to the heart. Decreases in intravascular volume limit venous return to the heart and cardiac output. The heart is the second component. Cardiac output is determined by heart rate, contractility, and loading conditions. Abnormalities in rhythm and heart rate may limit cardiac output. Impaired cardiac contractility decreases effective ventricular ejection and compromises stroke volume. Abnormalities in valvular function may also limit cardiac output. The third component is the resistance circuit; it consists of the arteriolar bed, where the major decreases in vascular resistance occur. Arteriolar tone plays an important role in ventricular loading conditions, arterial pressure, and distribution of systemic blood flow. Excessive decreases in arteriolar tone lead to hypotension and limit effective organ perfusion, whereas excessive increases in arteriolar tone impede cardiac ejection by increasing ventricular afterload. Differences in arteriolar tone between organs can result in maldistribution of blood flow and mismatching of blood supply with tissue metabolic demands. The capillaries are the fourth component. They are the site of nutrient exchange and fluid flux between the intravascular and extravascular spaces. Increases in capillary permeability result in tissue edema and loss of intravascular volume. Decreases in capillary cross-sectional area, secondary to either obstruction or impairment in endothelial cell function, compromise nutrient blood flow. The opening of arteriovenous connections, which bypass the capillary network, may play a role in tissue hypoperfusion. The venules are the fifth component. They are the site of the lowest shear stress in the circulatory system and are thus the site most prone to occlusion from alterations in cell rheology. Venular resistance contributes 10% to 15% of total vascular resistance. Increases in venular tone increase capillary hydrostatic pressures, thereby promoting the extravascular movement of fluid. The sixth component is the venous capacitance circuit. More than 80% of the total blood volume resides in large capacitance vessels. Increases in venous tone decrease venous capacitance, redistributing blood volume centrally and thereby increasing venous return to the heart. Decreases in venous tone increase venous capacitance and decrease effective arterial blood volume and venous return. The seventh component is mainstream patency. Obstruction of the systemic or pulmonary circuit

impedes ventricular ejection, while venous obstruction limits venous return to the ventricles.

Hemodynamic Assessment

Circulatory performance can be assessed from hemodynamic parameters. A low heart rate may limit cardiac output, whereas an increased heart rate can compromise stroke volumes by limiting ventricular filling times. Bradyarrhythmias indicate structural abnormalities, effects of drugs, hypoxia, or other metabolic stimuli. Severe bradyarrhythmias can also represent reflex-mediated responses, as occurs in cases of severe hemorrhagic shock and acute inferior wall myocardial infarction. Tachyarrhythmias may be due to underlying cardiac disease or pharmacologic or environmental stimuli. Alternatively, increases in the heart rate may reflect compensatory responses to maintain cardiac output.

In patients with circulatory shock, blood pressure should be monitored using intravascular measurements.⁴ Vasoconstriction related to compensatory mechanisms to maintain arterial pressure and the use of pharmacologic agents limits the accuracy of noninvasive measurements. This is particularly true in hypodynamic forms of circulatory failure.

For most vital organs, autoregulatory and neuronal mechanisms maintain blood flow independent of blood pressure at a mean arterial pressure of 60 to 130 mm Hg. At either higher or lower levels of pressure, blood flow becomes linearly dependent on blood pressure. Diseases such as hypertension can shift this relationship and increase the critical level of arterial pressure required for organ perfusion. Similarly, impaired autoregulatory mechanisms present in a variety of pathologic states expand the range of pressure-dependent blood flow.

The level of arterial pressure is not a reliable indicator of circulatory performance and tissue perfusion.^{5,6} In states of hypodynamic circulatory shock such as traumatic injury and cardiac failure, hypotension is a late marker of critical hypoperfusion. As cardiac output falls, blood pressure is initially maintained by increases in peripheral vascular resistance largely mediated by the sympathoadrenal system. It is only after these mechanisms have been exhausted that hypotension develops. Accordingly, tissue hypoperfusion may be present despite normal levels of blood pressure as blood flow is redirected toward more vital organs. Conversely, hypotension may exist without evidence of organ hypoperfusion. In some vasodilated states, increases in cardiac output maintain vital organ blood flow despite decreased levels of arterial pressure.

Pulmonary artery wedge pressure and central venous pressure are indirect measures of ventricular preload. These measurements correlate poorly with blood volume, end-diastolic volumes, and fluid responsiveness.⁷ Filling pressures are determined by ventricular compliance, venous return, and systolic function. Factors such as ventricular interactions, positive airway pressure, and intrinsic cardiac disease may decrease ventricular compliance and lead to an overestimation of ventricular preload. Echocardiographic techniques can provide a more accurate assessment of ventricular loading conditions, while dynamic indicators such as pulse pressure variation, stroke volume variation, changes in caval diameter, and passive leg raising may provide greater insight into fluid responsiveness.^{8,9}

Cardiac output can be measured by multiple techniques.⁴ Pulmonary artery thermodilution has been augmented by less invasive techniques including transpulmonary thermodilution and lithium

dilution, echocardiography, esophageal Doppler, and arterial pulse contour analysis. Echocardiographic measurements and esophageal Doppler can be used to assess ventricular ejection and also provide diagnostic information regarding the presence of pericardial tamponade and valvular function. The response of stroke volume to changes in ventricular loading during fluid infusion is also useful to assess cardiac contractility. A good response indicates preserved cardiac function, while lack of response may be related to either cardiac dysfunction or inadequate fluid volumes. However, the adequacy of cardiac output in meeting tissue metabolic demands must be assessed independently by monitoring indices of tissue perfusion and oxygen metabolism. A low cardiac output may be adequate when metabolic requirements are decreased—for example, in deep sedation or hypothermia. In contrast, an increased cardiac output may not be adequate when metabolic requirements are increased or maldistribution of blood flow exists, such as in septic shock.

Systemic vascular resistance is an indicator of arterial tone; it is calculated from cardiac output and arterial pressure. Increases in systemic vascular resistance are due to vasoconstriction and represent compensatory mechanisms directed at maintaining blood pressure in the setting of a decreased cardiac output. Excessive increases in vascular resistance increase ventricular afterload and the impedance to ejection. Decreases in vascular resistance are due to vasodilation, decreases in blood viscosity, or presence of arteriovenous connections. Vasodilation may be pathologic, as occurs in septic shock and liver disease, or it may be adaptive, as occurs in hyperdynamic stress following major surgery and traumatic injury. Venous tone is much harder to assess clinically. In most cases, changes in venous tone parallel changes in arterial tone. Modest increases in central venous pressures in the setting of large-volume infusion and the absence of intravascular volume loss suggest decreased venous tone.

■ CLASSIFICATION OF SHOCK

Hinshaw and Cox proposed a classification of circulatory shock involving four subsets: hypovolemic, cardiogenic, distributive, and obstructive.¹⁰ This classification can be simplified into two categories with typical hemodynamic profiles (Table 88-1). The first category, hypodynamic shock, includes the hypovolemic, cardiogenic, and obstructive shock subsets. The second category, hyperdynamic shock, includes the distributive shock subset.

The central features of hypodynamic shock are a low cardiac index and a high-resistance vasoconstricted state. Increased oxygen extraction and lactic acidosis usually parallel the decrease in cardiac output. In cases of hypodynamic shock, the development of organ dysfunction is directly related to inadequate global blood flow. Common causes of hypovolemic shock are hemorrhage, dehydration, and massive capillary leak. Acute decreases in blood volume of 25% result in tachycardia and orthostatic hypotension. The loss of 40% of blood volume is associated with a severe hypotension and clinical shock. Decreased filling pressures are the hallmark of hypovolemic shock, in contrast to cardiogenic shock in which filling pressures are elevated. Acute myocardial infarction involving 40% or more of ventricular mass is the most common cause of cardiogenic shock. Cardiomyopathies and severe valvular lesions are other important causes of cardiogenic shock.

Severe stress may also induce severe reversible cardiac dysfunction. Finally, obstructive shock is most commonly due to pericardial tamponade, acute pulmonary embolism, and tension pneumothorax. Dynamic obstruction to left ventricular output may also lead to circulatory shock. Since filling pressures are usually increased in these settings (owing to outflow obstruction, impaired ventricular filling, and decreased ventricular compliance), distinguishing between obstructive shock and cardiogenic shock can be difficult.

Hyperdynamic circulatory shock is characterized by a high cardiac index and a low-resistance vasodilated state. Filling pressures may be increased or normal, depending on volume status and myocardial competence. Common causes of hyperdynamic shock include sepsis, anaphylaxis, drug intoxications, spinal shock, and adrenal insufficiency. The underlying hemodynamic defect is maldistribution of blood flow and/or blood volume such that effective nutrient blood flow is compromised. In contrast to hypodynamic shock, oxygen extraction may be normal or decreased despite evidence of hypoperfusion.¹¹ Direct mediator-related effects coupled with tissue hypoperfusion lead to cellular injury and organ dysfunction in patients with septic shock.

A considerable overlap may exist between these different syndromes. Early in septic and anaphylactic shock, prior to fluid infusion, a significant hypovolemic component usually exists. Hypovolemia may also be present in a small group of patients presenting with shock secondary to acute myocardial infarction. In the presence of severe sepsis-related myocardial depression, patients with septic shock can develop a hypodynamic profile. Similarly, patients in cardiogenic shock after myocardial infarction and cardiac surgery may demonstrate significant vasodilation due to the activation of mediator cascades while on cardiopulmonary bypass.¹² Alternatively, dynamic left ventricular outflow obstruction related to systolic anterior movement of the mitral valve may complicate ischemic and stress-related cardiogenic shock.¹³

Progression of Shock

Critical reductions in tissue perfusion elicit a complex set of reflexes that are directed at maintaining cardiac output and arterial pressure.¹⁴ Activation of the sympathetic nervous system increases heart rate and contractility. The release of catecholamines, angiotensin, vasopressin, and endothelins increases arteriolar and venous tone, thereby increasing arterial blood pressure and shifting blood volume from the capacitance vessels to the central circulation. In addition, blood flow is redirected from skeletal muscle, subcutaneous tissue, and splanchnic circulation to the heart and brain. Vasopressin and activation of the renin-angiotensin system serve to enhance water and sodium retention, thereby protecting intravascular blood volume.

Progression of the shock state is marked by further declines in blood pressure that compromise coronary perfusion and cardiac performance. Increases in peripheral vascular resistance increase afterload and impede left ventricular ejection. Terminal phases of shock are marked by vasomotor dysfunction and loss of arteriolar tone with paradoxically increased venular resistance. The resulting increase in capillary hydrostatic pressure coupled and associated with increased microvascular permeability leads to a loss of intravascular volume with worsening of the shock state. Leukostasis and changes in erythrocyte rheology further impair microvascular blood flow.

TABLE 88-1 Circulatory Shock Hemodynamic Profiles

| | MAP | PAWP | CO | SVR | Svo ₂ | LACTATE |
|---|-----|------|----|-----|------------------|---------|
| HYPODYNAMIC | | | | | | |
| Hypovolemic hemorrhage, dehydration | ↓ | ↓ | ↓ | ↑ | ↓ | ↑ |
| Cardiogenic myocardial infarction | ↓ | ↑ | ↓ | ↑ | ↓ | ↑ |
| Obstructive pulmonary embolism, pericardial tamponade, tension pneumothorax | ↓ | ↔↑ | ↓ | ↑ | ↓ | ↑ |
| HYPERDYNAMIC | | | | | | |
| Distributive sepsis, adrenal insufficiency, anaphylaxis | ↓ | ↔↓ | ↔↑ | ↓ | ↔↑ | ↑ |

CO, cardiac output; MAP, mean arterial pressure; PAWP, pulmonary arterial wedge pressure; Svo₂, venous oxygen saturation; SVR, systemic vascular resistance.

This pathophysiology is altered in hyperdynamic forms of circulatory failure such as septic shock, in which inflammatory mediators play a prominent role.¹⁵ These patients are characterized by arterial and venous vasodilation coupled with an increased cardiac output. The influence of vasodilatory substances, such as nitric oxide, predominates over the effects of endogenous and exogenous vasopressor substances. In some forms of vasodilatory shock, inappropriately low levels of vasopressin and cortisol may contribute to refractoriness to catecholamines.¹² Decreases in capillary cross-sectional area, secondary to the interactions of activated leukocytes, platelets, endothelial cells, and the clotting cascade, limit effective nutrient blood flow despite the increase in cardiac output.¹⁶ Progressive hypotension, which is refractory to fluid infusion and vasopressors, results in worsening tissue hypoperfusion, acidosis, and organ failure. A hypodynamic circulation develops as a terminal event.

Oxidative Metabolism in Shock

The primary metabolic defect in circulatory shock is impaired oxidative metabolism with resulting cellular and organ failure. This impairment is most commonly due to decreases in tissue oxygen supply caused by either global decreases in blood flow or maldistribution of blood flow at a regional or microcirculatory level. Systemic oxygen consumption may initially be increased yet inadequate to meet tissue metabolic requirements; however, the terminal phases of all forms of shock are characterized by decreases in oxygen consumption. In experimental studies, mortality is directly related to the cumulated deficit in oxygen metabolism.¹⁷

Oxygen delivery is determined by cardiac output, hemoglobin concentration, and arterial oxygen saturation. Under normal circumstances, oxygen consumption is independent of oxygen delivery and cardiac output (Fig. 88-1). Increases in cellular oxygen extraction, from a normal level of 25% to a maximum of level of 80%, maintain oxygen consumption because blood flow is reduced. When oxygen

extraction is maximized, a critical level of oxygen delivery (DO_{2crit}) is reached below which oxygen consumption decreases and anaerobic metabolism ensues. Alterations in vasomotor reflexes caused by sepsis or drugs limit maximal oxygen extraction, resulting in critical tissue hypoxia and anaerobic metabolism at higher levels of oxygen delivery.¹⁸

Aerobic adenosine triphosphate (ATP) generation is dependent on glycolysis occurring in the cytoplasm and oxidative phosphorylation occurring in the mitochondria (Fig. 88-2). Under anaerobic conditions, ATP generation is limited to the two moles of ATP generated in the cytoplasm, compared with the 38 moles of ATP generated aerobically. The decreased entry of pyruvate into the citric acid cycle results in the accumulation of lactic acid and the generation of additional hydrogen ions from the hydrolysis of ATP. Accordingly, the presence of lactic acidosis serves as an indicator of critical cellular deficits in high-energy phosphate metabolism. The normal level of lactate is 0.4 to 1.2 mEq/L. Levels greater than 1.5 mEq/L are associated with an increased mortality rate in septic shock.¹⁹

Oxidative metabolism may also be impaired by mechanisms independent of tissue hypoperfusion. Inflammatory mediators, including nitric oxide, oxygen radicals, calcium, and tumor necrosis factor, impair mitochondrial function. Down-regulation of genes transcribing proteins important in mitochondrial biogenesis, mitochondrial swelling, and decreased mitochondrial complex activity has been observed in patients with septic shock.^{20,21} Serum from patients with septic shock has also been demonstrated to inhibit mitochondrial respiration and decrease cellular ATP concentration *in vitro*.²² Similarly, impaired mitochondrial function has been described in animal models of traumatic and hemorrhagic shock. The specific role of these mitochondrial abnormalities in organ dysfunction in shock remains to be determined.

The accumulation of tissue carbon dioxide (CO_2) parallels the decrease in oxygen metabolism in circulatory shock.²³ Increases in tissue CO_2 levels are manifested by venous hypercapnia and decreases in venous pH. The resulting widening of the arterial-venous CO_2 gradient is proportional to the degree of circulatory failure.²⁴ The normal

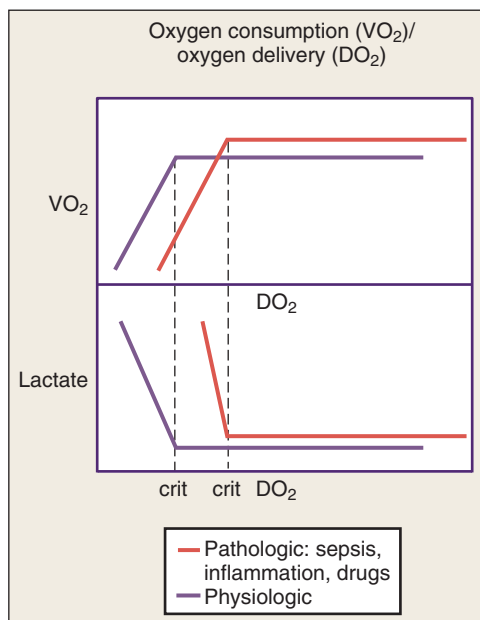


FIGURE 88-1 ■ Oxygen consumption–oxygen delivery relationships. Oxygen consumption (VO_2) is independent of oxygen delivery (DO_2) until a critical level of DO_2 is reached at which oxygen extraction is maximized. At that level of oxygen delivery (DO_{2crit}), VO_2 becomes linearly dependent on DO_2 , and anaerobic metabolism manifested by lactic acidosis ensues. This relationship shifts upward and to the right when the ability of the tissues to extract oxygen is impaired due to alterations in the distribution of blood flow.

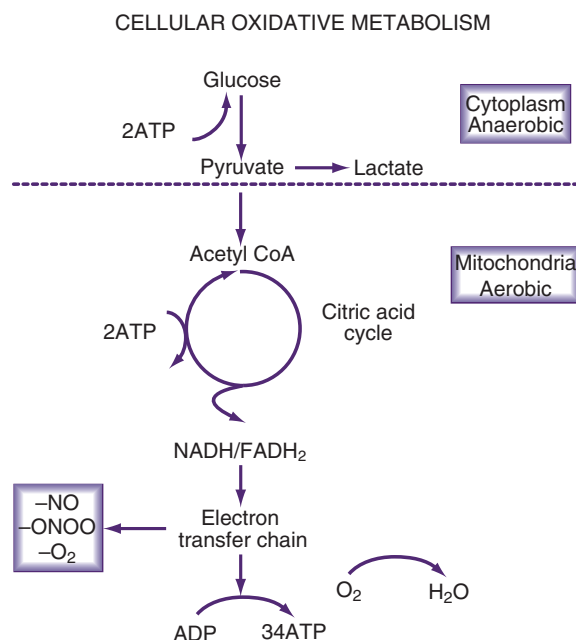


FIGURE 88-2 ■ Cellular oxidative metabolism. Glucose is metabolized anaerobically in the cytoplasm and aerobically in the mitochondria under conditions of normal tissue perfusion. Under conditions of shock, high-energy phosphate generation (ATP) is limited to anaerobic pathways. Nitric oxide (NO), peroxynitrite ($ONOO^-$), and superoxide (O_2^-) are potential inhibitors of the electron transfer chain.

gradient is less than 5 mm Hg, and it increases to 40 mm Hg during cardiac arrest. Decreased clearance of CO₂ generated by oxidative processes is responsible for the initial increase in tissue CO₂ levels. With the onset of anaerobic metabolism, a tissue CO₂ excess is generated from the titration of anaerobically derived acids by bicarbonate. The increase in tissue CO₂ levels has been associated with impaired myocardial performance *in vitro*.

Monitoring Perfusion Failure

Controversy exists over the optimal manner in which to monitor tissue perfusion in patients with circulatory shock. Commonly used parameters, such as heart rate, arterial pressure, and cardiac output, correlate poorly with survival in critically ill patients.^{5,6} This is particularly true in patients with septic shock and traumatic injury, in whom underlying deficits in tissue perfusion may exist despite initial resuscitative efforts.²⁵ These observations have led to the use of indices of tissue oxygen metabolism as markers of tissue perfusion and the adequacy of resuscitative efforts.

Mixed venous oxygen saturation (SvO₂), measured on blood taken from the pulmonary artery, is used as an index of tissue oxygenation. Venous blood is in equilibrium with the tissues. Mixed venous blood, representing a weighted mean of all the venous effluents, reflects overall tissue oxygenation. Since increased oxygen extraction is the primary compensatory mechanism to maintain oxygen consumption, decreases in SvO₂ are an early marker of compromised tissue perfusion. In cardiogenic shock, SvO₂ tracks cardiac function and systemic perfusion.²⁶ The same is not true in septic shock and other settings where the relationship between venous blood and tissue oxygenation is altered by maldistribution of blood flow.¹¹ In these circumstances, the ability of the tissues to extract oxygen is limited by decreases in effective nutrient flow such that SvO₂ may be normal or increased despite the presence of tissue hypoxia and anaerobic metabolism. Accordingly, while mixed venous desaturation is indicative of tissue hypoxia, normal levels do not preclude tissue hypoperfusion.

Central venous oxygen saturation (ScvO₂), measured in samples taken from the superior vena cava and right atrium, serves as an alternative to SvO₂. In critically ill patients, ScvO₂ is generally 5% higher than SvO₂; however, the correlation is inconsistent depending, in part, on the location of the tip of the central venous catheter. In patients with septic shock and baseline ScvO₂ of 48%, improved survival was demonstrated when therapy was titrated to ScvO₂ ≥70%.²⁷ Subsequent reports in patients who were better resuscitated with baseline ScvO₂ ≥70% failed to demonstrate the same benefit of ScvO₂ monitoring.^{28,29}

Lactate concentration is a useful marker of critical hypoperfusion. Increases in lactate levels indicate the presence of anaerobic metabolism and tissue energy deficits. Although the initial blood level of lactate has prognostic significance, the inability to clear lactate over time is more discriminating.^{30,31} In patients with septic shock, factors other than hypoperfusion may contribute to lactate accumulation. These factors include increased muscle ATPase activity, increased hepatic flux of alanine from skeletal muscle, decreased pyruvate dehydrogenase activity, decreased hepatic clearance of lactate, and dysfunctional mitochondrial respiration. Despite these concerns, increases in lactate concentration are associated with decreases in the intracellular redox potential in patients with septic shock, suggesting that it is a useful marker of cellular energy metabolism.³² When titration of therapy to ScvO₂ >70% was compared with achieving a lactate clearance of 10% over 6 hours in patients with septic shock, the outcome was similar.³³

Oxygen consumption and oxygen delivery are global markers of systemic oxygen metabolism. Oxygen consumption, a measure of overall metabolic requirements, is calculated from cardiac index, hemoglobin, and arterial and venous oxygen saturation. It can also be measured directly from expired gases. Oxygen delivery is calculated from cardiac output, hemoglobin, and arterial saturation; it is a measure of the total amount of oxygen being delivered to the tissues.

Although increased values of oxygen consumption and oxygen delivery have been observed in survivors compared with nonsurvivors, considerable overlap exists between the two groups. Efforts to titrate therapy to values associated with survival, “optimal goals,” have produced mixed results.³⁴ These differences, in part, reflect the varying metabolic requirements of individual patients.

The decrease in CO₂ clearance in circulatory shock can be used to monitor ongoing perfusion failure. Widening of the gap between central venous and arterial pCO₂ to >6 mm Hg can be used to identify patients who may not be adequately resuscitated despite ScvO₂ >70%.³⁵ End-tidal CO₂ measurements are useful in monitoring perfusion during cardiopulmonary resuscitation. Cardiac arrest results in marked decreases in pulmonary blood flow and accompanying decreases in CO₂ excretion. End-tidal CO₂ values move toward zero during arrest and increase with successful resuscitation.³⁶

There have been multiple attempts to use measures of local or regional perfusion as indices of overall systemic perfusion. Toe temperature, subcutaneous oxygen tensions, transcutaneous oxygen tension, and laser Doppler are some examples of regional measures previously studied. Gastric tonometry and, more recently, sublingual tonometry have been used to assess vascular beds for CO₂ excess as a marker of systemic hypoperfusion. Currently, attention has been focused on two measures of microvascular blood flow.³⁷ One approach is the use of near-infrared spectroscopy to assess the level of oxygenated hemoglobin in the thenar skeletal muscle. Both the actual value and the response of tissue hemoglobin saturation to reactive hyperemia have been reported to predict survival. Other techniques, such as orthogonal polarization spectral imaging and sidestream dark-field imaging, have been used to directly visualize microcirculatory flow. Decreases in capillary blood flow have been observed in patients with septic shock and cardiogenic shock, which are correlated with survival. Evidence of persistent hypoperfusion using these measurements has been reported in patients with septic shock despite improvement in systemic indices of perfusion. Whether titration of therapy to these measures of local perfusion will impact the outcome remains to be determined.

Organ Failure

The primary causes of organ dysfunction in circulatory shock are ischemic injury, mediator-related organ dysfunction, and reperfusion injury. Ischemic injury occurs when anaerobic metabolism ensues and high-energy phosphate production falls below the level required to maintain cellular pumps and membrane integrity. It is the major factor contributing to organ failure in patients with cardiogenic and hypovolemic shock. The direct effect of inflammatory mediators, coupled with an ischemic injury, plays a major role in organ dysfunction in septic shock. Tumor necrosis factor, nitric oxide, and superoxide radicals are examples of mediators directly affecting cellular and organ function. Reperfusion injury occurs upon restoration of tissue perfusion following an absence of blood flow (Fig. 88-3). The initial injury is related to the release of oxygen radicals, increased membrane permeability, and intracellular calcium accumulation. The later phase involves cytokines, activated neutrophils, endothelial cell dysfunction, and microvascular occlusion.³⁸ Reperfusion injury may be important in hemorrhagic and traumatic shock; its role in cardiogenic shock and septic shock is less clear.

Cardiac dysfunction is related to ischemia and myocardial necrosis in shock secondary to myocardial infarction. Reperfusion injury may play a role in patients following acute coronary revascularization. Myocardial depressant substances such as nitric oxide and cytokines cause myocardial depression in patients in septic shock and possibly in hemorrhagic shock.³⁹ Impaired responsiveness to catecholamines and adrenergic receptor down-regulation occur in septic and cardiogenic shock. Increases in pulmonary vascular resistance cause right ventricular failure in patients with pulmonary embolism and may be important in septic shock, particularly when acute respiratory distress syndrome is present.

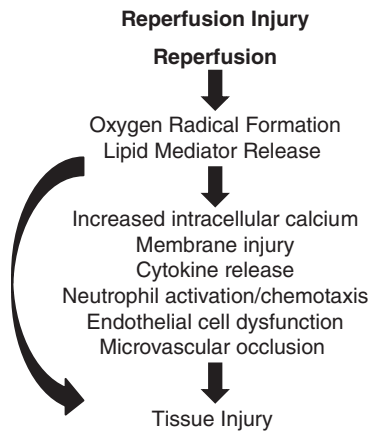


FIGURE 88-3 ■ Reperfusion injury. Under ischemic conditions, ATP is metabolized to hypoxanthine, and xanthine dehydrogenase is converted into xanthine oxidase. During reperfusion, superoxide is produced from hypoxanthine and oxygen by xanthine oxidase. Superoxide and its metabolites produce cellular injury and membrane disruption, resulting in the release of prostanoids and leukotrienes. The lipid mediators and oxygen radicals act as chemoattractants for neutrophils, which injure tissues through the release of elastases, proteases, and additional oxygen radicals.

Respiratory failure frequently complicates circulatory shock. Cardiac failure, fluid overload, and acute lung injury related to the release of inflammatory mediators and activation of neutrophils result in increased lung water and intrapulmonary shunt. Dead space may be increased due to either underlying disease and/or pulmonary vascular endothelial damage in acute lung injury syndromes. Decreased respiratory muscle perfusion, coupled with hypoxia and increased work of breathing, contributes to respiratory muscle failure. In patients with septic shock, inflammatory mediators may also directly impair respiratory muscle activity.⁴⁰

Renal dysfunction in shock is related to multiple mechanisms. Initially, as cardiac output decreases, glomerular filtration is maintained by increases in efferent arteriolar tone. Release of atrial natriuretic peptide because of increased atrial pressures may help protect renal blood flow in patients with cardiogenic shock. As shock progresses, the increases in afferent arteriolar tone result in renal ischemia and acute tubular necrosis. The activation of neutrophils, dendritic cells, and lymphocytes during sepsis/reperfusion also plays important roles in renal injury associated with shock.⁴¹

A characteristic pattern that involves centrilobar necrosis and marked transaminase elevation is observed in patients with ischemic hepatic injury associated with hypodynamic circulatory states.⁴² Activation of Kupffer cells and release of inflammatory mediators exacerbate ischemic injury in patients in septic and traumatic shock. In septic shock, canalicular cell function is impaired, resulting in intrahepatic cholestasis. Hepatic metabolic failure and impaired amino acid clearance are also features of septic shock.

Splanchnic mucosal blood flow is compromised early in shock, as blood flow gets redirected to more vital organs.⁴³ Splanchnic hypoperfusion related to shock and the use of vasopressors contribute to the development of stress ulceration, acalculous cholecystitis, intestinal necrosis, and pancreatitis. Loss of the integrity of the intestinal barrier leads to the release of inflammatory mediators into the mesenteric lymphatics and, less frequently, the translocation of bacteria, which in turn contribute to organ failure.

Thrombocytopenia is observed in a majority of patients with septic shock. The coagulation cascade is activated in septic and traumatic shock by the cytokines, tissue factors, and bacterial toxins. Disseminated intravascular coagulation is marked by impaired fibrinolysis and increased consumption of clotting factors. Clinical manifestations are

APPROACH TO CIRCULATORY SHOCK

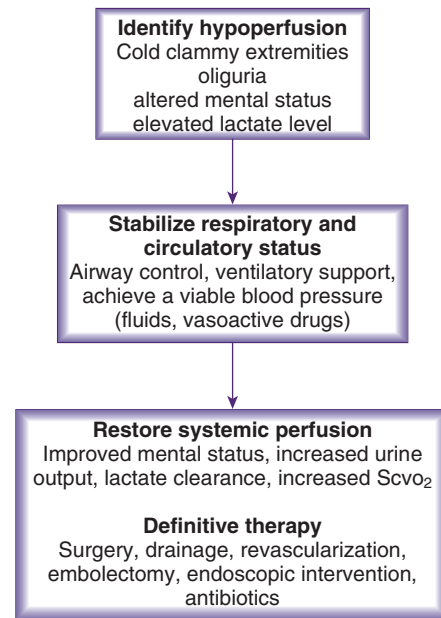


FIGURE 88-4 ■ Initial approach to patients with circulatory shock.

bleeding and microvascular thrombosis. Large-volume asanguineous fluid resuscitation may unmask these tendencies by restoring blood volume and additional hemodilution of clotting factors and platelets. The development of hypothermia exacerbates coagulopathies in patients with circulatory shock.

Disorientation and delirium are common in patients in shock. Hypotension, metabolic abnormalities, and hypoxia all contribute to neurologic dysfunction. Alterations in cerebral vascular reactivity and direct toxic effects of inflammatory mediators may also play a role in cerebral injury.⁴⁴ Severe hypotension, mean arterial pressure well below 60 mm Hg, can result in ischemic injury of the arterial border zones in the cortex and spinal cord.

Microvascular blood flow is impaired in all forms of circulatory failure.^{16,37,41} The microcirculation is characterized by heterogeneous blood flow and decreased capillary perfusion. Rheologic abnormalities of neutrophils and erythrocytes impede microvascular blood flow. Increased expression of neutrophil integrins, platelet P-selectin, and endothelial cell adhesion molecules results in cellular aggregation and microvascular obstruction. Decreased endothelial cell nitric oxide synthetase activity impairs normal vasodilatory reflexes and decreases the microvascular response to hypoxia.

Shock is associated with impairment of immunologic regulation of immunologic function. Immunosuppressive substances, including interleukin-10, prostaglandin E₂, and adenosine, are released that decrease cellular and humoral immunity. Altered signaling in afferent and efferent neural pathways contributes to impaired immune homeostasis.⁴⁵ Dendritic cell- and monocyte-mediated antigen processing is impaired, as is neutrophil function. Apoptosis of lymphocytes, dendritic cells, and monocytes is increased. A profile of decreased monocyte HLA-DR expression and impaired monocyte responsiveness to inflammatory stimuli has been associated with an increased risk of secondary infection and mortality.⁴⁶

CLINICAL ASPECTS OF SHOCK

Approach to Circulatory Shock

The approach to patients with circulatory shock involves restoration of cardiopulmonary stability and rapid assessment of the underlying disease process (Fig. 88-4). Patients should be assessed for clinical

evidence of organ hypoperfusion. Initial efforts should be directed at achieving a minimal level of blood pressure and ventilation associated with survival. The VIP approach prioritizes these efforts by focusing on ventilation, infusion, and pump activity.⁴⁷ Subsequent interventions should be focused on restoration of perfusion and organ function. A systematic approach, which incorporates physiologic endpoints, indices of systemic perfusion, and an algorithm for therapeutic interventions based on the pathophysiology of the underlying shock state,

results in the best outcomes.⁴ Definitive therapy depends on the cause of the shock state and may require additional diagnostic and therapeutic interventions. These efforts should be pursued in a timely manner, and, by necessity, may need to occur concurrently with resuscitative efforts. Finally, deviation from the expected clinical course and response to therapy should prompt a reassessment of the presumed cause of the shock state.

KEY POINTS

1. Circulatory shock is defined as a syndrome in which blood flow is inadequate to meet cellular metabolic requirements. The principal clinical manifestation of shock is that of organ hypoperfusion, which is most evident in the peripheral circulation, kidneys, and brain.
2. The development of shock is related to alterations in the major components of the circulatory system that regulate cardiovascular performance. These are intravascular volume, cardiac function, arteriolar resistance, capillary circulation, venules, venous capacitance circuit, and mainstream patency.
3. Circulatory performance can be assessed from the cardiac rate and rhythm, arterial blood pressure, cardiac filling pressures, cardiac output, and systemic vascular resistance. Although shock is frequently defined by hypotension, the level of arterial pressure is not a reliable indicator of circulatory performance and tissue perfusion.
4. Circulatory shock can be divided into four subsets: hypovolemic, cardiogenic, distributive, and obstructive. This classification can be simplified into two broad categories with typical hemodynamic profiles. The first category, hypodynamic shock, includes the hypovolemic, cardiogenic, and obstructive shock subsets. The second category, hyperdynamic shock, includes distributive shock. The central features of hypodynamic shock are a low cardiac output and vasoconstriction manifested by a high vascular resistance. Hyperdynamic circulatory shock is characterized by a high cardiac output and vasodilation manifested by a low vascular resistance.
5. The primary metabolic defect in circulatory shock is impaired oxidative metabolism. This impairment is most commonly caused by decreases in tissue oxygen supply owing to either global decreases in blood flow or maldistribution of blood flow. Cellular oxidative metabolism may also be impaired by mechanisms independent of tissue hypoperfusion. Accumulation of tissue CO₂ parallels the development of tissue hypoxia in circulatory shock.
6. Controversy exists over the optimal manner in which to monitor tissue perfusion in patients with circulatory shock. Commonly used variables such as heart rate, arterial pressure, and cardiac output correlate poorly with survival in critically ill patients. These observations have led to the use of indices of systemic oxygen metabolism as markers of tissue perfusion and the adequacy of resuscitative efforts.
7. The primary causes of organ dysfunction in circulatory shock are ischemic injury related to tissue hypoperfusion, mediator-related organ dysfunction, and reperfusion injury. The relative importance of these mechanisms varies with the cause of the shock state and the specific organ being examined.
8. The approach to patients with circulatory shock involves a rapid assessment of the underlying disease process and restoration of cardiopulmonary stability. The patient should be assessed for the etiology of the shock syndrome and evidence of organ hypoperfusion. Initial efforts to achieve cardiopulmonary stability should focus on ventilation, fluid infusion, and cardiac function. Restoration of systemic perfusion and definitive therapy directed at the etiology of the shock state should follow.

ANNOTATED REFERENCES

Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome in septic shock. *Lancet* 2002;360:219–23.

This study was one of the first studies to correlate evidence of mitochondrial dysfunction in patients with septic shock with nitric oxide-mediated pathways.

Hinshaw LB, Cox BG. The fundamental mechanisms of shock. New York: Plenum Press; 1972.

The subsets of shock described in this text formed the basis for all subsequent classifications of shock.

Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–77.

This study involved septic hypotensive patients. The study illustrated the importance of an integrated approach to resuscitating patients with shock, which included hemodynamic and perfusion-related endpoints.

Weil MH, Afifi AA. Experimental and clinical studies in lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). *Circulation* 1970;41:989–1000.

This was a classic study defining the importance of monitoring lactate in assessing perfusion failure in critically ill patients. A relationship between increased lactate levels and mortality was demonstrated. No added discrimination was observed when lactate levels were compared with lactate/pyruvate ratios.

Weil MH, Rackow EC, Trevino R, et al. Differences in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. *N Engl J Med* 1986;315:153–6.

This study was one of the first to reexamine the significance of CO₂ accumulation in patients with circulatory failure. Marked increases in mixed venous PCO₂ in patients during cardiac arrest were reported.

■ References for this chapter can be found at expertconsult.com.

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Circulatory failure is characterized by a decrease in cellular oxygen availability that is associated with a decrease in cellular partial pressure of oxygen (PO_2). When a critical PO_2 value is reached, oxidative phosphorylation is limited and leads to a shift from aerobic to anaerobic metabolism. The result is an increase in cellular and blood lactate concentrations associated with a decrease in adenosine triphosphate (ATP) synthesis. Adenosine diphosphate (ADP) and hydrogen ions accumulate and together with the elevated serum lactate levels leads to metabolic lactic acidosis. This state is called *dysoxia* and is accepted as a definition for “shock,” a state in which inadequate tissue oxygenation produces cellular injury. Shock often, but not always, results from a decrease in oxygen delivery (DO_2). A Task Force constituted by the European Society of Intensive Care Medicine has defined circulatory shock as a life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells.¹

Resuscitation from circulatory shock requires an emergency and global approach that is based on limited clinical features for establishing diagnosis and probabilistic therapy. The efficacy of this initial therapeutic strategy becomes part of the diagnostic approach: if the chosen therapy is successful, it retrospectively confirms the diagnosis. This initial diagnostic approach is essentially based on the physician's knowledge of global hemodynamics and oxygen-derived parameters. Rapidly available oxygen-derived biological markers can help with this process.

UNDERLYING PATHOPHYSIOLOGY OF GLOBAL FLOW AND OXYGEN DELIVERY

Addressing Global Adequacy of Tissue Oxygenation

Adequacy of tissue oxygenation is defined as an adapted oxygen supply (or DO_2) to oxygen demand.² Oxygen demand varies according to time and tissue type. Although oxygen demand cannot be measured or calculated, oxygen uptake or consumption ($\dot{V}O_2$) and DO_2 can both be quantified; they are linked by a simple relationship:

$$\dot{V}O_2 = DO_2 \times ERO_2$$

where ERO_2 represents the oxygen extraction ratio (ERO_2 in %; $\dot{V}O_2$ and DO_2 in mL O_2 /kg/min). DO_2 represents the total flow of oxygen in the arterial blood and is calculated as the product of cardiac output (\dot{Q}) and arterial oxygen content (CaO_2):

$$DO_2 = \dot{Q} \times CaO_2$$

with CaO_2 calculated as the product of hemoglobin (Hb, g/100 mL), arterial oxygen saturation (SaO_2 , %), and Hb O_2 capacity (1.39 mL O_2 /g Hb): $CaO_2 = Hb \times SaO_2 \times 1.39$.

Under physiologic control, oxygen demand equals $\dot{V}O_2$ (≈ 2.4 mL O_2 /kg/min for a 12 mL O_2 /kg/min DO_2 , which corresponds to a 20% ERO_2). The rate of oxygen delivered by blood is physiologically larger than that of $\dot{V}O_2$; DO_2 adapts to oxygen demand. When oxygen demand increases (e.g., during exercise), DO_2 adapts and increases.

During circulatory shock, as DO_2 declines secondary to a decrease in \dot{Q} and/or a decrease in CaO_2 , $\dot{V}O_2$ is maintained by a compensatory

increase in ERO_2 , $\dot{V}O_2$, and DO_2 , thus remaining independent. But as DO_2 decreases further, a critical point (DO_2 crit) is reached; ERO_2 can no longer compensate for the decrease in DO_2 , and at this critical level, $\dot{V}O_2$ becomes DO_2 dependent (Fig. 89-1). At this DO_2 crit (4 mL/kg/min), for a $\dot{V}O_2$ of about 2.4 mL/kg/min, ERO_2 reaches its critical point (ERO_2 crit) of 60%. When $\dot{V}O_2$ is higher, DO_2 crit is also higher. Increase in oxygen extraction occurs via two fundamental adaptive mechanisms³: (1) redistribution of blood flow among organs via an increase in sympathetic adrenergic tone and central vascular contraction (this is responsible for a decreased perfusion in organs with low ERO_2 , such as the skin and splanchnic area, and a maintained perfusion in organs with high ERO_2 , such as heart and brain) and (2) capillary recruitment within organs responsible for peripheral vasodilation (opposite to central vasoconstriction).

Using Mixed Venous Oxygen Saturation to Assess Adequacy of Global Tissue Oxygenation

In the clinical setting, mixed venous oxygen saturation (SvO_2) is used for assessing whole-body $\dot{V}O_2$ -to- DO_2 relationships. Indeed, according to the Fick equation, tissue $\dot{V}O_2$ is proportional to cardiac output:

$$\dot{V}O_2 = \text{cardiac output} \times (CaO_2 - CvO_2)$$

where CvO_2 is mixed venous blood oxygen content. To some extent, $\dot{V}O_2$ is approximately equal to cardiac output $\times (SaO_2 - SvO_2) \times Hb \times 1.39$, and SvO_2 is approximately equal to $SaO_2 - \dot{V}O_2 / (\dot{Q} \times Hb \times 1.39)$.

Four situations can be responsible for a decrease in SvO_2 : a decrease in SaO_2 (hypoxemia), Hb (anemia), cardiac output, or an increase in $\dot{V}O_2$ (like in exercise). At DO_2 crit, SvO_2 is about 40% (SvO_2 crit), with an ERO_2 of 60% and an SaO_2 of 100%. This SvO_2 crit has been identified in humans.⁴ It is important to emphasize that for the same decrease in CaO_2 (induced by a decrease in Hb or SaO_2), the decrease in SvO_2 will be more pronounced if cardiac output cannot adapt. Hence, SvO_2 represents the adequacy of global flow to the decrease in CaO_2 . A 40% SvO_2 is considered an imbalance between arterial blood oxygen supply and tissue oxygen demand with an evident risk of dysoxia. In the clinical setting, a decrease of SvO_2 of 5% from its normal value (77%-65%) is representative of a significant fall in DO_2 and/or an increase in oxygen demand (Fig. 89-2). If initial probabilistic treatment (fluid resuscitation, low-dose inotropes, and/or red blood cell transfusion) does not allow SvO_2 to be restored to a minimum of 65%, Hb, SaO_2 , and cardiac output should be individually measured to adapt to the appropriate treatment.

Assessing Global Flow

Global flow (i.e., cardiac output) is dependent on preload, myocardial contractility, afterload, and heart rate. Regional flow distribution is not homogeneous and is dependent on central and peripheral vascular tone, which ultimately results in composite systemic vascular resistances (SVR). As an oversimplification, mean arterial pressure (MAP) can be estimated as the product of cardiac output by SVR. When flow decreases, MAP remains stable and SVR increases; this corresponds to increased sympathetic adrenergic tone and central vascular contraction in low ERO_2 organs and preserved peripheral vasodilation in high ERO_2 organs. Overall, ERO_2 increases and SvO_2 decreases.

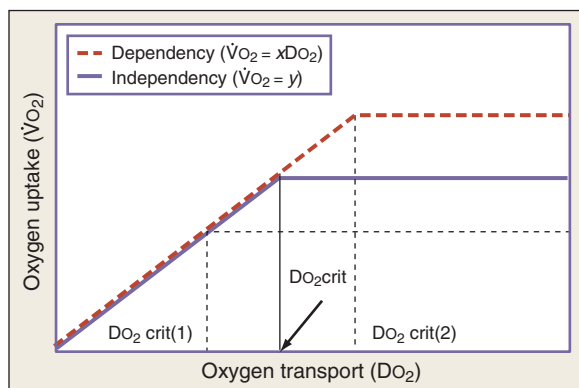


FIGURE 89-1 ■ O₂ uptake ($\dot{V}O_2$)-to-O₂ supply (DO₂) relationship.

When $\dot{V}O_2$ is supply independent ("independency"), following the relation $\dot{V}O_2 = y$, whole body O₂ needs are met. When $\dot{V}O_2$ becomes DO₂ dependent ("dependency"), according to the relation $\dot{V}O_2 = xDO_2$, $\dot{V}O_2$ starts to be linearly dependent on DO₂ at the critical DO₂ value (DO₂ crit), which corresponds to dysoxia (insufficient ATP synthesis as related to needs) and a shock state. DO₂ crit is influenced by global organism O₂ needs: when $\dot{V}O_2$ is decreased (e.g., by rest, sedation, hypothermia), the DO₂ crit is decreased as well (*lower dotted line; DO₂ crit[1]*); conversely, increased $\dot{V}O_2$ (e.g., by increased muscle activity, awakening, hyperthermia, sepsis) is associated with increased DO₂ crit (*upper dotted line; DO₂ crit[2]*).

Observation of inappropriate tissue perfusion (e.g., raised blood lactate level, metabolic acidosis, Svo₂ lower than 65%, decreased urinary flow) and its persistence despite probabilistic therapy (fluid, low-dose inotropes, red blood cells) should lead to optimizing flow according to the Frank-Starling curve. This can be assessed by invasive and noninvasive investigative procedures (see later).

During circulatory shock, $\dot{V}O_2$ -to-DO₂ dependency along with an increase in blood lactate levels implies oxygen debt. Several authors have reported that oxygen debt is related to the likelihood of multiple organ failure and mortality in postoperative or polytrauma patients.^{5,6} Patients who survive multiple organ failure have been shown to have a higher cardiac index, lower SVR, higher $\dot{V}O_2$, and higher Svo₂ than nonsurvivors.^{7,8} Rixen and Siegel⁶ demonstrated that the degree of tissue oxygen debt is related to an enhanced inflammatory response and associated with an increased risk of acute respiratory distress syndrome (ARDS) and higher mortality rates.

Several researches have emphasized the potential interest of using central venous oxygen saturation (Scvo₂) values for detecting global oxygenation impairment in experimental and clinical protocols.⁸⁻¹⁰ Furthermore, fluctuations between Svo₂ and Scvo₂ correlated relatively well, although absolute values differed.¹¹ Another important feature with Scvo₂ monitoring is that Scvo₂ can be continuously provided by central venous catheters equipped with optic fibers. In initial resuscitation of circulatory shock patients, insertion of a central venous catheter is a standard, rapid, and easy procedure.

In a landmark trial by Rivers et al., patients with septic shock were admitted to the emergency department and were randomized to either standard therapy (n = 133) or early goal-directed therapy (EGDT, n = 130) that targeted to achieve a central Scvo₂ of greater than 70%.¹² This study demonstrated a significant reduction in hospital mortality: 30.5% in the EGDT group compared with 46.5% in the standard therapy group (P = 0.009). An important point in this study was that 99.2% of patients receiving EGDT achieved their hemodynamic goals within the first 6 hours compared with 86% of those receiving standard therapy. This was the first study to demonstrate that early identification of patients with sepsis, associated with early initiation of GDT to achieve adequate tissue oxygenation by O₂ delivery (Scvo₂ monitoring), significantly improves mortality rates.¹² This study was further

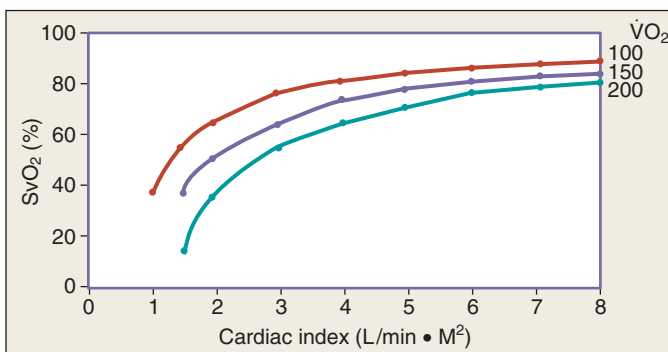


FIGURE 89-2 ■ Venous O₂ saturation (SvO₂)-to-cardiac index (CI) relationship.

According to the modified Fick equation, the relationship SvO₂/CI is curvilinear. Subsequently, when O₂ uptake ($\dot{V}O_2$) is constant, CI variations lead to large variations in SvO₂ when the initial CI value is low. In contrast, when initial CI values are already high, CI variations do not influence SvO₂ very much. These relationships are modified when CI variations are associated with large modifications in $\dot{V}O_2$.

validated by more than ten following trials.¹³ However, recent studies with large sample sizes showed more conflicting results. The ProCESS trial in the United States,¹⁴ the ARISE trial in Australia and New Zealand,¹⁵ and the ProMISE trial in England¹⁶ showed that EGDT did not significantly improve mortality in patients with septic shock compared with usual care. This can largely be explained by the difference in population between the study of Rivers et al. and these three most recent studies. In 10 years, practices have been significantly influenced by the impact of the Surviving Sepsis Campaign, which also contained some of the findings from the Rivers et al. study.¹⁷ In these three recent studies, patients had Scvo₂ at baseline greater than 70%, which is a very different result from that observed by Rivers et al.

DECIDING DIAGNOSTIC AND TREATMENT STRATEGY

Treatment strategy starts with an early and rapid estimation of O₂ deficit, rapidly followed by an early probabilistic treatment (Fig. 89-3). The response to this early probabilistic treatment (modification of lactate, arterial pH, Scvo₂, or Svo₂) then suggests which complementary investigation should be conducted (e.g., echocardiography, esophageal Doppler, computed tomography [CT] scan) and which type of monitoring needs to be installed (e.g., invasive systolic arterial blood pressure variations, noninvasive or invasive assessment of cardiac output). These will help refine the diagnosis and optimize treatment.

Diagnosing Shock Type

Quantitative Shock (Decreased DO₂)

Decreased Flow (Hypovolemic, Cardiogenic, Obstructive). The leading causes of decreased flow are decreased circulatory volume (absolute or relative hypovolemia) and cardiac pump failure. An obstructive cause (like in massive pulmonary embolism, tamponade, or tension pneumothorax) is less common.

Hypovolemia is "absolute" after severe hydration defects, plasma, or blood loss; it can be "relative" when fluid administration is insufficient to compensate a loss in vascular tone in the context of sepsis or anaphylaxis (or use of large doses of sedative drugs). In that context, there is an inadequacy between the content (volume) and vascular capacity, and abnormal sympathetic tone is associated with altered capillary recruitment. Therefore, relative hypovolemia is often associated with altered redistribution of flow among and within organs. It is important to note that shock can result from a mixture of quantitative and distributive features and a mixture of absolute and relative hypovolemia.

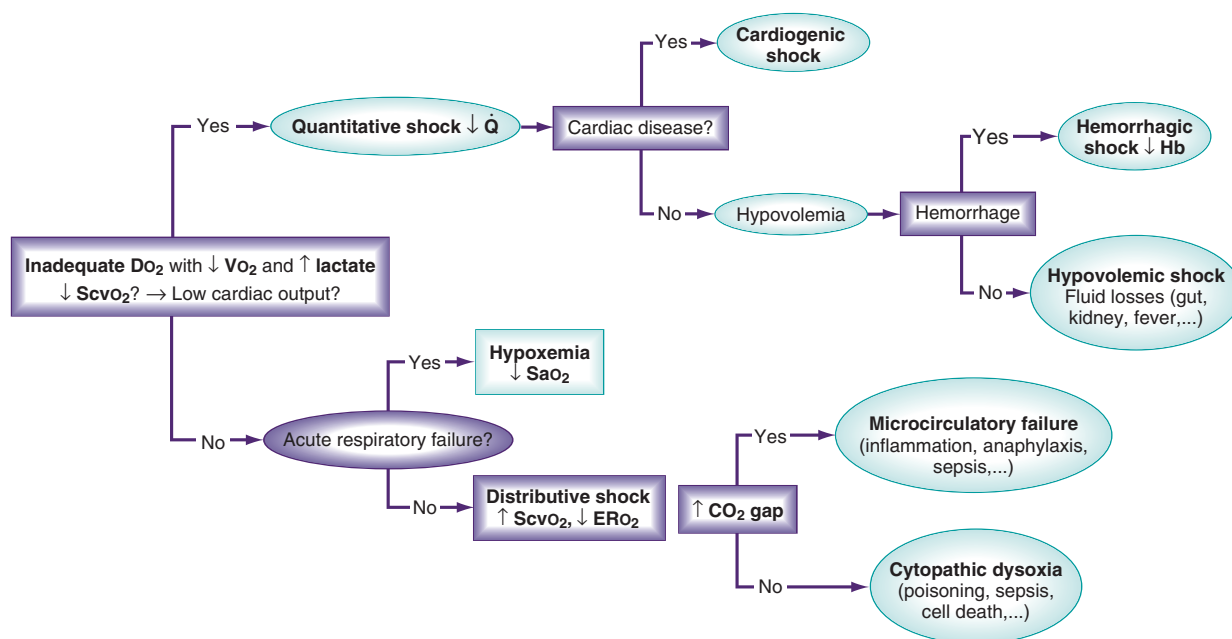


FIGURE 89-3 ■ Initial interpretation of a shock state. CO_2 gap, central venous-to-arterial CO_2 difference; DO_2 , O_2 supply; ERO_2 , oxygen extraction ratio; Hb, hemoglobin; Sao_2 , O_2 arterial saturation; Scvo_2 , central venous O_2 saturation; \dot{Q} , cardiac output; $\dot{\text{V}}\text{O}_2$, O_2 uptake.

Cardiac failure results from myogenic injury (infectious, viral, or ischemic disease), a major valvular disease, or a severe arrhythmia.

Decreased CaO_2 (Anemia, Hypoxemia, Poisoning). A decrease in Hb is not necessarily associated with hypovolemia. When associated with acute hemorrhage (hypovolemia), the decrease in DO_2 is magnified by the associated decrease in blood flow.

Hemoglobin capacity to carry O_2 can also be limited. During carbon monoxide poisoning, a decrease in DO_2 results from a loading competition on Hb between carbon monoxide and O_2 and is “maximized” by abnormal O_2 utilization (carbon monoxide interacts with oxidative phosphorylation) and a decrease in ERO_2 capabilities. In this particular case, shock is both quantitative and distributive.

In the presence of severe hypoxemia, because of an acute respiratory disorder, decreased Sao_2 leads to a decreased CaO_2 , and DO_2 that largely depends on an associated increase in cardiac output.

Distributive Shock (Decreased ERO_2)

This type of shock is linked to:

- Altered flow redistribution among organs secondary to inflammation, anaphylaxis, or some drugs (e.g., large doses of sedative agents)
- Decrease in capillary recruitment secondary to altered vascular reactivity, increased intravascular coagulation, increased blood cell adhesion, and/or endothelial edema
- Abnormal mitochondrial function (mitochondrial injury or dysfunction) described in “cytopathic hypoxia”¹⁸ or more precisely as cytopathic dysoxia, a situation in which cells cannot synthesize ATP, despite having sufficient global DO_2

Distributive shock may coexist with hypovolemic and/or cardiogenic shock. Because decreased ERO_2 is present, an elevated Svo_2 or Scvo_2 does not preclude that tissue hypoperfusion no longer exists. It is still possible to detect abnormalities in tissue perfusion through bedside microcirculatory exploration or by using the central venous-to-arterial carbon dioxide difference $\text{P}(\text{cv-a})\text{CO}_2$. In the latter, central venous PCO_2 is used as a surrogate for mixed venous PCO_2 .¹⁹ Central venous-to-arterial PCO_2 above 6 mm Hg can help in detecting septic shock patients who currently may remain inadequately resuscitated even though an Scvo_2 above 70% has been reached. In these patients, when compared to those who presented with a $\text{P}(\text{cv-a})\text{CO}_2$ below 6 mm

Hg, cardiac index was much smaller ($2.7 \pm 0.6 \text{ L/min/m}^2$ vs. $4.3 \pm 1.6 \text{ L/min/m}^2$), lactate concentration remained higher (7.5 ± 3.7 vs. $5.6 \pm 3.6 \text{ mmol/L}$), and organ failure score increases over a 24-hour time period. These results support the concept that hemodynamics requires further optimization in patients with impaired ERO_2 , and that targeting a $\text{P}(\text{cv-a})\text{CO}_2$ less than 6 mm Hg could be used as a complementary tool to do so (see Fig. 89-3). This was consistent with results found during abdominal surgery and in postoperative intensive care.^{20,21} In all studies, the threshold value was confirmed at around 6 mm Hg. $\text{P}(\text{cv-a})\text{CO}_2$ is associated with the arterial-venous oxygen content difference (Da-vO_2). The $\text{P}(\text{cv-a})\text{CO}_2/\text{Da-vO}_2$ ratio was proposed as a good monitoring variable in septic shock.²²

Choosing Appropriate Monitoring

Minimal monitoring consists of electrocardiography, pulse oximetry, and rapid arterial pressure recordings (every 5 minutes) and, soon after, a continuous and invasive recording (which facilitates the collection of arterial blood samples for blood gases and lactate levels). A central venous catheter allows measurement of central venous pressure, which often cannot help much in isolation (except when it remains lower than 5 mm Hg), but can help to guide fluid challenges. The central venous catheter facilitates infusion of drugs and fluids. It also allows for monitoring Scvo_2 , as discussed above.

Echocardiography cannot provide continuous hemodynamic data but allows for rapid identification of the type of hemodynamic disorder and has now been proposed as a first-line evaluation modality.²³ This information can be obtained rapidly even by physicians with minimal training (1- and 2-year training programs).²⁴ This is also the best modality to identify and characterize cardiac failure. In case of severe shock, where the patient is unresponsive to initial therapy, advanced hemodynamic monitoring is useful in identifying the key factors leading to hemodynamic abnormalities. Continuous or semi-continuous measurements of cardiac output and/or Svo_2 (or Scvo_2) as well as $\text{P}(\text{cv-a})\text{CO}_2$ are particularly useful to guide therapy and can also be nurse driven if strict medical protocols have been implemented.

A pulmonary artery catheter provides important hemodynamic variables including right atrial pressure (RAP), pulmonary artery

pressure (PAP), pulmonary artery occlusion pressure (PAOP), continuous cardiac output, and SvO₂ monitoring. Right atrial pressure and PAP is particularly useful in patients with right ventricular dysfunction. However, the data regarding the benefits from PAC in intensive care are conflicting. Former nonrandomized studies found an increased mortality and morbidity in patients monitored by PAC, but a meta-analysis of more than 5000 critically ill patients did not report any difference, in terms of safety and efficiency.²⁵

Transpulmonary thermodilution devices are somewhat less invasive than PAC. Continuous cardiac output measurement is provided by a combination of transpulmonary thermodilution and pulse contour analysis. A good agreement was reported with thermodilution cardiac output measured by PAC in unstable patients.²⁶ Beat-to-beat analysis improves the capacity to diagnose a decrease in cardiac output quickly and is more efficient in detecting short-term variations in cardiac output during therapeutic challenges. Transpulmonary thermodilution devices are able to assess extravascular lung water, a prognostic variable for mechanical ventilation weaning in patients with ARDS.²⁷ Therefore, in severe shock associated with ARDS, transpulmonary thermodilution devices may be useful.

Some devices are able to provide continuous cardiac output by pulse contour analysis without calibration. These are less invasive than PAC and transpulmonary thermodilution devices (they only need an artery catheter), but their reliability in terms of cardiac output in unstable patients, especially in septic shock, is still debated.^{28,29} More recently, noninvasive pulse contour analysis methods have been developed but are not reliable in patients in circulatory shock.³⁰ All these devices provide dynamic preload-dependency indices that are useful to guide fluid challenges.³¹ However, several events (arrhythmia, tidal volume less than 7 mL/kg⁻¹) limit this kind of evaluation.

Bioreactance is a noninvasive technique to assess cardiac output but is not reliable in critically ill patients.³² Transesophageal Doppler is a valuable technique to assess cardiac output but requires frequent replacement of the probe that is not suitable in most ICU patients; it is more adequate in the operating room.

Iterative blood gas analysis (another approach justifying insertion of an arterial line), metabolic acidosis and lactate concentration evaluation, are other ways to assess global tissue oxygenation and to complement ScvO₂ or SvO₂ measurements.

THERAPEUTIC PRINCIPLES: SYMPTOMATIC AND ETIOLOGIC TREATMENTS

Symptomatic Treatment

Emergency therapeutic principles of care need to be decided at the time the initial diagnostic strategy is considered. It is necessary to give supplemental O₂ and ventilatory support in response to acute respiratory failure either through a face mask or by endotracheal intubation. Acute circulatory failure is treated by initial fluid loading in the absence of left ventricular failure (see later). If decreased global contractility is present, inotropic support is considered. In case of anaphylactic shock, emergency treatment includes intravenous epinephrine to treat allergy-induced vasodilation.

Fluid loading is the first step in the treatment, and its first goal is to optimize left ventricular preload to improve Do₂ by increasing cardiac output.³³ There is, however, an associated risk of interstitial edema—in particular, pulmonary edema. Unless the patient has an acute lung injury, fluid loading aims at maximizing cardiac output³³ according to the Frank-Starling relationship, decreased lung gas exchange being detected by a decrease in SaO₂ (or by a decrease in its surrogate, pulse oximetry). When applicable, dynamic preload-dependency indices (arterial pulse pressure variations) should be preferred to static indices to guide fluid loading.³¹ Absolute value of CVP or PAOP should not be used alone to guide fluid therapy. Fluid administration should be titrated cautiously (except in severe hemor-

rhage) as fluid challenge. Of course, if cardiac output is monitored, stroke volume variations during fluid challenge must also be considered when applicable.

Normalization of hemoglobin concentration (Hb), by red blood cell transfusion is not required. Threshold values of 7 g/dL resulted in similar outcomes as higher thresholds in several randomized studies,^{34,35} but caution should be advised in patients with recent myocardial ischemia and high risk of coronary disease and in patients under extracorporeal life support (ECLS). In all cases, targeting an ScvO₂ larger than 70% may be a helpful guide for transfusion.³⁶

Catecholamines help in restoring perfusion pressure and maintaining cardiac output, thus allowing sufficient Do₂; this should allow regional flow distribution and improved ERO₂. All catecholamines are inotropes; they can be divided into (1) inodilators when they combine inotropic and vasodilatory properties (low-dose dopamine, any dose of dobutamine or dopexamine) or (2) inoconstrictors when they combine inotropic and vasoconstricting properties (high-dose dopamine, any dose of epinephrine or norepinephrine). Inodilators increase flow; inoconstrictors increase perfusion pressure. Because of variable individual sensitivity to catecholamines, dose titration is necessary.³⁷ More potent vasopressors such as vasopressin have been tested with conflicting results, in particular with regard to regional circulation. In a large multicenter, randomized, double-blind trial, vasopressin showed no benefit as a first-line vasopressor compared to norepinephrine in septic shock.³⁸ It is important to emphasize that a rise in blood pressure may not be a surrogate for clinical benefit. Indeed, in a large placebo-controlled clinical trial, administration of the nonselective nitric oxide inhibitor, N^G-methyl-L-arginine, during septic shock produced both significant increases in blood pressure and significant increases in mortality.³⁹

Some evidence exists to guide selection of the threshold for blood pressure maintenance. A MAP around 65 mm Hg is sufficient in most patients with septic shock.⁴⁰ However, in patients with a history of hypertension, a higher MAP is associated with a lower incidence of acute kidney injury.⁴⁰ Lower threshold is tolerated in severe bleeding without acute brain injury. Because increasing blood pressure through vasoconstriction may be associated with a decrease in flow, a tradeoff may exist between raising blood pressure and decreasing cardiac index that will vary depending on the specific vasopressor or combined inotrope/vasopressor.³⁷

Inotropic support should be considered in case of cardiac failure associated with impaired organ perfusion (low SvO₂, increased blood lactate level, high P(cv-a)CO₂, acute kidney injury), but not just facing a decrease in left ventricular ejection fraction. In case of refractory cardiac failure, ECLS should be considered, especially in case of primary cardiogenic shock (congenital or postischemic), postcardiotomy cardiogenic shock, and right ventricular failure associated with ARDS or massive pulmonary embolism.

Applying such principles for symptomatic treatment in septic shock patients has resulted in improving mortality. The longer a site was involved in a Surviving Sepsis Campaign program, the greater was the benefit. In a 7.5-year study, mortality rates dropped 0.7% per site for every 3 months of participation. Length of hospital and ICU stay decreased by 4% (95% CI, 1%-7%) for every 10% increase in site compliance with the Surviving Sepsis Campaign bundle.¹⁷

Other Therapeutic Principles

The importance of correction of metabolic acidosis and the use of intravenous bicarbonate for shock-induced anion gap acidosis has been overemphasized in the past. Indeed, clinical studies, including one randomized, prospective trial, failed to show any hemodynamic benefit from bicarbonate therapy either to increase cardiac output or to decrease vasopressor requirements, regardless of the degree of acidemia. Cardiac function does not appear to be significantly decreased when the arterial pH remains higher than 7.00. Bicarbonate infusion, apart from renal or digestive losses, is therefore not recommended, unless the patient has hyperkalemia.⁴¹

In patients with septic shock, stress-dose (low-dose) steroid therapy (hydrocortisone 200 mg/day) needs to be considered, especially if the decrease in blood pressure requires high or increasing concentrations of vasopressors, once appropriate antibiotics are being given or the infectious site is controlled.³³ Steroid therapy may be weaned once vasopressors are no longer required. Beyond 72 hours, absence of any hemodynamic improvement suggests that the hydrocortisone treatment is futile.

Although not oriented toward better circulatory efficacy, a number of treatments are essential in septic shock.³³ Control of the infectious source is essential. Empiric or probabilistic antibiotics must be directed against gram-negative microorganisms and potentially resistant pathogens. This justifies double or sometimes triple antibiotherapy. It theoretically offers the following advantages: widening the spectrum of activity, antibacterial synergy, increased bactericidal speed, and decreased risk for emergent resistant germs.

PROGNOSIS

The main prognostic factors for circulatory shock are the number of organ failures present on admission, delay in starting treatment, and response to symptomatic treatment. In cases of septic shock, control of the infectious source and the appropriate antibiotic therapy are essential prognostic factors. The early timing of GDT certainly influences the severity of multiple organ failure and the prognosis.

ANNOTATED REFERENCES

Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med* 2008;34:17–60.

The objective of the Surviving Sepsis Campaign, an international effort to increase awareness and improve outcome in patients with severe sepsis, was to develop management guidelines for severe sepsis and septic shock that would be of practical use for the bedside clinician. The process included a modified Delphi method, a consensus conference, several subsequent smaller meetings of subgroups and key individuals, teleconferences, and electronic-based discussion among subgroups and among the entire committee. Evidence-based recommendations, with their renewal in 2008, were made in 2004 regarding many aspects of the acute management of sepsis and septic shock that will hopefully translate into improved outcomes for the critically ill patient. The impact of these guidelines was formally tested and published in 2010 (see below).

Levy MM, Dellinger RP, Townsend SR, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Intensive Care Med* 2010;36:222–231.

The Surviving Sepsis Campaign (SSC or “the Campaign”) developed guidelines for management of severe sepsis and septic shock. A performance improvement initiative targeted changing clinical behavior (process improvement) via bundles based on key SSC guideline recommendations on process improvement and patient outcomes. A multifaceted intervention to facilitate compliance with selected guideline recommendations in the ICU, emergency departments, and wards of individual hospitals and regional hospital networks was implemented voluntarily in the United States, Europe, and South America. Elements of the guidelines were “bundled” into two sets of targets to be completed within 6 hours and within 24 hours. The Campaign was associated with sustained, continuous quality improvement in sepsis care. Although not necessarily cause and effect, a reduction in reported hospital mortality rates was associated with participation. Data from 15,022 subjects at 165 sites (included from January 2005 through March 2008) were analyzed to determine the compliance with bundle targets and association with hospital mortality. Compliance with the entire resuscitation bundle increased linearly from 10.9% in the first site quarter to 31.3% by the end of 2 years ($P < 0.0001$). Compliance with the entire management bundle started at 18.4% in the first quarter and increased to 36.1% by the end of 2 years ($P = 0.008$). Unadjusted hospital mortality decreased from 37% to 30.8% over 2 years ($P = 0.001$). The adjusted odds ratio for mortality improved the longer a site was in the Campaign, resulting in an adjusted absolute drop of 0.8% per quarter and 5.4% over 2 years (95% CI, 2.5%–8.4%).

References for this chapter can be found at expertconsult.com.

KEY POINTS

1. Circulatory shock occurs when a critical cellular partial pressure of oxygen (PO_2) is reached, a state at which inadequate tissue PO_2 produces cell dysoxia (cell oxygen consumption and ATP production are oxygen-limited) and injury.
2. Shock often, but not always, results from a decreased oxygen delivery (DO_2).
3. Initial resuscitation from circulatory shock consists of (1) addressing the global adequacy of tissue oxygenation, (2) assessing the global flow, (3) diagnosing the shock type, and (4) deciding the best probabilistic treatment.
4. Treatment aims at (1) reducing preload dependency, (2) restoring cardiac contractility, (3) improving perfusion pressure, (4) reaching oxygen supply-to-oxygen needs independency, and (5) eliminating disease sources (e.g., anaphylaxis, infection, myocardial ischemia).

Michard F, Boussat S, Chemla D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med* 2000;162:134–138.

In mechanically ventilated patients with acute circulatory failure related to sepsis, the authors investigated whether the respiratory changes in arterial pulse pressure (ΔPP) could be related to the effects of volume expansion (VE) on cardiac index. It was concluded that in that particular population of patients, analysis of ΔPP is a simple method for predicting and assessing the hemodynamic effects of VE.

Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–1377.

Goal-directed therapy involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the ICU. Early goal-directed therapy provided significant benefits with respect to outcome in patients with severe sepsis and septic shock.

Vallée F, Vallet B, Mathe O, et al. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? *Intensive Care Med* 2008;34:2218–2225.

This study tested the hypothesis that, in resuscitated septic shock patients, central venous-to-arterial carbon dioxide difference [$P(cv-a)CO_2$] may serve as a global index of tissue perfusion when the central venous oxygen saturation ($Scvo_2$) goal value has already been reached. In a prospective observational study, 50 consecutive septic shock patients with $Scvo_2 > 70\%$ were included immediately after their admission into the ICU (T0) following early resuscitation in the emergency unit. Patients were separated in Low $P(cv-a)CO_2$ group (Low gap; $n = 26$) and High $P(cv-a)CO_2$ group (High gap; $n = 24$) according to a threshold of 6 mm Hg at T0. Measurements were performed every 6 hours over 12 hours (T0, T6, T12). At T0, there was a significant difference between Low-gap patients and High-gap patients for cardiac index (4.3 ± 1.6 vs. 2.7 ± 0.8 L/min/m², $P < 0.0001$) but not for $Scvo_2$ values (78 ± 5 vs. $75 \pm 5\%$, $P = 0.07$). From T0 to T12, the clearance of lactate was significantly larger for the Low-gap group than for the High-gap group ($P < 0.05$), as well as the decrease of SOFA score after 24 hours ($P < 0.01$). At T0, T6, and T12, cardiac index and $P(cv-a)CO_2$ values were inversely correlated ($P < 0.0001$). Therefore, when the 70% $Scvo_2$ goal is reached, the presence of a $P(cv-a)CO_2 > 6$ mm Hg might serve as a useful tool to identify patients who remain inadequately resuscitated.

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RATIONALE FOR USING INOTROPIC THERAPY IN THE CRITICALLY ILL

Two different objectives for using inotropes in the critically ill have been considered: (1) the attempt to improve cardiac function in patients with low blood flow related to reduced myocardial contractility and (2) the attempt to achieve supranormal values of cardiac output in order to prevent or reduce oxygen debt; in this situation, inotropes might be given after volume resuscitation, even in the absence of formally documented myocardial depression.

Use of Inotropes for Reversing Impaired Myocardial Contractility

The first category of situations where inotropic therapy is generally considered includes cardiogenic shock, acute heart failure, or acute exacerbation of chronic heart failure. However, although the use of such therapy in these clinical conditions seems logical on a classic pathophysiologic basis, no demonstration of a beneficial impact on morbidity and mortality can be found in the literature. Moreover, almost all the commercially available inotropes have been shown to be associated with an increased mortality rate when given on a long-term basis to patients with chronic heart failure. It has been postulated that the long-term use of inotropes leads to the deterioration of left ventricular function through the acceleration of myocardial cell apoptosis.¹ Additionally, the beneficial effects on the mortality rate with agents known to have negative inotropic effects such as beta-blockers is now well established in patients with chronic heart failure with preserved ejection fraction² or reduced ejection fraction.³ Therefore, inotropic therapy is generally reserved for patients with cardiogenic shock or those with advanced heart failure whose condition is refractory to standard therapy including diuretics, digoxin, beta-blockers, and angiotensin-converting enzyme inhibitors. Under these conditions, clinicians can expect short-term positive effects of intravenous inotropic therapy allowing cardiovascular stabilization. This therapy can also be used in patients with refractory heart failure who are waiting for mechanical circulatory support (left ventricular assist devices, extracorporeal membrane oxygenation) and/or cardiac transplantation. In those with potentially reversible causes of acute heart failure (such as myocardial infarction or acute myocarditis), short-term inotropic therapy must be considered as an appropriate bridge to coronary revascularization or recovery. The development of bedside echocardiography in the intensive care unit (ICU) should allow the appropriate use of inotropic therapy since this method provides a more accurate assessment of systolic cardiac function than traditional invasive methods as pulmonary artery catheterization.

Use of Inotropes for Achieving Supranormal Levels of Oxygen Delivery or for Being Incorporated in a Goal-Directed Therapeutic Approach

High-Risk Surgical Patients

The concept of attempting to achieve supranormal hemodynamic endpoints emerged from studies in high-risk surgical patients. In a

prospective study in high-risk patients undergoing surgery, Shoemaker et al. showed that the use of supranormal hemodynamic values as therapeutic endpoints was associated with a reduction in mortality rate from 33% to 4%.⁴ In the protocol group, dobutamine and dopamine were given as inotropic drugs, even in the absence of evidence of reduced cardiac contractility, when volume resuscitation (and packed red blood cells, if necessary) failed to achieve supranormal values of oxygen delivery⁴ (>600 mL/min/m²). Thereafter, some debate concerning the perioperative fluid management strategy has emerged, especially during abdominal surgery. On the one hand, restricted perioperative fluid management could decrease the rate of postoperative complications and promote faster recovery.⁵⁻⁷ On the other hand, randomized trials did not confirm the supposed benefits of fluid restriction on recovery after elective surgery.^{8,9} Excessive fluid restriction could lead to hypovolemia and more postoperative complications as anastomotic leaks and sepsis.¹⁰

In fact, the most important point was not the use of the perioperative fluid strategy itself but rather the use of a goal-directed strategy based on stroke volume,¹¹⁻¹³ oxygen delivery index,^{14,15} or cardiac index.¹⁶ In these randomized studies, the volume of intraoperative fluids was decreased,^{14,15} unchanged,¹⁶ or increased.¹¹⁻¹³ Nevertheless, in all these studies, postoperative complications or hospital length of stay was decreased. Two reviews confirmed that a deliberate perioperative increase in oxygen delivery above supranormal values using fluid infusion and various inotropic drugs (dobutamine, dopamine, epinephrine, dopexamine) in high-risk patients undergoing surgery was associated with a decreased mortality rate and postoperative complications.^{17,18} It is important to emphasize that (1) benefits are most pronounced in patients receiving fluid and inotropic therapy as opposed to fluids alone to achieve supranormal values of cardiac index or oxygen delivery with the use of minimally invasive cardiac output monitors,¹⁹ (2) benefits related to the use of an intraoperative goal-directed therapy could also concern low- and moderate-risk patients,²⁰ and (3) such an early goal-directed therapy (EGDT) is not considered after complications have already developed.¹⁸ However, more recently, the interest of perioperative goal-directed therapy has been questioned.^{21,22} In a pragmatic, multicenter randomized trial in high-risk patients undergoing major gastrointestinal surgery, Pearse et al. assessed the clinical effectiveness of a deliberate perioperative strategy including fluid administration and dopexamine to achieve and maintain a maximal stroke volume.²² When compared to usual care, goal-directed therapy was not associated with a significant reduction in moderate or major postoperative complications.²² Nevertheless, after incorporating these results into an updated systematic review and metaanalysis, the deliberate perioperative strategy was associated with a significant reduction in the percentage of patients who developed postoperative complications.²² It is important to note that in the group of usual care, fluid administration was based on central venous pressures and could be considered, in part, as goal-directed therapy.²² It remains unclear, however, whether potential benefits could be related to the increased oxygen delivery per se or other antiinflammatory effects of catecholamines.²³ In this regard, it has been demonstrated that the increased oxygen delivery per se improved microvascular flow and tissue oxygenation.²⁴ Nevertheless, an experimental study of murine septic shock has shown that dopexamine infusion per se reduces the systemic inflammatory response, attenuates leukocyte infiltration, and prevents hepatic and renal injury at doses that have no effects on global or

regional hemodynamics.²⁵ The issue of drug dosage is also essential. A recent metaanalysis has suggested that in the setting of major surgery, dopexamine at low doses, but not at high doses, improves outcome.²⁶ From all these findings, it is still reasonable to consider the increase in cardiac output and oxygen delivery toward supranormal values during the perioperative period in high-risk patients undergoing elective major surgery.

Critically Ill Patients

It is debatable whether a supranormal hemodynamic target approach can be applied to patients admitted to the ICU for acute illnesses. On the one hand, a pathologic oxygen consumption/supply dependency, presumably due to impaired oxygen extraction capacities, has been reported in various categories of acute illnesses such as sepsis²⁷ and acute respiratory distress syndrome.²⁸ Such a phenomenon was reported to correlate with the presence of increased blood lactate, to be a marker of global tissue hypoxia,²⁷ and to be associated with a poor outcome.²⁹ This so-called pathologic oxygen consumption/supply dependency would incite the clinician to increase oxygen delivery toward supranormal values to overpass its critical level. However, such an aggressive therapeutic approach has been seriously questioned since the publication of randomized clinical trials performed in patients with acute illnesses and who did not demonstrate any benefit from the deliberate manipulation of hemodynamic variables toward values higher than physiologic values.^{30,31} In one of these studies, the mortality rate was higher in the group of patients assigned to receive an aggressive treatment aimed at achieving supranormal values of oxygen delivery.³⁰ It was postulated that the deleterious consequences of the use of high doses of dobutamine in patients in the protocol group were responsible for the increased mortality rate. It should be noted that (1) the patients in the protocol group received high doses of the inotropic agent despite no evidence of any deficit of inotropic function and that (2), in most of these patients, the aggressive inotropic support failed to achieve the target value of oxygen consumption (170 mL/min/m^2). The later analysis of the subgroup of septic patients in a study showed that survivors were characterized by their ability to increase both oxygen delivery and oxygen consumption, regardless of their group of randomization.³² Nonsurviving patients were characterized by their inability to increase oxygen consumption despite the increase in oxygen delivery, suggesting a more marked impairment of peripheral oxygen extraction in nonsurvivors than in survivors.³² In addition, the ability to increase cardiac output and oxygen delivery was also significantly reduced in nonsurvivors than in survivors, suggesting a decrease in cardiac reserve in patients who will die.³² This is not a surprising finding since the degree of myocardial dysfunction in septic shock correlates with an increased risk of death. In this regard, it has been suggested that the response to a dobutamine challenge has a prognostic value in septic patients since in two prospective studies survivors were able to increase both oxygen consumption and oxygen delivery in response to dobutamine, while nonsurvivors were unable to increase either oxygen delivery or oxygen consumption or both.^{33,34}

Data from all the results of randomized controlled studies indicate that a deliberative attempt to achieve supranormal hemodynamic targets in the general population of critically ill patients is no longer recommended.^{35,36} However, in the early phase of septic shock with low blood flow and oxygen delivery, an aggressive hemodynamic therapy, including inotropes, aimed at rapidly normalizing the central venous oxygen saturation (ScvO_2) as a surrogate of oxygen delivery, was demonstrated to result in a better outcome in a monocenter randomized controlled trial.³⁷ This result has led to the popularity of the concept of EGDT with ScvO_2 as the main hemodynamic target. Nevertheless, three recent multicenter randomized studies have shown that EGDT using ScvO_2 did not reduce all-cause mortality,³⁸⁻⁴⁰ duration of organ support, or hospital length of stay.^{38,40} However, compared to the study by Rivers et al.,³⁷ patients were fluid resuscitated before randomization, such that the average baseline ScvO_2 was already higher than 70% (the target of the EGDT arm). Such a fact

certainly accounted for the absence of superiority of EGDT over the control arms in these studies.³⁸⁻⁴⁰ This clearly cannot rule out the strategy of increasing oxygen delivery and targeting ScvO_2 higher than 70% when ScvO_2 is lower than 70% as this was the case in majority of the patients in the study by Rivers et al.³⁷ Thus, in the early phase of septic shock and maybe in other acute illnesses, it could be essential to rapidly restore normal global blood flow conditions to avoid further deleterious consequences of systemic hypoperfusion. In later stages of the disease, with inflammatory processes and organ dysfunction already developed, no evidence of benefit from a further increase in oxygen delivery has been shown in the literature. Nevertheless, it seems likely that cardiac output should be kept in the normal range by using fluids and/or inotropes to prevent worsening of the insult. It should be stressed that even in the EGDT approach, their use should not only be based on ScvO_2 but also on the presence of established cardiac dysfunction, which is at best diagnosed on echocardiography³⁶ and after checking that hypovolemia and hypotension have been already corrected.

PHARMACOLOGIC PROPERTIES OF INOTROPIC AGENTS

Different inotropic drugs are available. Some of them act on adrenergic receptors located at the surface of the cardiomyocytes, while others exert their effects into the myocardial cell.

Adrenergic Signaling

Natural as well as synthetic catecholamines increase the Ca^{2+} cytosolic concentration, which is directly related to the force of contraction (Fig. 90-1). Ca^{2+} fixes on the troponin C Ca^{2+} -specific binding site, inducing a conformational change that leads to the fixation of the myosin head to the actin filament. Hydrolysis of the adenosine triphosphate (ATP)

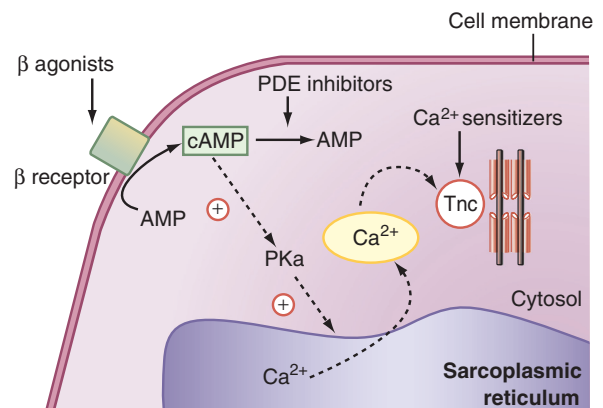


FIGURE 90-1 ■ Mechanisms of action of inotropic agents at the cellular level. Schematic representation. Beta-agonist agents fix the beta receptor and stimulate the formation of cyclic AMP (cAMP) from AMP through adenylate cyclase. Cyclic AMP activates protein kinase A (PKA), which provokes the extrusion of Ca^{2+} from the sarcoplasmic reticulum into the cytosol through phosphorylated ryanodine receptors. Ca^{2+} fixes troponin C (Tnc) and finally activates the fixation of actin on myosin filaments. Phosphodiesterase (PDE) inhibitors also increase the cAMP concentration by inhibiting its degradation. Ca^{2+} sensitizers increase inotropism through the enhancement of troponin C sensitivity for Ca^{2+} . Cardiac myosin activators increase the activity of the ATPase of the myofibrils, increasing the contractile force of the cardiomyocytes without increasing the amount of ATP molecules required for contraction. Istaroxime inhibits Na^+/K^+ ATPase, increasing the activity of the sarcoplasmic reticulum Ca^{2+} ATPase pump and increasing the reuptake of Ca^{2+} by the sarcoplasmic reticulum.

molecule located on the myosin head to adenosine diphosphate (ADP) simultaneously induces the flexion of the myosin neck and the shortening of the contractile apparatus.

A rapid overview of the physiologic response to adrenergic receptor stimulation is essential to understand the pharmacologic properties of these drugs. Receptors of the adrenergic system are classed as α_1 , α_2 , β_1 , β_2 , and dopaminergic receptors. Activation of the β_1 receptors and, to a lesser degree, the α_1 receptors, is responsible for the inotropic effect of adrenergic agents.

Beta1-Adrenergic Receptors

Beta-adrenergic receptors are transmembrane proteins located in the sarcolemma. The β_1 receptor subtype is mainly represented in the human heart. Its stimulation induces inotropic, lusitropic, chronotropic, and dromotropic effects that result from the enhancement in Ca^{2+} cytosolic concentration. Binding of a β_1 -agonist agent to its receptor stimulates the Gs protein. Guanosine diphosphate, normally fixed to the stimulatory α_s subunit of the Gs protein, is replaced by guanosine triphosphate, and the α_s -guanosine triphosphate complex binds to adenyl cyclase, which then becomes activated. Cyclic adenosine monophosphate (cAMP) is formed from ATP and activates protein kinase A. Protein kinase A phosphorylates and activates several cellular structures as follows:

- The ryanodine receptors of the sarcoplasmic reticulum, leading to the enhanced extrusion of Ca^{2+} out of the sarcoplasmic reticulum. Indeed, the main part of the Ca^{2+} cytosolic content needed for contraction is provided by the sarcoplasmic Ca^{2+} store. The entry of Ca^{2+} through the membrane L-type channels modifies the molecular conformation of the ryanodine receptor of the sarcoplasmic reticulum. Parts of these ryanodine receptors are Ca^{2+} channels that enable the massive release of Ca^{2+} out of the sarcoplasmic reticulum (see Fig. 90-1).
- The sarcolemmal L-type Ca^{2+} channels, increasing their opening time. This leads to an increased amount of cytosolic Ca^{2+} available for sarcoplasmic reticulum Ca^{2+} release and for contraction. The increase in intracytosolic Ca^{2+} concentration also leads to the activation of calmodulin. This ubiquitous protein enables the phosphorylation of other proteins once it has fixed Ca^{2+} .
- The myosin light chain through the myosin light chain ATPase. This phosphorylation enhances the responsiveness of the cardiac contractile protein to Ca^{2+} and helps increase the affinity of myosin for actin, thus participating in the inotropic effect.
- The phospholamban and the sarcolemmal $\text{Na}^+/\text{Ca}^{2+}$ exchanger, leading to a faster decrease in Ca^{2+} cytosolic concentration after contraction and accounting for the lusitropic effect. Indeed, relaxation is dependent of Ca^{2+} reuptake by the sarcoplasmic reticulum through the sarcoendoplasmic reticulum Ca^{2+} ATPase pump. The activity of sarcoendoplasmic reticulum Ca^{2+} ATPase is normally inhibited by phospholamban located in the sarcoplasmic reticulum membrane near the Ca^{2+} pump. The phosphorylation of phospholamban relieves this inhibition, and Ca^{2+} uptake by the sarcoplasmic reticulum is thus stimulated.

Beta2-Adrenergic Receptors

The β_2 receptor subtype is mainly represented in noncardiac structures. Beta2-adrenergic stimulation induces arterial and venous relaxation. The effects of β_2 stimulation in vascular smooth muscle result from a different activation pathway: once the Ca^{2+} intracytosolic concentration increases, it fixes the calmodulin regulatory protein, and the Ca^{2+} -calmodulin complex activates the myosin light chain kinase, leading to the inhibition of phosphorylation of the myosin light chain and finally smooth muscle relaxation.

Alpha-Adrenergic Receptors

When an agonist fixes the α_1 -receptor, Gh, which is one of the G-protein family, stimulates phospholipase C, which splits phosphatidyl inositol into inositol triphosphate and 1,2-diacylglycerol. Inositol triphosphate stimulates the release of Ca^{2+} from the sarcoplasmic

reticulum. Alpha2-adrenoreceptor stimulation inhibits adenylate cyclase and reduces cAMP intracellular concentration. Alpha adrenoreceptors are not prominent in the cardiac tissue but are in the vascular wall. Cardiac α_1 -stimulation induces a positive inotropic effect; α_1 and α_2 stimulations induce potent arterial and venous constriction.

Pharmacologic Properties of Inotropic Agents Used in Clinical Practice

Epinephrine

Epinephrine is the main physiologic adrenergic hormone of the adrenal medullary gland. It is a potent stimulator of α , β_1 , and β_2 receptors. The α -adrenergic effect is responsible for a marked arterial and venous vasoconstriction. Epinephrine increases systolic arterial pressure, but its effect on vasculature is partly counteracted by β_2 -mediated vasodilation. Diastolic blood pressure is thus only slightly affected by epinephrine, and the increase in mean arterial pressure (MAP) is less than that with norepinephrine.

Through cardiac β_1 stimulation, epinephrine increases heart rate and inotropism. The effects of the combination of the latter, along with the α -mediated venous constriction promoting venous return and cardiac preload, results in an increase in cardiac output. Epinephrine also facilitates ventricular relaxation and enhanced coronary blood flow through the increase in myocardial oxygen consumption.

Norepinephrine

Norepinephrine is the physiologic mediator released by the postganglionic adrenergic nerves. It is a potent α - and β_1 -adrenergic agonist, but it has little activity on β_2 receptors. Through its α -adrenergic effect, norepinephrine induces potent arterial and venous constriction. It increases systolic as well as diastolic blood pressure, left ventricular afterload, and cardiac filling pressures. Its α -adrenergic effect also induces the reduction of peripheral venous capacitance and thus results in decreased unstressed venous blood volume and increased stressed venous blood volume. This is responsible for increased mean systemic filling pressure, venous return pressure gradient, and venous return.^{41,42} β_1 stimulation results in a positive inotropic effect and an increase in stroke volume. However, the chronotropic effect is counteracted by baroreflex stimulation following vasoconstriction. Consequently, the heart rate is unchanged or reduced, and the cardiac output can be unchanged. The coronary blood flow is enhanced by norepinephrine because of coronary vasodilation secondary to enhanced cardiac metabolism and the normalization of diastolic blood pressure when low.

Dopamine

Dopamine is the immediate physiologic precursor of norepinephrine and epinephrine. The cardiovascular effects of dopamine are mediated by several types of receptors that are activated at different dopamine concentrations and by norepinephrine produced by the transformation of dopamine.

At low rates of administration ($<5 \mu\text{g/kg/min}$), dopamine activates D1 receptors located in renal, mesenteric, cerebral, and coronary vessels and induces vasodilation without affecting arterial blood pressure. At higher and intermediate rates of administration ($5\text{--}10 \mu\text{g/kg/min}$), dopamine predominantly stimulates the β_1 -adrenergic receptor and thus enhances inotropism and increases heart rate. At such rates of infusion, dopamine increases systolic blood pressure without altering diastolic blood pressure because stroke volume is enhanced and arterial vascular tone is only slightly altered. Norepinephrine resulting from dopamine transformation contributes to these cardiovascular effects. At higher rates of administration ($10\text{--}20 \mu\text{g/kg/min}$), dopamine predominantly activates vascular α_1 -adrenergic receptors and induces arterial and venous vasoconstriction, counteracting D1-receptor-mediated vasodilation. This vasoconstriction increases arterial blood pressure, venous return, and cardiac filling pressures. At higher rates of administration, the hemodynamic effects of dopamine are similar to those of norepinephrine.

Dobutamine

Dobutamine is a synthetic adrenergic agonist derived from dopamine. Its effects on adrenergic receptors are complex but do not result from endogenous transformation to norepinephrine. Dobutamine simultaneously activates different adrenergic receptors with some opposite effects. In fact, the clinically used drug is a racemic mixture of a (–) enantiomer, activating α_1 -adrenergic receptors, and of a (+) enantiomer, activating β_1 and β_2 receptors. The α_1 - and β_1 -adrenergic stimulation results in inotropic and chronotropic effects. Dobutamine does not exert any intrinsic vascular effect because the vasoconstriction induced by α_1 stimulation is counteracted by the β_2 vasodilating effect.

Dopexamine

Dopexamine is a synthetic catecholamine inducing β_2 - and dopaminergic-receptor activation, with no effect on α -adrenergic receptors and a weak direct effect on β_1 -adrenergic receptors. It also exerts indirect effects through the inhibition of the neuronal reuptake of norepinephrine. Its administration induces vasodilation and the inotropic effect with substantially increased stroke volume.

Isoproterenol

Isoproterenol (or isoprenaline) is a potent synthetic β -adrenergic agonist with a very low affinity for α -adrenergic receptors. Through its potent β_2 vasodilating effect, it induces a fall in diastolic and mean blood pressure, whereas the systolic blood pressure is increased owing to the increase in stroke volume related to its β_1 -adrenergic activation. The combination of the latter effect and the marked increase in heart rate leads to an enhanced cardiac output. The resulting increase in myocardial oxygen consumption is not compensated by coronary blood flow enhancement so that isoproterenol infusion may lead to myocardial ischemia, especially if there is preexisting coronary artery disease. Because of its proischemic and hypotensive effects, isoproterenol is no longer used as an inotropic agent in clinical practice in the absence of bradycardia.

Phosphodiesterase Inhibitors

Despite the major role of catecholamines in the management of critically ill patients with inadequate cardiac output, problems such as tachycardia, arrhythmias, increased myocardial oxygen consumption, excessive vasoconstriction, or loss of effectiveness with prolonged exposure to β -agonists may occur. Thus, other inotropic drugs as phosphodiesterase inhibitors (milrinone and enoximone) have been proposed for the management of myocardial dysfunction. These synthetic drugs inhibit the peak III isoform of phosphodiesterase, which catalyzes cAMP (see Fig. 90-1). By increasing intracellular cAMP concentration, they induce a potent vasodilation of the arterial and venous system through the relaxation of vascular smooth muscle. The left ventricular preload is reduced to a greater extent than with dobutamine. At the cardiac level, phosphodiesterase inhibitors induce an inotropic effect similar to that induced by dobutamine. The heart rate is increased only at high rates of administration. The resulting effect is an increase in cardiac output. Because the enhancement of cAMP intracellular concentration also promotes the reuptake of Ca^{2+} by the sarcoplasmic reticulum, phosphodiesterase inhibitors facilitate ventricular relaxation. Finally, since β -agonists exert their action by increasing the production of cAMP, phosphodiesterase inhibition could enhance their adrenergic effects. This is the pharmacologic basis for the synergic association of β -agonists and phosphodiesterase inhibitors.

Ca^{2+} Sensitizers

Ca^{2+} sensitizers increase the sensitivity of troponin C for Ca^{2+} and, hence, the force and the duration of cardiomyocyte contraction (see Fig. 90-1). Levosimendan is the leading drug of this therapeutic class. The advantage of levosimendan over classical inotropes would be to increase the force of contraction without enhancing the influx of Ca^{2+} into the cytosol and thus without increasing the risk of arrhythmias

related to this ionic alteration. Some degree of phosphodiesterase III inhibitory activity probably also contributes to the inotropic effect of these drugs. It also induces vasodilation by opening ATP-dependent K^+ channels.⁴³

Cardiac Myosin Activators

Cardiac myosin activators belong to a new class of inotropes. They increase the activity of ATPase of the myofibrils, increasing the contractile force of the cardiomyocytes without increasing the concentration of ATP molecules required for contraction, i.e., without increasing the myocardial oxygen consumption.⁴⁴ Additionally, these substances increase the cardiac contractile force without the potentially deleterious increase in intracytoplasmic Ca^{2+} concentration. Cardiac myosine activators have been tested in animal studies in which their inotropic properties have been well demonstrated.⁴⁵ In humans, two recent studies have demonstrated that cardiac myosin activators are a valuable new class of therapeutic agents in systolic heart failure.^{46,47} Cardiac myosin activators are well tolerated,^{46,47} including during exercise in patients with ischemic cardiomyopathy.⁴⁸ These agents improve cardiac systolic function in a dose- and concentration-related manner,^{46,47} without significant changes in diastolic function.⁴⁷ Studies in patients hospitalized for acute heart failure are ongoing (available at: www.clinicaltrials.gov, identifier: NCT01300013).

Istaroxime

Istaroxime is a new drug that inhibits Na^+/K^+ -ATPase, increasing the activity of the sarcoendoplasmic reticulum Ca^{2+} ATPase pump by relieving phospholamban inhibition.⁴⁹ It induces some inotropic and lusitropic effects.⁵⁰ In animals, istaroxime was demonstrated to decrease the end-diastolic volume of the left ventricle and increase the left ventricular ejection fraction. In patients with decompensated heart failure without hypotension, istaroxime decreased the pulmonary artery occlusion pressure and improved the diastolic function of the left ventricle.⁵¹ In patients with acute heart failure, istaroxime decreased pulmonary artery occlusion pressure, decreased heart rate in a dose-dependent manner, and increased systolic blood pressure without any effects on neurohormones or troponin levels.⁵² This drug still needs further clinical evaluation.

Nitric Oxide Donors

Nitric oxide donors improve cardiac function by direct positive cAMP-independent lusitropic and inotropic effects.⁵³ These drugs enhance sarcoendoplasmic reticulum Ca^{2+} uptake via modifications of phospholamban, sarcoendoplasmic reticulum Ca^{2+} ATPase pump, and ryanodine receptor. Moreover, nitric oxide donors improve myofilament Ca^{2+} sensitivity.⁵⁴ A human study has shown that nitric oxide donors increase cardiac output and decrease both right and left filling pressures in patients with systolic heart failure without any adverse effects.⁵⁴ This pharmacologic class also still needs further clinical evaluation.

Decrease in Beta-Adrenergic Response

It is well recognized that the response to β -adrenergic stimulation is decreased in chronic cardiac failure. This may be a response to the increased activity of the sympathetic nervous system, which may itself be a response to the reduced cardiac output. Therefore, this negative retrocontrol of the β -adrenergic response could act as a protection against excessive adrenergic stimulation. The cellular mechanisms involved are a downregulation of β_1 -adrenergic receptors and a stimulation of the G_i protein of the adenylyl cyclase system. The decrease in β_1 -adrenergic receptors could result from a decrease in β -adrenergic receptor mRNA and to an increased internalization and degradation of these receptors. These latter mechanisms are mainly related to the phosphorylation of β_1 -adrenergic receptors by the β -adrenoreceptor kinase, which is activated. The high level of nitric oxide (NO) production during heart failure contributes to the attenuation of the β -adrenergic response. The effects of exogenous

catecholamines during exacerbations of chronic heart failure can thus be reduced.

Similarly, there is evidence for a decreased responsiveness of the myocardium to beta-adrenergic stimulation during septic shock.⁵⁵ This phenomenon may occur more likely in the later phase (>24 hours) than in the early phase of the septic process.⁵⁶ This may be explained by the inhibition of adenylyl cyclase activation due to an overexpression of the Gi protein⁵⁷ at the gene level.⁵⁸

HEMODYNAMIC EFFECTS OF INOTROPIC AGENTS IN CRITICALLY ILL PATIENTS

Effects on Cardiac Output

Dobutamine

Dobutamine is the beta-adrenergic agent most widely used in critically ill patients when an increase in cardiac output through an increase in myocardial contractility is desired.

In patients with acute heart failure, dobutamine increases cardiac output and heart rate and decreases pulmonary artery occlusion pressure through a dose-response manner (from 0 to 15 $\mu\text{g/kg/min}$).⁵⁹ In patients with cardiogenic shock, dobutamine is also able to increase cardiac output while decreasing pulmonary artery occlusion pressure.⁶⁰

In patients with septic shock and depressed myocardial function, dobutamine is expected to increase stroke volume and heart rate owing to its beta1-adrenergic properties and exert a vasodilatory effect owing to its beta2-adrenergic properties. Accordingly, an increase in cardiac output and a decrease in systemic vascular resistance (SVR) with dobutamine were reported in septic patients.^{61,62} This emphasizes the need to give a potent vasopressor agent to patients with septic shock when dobutamine is administered to support cardiac function in the presence of depressed myocardial contractility. One potential advantage of dobutamine is a decrease in cardiac filling pressures that could allow an additional volume infusion to improve further cardiac output when necessary. A change from dopamine to dobutamine was shown to result in lower right and left ventricular filling pressures and an increase in right ventricular ejection fraction for the same pulmonary artery pressure and right ventricular end-diastolic volume, suggesting that dobutamine exerts a more favorable effect on cardiac contractility than dopamine.⁶³ This has justified the recommendation to administer dobutamine rather than dopamine when the use of inotropic drugs is judged necessary in patients with severe sepsis or septic shock.^{35,36} However, because of the alteration of the beta1-adrenergic pathway in the septic heart, the effect on stroke volume and cardiac output of a beta1 agonist agent such as dobutamine may be attenuated in patients with sepsis compared with those without sepsis. In this regard, infusion of dobutamine at 5 $\mu\text{g/kg/min}$, a dose able to increase cardiac output substantially in patients with acute heart failure,⁵⁹ has been reported to exert variable effects in the context of sepsis. For example, dobutamine at 5 $\mu\text{g/kg/min}$ was reported to induce a substantial increase in cardiac output in some studies in patients with severe sepsis^{61,64} but to have no significant effect on cardiac output in some studies investigating patients with septic shock.⁶⁵⁻⁶⁹ It is likely that these differences in response to dobutamine were related to various individual factors including differences in the vasopressor coadministered and in the degree of myocardial depression and/or beta-receptor downregulation. In this regard, Silverman et al. showed that incremental doses of dobutamine (0, 5, 10 $\mu\text{g/kg/min}$) produced a dose-related increase in cardiac output in patients with sepsis without shock but no increase in cardiac output in patients with septic shock, even for the highest dose.⁵⁵ Interestingly, they also found that the post-beta-adrenergic receptor signal transmission was impaired only in patients of the septic shock group and that impairment of beta-adrenergic receptor responsiveness found in both groups was significantly more marked in the septic shock group.⁵⁵ These findings, which allow divergent results of numerous studies to be reconciled,^{61,64-72} emphasize the unpredictability of the

effects of beta-agonist agents in patients with sepsis. It must be stressed that the absence of positive cardiac response to dobutamine seems to be a marker of poor outcome in septic shock patients.^{33,34,69} Because dobutamine also has potentially harmful effects (e.g., myocardial ischemia, cardiac arrhythmias), monitoring its effects on cardiac output to check its efficacy is mandatory, especially in patients who are not responding to initial therapy.³⁶

Dopamine

In patients with acute heart failure, dopamine increased stroke volume and cardiac output at 4 $\mu\text{g/kg/min}$ but not at higher doses, presumably because of an increase in left ventricular afterload. It was also reported that pulmonary artery occlusion pressure increased with dopamine while it decreased with dobutamine.⁷³ Similar results were observed in patients with cardiogenic shock receiving a dose of 15 $\mu\text{g/kg/min}$ of either agent.⁶⁰

In patients with septic shock, it was reported that the restoration of an adequate MAP with dopamine was mainly produced by the increase in cardiac output, whereas minimal effects on SVR were observed despite relatively high doses of this agent.⁷⁴ Dopamine was even demonstrated to increase cardiac output markedly while SVR fell in septic patients without shock.⁷⁵ Conversely, in another study in patients with severe septic shock, cardiac output did not increase significantly with dopamine at doses of up to 25 $\mu\text{g/kg/min}$ while SVR either did not change or significantly increased.⁷⁶ This emphasizes the great heterogeneity of the response to dopamine among patients with sepsis. This also emphasizes the difficulty to predict clinical hemodynamic effects from pharmacologic properties owing to interindividual differences in terms of the severity of the insult, underlying diseases, comorbidities, integrity of the neuro-vegetative status, drugs concomitantly prescribed, and other factors.

Epinephrine and Norepinephrine

Although these agents have beta1-adrenergic properties and are thus able to increase myocardial contractility, they are used as vasoconstrictive agents in case of severe hypotension since they also have potent alpha-adrenergic properties. Nevertheless, significant increases in cardiac output with these drugs have been reported in patients with sepsis.^{74,77,78} In this regard, norepinephrine was shown to increase cardiac output to the same extent as dopamine for the same increase in MAP.⁷⁴ However, the effects of norepinephrine on cardiac output depends on its effect on cardiac preload^{79,80} through an increase in mean systemic filling pressure.⁴¹ By contrast, epinephrine appeared as a potent inotropic agent in most studies in patients with sepsis.^{67,81-83}

Dopexamine

The pharmacologic properties of dopexamine should result in a combination of inotropic, afterload-reducing, and renal vasodilating effects, which could be useful for the management of the acute exacerbation of congestive heart failure. In this regard, dopexamine was reported to substantially increase cardiac output in patients with heart failure without altering blood pressure: at doses of up to 4 $\mu\text{g/kg/min}$, the majority of the effects resulted from an increase in stroke volume. At higher doses, the increase in heart rate made a greater contribution.⁸⁴ In cases of human sepsis, dopexamine produced a dose-dependent increase in stroke volume and heart rate but a dose-dependent decrease in SVR.⁸⁵ This underlines the marked vasodilating effect of this drug, which should not be administered in severe sepsis in the absence of a potent vasopressor. Under these conditions, dopexamine, at doses ranging from 1 to 4 $\mu\text{g/kg/min}$, could still enhance cardiac output without altering blood pressure.⁸⁶

Phosphodiesterase Inhibitors

In patients with heart failure, phosphodiesterase inhibitors significantly increased cardiac output and stroke volume, while blood pressure slightly decreased due to a decrease in SVR, confirming the combined inotropic and vasodilating effects of these agents.⁸⁷ Because of the ability of beta-agonist agents to increase cAMP levels, thereby

providing an increased substrate for phosphodiesterase inhibitors, the combination of these two types of drugs would be attractive. Synergic effects on the cardiac output of dobutamine and enoximone have been observed in patients with heart failure.⁸⁸

Ca²⁺ Sensitizers

It has been well demonstrated that levosimendan induces some beneficial hemodynamic effects in patients with acute heart failure, with an enhanced cardiac output and a decreased pulmonary artery occlusion pressure.⁸⁹ In the LIDO study, levosimendan was shown to improve hemodynamic performance more effectively than dobutamine in patients with low-output heart failure.⁸⁹ Unlike dobutamine, levosimendan can keep its effects on cardiac performance in patients receiving beta-blockers.⁸⁹

Istaroxime

Only few clinical trials studied the effect of istaroxime, a new inotropic-lusitropic agent. Two studies demonstrated that in patients with systolic heart failure, istaroxime increased cardiac index^{52,90} and decreased pulmonary artery occlusion pressure and heart rate.⁵²

Effects on Arterial Oxygen Content

The aim of inotropic therapy in critically ill patients with reduced cardiac contractility is not only to increase cardiac output but also to ultimately improve oxygen delivery to the tissues. Thus, attention should be paid to the effects of these drugs on arterial oxygen content. Inotropes may affect arterial oxygen tension through several mechanisms. First, the reduction in lung filtration pressure resulting from an improvement in cardiac function may decrease intrapulmonary shunt fraction and thus improve arterial oxygenation. Second, the increase in cardiac output may result in an increased venous admixture.⁹¹ On the other hand, the increased mixed venous blood oxygen tension resulting from increased cardiac output may improve arterial oxygenation in the presence of ventilation/perfusion mismatching and may thus compensate for the increased venous admixture. Accordingly, when looking at published data, it appears that even if the venous admixture increased with the administration of an inotropic agent, no significant change in arterial oxygen tension was observed.^{92,93} Therefore, when an inotropic agent increases cardiac output in critically ill patients, it generally increases oxygen delivery to the same extent.^{61,74,94,95}

Effects on Tissue Oxygen Utilization

Even though an inotropic agent results in a large increase in oxygen delivery, its effectiveness in reducing oxygen deficit depends on its capacity to provide oxygen in the most hypoxic tissues. This concern is particularly crucial since, first, the redistribution of blood flow is a characteristic pattern of shock states and, second, inotropic drugs may also have vasoactive properties that interact with blood flow distribution.

Cardiogenic Shock

In this setting, the redistribution of blood flow is recognized as a potent compensatory mechanism, which, in response to reduced global oxygen delivery, attempts to redirect blood flow from nonvital organs with a low oxygen extraction ratio toward vital organs with a high oxygen extraction ratio such as the heart or the brain. It must be kept in mind that the administration of drugs with vasoactive properties may interfere with the vasoregulation of regional blood flow. The extent to which this interference is beneficial in increasing oxygen supply and oxygen consumption in hypoxic areas remains speculative. This emphasizes the need to monitor, as far as possible, the perfusion and/or function of critical organs.

Septic Shock

The maldistribution of flow at the macrocirculatory level and the microcirculatory level mainly contributes to defective tissue utilization

and eventually to tissue oxygen debt in sepsis, even when systemic oxygen delivery is greater than normal. Besides sepsis-induced microthrombosis, sepsis-induced alteration in vascular reactivity is a major cause of the altered distribution of blood flow between and within organs. In addition, severe sepsis can modify the impact of endogenous catecholamines and adrenergic drugs on regional blood flows, given that a depressed vascular responsiveness to vasoactive agent is likely to occur in this setting. This hypothesis may account for the absence of the reduction of renal blood flow observed during norepinephrine administration in bacteriemic animals in comparison with controls.⁹⁶

In case of human sepsis, numerous studies examined the effects of adrenergic agents on splanchnic perfusion. Their findings have sometimes varied either because of differences in the methods used for assessing this regional circulation (e.g., gastric tonometry, laser-Doppler flowmetry, indocyanin green dilution) or because of the heterogeneity of the studied populations (e.g., differences in the severity of the septic insult, underlying diseases, or therapy coadministered). However, from the findings of majority of these studies, some reasonable conclusions can be drawn. First, dobutamine is likely to exert a beneficial effect on gut mucosal perfusion,^{62,65,67,71,97} probably via a beta2-adrenergic effect.⁹⁸ Dobutamine may also improve hepatic microcirculation via a beta1-adrenergic effect.⁹⁹ Second, dopamine may have deleterious effects on gut mucosal perfusion,⁷⁴ despite its potential vasodilating action through mesenteric dopaminergic receptors. Third, epinephrine is probably the adrenergic agent with the least desirable effects on the splanchnic vasculature as most studies showed a lower splanchnic blood flow with epinephrine than norepinephrine alone¹⁰⁰ or in combination with dobutamine,^{65,67,101} even for similar global hemodynamic effects. Fourth, dopexamine can exert a favorable effect on splanchnic perfusion¹⁰² comparable to that of dobutamine⁶⁶ and that is likely to be related to a beta2-adrenergic effect.

Regarding the effects of inotropic agents on renal circulation in patients with sepsis, two major points must be kept in mind. First, an alpha-adrenergic agent such as norepinephrine is able to increase renal blood flow and urine output,^{76,103-105} despite its potential vasoconstricting effect on the afferent glomerular arteries. This is probably due to the beneficial effect of increasing MAP when the renal blood flow is dependent of its perfusion pressure as it occurs in the presence of profound systemic hypotension. Otherwise, the sepsis-induced depressed responsiveness of afferent glomerular arteries to the action of norepinephrine cannot be excluded. Accordingly, there is more evidence that norepinephrine increases, rather than decreases, renal blood flow and urine output when given to patients with sepsis to increase the MAP toward normal values.^{76,103,104,106} Moreover, it has been demonstrated in patients with septic shock that elevating the MAP to up to 85 mm Hg with incremental doses of norepinephrine was not associated with a decrease in urine output.^{105,107,108} Second, although dopamine at low doses (<5 µg/kg/min) is pharmacologically able to vasodilate renal arteries through its action on dopaminergic receptors, the systematic administration of low doses of dopamine in critically ill patients, including patients with sepsis, does not result in improved outcome¹⁰⁹ and must no longer be recommended. Finally, no study focused on the renal effects of levosimendan in patients with septic shock. Nevertheless, a recent study showed that in postoperative cardiac patients, levosimendan infusion increased both renal blood flow and glomerular filtration, likely via its vasodilatory effects.¹¹⁰

Catecholamines can also exert proper effects on the microcirculation. First, the administration of 5 µg/kg/min of dobutamine was shown to improve sublingual microvessel perfusion measured with orthogonal polarizing spectral imaging in patients with septic shock.¹¹¹ Interestingly, these changes were independent of changes in systemic hemodynamic variables.¹¹¹ The improvement of sublingual microcirculation seems to occur only in patients with severe alterations at baseline.¹¹² Nevertheless, the effect of dobutamine on microcirculation is still debated. The administration of 5 µg/kg/min in patients with sepsis having hyperlactatemia and a cardiac index of greater than or equal to 2.5 L/min/m² failed to improve sublingual perfused vessel density or microvascular flow index, in spite of a significant increase

in systemic hemodynamics.⁹⁴ Compared to the administration of 5 µg/kg/min of dobutamine, an infusion of low doses of levosimendan improved sublingual microcirculatory blood flow patients with septic shock, probably via its vasodilatory effects.¹¹³ Two studies showed no significant effect of increasing MAP with norepinephrine on sublingual microvessels in patients with septic shock who had already been resuscitated.^{77,78} However, another study, conducted in patients with septic shock requiring norepinephrine for arterial hypotension resistant to fluid administration demonstrated that increasing the MAP from 65 to 85 mm Hg by titrating norepinephrine doses allowed the improvement of sublingual microvessel circulation.¹¹⁴ Thus, at least nonworsening or even improvement of microcirculation can result from norepinephrine infusion in patients with septic shock even when a MAP of up to 85 mm Hg is targeted. It is noteworthy that in patients with septic shock patients having a history of chronic hypertension, improved sublingual microcirculation was reported when the usual patient's level (averaged value 93 mm Hg) was targeted compared to 65 mm Hg.¹¹⁵ This result is in agreement with the results of a multicenter randomized clinical trial showing that this specific population of patients may benefit from a higher MAP target, at least in terms of renal function, than the population of patients with no chronic hypertension.¹¹⁶ Finally, inotropic drugs may also exert nonhemodynamic effects that could affect cellular metabolism and/or organ function.^{23,117} For example, the administration of epinephrine in patients with septic shock was demonstrated to increase blood lactate level independently of tissue hypoxia, by the stimulation of skeletal muscle cell Na⁺/K⁺-ATPase, which accelerates aerobic glycolysis and thus the production of pyruvate and hence of lactate into the cell.¹¹⁸ This metabolic effect is assumed to be related to the activation of the beta2-adrenergic receptors located at the surface of the skeletal muscle cells.¹¹⁹ In addition, catecholamines may modulate cytokine response to sepsis, trauma, or major surgery through beta-adrenergic receptor activation.²³ It remains to be evaluated whether this effect (inhibition of proinflammatory cytokines and enhancement of proinflammatory cytokine production) plays a beneficial role in the reversal of tissue hypoxia and organ dysfunction.

MAIN INDICATIONS OF INOTROPIC THERAPY IN PATIENTS WITH CIRCULATORY FAILURE

Acute Heart Failure and Cardiogenic Shock

For the American College of Cardiology Federation/American Heart Association, inotropic agents should be considered in patients with heart failure, in those who are refractory to other therapies, and in those who are suffering consequences from end-organ hypoperfusion.¹²⁰ In practice, inotropes should be restricted to patients with systolic dysfunction who have a low cardiac index and evidence of systemic hypoperfusion and/or congestion.¹²⁰ In the European Society of Cardiology guidelines, inotropes should be considered in patients with acute heart failure and in patients having hypotension (systolic blood pressure <85 mm Hg) and/or hypoperfusion to increase cardiac output, increase blood pressure, and improve peripheral perfusion.¹²¹ Overall, these indications clearly limit the use of inotropic agents to patients with acute heart failure and low systolic blood pressure, most likely to have increased mortality rates with a strong inverse correlation between systolic blood pressure and survival.¹²²

For the European Society of Cardiology, dobutamine is currently the first-line inotropic agent in the presence of acute heart failure with low systolic arterial blood pressure.¹²¹ For the American Heart Association, dobutamine and dopamine are both cited as inotropic agents.¹²⁰ Accordingly, the SHOCK trial registry (1190 patients) reported that dopamine and dobutamine were used in 89% and 70%, respectively, of patients with cardiogenic shock due to massive acute myocardial infarction.¹²³ However, the use of dopamine is still a matter of debate. In a study comparing dopamine and norepinephrine as the first-line

vasopressor agent in the treatment of shock, the use of dopamine was associated with a greater number of cardiac arrhythmias.¹²⁴ In addition, in a predefined subgroup analysis, the authors reported that the use of dopamine was associated with an increased risk of death in the subgroup of 280 patients with cardiogenic shock.¹²⁴

Finally, a recent multicenter placebo-controlled clinical trial demonstrated that the use of low-dose dopamine in patients with acute heart failure and renal dysfunction had no significant effect on the 72-hours' cumulative urine volume and did not improve renal function, assessed by the change in cystatin C levels.¹²⁵

Epinephrine was compared to the combination of norepinephrine and dobutamine in patients with dopamine-resistant cardiogenic shock—for example, with a cardiac index of less than 2.2 L/min/m² and a MAP of less than 60 mm Hg.¹²⁶ Epinephrine or norepinephrine-dobutamine were titrated to obtain a MAP of greater than 65 mm Hg.¹²⁶ Epinephrine infusion was as effective as the combination of norepinephrine and dobutamine to improve cardiac index and oxygen-derived parameters. Nevertheless, epinephrine infusion induced arrhythmia, increased blood lactate level, and impaired splanchnic circulation.¹²⁶

It must be stressed that the intravenous administration of catecholamines such as dobutamine is associated with an increased risk of death in patients with acute heart failure.¹²⁷⁻¹²⁹ This emphasizes their restrictive use to patients in whom pump failure results in severe hypotension and peripheral hypoperfusion.^{120,121}

Phosphodiesterase inhibitors have been proposed as an alternative to beta-adrenergic agents. However, results of trials of long-term oral phosphodiesterase inhibitor therapy in chronic heart failure and of the OPTIME-CHF study in the acute decompensation of congestive heart failure¹³⁰ have been disappointing. Thus, the use of these agents is limited to few categories of patients: (1) patients with advanced heart failure awaiting transplantation in whom intravenous milrinone could be better tolerated than dobutamine and its use may allow the continuation of beta-blocker therapy controlling arrhythmias or myocardial ischemia,¹³¹ (2) patients with acute decompensation of chronic heart failure unable to achieve stabilization with the standard treatment, and (3) patients with long-term beta-blocker use, in whom short-term intravenous milrinone may even be preferred to dobutamine. Enoximone, another phosphodiesterase inhibitor, has been tested in patients with advanced heart failure. As for milrinone, the results are disappointing. Low doses of enoximone could not improve all-cause mortality or the 6-min walk test distance.¹³² There is now clear evidence that phosphodiesterase inhibitors such as beta-agonists can exert both short-term beneficial hemodynamic effects and serious adverse effects that make them deleterious in terms of long-term outcome. It is likely that their adverse effects (e.g., arrhythmias, increased risk of myocardial ischemia) are related to the increased cAMP concentration in the cytosol of the cardiomyocyte.¹³³

The initial enthusiasm in the use of Ca²⁺ sensitizers in patients with heart failure has attenuated in recent years. In the LIDO study, compared to dobutamine, levosimendan significantly decreased mortality rate and improved the hemodynamic condition.⁸⁹ Nevertheless, these positive results have been contradicted in two large-scale studies. In the REVIVE study,¹³⁴ even though levosimendan improved the composite judgment criteria of clinical signs of heart failure at 5 days compared to placebo, the mortality rate was not significantly changed. In the SURVIVE study,¹³⁵ levosimendan was not better than dobutamine in increasing the survival rate in patients with acute heart failure requiring an inotropic support. A meta-analysis concluded that in patients with acute severe heart failure, levosimendan improved hemodynamic parameters when compared with placebo, without showing evidence of survival benefit.¹³⁶ However, a more recent meta-analysis demonstrated that levosimendan reduced mortality rate when compared to dobutamine and decreased hospital length of stay in the overall population of cardiologic patients, including but not restricted to patients with heart failure.¹³⁷ Furthermore, another topic of interest of levosimendan may be patients with heart failure receiving concomitant use of beta-blocker therapy, a situation where higher doses of dobutamine are usually required to have some efficacy. In such patients,

dobutamine was shown to be as effective as levosimendan in the first 24 hours of treatment to increase cardiac index and decrease pulmonary artery occlusion pressure.¹³⁸ However, at 48 hours, levosimendan still efficiently improved hemodynamics while dobutamine did not.¹³⁸ Moreover, when compared with placebo, levosimendan improved contractility in patients with acute heart failure following myocardial infarction,¹³⁹ and levosimendan provided rapid and durable symptomatic relief.¹⁴⁰ Nevertheless, levosimendan induced hypotension^{139,140} or cardiac arrhythmias.¹⁴⁰ Finally, a recent systematic review found no significant beneficial effects of levosimendan for low cardiac output syndromes in the general population of critically ill patients.¹⁴¹ Currently, all these disappointing results have impeded the commercialization of levosimendan in many countries.

NO synthase inhibitors have been proposed to be used in patients with cardiogenic shock, in whom NO production is increased and may exert deleterious effects on cardiac function and vascular tone.¹⁴² Tilarginine is a nonselective NO synthase inhibitor developed for treating acute heart failure. However, in the TRIUMPH study, tilarginine was unable to improve the survival rate in patients with cardiogenic shock at 3 months in comparison with placebo.¹⁴³ These negative results have interrupted the clinical development of this new drug.

Septic Shock

Treating or not treating septic-induced myocardial depression has been a matter of debate. First, it has been thought that left ventricular dilation and low ventricular ejection fraction denote adaptive mechanisms and then, if so, treating it is questionable. In this regard, left ventricular ejection fraction was reported to be lower and left ventricular end-diastolic volume to be higher in survivors,^{144,145} although a meta-analysis showed no difference between survivors for the two parameters. Second, owing to the potential, but not constant, hyporesponsiveness of the beta receptors, the efficacy of beta-agonists is not guaranteed. Third, side effects may occur with these drugs (tachycardia, arrhythmias, and hypotension). It must be stressed that there is an association of inotrope use during septic shock with mortality.¹⁴⁶ For all these reasons, inotropes and among them, dobutamine, should be not systematically administered even when a septic myocardial depression is suspected. It should be reserved for situations where cardiac dysfunction is accompanied by a low or inadequate cardiac output and signs of tissue hypoperfusion, in spite of preload optimization.³⁶ Bidimensional echocardiography¹⁴⁷ is the best tool to diagnose a severe decrease in cardiac contractility. However, bedside echocardiography is not available in all general ICUs; hence, the Surviving Sepsis Campaign recommends the use of dobutamine in septic shock in cases of (a) a myocardial dysfunction as suggested by elevated cardiac filling pressures and low CO or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP.³⁵ Since dobutamine can exert vasodilatory effects, its use requires the concomitant use of a vasopressor such as norepinephrine. In septic shock, it is clearly recommended to use norepinephrine as the first-choice agent rather than dopamine since the latter is associated with increased mortality.¹⁴⁸ Epinephrine is a potent inotrope with vasopressive properties that could be used as an alternative of the combination of dobuta-

mine and norepinephrine. A randomized study in patients with septic shock and a presumed cardiac dysfunction found no significant difference in patient outcome between epinephrine alone and a combination of norepinephrine and dobutamine.¹⁴⁹ However, this study has been criticized for a lack of statistical power. In the condition of depressed vascular tone and reduced myocardial function, despite similar effects on systemic blood flow and pressure, epinephrine was shown to be inferior to the combination of dobutamine and norepinephrine in terms of splanchnic perfusion^{65,67,101} or to norepinephrine alone in terms of myocardial oxygen consumption.¹⁵⁰ Recently, a meta-analysis showed that the use of norepinephrine in patients with sepsis reduced mortality rate whereas the use of epinephrine did not.¹⁵¹ For all these reasons, epinephrine is not recommended as the first-choice drug when the treatment of impaired cardiac contractility is considered.⁴³ The use of levosimendan has been proposed as an alternative to dobutamine in case of severe septic myocardial depression that no longer responds to dobutamine administration.¹⁵² The rationale for using levosimendan is that the sensitivity of Ca^{2+} to myofilament is reduced during sepsis probably because of an abnormal phosphorylation of the troponin complex at the site where the Ca^{2+} ion binds to troponin C.¹⁵³ Because levosimendan can improve not only left ventricular function but also right ventricular performance through pulmonary vasodilation,^{154,155} it might be useful in cases of septic myocardial depression with associated lung injury. A recent meta-analysis including seven clinical studies in patients with severe sepsis and septic shock (246 patients) showed that levosimendan was associated with a significant reduction in mortality rate compared with standard inotropic therapy.¹⁵⁶ A multicenter randomized double-blind, parallel-group, placebo-controlled trial is ongoing to assess the efficacy of levosimendan to reduce organ failure, including cardiac dysfunction, in patients with septic shock.¹⁵⁷

It is important to note that the concept of using beta-blockers in septic conditions to prevent systemic adrenergic activation has recently emerged. In an experimental model, esmolol infusion had no significant effect on cardiac index or systemic arterial pressure and may prevent septic cardiac dysfunction by a preload effect induced by the decrease in heart rate.¹⁵⁸ In patients with septic shock, esmolol infusion was associated with a preserved stroke volume and microcirculation and a decrease in norepinephrine requirement.¹⁵⁹ In this regard, a randomized clinical trial was conducted in patients with septic shock and heart rate of greater than 90 beats/min. Esmolol infusion decreased heart rate, increased stroke volume and left ventricular stroke work index, and decreased arterial blood lactate level and fluid requirements. Although mortality rate was not the primary endpoint, it should be noted that esmolol infusion was associated with a significant decrease in 28-day mortality.¹⁶⁰ Nevertheless, patients with severe cardiac dysfunction (i.e., cardiac index ≤ 2.2 L/min/m² in the presence of a pulmonary artery occlusion pressure >18 mm Hg) were excluded. As a consequence, the presence of cardiac dysfunction during sepsis cannot be considered as an indication for beta-blockers and should be still considered as a contraindication for their use.

In summary, given all the available data, it is still recommended to choose the combination of norepinephrine and dobutamine when inotropic therapy is given to reverse cardiac dysfunction in severe sepsis.³⁵

KEY POINTS

1. Inotropic therapy is considered in patients with cardiogenic shock or in those with advanced heart failure whose condition is refractory to standard therapy. In these situations, clinicians expect short-term positive effects of intravenous inotropic drugs, allowing cardiovascular stabilization.
2. Inotropic therapy might also be considered in high-risk surgical patients, even in the absence of formally documented myocardial depression, to achieve supranormal levels of oxygen delivery during the perioperative period to prevent tissue hypoxia and organ dysfunction. Such a therapeutic attitude, which is still debated in the perioperative context, is not recommended routinely for critically ill patients with established circulatory shock.
3. Most inotropic agents enhance myocardial contractility by increasing the Ca^{2+} concentration in the cytosol of cardiomyocytes

Continued

KEY POINTS—cont'd

- after producing an increase in cytosolic cyclic adenosine monophosphate (cAMP) concentration. Synthetic and natural catecholamines enhance cAMP formation after fixing beta1-adrenergic receptors at the cellular surface while phosphodiesterase inhibitors decrease cyclic AMP degradation.
4. Beta1-adrenergic agents, such as dobutamine, dopamine, and epinephrine, are the most potent inotropic agents.
 5. Because of the downregulation of beta1-adrenergic receptors, the myocardial effects of exogenous catecholamines can be attenuated after a few days of administration.
 6. Sepsis-induced decreased responsiveness of the myocardium to beta-adrenergic stimulation may also result in the attenuation of

cardiac effects of exogenous catecholamine administration in patients suffering from septic shock.

7. The drugs given to increase cardiac contractility may also exert vasoactive effects that may interfere with the regulation of regional blood flow. The extent to which this interference is beneficial in increasing oxygen supply in hypoxic areas remains speculative. This emphasizes the need to monitor, as far as possible, the perfusion and/or function of critical organs when such agents are given to patients in circulatory shock.

ANNOTATED REFERENCES

De Backer D, Aldecoa C, Njimi H, Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis. *Crit Care Med* 2012;40:725-30.

The objective of this meta-analysis was to evaluate the effects of norepinephrine and dopamine on outcome and adverse events in patients with septic shock. Six randomized studies (1408 patients) were included. Dopamine administration was associated with greater mortality and a higher incidence of cardiac arrhythmic events compared to norepinephrine administration. This paper is important since it greatly contributed to change the guidelines of the Surviving Sepsis Campaign, which now recommends to use of norepinephrine as a first-choice vasopressor and to restrict the use of dopamine to highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia).

Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, Higgins AM, Holdgate A, Howe BD, Webb SA, Williams P. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014;371:1496-506.

In this multicenter clinical trial, 1600 patients presenting to the emergency department with early septic shock were randomly assigned to receive either early goal-directed therapy (EGDT) or usual care. EGDT did not reduce all-cause mortality at 90 days. This paper as well as the Process (ref) and Promise (Ref) papers have substantially questioned the interest of using EGDT including Scvo₂ in the early phase of septic shock.

Hayes MA, Timmins AC, Yau E, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994;330:1717-22.

This randomized study showed that attempting to achieve supranormal values of oxygen delivery in patients with an established critical illness may worsen rather than improve outcome.

Mebazaa A, Nieminen MS, Packer M, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. *JAMA* 2007;297:1883-91.

In 1327 patients with acute decompensated heart failure requiring inotropic support, levosimendan was compared to dobutamine in a randomized double-blind design. Despite an initial reduction in plasma B-type natriuretic peptide level in patients receiving levosimendan, levosimendan did not significantly reduce all-cause mortality at 180 days or affect any secondary clinical outcomes. These disappointing results impeded commercialization of levosimendan in many countries over the world.

Morelli A, De Castro S, Teboul JL, et al. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. *Intensive Care Med* 2005;31:638-44.

In 28 septic patients with persisting cardiac dysfunction after 48 h of dobutamine administration, compared to dobutamine continuation, levosimendan improved systemic hemodynamics, improved gastric mucosal perfusion and renal function, and decreased lactate. This study suggests that levosimendan might be an alternative to dobutamine for treating sepsis-induced cardiac dysfunction.

Silverman HJ, Penaranda R, Orens JB, et al. Impaired beta-adrenergic receptor stimulation of cyclic adenosine monophosphate in human septic shock: association with myocardial hyporesponsiveness to catecholamines. *Crit Care Med* 1993;21:31-9.

This clinical study demonstrated that patients with septic shock exhibit a decreased hemodynamic response to dobutamine when compared to septic patients without shock. Moreover, the stimulation of circulating lymphocytes of the studied population showed that in patients with septic shock, the degree of impairment of beta-adrenergic receptor responsiveness as well as that of post-beta-adrenergic receptor signal transmission was greater than in septic patients without shock. This study provides strong evidence of a septic shock-related myocardial hyporesponsiveness to catecholamines that may contribute to the reduced myocardial performance observed in this critical illness.

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Heart disease remains the leading cause of death in both men and women among African Americans, Hispanics, and Caucasians in the United States, accounting for 1 in 7 deaths annually. Coronary artery disease was responsible for more than 375,000 deaths in 2011 as well as 650,000 admissions for a first-time acute myocardial infarction (AMI) and 300,000 recurrent infarctions.¹ Primary and secondary prevention strategies have been attributed to an overall decrease in the incidence of AMI in the United States since 1999.² Despite these encouraging data, the high incidence of obesity and heart disease among an ever-growing elderly population still accounts for a staggering number of patients who continue to require treatment for cardiogenic shock (CS) and heart failure (HF), with HF listed in over 1 in 9 death certificates.¹ The incidence of CS in myocardial infarction (CSMI) has remained relatively constant in recent decades (~7%) and remains the leading cause of death in patients with AMI.³

The lethality of CS and limited availability of donor hearts for patients with chronic HF has been the impetus for the ongoing search for an ideal form of mechanical circulatory support (MCS) over the past 60 years. The complexity and heterogeneity of this patient population have led to the development of a vast array of devices, none of which has proven optimal for support in all patients across the spectrum. The biological barriers to MCS present a constant challenge to clinicians, and the types of MCSs available are continually evolving. Accurate statistics on the worldwide utilization of all types of MCSs for CS are not known. Nonetheless, MCS remains an important adjunct in the treatment of CS and HF, with many devices demonstrating significant improvement in survival and quality of life. The lack of large prospective, randomized controlled trials (RCTs) that demonstrate clear survival advantages for many of these devices can make it difficult to discern which, if any, MCS should be used in a given clinical situation. Accordingly, the current indications, benefits, and limitations of MCS are outlined in this chapter.

HISTORY OF MECHANICAL CIRCULATORY SUPPORT

The evolution of MCS dates to the early 1950s when Gibbon developed the prototype cardiopulmonary bypass (CPB) apparatus.⁴ In the years that followed, Lillehei, Kirklin, and others applied the heart-lung machine to facilitate open-heart surgery; their pioneering work and early observations led directly to the development of modern MCS systems.⁵⁻⁷ Their initial publications introduced the concept that left ventricular (LV) decompression and myocardial rest could afford enhanced cardiac recovery after the insult of open-heart surgery. Clinical use of extracorporeal CPB for heart surgery became widespread in the early 1960s. Simultaneously, several groups of investigators were testing means of MCS for use outside the operating room to support patients in CS. The current modes of MCS are derivations of those originally developed.

The decision on the type of MCS used is based on the acuity of the patient's presentation and the overall goals of therapy. This decision often changes as the patient's clinical picture evolves. MCS devices include the intraaortic balloon pump (IABP), continuous flow pumps with or without an oxygenator, and pulsatile pumps. Temporary MCS devices are utilized in CS as a bridge to recovery (BTR),

bridge-to-bridge ("double bridge") with a long-term implantable MCS device, bridge to transplant (BTT), or until definitive corrective surgery can be performed. Some temporary MCS devices can be inserted percutaneously, while others require surgical implantation. Long-term MCS devices are used as a BTR, a BTT, or as the definitive means of treatment for the patient's remaining lifespan—that is, destination therapy (DT). These devices have been employed for a variety of causes of CS including AMI, inability to wean from CPB (postcardiotomy failure), acute decompensation of chronic HF, acute myocarditis, peripartum cardiomyopathy, HF secondary to acute or chronic valvular heart disease, and congenital heart defects.

History of Aortic Counterpulsation

The concept of arterial counterpulsation was introduced in 1961 by Clauss and coworkers. It involved use of an external "ventricular" chamber that filled with blood from a catheter in the iliac artery and was subsequently compressed by a piston. Compression of the "ventricle" was synchronized to either the QRS complex of an electrocardiogram (ECG) or the impulse of a pacemaker so that a counterpulse of blood was delivered into the arterial system during diastole.⁸ It was demonstrated in dogs that cardiac stroke work and LV end-systolic pressures were substantially reduced with the use of a counterpulsation into the aorta. The following year, Mouloupoulos and associates adapted the model to create an IABP that could provide a similar counterpulsation without the need for blood reservoirs.⁹ The investigators used a balloon that was rapidly inflated and deflated with carbon dioxide during native diastole. The IABP was subsequently adapted and described for clinical use by Kantrowitz and colleagues in 1968.¹⁰ There is little difference in the modern IABP and that originally described, other than the availability of different-sized balloons (30- to 50-mL balloons), the use of helium instead of carbon dioxide, and subtle differences in the materials used to make the catheters.

History of Mechanical Assist Devices

The need for effective MCS devices became apparent in the 1950s during the development of CPB for open-heart surgery. The first attempt at isolated extracorporeal LV support was with a simple roller pump in 1962.¹¹ Initial attempts with prolonged postoperative CPB demonstrated that the bypass circuit was damaging to both end organ function and blood constituents after several hours of use.¹² Subsequently, femoral venous-to-femoral arterial CPB was successfully used by Spencer and colleagues in four patients with postcardiotomy cardiac failure.¹³ Simultaneous to Spencer and colleagues' work with extracorporeal systems, DeBakey designed the first intracorporeal LV assist device (LVAD), the DeBakey blood pump.¹⁴ A remodeled extracorporeal version was subsequently used for postcardiotomy failure in a 37-year-old woman after aortic and mitral valve replacements. The device was needed for 10 days, and the patient survived.¹⁵

By 1972, investigators at the Texas Heart Institute had developed a pneumatically driven LVAD designed to be implanted in the abdomen.¹⁶ This device had a blood chamber compressed by pulses of air delivered into the pump by a percutaneous driveline. Modern devices have chamber compression that is electrically powered via percutaneous drivelines. Paracorporeal, pneumatically driven devices were a parallel

development. Paramount to the evolution of these devices was the sponsorship of the Artificial Heart Program of the National Heart, Lung, and Blood Institute, which was chartered in 1964.

By the 1960s, continuous flow, as compared to pulsatile, pumps were under development.^{17,18} Over the subsequent 15 years, continuous flow centrifugal pumps were perfected and introduced into clinical use. These pumps work on the principle of a forced, constrained vortex devised from three magnetic cones.^{19,20} They have been shown to be useful in a variety of clinical settings where short-term MCS is needed and an IABP is inadequate. Several types of small, axial-flow, or rotary pumps have also been developed, including some that allow for percutaneous deployment.²¹⁻³⁴ These pumps generally contain a magnetically suspended impeller that rotates at extremely fast rates (25,000 to 35,000 rpm). The axial rotary pump technology has some potential advantages over pulsatile devices: they are quite small with few moving parts and do not require a compliance chamber. The latest generation of rotary pump technology utilizes fully magnetically levitated rotors that completely eliminate the need for seals or bearings. This technology reduces the risk of damage to blood elements and may lead to lower rates of thromboembolism.

CURRENT USE OF MECHANICAL CIRCULATORY SUPPORT DEVICES

Temporary Mechanical Circulatory Support

Percutaneous Insertion

Intraaortic Balloon Pump. The physiologic rationale for the efficacy of the IABP is that balloon deflation provides a rapid, synchronized reduction in impedance (afterload) during isovolemic LV contraction. This is followed by a rapid, synchronized increase in aortic pressure during isovolemic LV relaxation (diastolic augmentation) caused by balloon inflation. In combination, these events achieve two important goals. First, LV systolic unloading directly reduces stroke work, which in turn reduces myocardial oxygen consumption during the cardiac cycle. Second, diastolic augmentation raises arterial blood pressure and provides better coronary arterial perfusion during diastole, yielding increased oxygen delivery to the myocardium. The IABP does not directly move or redistribute blood flow; however, peak diastolic coronary flow velocity can be increased as much as 87% with IABP augmentation and peak diastolic flow velocity by as much as 117%.³⁵ Since its introduction into clinical use in 1968, the IABP has remained an important adjunct to supporting patients in CS. Myocardial recovery is promoted by the reduction of cardiac work and the simultaneous increase in myocardial oxygen supply. However, therapeutic success is dependent on the patient having a minimum degree of LV function that, in combination with IABP support, facilitates an adequate cardiac output (CO) to sustain end organ function. When this minimal CO is not met, alternative MCS must be considered.

The absolute indications for IABP placement include CS, uncontrolled angina pectoris, acute postinfarction ventricular septal defect (VSD),³⁶ postinfarction mitral regurgitation (MR) secondary to papillary muscle rupture, and postcardiotomy left-sided HF with low CO. In these settings, IABP should be considered as a primary therapy that should not be delayed until signs of systemic malperfusion are clinically evident. It is important to recognize that blood pressure alone is not an adequate indication of hemodynamic or cardiac stability. Limb perfusion, renal function, mental status, and even gastrointestinal function need to be considered in the assessment of adequate resuscitation and homeostasis. Additional measurable indices include arterial (SaO₂) and mixed venous oxygen saturation (SvO₂), acid-base status, urine output, and body temperature. A multivariate analysis of data accrued from 391 postcardiotomy patients requiring an IABP demonstrated that epinephrine requirements greater than 0.5 µg/kg/min, a left atrial pressure greater than 15 mm Hg, urine output less than 100 mL/h, and SvO₂ less than 60% correlated with mortality.³⁷

These criteria were used to help predict mortality and the need for subsequent MCS.

Other relative indications for IABP use include (1) high-risk, catheter-based interventional procedures such as left main coronary artery angioplasty, (2) after unsuccessful attempts at catheter-based intervention in patients with poorly controlled ventricular arrhythmias and concomitant poor LV function, and (3) in settings of persistent stunned, ischemic myocardium. These are circumstances in which reduction of LV systolic wall tension and oxygen consumption by the IABP might enhance myocardial recovery after intervention. The Benchmark Counterpulsation Outcomes Registry of IABP use in 22,663 patients from 250 hospitals worldwide demonstrated that CS and high-risk angioplasty were the most common indications for utilization of the device.³⁸ Table 91-1 depicts a further characterization of the Benchmark report with respect to indications for use of the IABP and subsequent interventions.³⁹

The optimal site of insertion of an IABP is a common femoral artery that can be accessed either percutaneously with the Seldinger technique or by surgical cutdown. Modern intraaortic balloon catheters are available for adults and children, according to the appropriate size and length for a given height and weight of the patient. Adult intraaortic balloons have a range in volume filled between 30 and 50 mL, with a standard balloon size holding 40 mL of helium. IABP catheters placed through the femoral artery are positioned so that the tip is just distal to the takeoff of the left subclavian artery in the proximal descending thoracic aorta. Optimally, the tip of the catheter should be positioned with transesophageal echocardiographic or fluoroscopic guidance.⁴⁰ To reduce the diameter of femoral cannulation, the sheathless IABP technique can be utilized and is our preferred method.⁴¹

Inflation of the balloon should be timed with closure of the aortic valve (at the dicrotic notch of the aortic pressure tracing) and should be inflated to nearly occlude the descending thoracic aorta. Timing can be synchronized in one of three ways: (1) using an arterial (preferably aortic) pressure tracing in synchrony with the dicrotic notch, (2) using the descent of the R wave on a rhythm tracing, or (3) timed after a ventricular pacing spike when a pacemaker is in use.⁴²⁻⁴⁶ The optimal physiologic benefit of the IABP is significantly improved by proper timing of inflation and deflation, which can be difficult when there is an accelerated heart rate, cardiac rhythm disturbances, atrioventricular dyssynchrony, or low mean arterial pressure. Timing should be adjusted to maximize diastolic augmentation; hence, deflation should be as late as possible but just before opening of the aortic valve. If this cannot be gauged by pressure tracing, it can be timed to the onset of the R wave on ECG tracing or with the use of M-mode echocardiography.⁴⁷

When femoral arterial cannulation is not desirable due to aortoiliac occlusive disease or extensive peripheral vascular disease (PVD), the subclavian artery or the ascending aorta can be utilized.⁴⁸⁻⁵² With either technique, the IABP catheter is advanced antegrade down the descending thoracic aorta so that the balloon tip sits above the level of the diaphragmatic hiatus, and the most proximal end of the balloon is distal to the takeoff of the left subclavian artery. These antegrade balloons should always be placed with either fluoroscopic or echocardiographic guidance. They should be removed with open arterial repair in all cases.

IABP catheters should not be left in place after weaning because of the risk of thrombus formation and embolization. An IABP should be weaned stepwise from a rate that is equivalent to heart rate (1:1) down to a ratio of 1:4 just before removal. Balloon catheters placed via the open surgical technique should also be removed surgically. Percutaneous removal of catheters placed in the iliac artery above the inguinal ligament (often done in obese individuals) can result in significant retroperitoneal bleeding. Consideration of operative removal is warranted.

Relative contraindications to IABP use include severe atherosclerotic disease of the descending thoracic aorta, descending aortic dissection or aneurysm, recent descending thoracic aortic surgery, and mild to moderate aortic insufficiency. Severe aortic insufficiency is

TABLE 91-1 Indications for Use

| | TOTAL POPULATION (N = 16,909) | DIAGNOSTIC CATHETERIZATION (N = 1576) | CATHETERIZATION ONLY AND PCI ONLY (N = 3882) | SURGERY | | NO INTERVENTION (N = 1186) |
|--|-------------------------------------|---|--|--------------------|------------------------|----------------------------------|
| | | | | CABG (N = 9179) | NON-CABG (N = 1086) | |
| Support and stabilization (%) | 20.6 | 21.4 | 54.4 | 9.7 | 5.0 | 7.8 |
| Cardiogenic shock (%) | 18.8 | 33.1 | 23.7 | 12.3 | 23.8 | 29.4 |
| Weaning from cardiopulmonary bypass (%) | 16.1 | 0.4 | 0.1 | 24.9 | 31.4 | 7.1 |
| Preop: high-risk CABG (%) | 13.0 | 4.6 | 0.2 | 22.1 | 6.4 | 1.9 |
| Refractory unstable angina (%) | 12.3 | 15.3 | 8.3 | 15.8 | 2.2 | 3.0 |
| Refractory ventricular failure (%) | 6.5 | 9.1 | 2.5 | 5.9 | 15.7 | 12.7 |
| Mechanical complication due to AMI (%) | 5.5 | 9.8 | 7.0 | 4.2 | 5.2 | 5.1 |
| Ischemia related to intractable VA (%) | 1.7 | 1.6 | 1.5 | 1.9 | 1.7 | 1.6 |
| Cardiac support for high-risk general surgery (%) | 0.9 | 2.1 | 0.2 | 0.5 | 4.3 | 1.1 |
| Other (%) | 0.8 | 0.7 | 0.2 | 0.8 | 2.5 | 2.0 |
| Intraoperative pulsatile flow (%) | 0.4 | 0.1 | 0.1 | 0.7 | 0.5 | 0.2 |
| Missing indication (%) | 3.3 | 1.8 | 1.9 | 1.2 | 1.5 | 28.1 |

AMI, acute myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; VA, ventricular arrhythmias.

Modified from Ferguson JJ 3rd, Cohen M, Freedman RJ Jr, et al. The current practice of intra-aortic balloon counterpulsation: results from the Benchmark Registry. *J Am Coll Cardiol* 2001;38:1456–1462.

an absolute contraindication to use because diastolic augmentation cannot be accomplished and LV end-diastolic volume and pressure are actually increased rather than decreased.

The overall complication rate of IABP utilization is between 5% and 10%. Major complications occur at a rate of about 3% and include severe bleeding, major limb ischemia or amputation, infection, visceral or spinal cord ischemia, and attributable IABP mortality.^{38,53} In the Benchmark registry, rates of complications were quite low; the most common complications were access site bleeding (4.3%) and limb ischemia (2.3%). The rates of amputation, stroke, visceral or spinal cord ischemia, and IABP-related mortality were all 0.1% or less.³⁹ Intraaortic balloon entrapment is a rare complication.^{54–56} The incidence of major vascular complications according to the STS National Database (1996–1997) and the Benchmark Registry (1997–1999) was 5.4% and 1.4%, respectively.^{39,53} Ipsilateral limb ischemia should be immediately addressed after its recognition. This usually requires removal of the IABP with replacement at another location if it is still indicated. The ischemic limb may require thrombectomy with or without revascularization and fasciotomy.^{57–63}

Despite the widespread use of IABP in thousands of patients worldwide each year, no prospective RCT has ever demonstrated a survival benefit with IABP use in a patient population undergoing high-risk catheter intervention. The use of an IABP had no impact on mortality rates in a population of patients without hemodynamic instability undergoing high-risk angioplasty randomized in a prospective trial reported in 1997.⁶⁴ In contrast, the SHOCK trial showed that early revascularization in CSMI, often facilitated by IABP use (86%), yielded a lower 6-month mortality rate (50%) than that with medical therapy alone (63%).³ Additional studies have shown that in patients undergoing urgent or emergent revascularization after an AMI, those supported preoperatively with an IABP had a lower operative mortality than those in whom an IABP was not used (5.3%–8.8% vs. 11.8%–28.2%).^{53,65} These data seem to justify a strategy of aggressive IABP use to facilitate early revascularization in a postinfarction patient. The Second Angioplasty in Myocardial Infarction (PAMI-II) Trial data examined high-risk patients with AMI revascularized by percutaneous coronary intervention (PCI) only and demonstrated a modest survival advantage at 6 months with the use of periprocedural IABP

support.⁶⁴ When evaluating hospital mortality rates among patients undergoing coronary artery bypass graft (CABG) and/or valve surgery who received preoperative IABP or required intraoperative/postoperative IABP support, the mortality rate was significantly lower among patients supported preoperatively as depicted in [Table 91-2](#).^{39,53} Hence, there appeared to be a survival advantage to earlier IABP support for patients with CSMI who undergo revascularization. In the setting of an acute VSD or acute MR after an AMI, IABP support can offer a dramatic improvement in the hemodynamic response of the patient.^{66–71} [Figures 91-1](#) and [91-2](#) stratify hospital mortality rates associated with IABP use in patients with AMI by principal usage indication or by performance of PCI or CABG. It is clear that the mortality rate of patients in CSMI remains high at 39%. However, these studies suggest that IABP support, combined with revascularization, portends a better prognosis than adjunctive IABP use with medical therapy alone.³⁸ This benefit is likely greatest in those who are revascularized and present with Class 3 or 4 HF.⁷² A recent meta-analysis of 16 studies demonstrated a significant survival benefit for the use of IABP in CSMI (RR: 0.78; CI: 0.60–0.86; $P < 0.0004$).⁷³ However, no benefit was seen in patients with high-risk AMI that was not complicated by CS.

Conversely, a recent Cochrane Database meta-analysis of six RCTs reviewed the use of IABP in CSMI in 190 patients and found no significant improvement in in-hospital, 30-day, or 6-month all-cause mortality.⁷⁴ An update of the review in 2015 drew the same conclusions.⁷⁵ A meta-analysis of cohort studies of IABP use in patients in CSMI by Sjauw et al. found an 18% decrease in 30-day mortality in patients treated with thrombolysis and IABP. However, in patients treated with PCI, they noted a 6% increase in mortality associated with the additional use of an IABP.⁷⁶ In the prospective IABP-SHOCK II Trial, 600 patients in CSMI were randomized with and without placement of IABP after undergoing revascularization, primarily with PCI (>95%).⁷⁷ No difference in the primary endpoint of 30-day, all-cause mortality was seen (39.7% IABP, 41.3% control). However, a 10% crossover to the IABP arm was noted. Additionally, a meta-analysis of 12 RCTs found no improvement in 30-day mortality with the use of IABP in patients with AMI, regardless of whether or not the patients suffered from CS.⁷⁸ From this compilation of results, it may

TABLE 91-2

Hospital Mortality (Outcome Parameter) for Patients Undergoing Cardiac Surgery Who Either Received Preoperative IABP or Intra-/Postoperative IABP Support

| TYPE OF THERAPY | BENCHMARK REGISTRY 1997-1999 MORTALITY/ TOTAL OPERATIONS WITH IABP, N (%) | STS NATIONAL DATABASE 1996-1997 MORTALITY/ TOTAL OPERATIONS WITH IABP, N (%) | STS NATIONAL DATABASE 1996-1997 MORTALITY/ TOTAL OPERATIONS WITHOUT IABP, N (%) |
|-----------------------------------|--|---|--|
| Preoperative IABP | 8.8 (329/3721) | 9.5 (2487/26,077) | 2.9 (10,919/378,810) |
| Intraoperative/postoperative IABP | 28.2 (954/3380) | 23.6 (3528/14,933) | 2.5 (9878/389,954) |

Based on data from the Benchmark Counterpulsation Registry 1997-1999 and the STS National Database 1996-1997 compared with hospital mortality for patients who had neither preoperative nor intraoperative/postoperative IABP support.

From Christenson JT, Cohen M, Ferguson JJ 3rd, et al. Trends in intraaortic balloon counterpulsation: complications and outcomes in cardiac surgery. *Ann Thorac Surg* 2002;74:1086-1090. Tab 4.

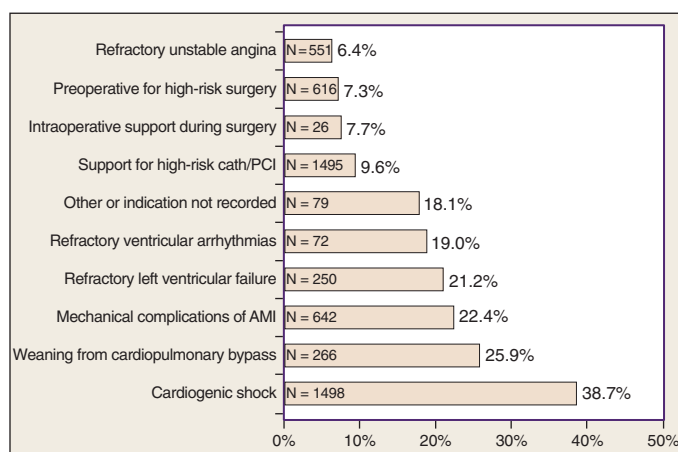


FIGURE 91-1 ■ In-hospital mortality of 5495 patients with acute myocardial infarction (AMI) requiring intraaortic balloon pump counterpulsation, stratified by principal usage indication. PCI, percutaneous coronary intervention. (From Stone GW, Ohman EM, Miller MF, et al. Contemporary utilization and outcomes of intra-aortic balloon counterpulsation in acute myocardial infarction: the Benchmark registry. *J Am Coll Cardiol* 2003;41:1940-1945.)

be concluded that the use of IABP in CSMI has little benefit in any treatment strategy that does not employ the use of early revascularization (primarily with PCI). Furthermore, improvement in the patient's hemodynamics often seen with the use of IABP does not suffice as a surrogate marker for survival in patients in CSMI. An IABP should be placed in the case of acute postinfarction VSD or acute MR without delay. Along with early revascularization, it should be considered in the armamentarium of MCS in patients in CSMI until further RCTs more clearly delineate those patients who are most likely to derive benefit.

Extracorporeal Membrane Oxygenation (ECMO). Since the 1970s, ECMO has been utilized in the adult population for short-term (1 to 10 days) MCS when CS is complicated by concomitant pulmonary insufficiency. It provides full cardiopulmonary support to allow reversal of the systemic malperfusion that occurs in CS until definitive surgical correction is performed. It can also serve as a BTR, a BTT, or a bridge-to-bridge to longer term MCS (i.e., VAD).⁷⁹⁻⁸¹ It may be employed for a period of 1 to 3 days in cases when the neurologic status of a patient is unclear and longer term support may not be appropriate until this status is clarified.

The ECMO circuit consists of inflow and outflow cannulas, a continuous flow centrifugal pump, a hollow-fiber oxygenator, and a heat exchanger. Historically, roller pumps and centrifugal pumps have both been utilized. Roller pumps remain in widespread use for CPB

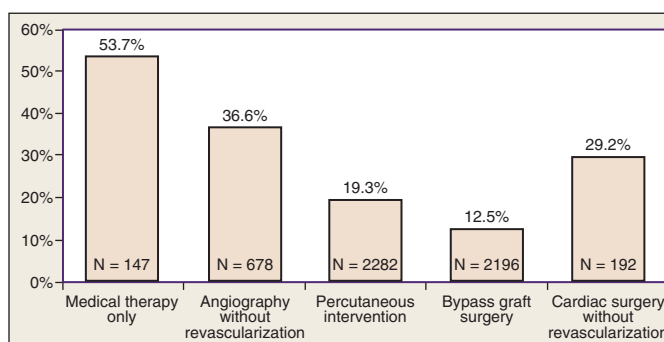


FIGURE 91-2 ■ In-hospital mortality stratified by the performance of angiography and percutaneous or surgical coronary revascularization. (From Stone GW, Ohman EM, Miller MF, et al. Contemporary utilization and outcomes of intra-aortic balloon counterpulsation in acute myocardial infarction: the Benchmark registry. *J Am Coll Cardiol* 2003;41:1940-1945.)

during cardiac surgery; applications outside the operating room have been virtually abandoned due to higher rates of circuit disruption, particle emboli, and hemolysis.^{82,83} Bio-Medicus Biopump (Medtronic, Corp., Minneapolis, MN) and CentriMag (Levitronix LLC, Waltham, MA) are two centrifugal pumps commonly used in ECMO circuits. The Bio-Medicus Biopump generates a constrained vortex within an acrylic shell that houses concentric magnetic cones. The cones rotate as a magnetic rotary motor spins adjacent to the base of the cones^{19,20,84} and can generate very high flows with less trauma to blood cells than roller pumps.^{83,85,86} The cannulation strategy most often used in acute CS is peripherally via the femoral vessels with either the percutaneous Seldinger or surgical technique. Alternatively, central cannulation via the right atrium (RA) and aorta is used to provide temporary MCS in the case of postcardiotomy failure. When faced with postcardiotomy ventricular failure, MCS with these pumps can facilitate patient stabilization for subsequent transport to a tertiary medical center for VAD placement. A recent addition to the array of ECMO systems is CardioHelp (Maquet Cardiopulmonary AG, Hechingen, Germany). It is a miniaturized system that combines the pump and oxygenator in a single unit (Fig. 91-3). It can be easily carried in one hand, making it ideal for patients who require urgent interhospital transport.⁸⁷

Disadvantages in using the peripheral cardiopulmonary support or ECMO include the greater potential for ipsilateral limb complications, higher rates of hemolysis, the requirement for anticoagulation to prevent thrombosis of the oxygenator and circuit, and failure to adequately decompress the left ventricle.⁸⁸⁻⁹⁴ Inadequate LV decompression with peripheral cardiopulmonary support/ECMO systems may be the mechanism responsible for some treatment failures.



FIGURE 91-3 ■ (A) Front view of the Maquet CardioHelp console. The line set can be seen hanging on the wall behind the pump. The device can be carried with one hand by the handle as seen on top of the device. (B) View of the back of the CardioHelp demonstrating the oxygenator directly attached to the pump, creating a compact unit that is very amenable to transport. (With permission from Maquet BV, Rastatt, Germany.)

Regardless of the etiology of CS, a rested ventricle (i.e., decompressed) has a better chance of recovery than a distended ventricle. Lower extremity ischemia may be resolved or prevented by placing an additional perfusion cannula (8 to 14F) down the ipsilateral superficial femoral artery.⁹⁵ Alternatively, limb ischemia may be prevented with the use of an 8-mm T-graft sutured to the side of the femoral artery.⁹⁶ However, this increases the complexity of instituting ECMO and can be impractical in CS.

The use of ECMO in the adult population for reasons other than primary cardiac failure with secondary pulmonary insufficiency has limited advantages over conventional therapies.^{97,98} However, a substantial subset of patients who present with CS and are initially resuscitated with cardiopulmonary support/ECMO survive to revascularization, transplantation, or recovery, with survival rates as high as 75%.⁹⁹⁻¹⁰⁹ ECMO used as a bridge to VAD placement for profound CS ("double bridge" mechanical assistance) can yield survival rates higher than 40%.¹¹⁰ This strategy is pragmatic and offers immediate end organ support while a subsequent definitive treatment plan can be designed. In an outcome study by Combes et al., early predictors of death on ECMO support include hepatic failure, renal failure, or placement of ECMO while undergoing CPR. Of the greater than 40% who did survive to discharge, many reported continued physical and social problems, including the ability to return to work.¹¹¹ This underscores the importance of long-term follow-up and the need for continued psychosocial support of these patients.

Improvements in pump and oxygenator technology have made EMCO a relatively simple means to establish MCS, allowing reversal of end organ malperfusion that inevitably accompanies CS not promptly corrected with medical therapy alone. However, complications of bleeding, infection, stroke, and limb ischemia increase with time and limit this means of support to approximately 7 days.¹¹² As with any form of MCS, the plan for separation from support or transition to a more permanent means begins upon institution of ECMO. Once end organ malperfusion has been corrected, the feasibility of ECMO weaning is determined on a daily basis. Weaning trials are guided based on the patient's hemodynamic parameters, oxygenation, and ventilation. Pulmonary and circulatory support can be weaned independently or simultaneously. Pulmonary weaning consists of increasing support from mechanical ventilation, while the amount of

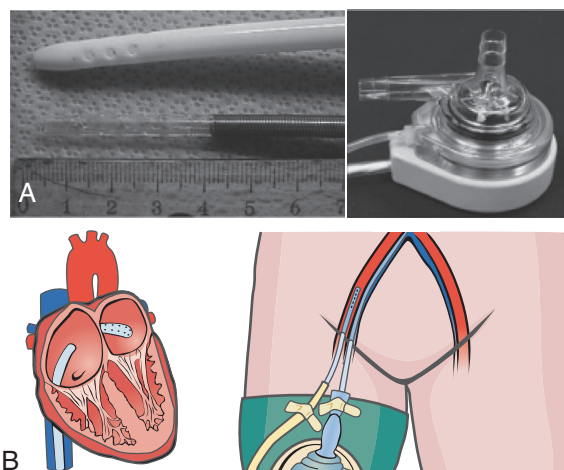


FIGURE 91-4 ■ (A) Components of the TandemHeart device: 21F left atrial drainage cannula and 15-17F femoral arterial cannula (left); continuous flow centrifugal pump (right). (B) Schematic demonstrating transeptal left atrial drainage and femoral access points. (From Windecker S. Percutaneous left ventricular assist devices for treatment of patients with cardiogenic shock. *Curr Opin Crit Care* 13:521-527. Copyright 2007, Lippincott Williams & Wilkins.)

oxygenation and ventilation provided by ECMO is dialed down. Circulatory weaning is done by gradually decreasing the amount of pump flow in a stepwise fashion, while assessing hemodynamic parameters. This is also guided by the use of transthoracic or transesophageal echocardiography to evaluate the cardiac response to ventricular loading that occurs with decreasing pump flow. Once it is determined that the patient can maintain adequate perfusion and pulmonary function, a plan is made to separate the patient from ECMO and remove the cannulas. The cannulas are most often removed in the operating room with direct vascular repair of the femoral vessels. If the patient cannot be successfully weaned from EMCO, the plan for conversion to VAD or transplant is undertaken. This period of support, weaning, and determining the long-term strategy is done with the collaboration of a multidisciplinary team of surgeons, cardiologists, and critical care providers.

TandemHeart. The TandemHeart System (Cardiac Assist, Inc., Pittsburgh, PA) is an external centrifugal pump system that allows for percutaneous LV support by pumping blood from the left atrium into the femoral artery (Fig. 91-4).¹¹³ Placement of the 21F venous inflow cannula is performed in the cardiac catheterization laboratory by accessing the femoral vein percutaneously and positioning the cannula tip in the left atrium via an atrial transeptal puncture. Outflow is established into the contralateral or ipsilateral femoral artery via a 15F or 17F cannula. The centrifugal pump is strapped to the thigh adjacent to the arterial cannula. The device contains a built-in heparin delivery system to decrease thrombin formation. An experienced team can establish MCS with TandemHeart in as little as 1 hour.¹¹⁴ However, this is still longer than required for institution of ECMO. Therefore, its use may be limited in truly emergent cases and in conditions requiring CPR.

Contraindications to placement of TandemHeart include severe PVD and isolated right ventricular (RV) failure. It also cannot be used in the presence of a VSD due to the potential for right-to-left shunting.¹¹⁵ Right-to-left shunting is a known complication that can also occur if the transeptal cannula becomes dislodged into the RA. Other complications include limb ischemia and thromboembolism.

TandemHeart has mostly been utilized as an MCS in CS.¹¹⁶⁻¹¹⁸ Support has been employed for various indications including postcardiotomy failure,¹¹⁹⁻¹²¹ until corrective valvular surgery is performed,¹²²⁻¹²⁴

until recovery of fulminant myocarditis,^{125,126} or as a bridge to LVAD or BTT.^{118,127,128} It has also been utilized successfully for MCS during high-risk PCI.¹²⁹⁻¹³² TandemHeart has been shown to be a more effective means of improving hemodynamic parameters in CS than IABP; however, no improvement in 30-day mortality has been demonstrated.^{133,134}

Impella Recover. The most recent addition to the armamentarium for acute short-term MCS is the Impella Recover axial flow pump (Abiomed, Inc., Danvers, MA) (Fig. 91-5). The device is placed retrograde across the aortic valve with the tip situated in the LV. It can be placed percutaneously or surgically via the femoral artery under fluoroscopic guidance. It may also be placed surgically via an 8-mm T-graft sewn to the subclavian artery^{135,136} or directly into the ascending aorta during cardiac surgery. There are two versions of Impella: the 2.5 and 5.0 (flow rates of 2.5 and 5.0 L/min, respectively). While the 2.5 can be placed percutaneously or surgically, the larger 5.0 requires surgical placement. Contraindications for the use of Impella include patients with severe aortic stenosis and those who have had a previous mechanical aortic valve replacement. Severe PVD may make percutaneous deployment impossible or mandate a surgical cutdown for placement.

Similar to other devices, Impella has been used for MCS for several indications including high-risk PCI,¹³⁷⁻¹³⁹ postcardiotomy failure,¹⁴⁰⁻¹⁴²

CSMI,^{117,143-146} severe allograft rejection following heart transplant,^{147,148} myocarditis,^{149,150} and as a bridge to placement of a long-term device, BTR, or BTT.¹¹⁷ RCTs comparing support with Impella 2.5 versus IABP in CSMI have demonstrated improved hemodynamic and laboratory parameters (CI, mean arterial pressure, serum lactate levels) with the use of Impella.^{133,151} However, this did not translate into improved 30-day survival. In contrast, the recent PROTECT-II randomized trial comparing these two devices in high-risk PCI demonstrated lower rates of the two composite endpoints of major adverse events (MAE) and major adverse cardiac and cerebral events (MACCE = death, stroke, myocardial infarction, and repeat revascularization).¹³⁷ At the 3-month follow-up, the rates of both composite endpoints were lower in the Impella group than in the IABP group (MAE, 37% vs. 49%, $P = 0.014$; MACCE, 22% vs. 31%, $P = 0.034$) at 3 months.

Surgical Insertion

Short-term MCS using continuous-flow pumps for CS is a relatively simple means of establishing immediate and complete MCS, requiring no additional equipment other than that needed for standard CPB support during cardiac surgery. As previously discussed, some MCS pumps can be utilized with percutaneous cannulation for ECMO support. These same pumps may be placed by surgical insertion. The most common indication for temporary MCS where surgical insertion is used is for postcardiotomy CS. This can be achieved by conversion from the CPB circuit used during the primary cardiac operation to a temporary VAD system, using the existing cannulas in the RA and aorta. Temporary VAD support may be required for several days to allow myocardial recovery. If the decision is made to leave the chest open, the cannulas can be brought out through the lower portion of the sternotomy incision and covered with a sealed temporary dressing. Alternatively, they can be brought out through separate incisions inferior to the sternotomy, allowing the sternum to be closed temporarily. The patient can then be brought back to the operating room within several days to explant the cannulas once cardiac recovery has occurred or converted to a long-term LVAD. In addition, MCS in postcardiotomy failure can be carried out by converting to peripheral cannulation. This allows for definitive closure of the chest, provided the patient can be successfully weaned from MCS and will not require a long-term VAD or transplant. Postcardiotomy MCS can be withdrawn in cases where severe multiorgan failure ensues despite therapy or conversion to long-term MCS is not appropriate (advanced age, lack of appropriate psychosocial support). However, it is best to determine candidacy for long-term MCS and discuss the goals of treatment prior to performing any high-risk surgical case.

CentriMag Ventricular Assist. The CentriMag system utilizes fully magnetically levitated technology (Fig. 91-6) to provide MCS in a fashion similar to the BioMedicus Biopump. The CentriMag system has many advantages that make it attractive for temporary MCS in the acute setting.¹⁵² These advantages include ease of implantation, direct outflow cannulation of the ventricle for improved decompression, minimal need for anticoagulation, and less damage to blood elements compared to traditional devices such as the Bio-Medicus pump. It has been used effectively for uni- or biventricular support in the setting of postcardiotomy failure as a bridge to decision, BTR, or bridge to a long-term MCS device. For patients with concomitant pulmonary insufficiency, an oxygenator may be spliced into the circuit, effectively converting it to an ECMO system.

ABIOMED BVS 5000 and AB 5000. The ABIOMED biventricular system (Abiomed, Inc., Danvers, MA) is a pulsatile, temporary MCS system that is available in two versions. The FDA-approved ABIOMED AB 5000 “ventricle” replaces the previously utilized BVS 5000, which was developed in the 1980s and was granted approval for use for postcardiotomy HF by the U.S. Food and Drug Administration in 1992.¹⁰⁷ Since that time, indications for the device have been broadened to include patients with either postcardiotomy shock or precardiotomy shock who do not adequately respond to inotropes and an IABP. The ABIOMED system is a pneumatically driven, dual-chamber blood

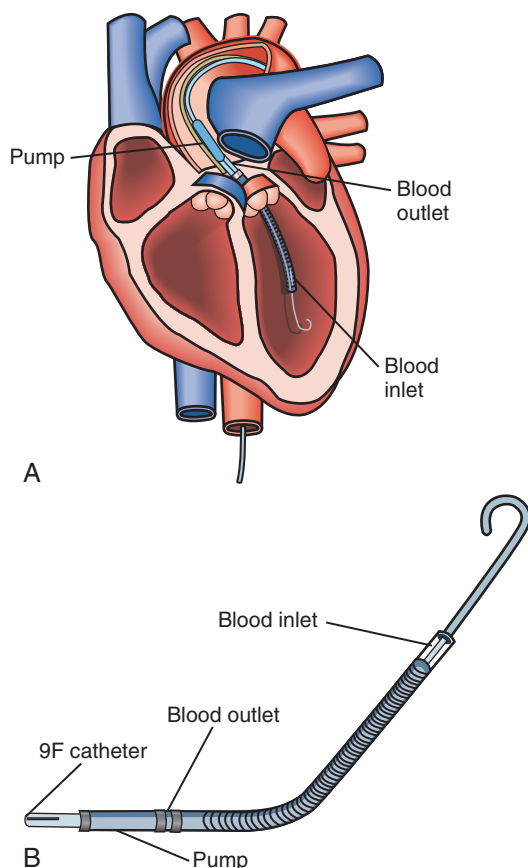


FIGURE 91-5 ■ (A) Schematic demonstrating retrograde placement of the Impella Recover LP 2.5 device across the aortic valve. (B) Components of the device. Blood from the ventricle enters the inlet portion of the device and is propelled by a 12F microaxial pump to the outlet portion positioned in the ascending aorta, establishing left ventricular decompression. (From Windecker S. Percutaneous left ventricular assist devices for treatment of patients with cardiogenic shock. *Curr Opin Crit Care* 13:521–527. Copyright 2007, Lippincott Williams & Wilkins.)

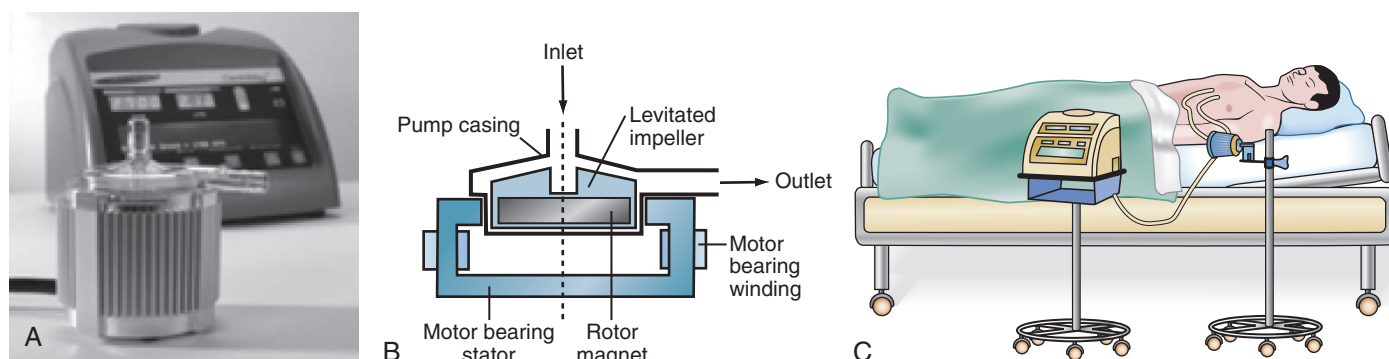


FIGURE 91-6 ■ (A) Levitronix CentriMag rotor and bearingless pump. (B) A schematic representation of the pump, and (C) console as seen in clinical use. (From Bhama J, Kormos RL, Toyoda Y, et al. Clinical experience utilizing the Levitronix CentriMag system for temporary right ventricular mechanical circulatory support. *J Heart Lung Transplant* 2008;28:971–976. Copyright 2009, International Society of Heart and Lung Transplantation.)

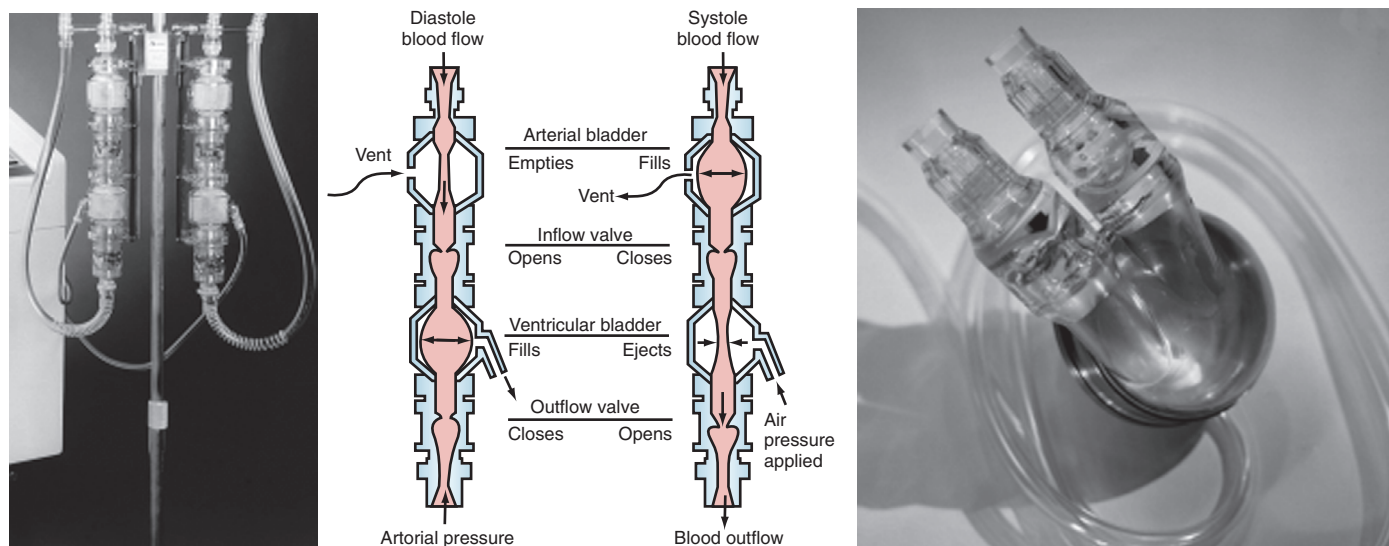


FIGURE 91-7 ■ The ABIOMED BVS 5000 and AB 5000. Left, In the BVS5000 model, the atrial chamber empties through a one-way valve into the ventricular chamber (diastole). The pneumatically driven pump compresses the ventricular chamber, and blood flows through a one-way valve into the patient (systole). The atrial chamber fills by gravity during pump systole. Right, In the AB 5000 model, a single ventricular blood chamber fills by vacuum assistance, and blood is ejected by pneumatic inflation of a polyurethane bladder housed within the pump casing. (From Couper GS, Dekkers RJ, Adams DH. The logistics and cost-effectiveness of circulatory support: advantages of the ABIOMED BVS 5000. *Ann Thorac Surg* 1999;68:646–649. Copyright 1999, The Society of Thoracic Surgeons; Moazami N, McCarthy PM. Temporary circulatory support. In: Cohn LH, Edmunds LH Jr, editors. *Cardiac surgery in the adult*. New York, McGraw-Hill; 2003.)

pump that delivers pulsatile flow. The pumps, as depicted in Figure 91-7, are extracorporeal (BVS5000) or paracorporeal (AB5000). The BVS5000 is generally useful for short-term (<7–10 days) support because of the increased risk of thromboembolic complications or device malfunction beyond this period. If longer support (2–3 months) is necessary, the ABIOMED pump can be exchanged with AB5000 or converted to a long-term VAD system such as Thoratec PVAD or HeartMate.

ABIOMED VADs have been placed for precardiotomy or postcardiotomy cardiac failure.^{153–157} Survival and hospital discharge rates have ranged from 20% to 45%, depending on the indication for the ABIOMED and the hemodynamic condition of the patient before surgery.^{154–157} The most common complications directly attributed

to this VAD include bleeding, stroke, and infection, with rates of 20% to 40%.^{154,155,157} Advancements in pump technology have contributed to the ABIOMED system's waning importance in the field of MCS.

Long-Term Ventricular Assist Devices

Pulsatile Devices

Early evidence suggested that pulsatile MCS offers improved end-organ perfusion and lymphatic flow and was thus beneficial.^{157–159} VADs that utilize direct cardiac outflow cannulation (VAD inflow) provide better ventricular decompression and rest than peripheral bypass support systems. Several MCS devices achieve these goals,

including the previously mentioned temporary, extracorporeal ABIOMED AB 5000. Long-term pulsatile devices from the Thoratec Corporation (Pleasanton, CA) include the paracorporeal Thoratec PVAD and two implantable, intracorporeal devices: Thoratec IVAD and HeartMate XVE LVAD. Last, full cardiac replacement has been achieved with pulsatile CardioWest Total Artificial Heart (SynCardia Systems, Inc., Tucson, AZ). These devices have been used for BTR, BTT, or DT.

Thoratec Paracorporeal Ventricular Assist Device. The Thoratec paracorporeal VAD (PVAD) system is composed of a single chamber with a seamless polyurethane bladder housed in a rigid casing (Fig. 91-8, A).¹⁶⁰ VAD inflow cannulas are either atrial or ventricular. Outflow cannulas have a polyester graft attached for direct connection to the aorta or pulmonary artery, similar to the ABIOMED cannulas. Mechanical tilting disk valves at both the inflow and outflow connections ensure unidirectional flow and require anticoagulation. A pneumatic driveline is connected to the rigid casing and supplies alternating vacuum and pressure to facilitate bladder filling and emptying, respectively. The pump can be adjusted to accommodate changing preload and afterload.

The Thoratec PVAD is similar to ABIOMED but is more portable and has the potential for outpatient use in patients as a BTR or BTT.¹⁶⁰⁻¹⁶³ Two advantages to the Thoratec PVAD system are the ability of secure ventricular inflow (VAD) cannulation and the applicability of long-term utilization. LV cannulation provides better ventricular decompression than left atrial cannulation.¹⁶⁴⁻¹⁶⁸ This is important because LV distention or inadequate decompression will limit ventricular recovery in some patients. Ventricular cannulation also provides better VAD performance and reduces the risk of thrombotic complications, particularly in the setting of AMI.^{106,166-168} RV cannulation provides similar advantages over right atrial (RA) cannulation. However, these advantages may not be manifest if the tricuspid valve is left intact, because the tricuspid leaflets are often in close proximity to the cannulation tip and can obstruct VAD inflow.¹⁶⁹ In this situation, the advantages and disadvantages of RV versus RA cannulation must be weighed to direct the best approach.

As of July 2012, over 5000 Thoratec PVADs have been placed worldwide in 277 centers over the last 30 years.¹⁷⁰ More than half of the patients received biventricular support. Survival and hospital discharge rates vary widely between 20% and 80%, depending on the etiology of shock and the medical center.^{99,110,160,164,171-173} Cases of acute fulminant myocarditis with CS are among the best situations for VAD support with the Thoratec PVAD system, having an 88% recovery-with-discharge rate.⁹⁹ Complications of the Thoratec PVAD system are similar to other extracorporeal VAD systems when used for treatment of CS and include infection, stroke, bleeding, and acute renal failure. The rates of these complications vary among different series but range from 10% to 60%.^{160,164,171,172,174-178}

Thoratec Intracorporeal Ventricular Assist Device. Options for pulsatile intracorporeal long-term support include the Thoratec implantable VAD (IVAD) and Thoratec HeartMate XVE LVAD. The Thoratec IVAD is an implantable version of the Thoratec PVAD with identical internal components. The major difference is a smooth polished titanium housing that facilitates implantability (Fig. 91-8, B). Advantages of the IVAD over the PVAD are the decreased risk of infection due to the lack of cannulas exiting the skin and improved patient mobility.

HeartMate XVE LVAD. HeartMate XVE has a fully implanted pusher-plate blood pump with externalized drivelines (Fig. 91-9). It uses bioprosthetic porcine valves to ensure unidirectional flow. The HeartMate XVE has a flexible polyurethane diaphragm that pushes against a titanium alloy housing generating a maximum stroke volume of 83 mL. A unique feature of this device is the blood contact surface, which is textured with polyurethane fibrils on the diaphragm side and sintered titanium spheres on the housing. Fibrin and cellular components react and bond to the surface, creating a pseudointima, precluding the need for anticoagulation. Antiplatelet therapy is recommended.

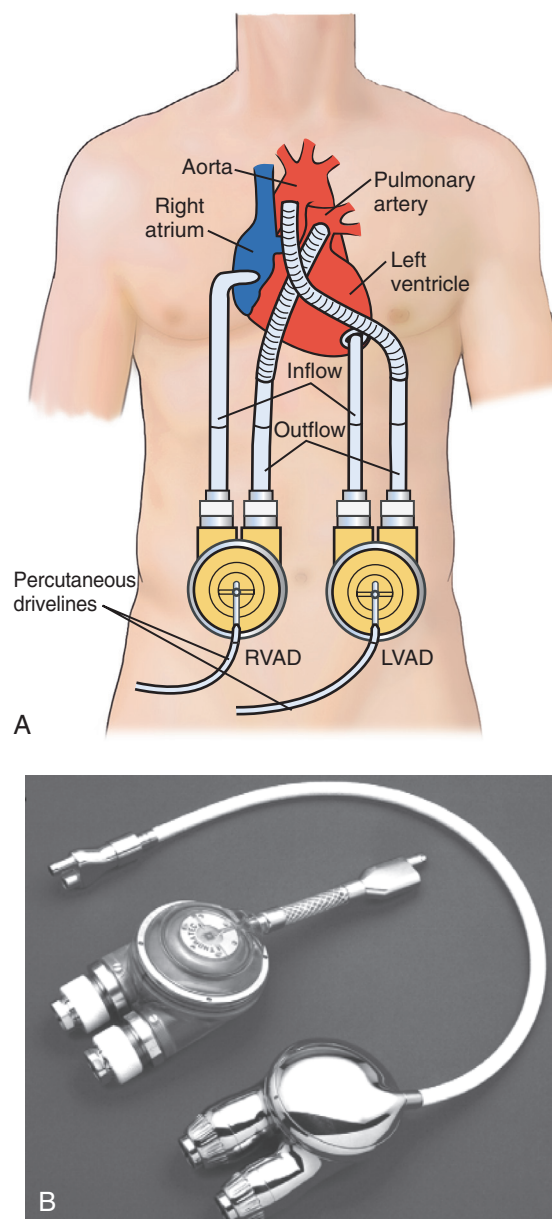


FIGURE 91-8 ■ Thoratec ventricular assist system: a pneumatically powered system configured for uni- or biventricular support with paracorporeal (PVAD) and intracorporeal (IVAD) options. (A) Schematic demonstrating configuration for right and left ventricular support. (B) The IVAD (below) shown next to a PVAD (above). The smooth, contoured, polished titanium housing and the polyester velour-covered driveline allow for implantability with the IVAD. (From Hunt SA, Frazier OH. Mechanical circulatory support and cardiac transplantation. *Circulation* 1998;97:2079–2090. Copyright 1998, American Heart Association; Slaughter MS, Tsui SS, El-Banayosy A, et al. Results of a multicenter clinical trial with the Thoratec Implantable Ventricular Assist Device. *J Thorac Cardiovasc Surg* 2007;133:1573–1580. Copyright 2007, The American Association for Thoracic Surgery.)

HeartMate XVE was the first implantable device approved for both BTT and DT.¹⁷⁹ The landmark REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) compared the use of the HeartMate XVE versus optimal medical therapy in patients with New York Heart Association class IV HF who were not eligible for transplant.¹⁸⁰ Survival at 1 year was 52%

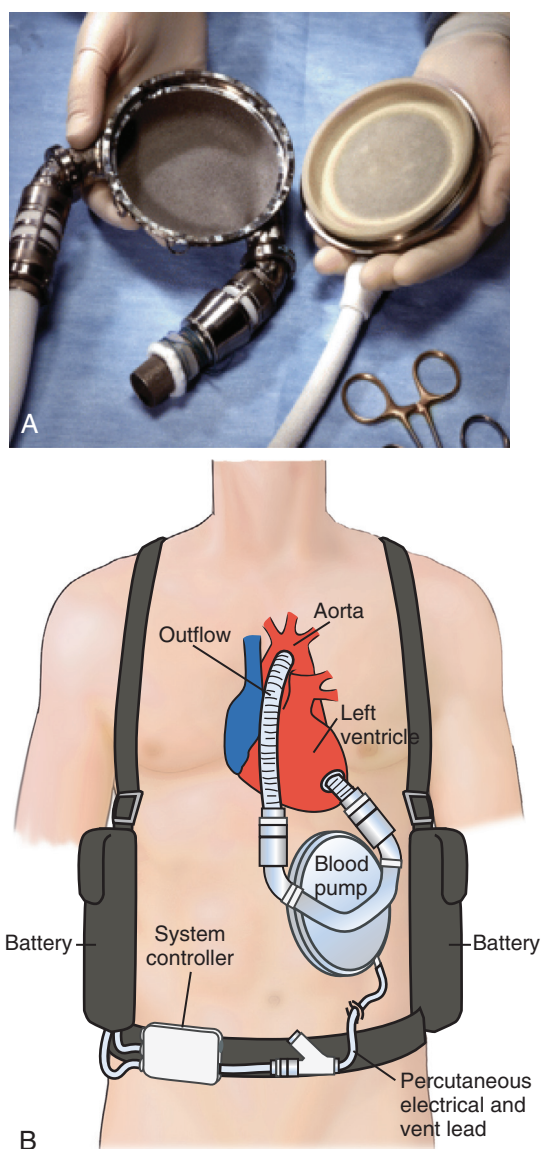


FIGURE 91-9 ■ The HeartMate vented electric left ventricular assist device (HeartMate XVE): an intracorporeal, electrically powered system. (A) Textured surface designed to reduce thrombogenicity. (B) Schematic demonstrating position of pump and related components. (From Loisance D. Mechanical circulatory support: a clinical reality. *Asian Cardiovasc Thorac Ann* 2008;16:419–431. Copyright 2008, Asia Publishing EXchange Ltd.; Hunt SA, Frazier OH. Mechanical circulatory support and cardiac transplantation. *Circulation* 1998;97:2079–2090. Copyright 1998, American Heart Association.)

with the device compared to 25% with medical therapy ($P = 0.002$). Rates at 2 years were 23% and 8%, respectively ($P = 0.09$). Use of the device as also associated with significantly improved quality of life at one year.

Thoratec IVAD and HeartMate XVE both have variable modes that can generate fixed rates or demand-sensitive rates. Both are approved for use for the treatment of end-stage HF, but they may have a selective role for CS. These devices are practical alternatives for use in a “double-bridge” setting with initial resuscitation using a temporary device (i.e., ECMO/cardiopulmonary support or ABIOMED) for stabilization and pulmonary recovery.^{105,109,110,181,182} Results with these devices have been favorable and, in certain subsets of patients, better than longer term

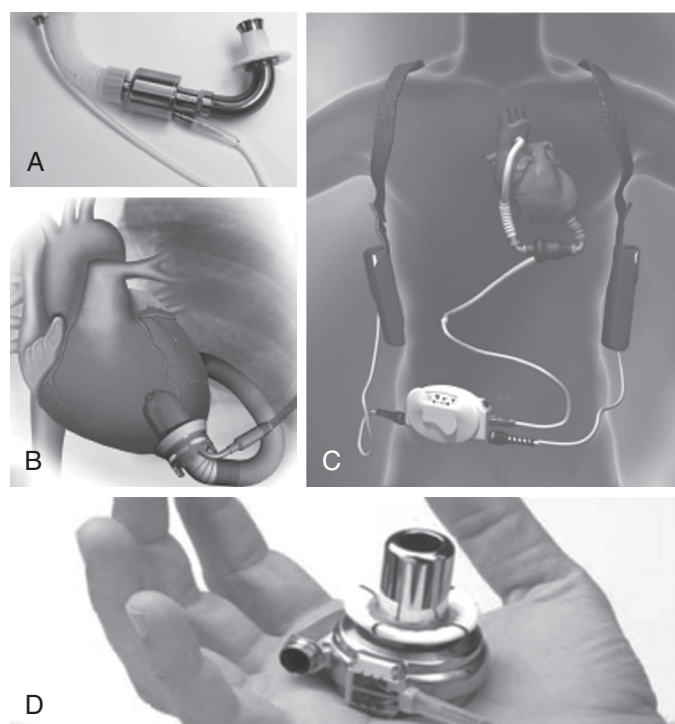


FIGURE 91-10 ■ Implantable continuous-flow ventricular assist devices currently in clinical use: (A) MicroMed-DeBakey, (B) Jarvik 2000, (C) HeartMate II, and (D) HeartWare. (From Mitter N, Sheinberg R. Update on ventricular assist devices. *Curr Opin Anaesthesiol* 23:57–66. Copyright 2010, Wolters Kluwer Health, Lippincott Williams & Wilkins.)

support with other systems.^{99,177,183–188} Complications have been similar to other VADs and include bleeding, infection, stroke, thrombotic complications, and renal insufficiency.

CardioWest Total Artificial Heart (SynCardia TAH). SynCardia TAH is a pneumatic pulsatile pump used to completely replace cardiac function in cases of severe biventricular myocardial damage. It is indicated as a BTT and was first used successfully in 1985.¹⁸⁹ It is a large device that resides orthotopically within the pericardium. It has limited use in acute CS.

Continuous-Flow Left Ventricular Assist Devices

In the continued search for smaller, implantable LVADs with increased durability, there have been many advances in technology that have led to an array of continuous flow (nonpulsatile) pumps, each with unique features (Fig. 91-10).¹⁹⁰ These axial or centrifugal flow pumps are smaller and more durable than pulsatile devices, making them well suited for long-term support as a BTT, BTR, or DT.^{191–194} They are placed within the pericardium or in a preperitoneal pocket, with only an external driveline exposed to provide power and device control. These devices are relatively costly, provide isolated LV support, and require specialized training to implant. Consequently, they have not yet received widespread use for acute CS. However, they may be ideally suited as a bridge-to-bridge after resolution of the shock state with a temporary MCS device. These devices will continue to play a significant role in HF management and are briefly outlined.

HeartMate II (HMII). HeartMate II (Thoratec Corp.) is an implantable axial flow LVAD that has been used as a BTT and DT.^{191,195,196} The device is implanted in a preperitoneal pocket with the inflow cannula situated in the LV apex. Outflow is via a graft anastomosed to the ascending aorta. The device was approved for DT by the FDA in 2010. A prospective postapproval study confirmed the efficacy of the device and demonstrated a reduction in the median length of

stay by 6 days as compared to the pivotal DT trial.¹⁹⁷ Results of the recent ROADMAP trial were presented at the International Society of Heart and Lung Transplantation.¹⁹⁸ Functionally limited HF patients treated with the HMII LVAD had significant improvement in the primary outcome composite of survival and improvement in a 6-minute walk test at 1 year compared to similar patients treated with optimal medical therapy.

Jarvik 2000. Jarvik 2000 (Jarvik Heart Inc., New York, NY) is an implantable axial flow pump used as a BTT and for DT.^{193,199,200} It is unique in that the pump itself resides within the LV cavity, providing outflow via the LV apex to a graft anastomosed to the ascending or descending thoracic aorta. It is a DC battery-powered device, utilizing AC power only to recharge the batteries.

HeartWare Ventricular Assist Device (HVAD). The HVAD (HeartWare, Inc., Framingham, MA) is a centrifugal pump that is implanted within the pericardial space. The pump is attached directly to the LV apex where inflow is provided. Outflow is via a graft sewn to the ascending aorta. Based on results from the ADVANCE clinical trial, the HVAD has now received FDA approval as a BTT device.²⁰¹

DuraHeart. DuraHeart LVAS (Terumo Heart, Inc., Ann Arbor, MI) is a magnetically levitated centrifugal pump utilized as a BTT.²⁰² It is implanted in a preperitoneal pocket. Inflow is via a titanium conduit placed in the LV apex, and outflow is via a graft anastomosed to the ascending aorta. The inner surface is coated with covalently bonded heparin. Ambulation is improved with the use of battery power.

INCOR. The INCOR LVAD (Berlin Heart AG, Berlin, Germany) is an axial flow pump that is placed in a preperitoneal pocket. Inflow is via the LV and outflow via the ascending aorta. The device is powered via a percutaneous driveline that can use either AC or DC sources. The most experience with the Berlin Heart has mainly been in Europe. It has been used as a BTR, BTT, and for DT.²⁰³⁻²⁰⁵

Levacor. The Levacor VAD (Worldheart Corp., Salt Lake City, UT) is a centrifugal pump placed in a preperitoneal pocket. The outer surface of the inflow cannula is coated with titanium microspheres to create a textured surface that will encourage tissue in-growth and promote fixation within the LV. Outflow is to the ascending aorta. A percutaneous drive-line provides power and control to the pump. It is powered with either AC or DC power to increase ambulatory operation. Initial experiences with the pump have been favorable.^{194,206,207}

Synergy Micropump. The Synergy micropump (CircuLite, Inc., Saddle Brook, NJ) is a miniature axial flow LVAD that is only slightly larger than an AA battery. It is a partial LVAD designed to augment flow in patients with NYHA class IIIb or IV HF.^{208,209} It placed in a subcutaneous pocket on the right anterior chest wall. Inflow is from a graft sewn to the left atrium, and outflow is via a graft sewn to the right subclavian artery. The device is battery powered via a driveline that exists in the upper abdomen.

TREATMENT OF CARDIOGENIC SHOCK: AN ALGORITHM FOR MECHANICAL CIRCULATORY SUPPORT

The hallmarks of CS are low CO, hypotension, peripheral vasoconstriction, cold extremities, poor urine output, and altered mental status. As the pathophysiologic state progresses, pulmonary insufficiency and pulmonary edema ensue. Extrinsic causes of CS most commonly manifest as circulatory collapse secondary to pericardial tamponade. Acute tamponade is easily diagnosed by echocardiography and requires surgical or percutaneous evacuation and subsequent treatment of that which caused the tamponade (e.g., traumatic injury, aortic dissection, ruptured aneurysm). Extrinsic causes of CS usually require immediate surgical intervention but rarely necessitate mechanical assistance. However, intrinsic causes of CS can be refractory to both medical and surgical therapies and may require MCS. Intrinsic causes can be divided into four pathophysiologic classifications: (1) acute valvular insufficiency, (2) CSMI, (3) acute myocarditis, and (4) postcardiotomy

cardiac failure. Irrespective of the etiology of CS, the approach toward the initial management of patients should be fairly uniform. A suggested management algorithm is outlined in Figure 91-11.

First, insertion of a pulmonary arterial balloon catheter and echocardiography should be done to help formulate a differential diagnosis. Severe valvular insufficiency or a VSD can usually be effectively excluded at this juncture. If severe aortic insufficiency is present, chronotropic control (heart rate 80 to 100 beats/min) and afterload reduction with inotropic support should be the initial maneuvers. An IABP is contraindicated because aortic regurgitation will worsen; these patients should be prepared for immediate aortic valve replacement. For patients with acute MR or a VSD, an IABP should be placed immediately in conjunction with inotropic support and afterload reduction. Surgical intervention should proceed emergently. Cardiac catheterization is pursued preoperatively in order to identify coronary lesions that would require CABG only if the patient can be adequately stabilized.

Acute fulminant myocarditis usually presents in a previously healthy individual with no history of cardiac disease. Patients with presumed myocarditis who do not stabilize after the insertion of an IABP and concomitant inotropic infusion should be diverted to VAD support expeditiously. A remarkable percentage of these patients will recover if adequately supported during the acute phase of this disease. Short-term to intermediate-term VADs are optimal in these patients because of the ease of their insertion and removal and the anticipation for relatively short-term recovery. Giant cell myocarditis is one exception to this rule, because most patients with this diagnosis will require transplantation.²¹⁰⁻²¹³

CSMI requires pharmacologic support along with emergent cardiac catheterization and PCI as indicated. MCS can be rapidly instituted with IABP placement and should be considered in conjunction with PCI. If a mechanical complication (i.e., severe MR or VSD) has occurred, an IABP should be placed without delay. Urgent surgical intervention is usually required for these mechanical complications. The culprit vessel resulting in the AMI is treated immediately with PCI. The number of diseased arteries remaining and the clinical status usually determine subsequent allocation to further PCI or CABG. This can be accomplished several days later, once the myocardium is recovered and the shock state has resolved. Patients who remain in CS after AMI, despite PCI, IABP, and inotropic support, should be considered for VAD support.

Postcardiotomy CS should be managed intraoperatively with an initial trial of IABP and inotropic support. If there is persistent shock or an inability to be weaned from CPB, VAD implantation is the next therapeutic step, provided a meaningful recovery is predictable or a plan for transplantation or permanent therapy can be clarified. The general recommendation for implantation of a VAD for postcardiotomy failure is within 1 hour of the first failed attempt to wean from CPB.

The mode of MCS used for CS is determined by a number of factors. First is the degree of pulmonary insufficiency. If there is pulmonary failure with a very large alveolar-to-arterial oxygen gradient on maximal ventilatory support, ECMO support is indicated. A small percentage of ECMO patients in this setting will recover, some will require VAD placement as a BTT, fewer still will bridge to VAD and then to recovery. If the degree of pulmonary insufficiency is limited to pulmonary edema that is likely to recover with adequate CO, patients should undergo VAD placement directly. The choice of VAD in this situation is also dependent on several factors, including the predicted need for short- or longer term support, the need for univentricular versus biventricular support, the chance of ventricular recovery, the institutional experience with different devices, device availability, and the relative risks of anticoagulation.

The ABIOMED and Levitronix CentriMag systems are attractive options for postcardiotomy cardiac failure in those patients predicted to recover within days to a week of surgery, for cases when neurologic function is not known or is markedly compromised, and for patients who are not candidates for transplantation but may BTR or bridge to

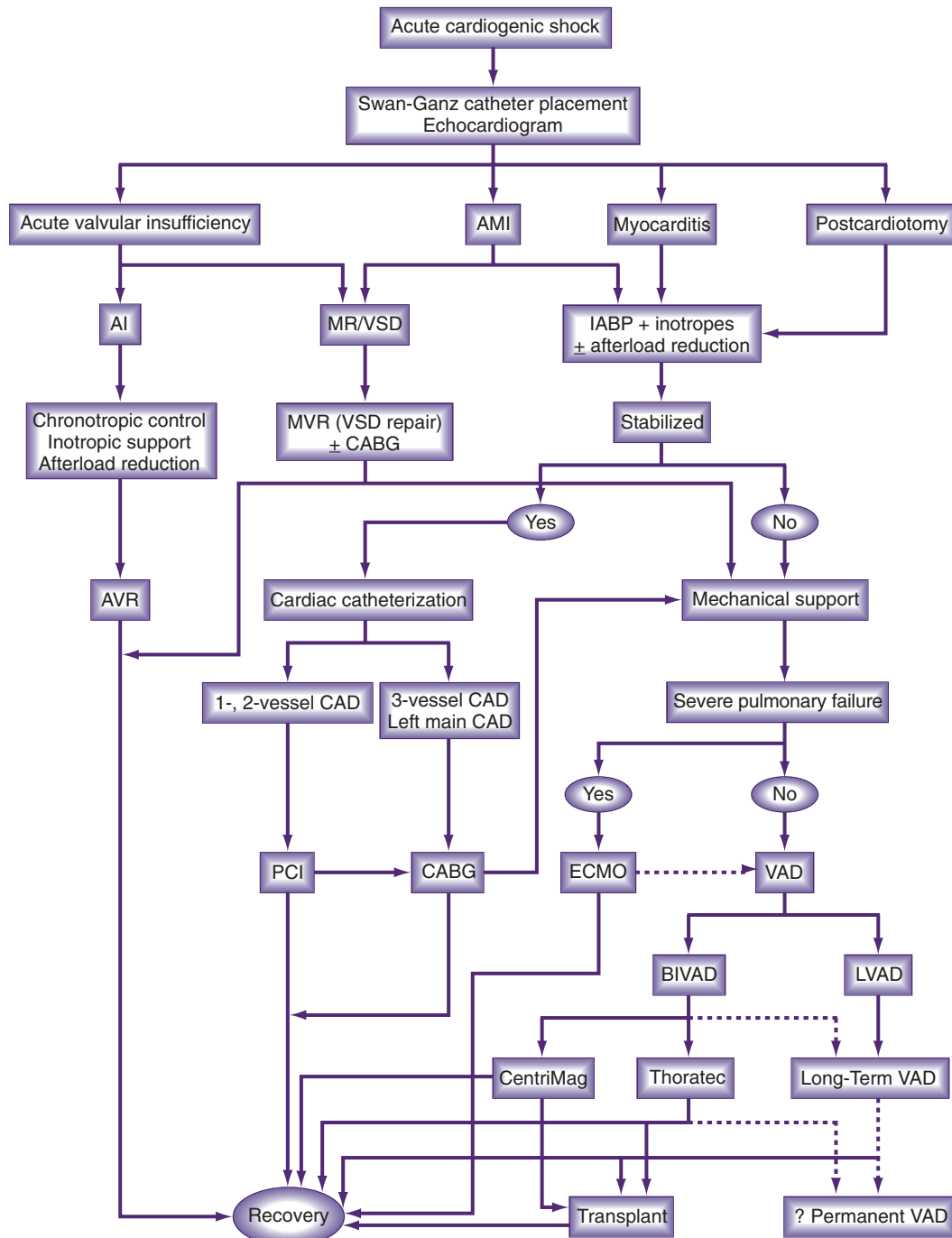


FIGURE 91-11 ■ Algorithm for the management of acute cardiogenic shock.

a long-term and ambulatory device once stabilized. Both are easy to insert. Therefore, in cases of profound CS when operative brevity is paramount, these devices may be beneficial. Additionally, both allow for atrial cannulation, which may make conversion to other long-term VAD systems technically easier.

The Thoratec PVAD system is the most versatile VAD and remains the support used most frequently for the treatment of refractory CS. The device is relatively easy to install, may be used for short-term or long-term uni- or biventricular support, and allows the potential for ambulation. VAD inflow cannulation can be either via the atria or ventricles. Ventricular cannulation is preferable even in the case of AMI because of its hemodynamic efficiency, reliability, and better ventricular decompression. Despite the friability of freshly infarcted

myocardium, the Thoratec ventricular cannulas are safe to insert through infarcted tissue. Once a patient is stabilized with the Thoratec system, a management strategy can be mapped out as BTR, BTT, or permanent therapy with an intracorporeal device.

Initial placement of implantable pulsatile or continuous-flow VADs (e.g., HeartMate XVE or HeartMate II) for MCS in patients with CS is generally not indicated. These devices may be used as a second bridge (“bridge-to-bridge”) toward recovery, BTT, or permanency. There may be a select group of patients in whom these intracorporeal VADs have a primary role in CS: (1) patients who require a larger CO than other devices can generate (large individuals needing a CO greater than 6 L/min to reverse the shock state); (2) patients who are more stable, can sustain longer operative times, and are unlikely to achieve myocardial

recovery; and (3) patients in whom anticoagulation is contraindicated, making the HeartMate XVE device potentially safer.

CONCLUSION

CS remains a lethal problem with a mortality rate as high as 75%.^{3,214,215} Patients who cannot be stabilized with inotropic support and an IABP should be considered for MCS with a VAD. The ideal assist device that can be easily placed, is versatile, portable, has minimal risk of complication, offers a normal CO with physiologically equivalent characteristics such as pulsatile flow, and is easily removed does not yet exist. Currently, there are three modes of MCS that have received widespread use in the patient population with CS, including ECMO/cardiopulmonary support, the ABIOMED AB 5000, and the Thoratec PVAD system. Implantable devices such as the HeartMate LVAS XVE and HeartMate II have occasionally been used in this moribund population but have a more defined role in the subacute and chronic HF population.

The use of MCS for acute CS has facilitated impressive improvements in survival for certain disease cohorts such as those with

acute myocarditis, with survival rates over 70%.⁹⁹ VADs have had less remarkable an impact on patients with postcardiotomy shock or CSMI,¹⁰⁶ but results in these patient populations are improving annually. Inherent to achieving better results is our understanding that patients who present with CS typically have significant underlying comorbidities with multiple-system organ dysfunction and marked derangements in both coagulation and inflammatory mediators that complicate management. They need to be approached by an integrated multidisciplinary team, including cardiologists, cardiac surgeons, anesthesiologists, critical care specialists, and experienced nursing staff to implement efficient and decisive treatment plans. These integrated systems offer the greatest chance for success. The future holds exciting promise with the rapid expansion of 3D printing technology, which is now capable of producing a titanium LVAD within a few hours. Transcutaneous energy transfer (TET) systems may someday obviate the need for percutaneous drive lines. As technologies expand and improve exponentially every year, it is clear that MCS will continue to play a pivotal role in the management of these difficult patients.

KEY POINTS

1. The leading cause of death among hospitalized patients with AMI continues to be CS. Mortality remains high at approximately 40%.
2. The hallmarks of CS and low CO are hypotension, peripheral vasoconstriction, cold extremities, poor urine output, and altered mental status.
3. Intrinsic causes of CS can be divided into four pathophysiologic classifications: (a) acute valvular insufficiency, (b) acute myocardial infarction, (c) acute myocarditis, and (d) postcardiotomy cardiac failure.
4. Echocardiography should be done to help formulate a differential diagnosis, and insertion of a pulmonary artery balloon catheter should be considered.
5. CSMI requires immediate cardiac catheterization. Concomitant IABP placement should be considered in addition to pharmacologic support.
6. Pioneering surgeons recognized by the 1960s that LV decompression and myocardial rest could afford enhanced cardiac recovery after the insult of open-heart surgery.
7. The physiologic rationale for the efficacy of the IABP includes (a) LV systolic unloading directly reduces stroke work, which in turn reduces myocardial oxygen consumption during the cardiac cycle, and (b) diastolic augmentation, which raises arterial blood pressure and provides better coronary arterial perfusion during diastole, yielding increased oxygen delivery to the myocardium.
8. The absolute indications for IABP placement include CS, uncontrolled angina pectoris, acute postinfarction VSD or MR, and postcardiotomy left-sided HF with low CO.
9. Relative contraindications to IABP use include severe atheromatous and atherosclerotic descending thoracic aorta, descending aortic aneurysm, recent descending thoracic aortic surgery, and mild to moderate aortic insufficiency.
10. IABP support, combined with revascularization, portends a better prognosis than adjunctive IABP use with medical therapy alone.
11. Short-term cardiopulmonary support for CS is as an important adjunctive therapy. It is a relatively simple means of establishing immediate and complete circulatory support, requiring no additional equipment other than that needed for standard cardiopulmonary bypass support during cardiac surgery.
12. Initial placement of implantable VADs (e.g., HeartMate) for MCS in patients with CS is generally not indicated. These devices are best suited as a bridge-to-bridge once the shock state has resolved, often with a temporary MCS device.

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ANATOMY AND PHYSIOLOGY OF THE PORTAL SYSTEM

The term *portal system* refers to a venous system that begins and ends in capillaries. The portal venous system commences in the capillaries of the intestine and ends in the hepatic sinusoids. The portal venous system drains blood from the gastrointestinal (GI) tract, pancreas, gallbladder, and spleen. The portal vein originates from the confluence of the splenic vein and the superior mesenteric vein. The inferior mesenteric vein and short gastric veins drain into the splenic veins. The superior mesenteric vein drains all the blood from the small bowel and the right colon while the inferior mesenteric vein drains the blood from the remainder of the colon and most of the rectum. Flow in the portal vein is normally about 1 L/min (approximately 20% cardiac output) with a mean pressure of 7 mm Hg. Although the blood in the portal vein is the outflow from capillary beds and therefore has relatively low oxygen content, 70% of hepatic oxygenation is derived from the portal flow. The blood flowing through the hepatic artery supplies the remainder of hepatic oxygen consumption and is the primary blood supply to the biliary tree. The portal vein carries a high concentration of nutrients and hormones, facilitating the liver's central role in fat, carbohydrate, drug, and protein metabolism. Toxic substances are removed by hepatocytes, and bacteria (and bacterial products) are removed by Kupffer cells. Portal venous blood and hepatic arterial blood mix at the sinusoidal level, and there exists an adenosine-mediated local hepatic arterial autoregulatory "buffer response" that increases arterial inflow in response to low portal flow; however, the total hepatic flow is decreased. This buffer response is also dysregulated in sepsis.

Postsinusoidal blood drains through hepatic venules into hepatic veins and then into the inferior vena cava to return to the systemic circulation. A variety of pathologic processes can result in portal venous flow becoming "obstructed." Regardless of the cause (i.e., intra- or extrahepatic obstruction), this resistance to portal flow increases portal pressure and leads to the development of what is called the *portal hypertension syndrome*, which is characterized by the formation of portosystemic collaterals. Under these circumstances, only a portion of the blood flow that originates within the portal system reaches the liver; the remainder is diverted through collaterals and enters the systemic circulation directly.

In the setting of portal hypertension, collaterals will often form. The major sites of collateral remodeling are in the gastroesophageal region. Most commonly, these vessels, often called varices, form between the inferior mesenteric vein and the hemorrhoidal vein, at the umbilical vein, and along the anterior abdominal wall. Of note, collateral vessels may also develop at the sites of previous or current colostomy stomas, in which case they are termed ectopic varices. In addition to the formation of discrete collateral vessels, there are also more generalized changes within the GI tract, leading to vascular ectasia or portal hypertensive enteropathy. Bleeding may result from varices or portal hypertensive enteropathy.

Patients with portal hypertension exhibit characteristic splanchnic and systemic circulatory changes. The key to these manifestations is abnormal vasodilation. Decreased arteriolar tone in the splanchnic vessels leads to splanchnic hyperemia and hypervolemia but also a reduction in effective central blood volume, with the majority of the

excess blood volume residing within the splanchnic bed. These circulatory changes prompt systemic homeostatic responses, with activation of the vasoconstrictor and sodium-retaining mechanisms. Overall, these changes comprise a hyperdynamic circulation characterized by increased cardiac output and heart rate to maintain blood pressure despite decreased systemic vascular resistance, with an overall increase in total plasma volume.

THE PATHOPHYSIOLOGY OF PORTAL HYPERTENSION

The primary pathophysiologic derangements in portal hypertension can be expressed by Ohm's law, $V = IR$, where V is pressure, I is flow, and R is resistance. This equation demonstrates that with increased resistance and stable flow, pressure must increase. In portal hypertension, this is complicated by multiple other general derangements and alterations in homeostasis. Moreover, as the compensation for portal hypertension ensues, splanchnic blood flow increases along with increased resistance, adding to the elevated portal pressure. In addition to these mechanical forces on the portal vessels, when liver disease is involved, a reduction in synthetic capacity of the liver leads to decreased albumin synthesis and subsequent decreased total intravascular oncotic pressure. Combined with hyponatremia, these factors further contribute to increased portal pressures. In the setting of cirrhosis, animal data reveal there is an intrahepatic component of the portal resistances that is dynamic and consists of a constrictive and fibrogenic phenomenon that is associated with the alterations in hepatic stellate cells.¹ Various vasoactive substances and neurohormones further influence this system, adding more components to portal hypertension. Further details are beyond the scope of this review. [Table 92-1](#) summarizes some of the basic pathophysiologic findings of cirrhosis and portal hypertension.

DIAGNOSIS OF PORTAL HYPERTENSION

PHT is defined as a portal pressure that is 5 mm Hg greater than the pressure measured in the inferior vena cava or a pressure of more than 15 mm Hg in the splenic vein or portal pressure measured at surgery. If the gradient is greater than 10 mm Hg, then clinically significant PHT is present. The direct consequences of PHT are the formation of portosystemic collaterals and splenomegaly. Portosystemic collaterals can become clinically apparent as gastric or esophageal varices, umbilical vein recanalization, retroperitoneal collaterals, and rectal or ileostomy varices. The complications of PHT are variceal bleeding, gastropathy, hyperdynamic circulation, ascites, hepatic hydrothorax, hepatorenal syndrome (HRS), hypersplenism, and hepatic encephalopathy. The most clinically significant complication will be discussed in the sections to follow. Varices are rarely seen if the gradient is less than 10 mm Hg. Variceal bleeding is not observed if the pressure gradient is less than 12 mm Hg, and protection from variceal bleeding is gained if the pressure gradient can be manipulated to less than 12 mm Hg or a 20% reduction in pressure is achieved.

Direct measurement of the hepatic vein wedge pressure of the portal venous pressure requires invasive means, most often transjugular catheterization. The advantage of this approach is that caval and hepatic venous pressures can be measured during the same procedure.

Less frequently, a transhepatic approach is directly (by cannulating a branch of the superior mesenteric vein) at the time of a surgical procedure. Very rarely, splenic pulp pressure is measured.

Indirect measurements also can be used to assess the portal pressure gradient. This procedure involves measurement of the free and wedged hepatic venous pressure using catheterization of the right hepatic vein. Wedged hepatic venous pressure (measured using a balloon-tipped catheter) reflects the pressure in a static column of blood from the hepatic vein to the sinusoid. It is an assessment of sinusoidal pressure rather than portal venous pressure and therefore may underestimate the portal pressure gradient in disease states

TABLE 92-1 Pathophysiologic Changes in Portal Hypertension

| PATHOPHYSIOLOGIC CHANGE | SPECIFICS |
|--|--|
| Hepatic resistance | Passive, mechanical component: 60%-70% Active, dynamic component: 30%-40% |
| Portal hypertension | |
| Shunts | |
| Splanchnic vasodilation | |
| Increased portal inflow | |
| Decrease in effective circulating volume; redistribution total blood volume | |
| Increase in endogenous vasopressors (RAA, SNS, VP) | Increase in endothelin-1 Angiotensin II Norepinephrine Vasopressin PGF-2 alpha |
| Decrease in NO, CO | |

characterized by presinusoidal hypertension. The free hepatic venous pressure is obtained with the catheter in the hepatic vein and gives an assessment of caval pressure. Free hepatic venous pressure is not elevated in patients with diseases characterized by presinusoidal and sinusoidal PHT, but it is characteristically raised in posthepatic (or extrahepatic postsinusoidal) etiologies. The gradient between the two measurements is called the *hepatic venous pressure gradient* and is the most commonly quoted parameter in the medical literature regarding the management of PHT. Both the absolute value of the hepatic venous pressure gradient and the change in the hepatic venous pressure gradient with pharmacotherapy have prognostic significance related to the risk of variceal bleeding. It is important to understand the true definitions of these various pressures so that the data obtained from the various measurements can be properly interpreted. If the proceduralist is less familiar with the nuances and meaning of the values obtained, incorrect conclusions will be drawn. In the [Table 92-2](#), we list some of the most common etiologies of portal hypertension classified by site of increased resistance.

GI BLEEDING

GI bleeding can always be life-threatening in the critical care setting. However, this is especially true when cirrhosis and portal hypertension exist. The causes of GI bleeding are many, and we will restrict the discussion to the more common scenarios. In the diagnostic and therapeutic algorithms, acute bleeding in decompensated chronic liver disease usually associated with cirrhosis can present as upper or lower GI bleeding. Although the diagnostic algorithms are similar for GI bleeding in the presence or absence of cirrhosis, the etiologies by percentage vary considerably. The chart below ([Fig. 92-1, A](#)) demonstrates this variability. In general, 73.2% of all patients presenting with GI bleeding in the ER will be noncirrhotic, and 26.8% will be cirrhotic. Of note, in cirrhotic patients, approximately 50% of all bleeding will be secondary to esophageal varices whereas in noncirrhotics, bleeding is most commonly due to bleeding gastric ulcers ([Fig. 92-1B](#)).

GI bleeding in the portal hypertensive patient most often is found by the observation of melena and/or hematemesis in combination with a dropping hematocrit and possibly hemodynamic instability. Most would recommend the initial placement of a nasogastric tube to determine, if, in fact, the seemingly obvious source is an upper GI bleed. This should be simultaneously accompanied by a request for and

TABLE 92-2 Etiology of Portal Hypertension Grouped by Location of Insult

| SITE OF INCREASED RESISTANCE | CONDITION | FHP | WHVP | HVPG | SPP |
|--|---|------------|-------------------|-------------------|------------|
| Presinusoidal (extrahepatic) | Extrahepatic portal, splenic, or mesenteric vein thrombosis | Normal | Normal | Normal | Increased |
| Presinusoidal (intrahepatic) | Early primary biliary cirrhosis | Normal | Normal/raised (?) | Normal/raised (?) | Increased |
| Presinusoidal (intrahepatic) | PSC | Normal | Normal/raised (?) | Normal/raised (?) | Increased |
| Presinusoidal (intrahepatic) | Sarcoid | Normal | Normal/raised (?) | Normal/raised (?) | Increased |
| Presinusoidal (intrahepatic) | Schistosomiasis | Normal | Normal/raised (?) | Normal/raised (?) | Increased |
| Presinusoidal (intrahepatic) | Congestive heart failure | Normal | Normal/raised (?) | Normal/raised (?) | Increased |
| Presinusoidal (intrahepatic) | Noncirrhotic portal fibrosis | Normal | Normal/raised (?) | Normal/raised (?) | Increased |
| Intrahepatic sinusoidal | Cirrhosis (any etiology) | Normal | Increased | Increased | Increased |
| Intrahepatic sinusoidal | Alcoholic hepatitis | Normal | Increased | Increased | Increased |
| Intrahepatic sinusoidal | Fulminant liver failure (any etiology) | Normal | Increased | Increased | Increased |
| Extrahepatic postsinusoidal hypertension | Budd-Chiari syndrome | Increased | Increased | Normal | Increased |
| Extrahepatic postsinusoidal hypertension | Constrictive pericarditis | Increased | Increased | Normal | Increased |
| Extrahepatic postsinusoidal hypertension | Inferior vena cava obstruction | Increased | Increased | Normal | Increased |
| Extrahepatic postsinusoidal hypertension | Congenital inferior vena cava web | Increased | Increased | Normal | Increased |
| Extrahepatic postsinusoidal hypertension | Right heart failure | Increased | Increased | Normal | Increased |

FHP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; SPP, systolic pulse pressure; WHVP, wedged hepatic venous pressure.

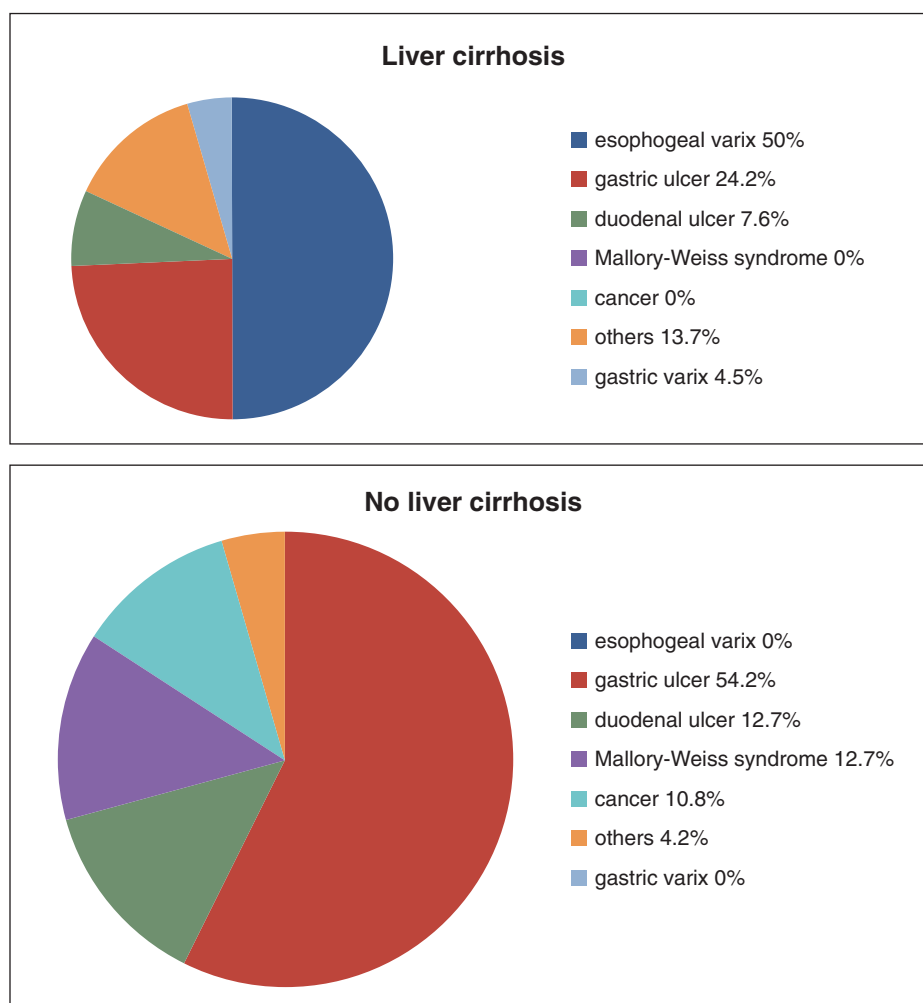


FIGURE 92-1 ■ Gastrointestinal bleeding in the presence and absence of cirrhosis.

preparation for upper GI endoscopy. Of note, in the critical care setting, some assumed upper GI bleeding episodes can actually be from another site of bleeding and not truly from the upper GI tract. In other words, the critical care practitioner must not miss another source of bleeding that is masquerading as an upper GI bleed. Most notably, bleeding can come from the soft palate hemoptysis, the sinuses, or the nasopharyngeal region. GI bleeding may also manifest as esophageal necrosis or perforation, possibly associated with previous banding therapy, and may only manifest with subtleties (e.g., pneumomediastinum). Therefore, there must be a heightened level of suspicion in patients who have a history of these typically routine interventions. Hemobilia is another rare consequence of hepatic interventions, such as a transjugular intrahepatic portosystemic shunt (TIPS) procedure, endoscopic retrograde cholangiopancreatography (ERCP), or liver biopsy in a cirrhotic patient, which can present as a massive upper GI bleed.

Upper GI bleeding is diagnosed in the majority of cases with endoscopy, and immediate therapeutic options are available. Importantly, a secure airway must be in place before attempting endoscopy in critically ill patients. Endoscopic intervention options include epinephrine injection, thrombin injection, and thermocoagulation for ulcers or Dieulafoy lesions. For variceal bleeding, therapeutic maneuvers include banding, endoclips, sclerosants, and thrombin injections. Complications of endoscopy therapy include aspiration, side effects from sedation, perforation, and increased bleeding while attempting a therapeutic intervention.

The next diagnostic opportunity is usually the visceral angiography. This is often prompted by ambiguous findings on endoscopy or the

inability to implement control of the hemorrhage. In many institutions, CT angiography has replaced direct angiography as the initial diagnostic maneuver and has been shown to be more sensitive. A tagged red blood cell scan can often direct the therapy for slower bleeding emanating distally to the ligament of Treitz (Table 92-3).

Hemodynamic instability, especially from upper GI bleeding in the cirrhotic patients, may require additional aggressive interventions. Therapeutic maneuvers such as the Blakemore tube may be employed, even empirically. If there is a history of hemorrhage or an unknown presence of varices in a patient, this can often be lifesaving. Of course, a mechanical means to address hemorrhage would be accompanied by medical management. Medical management of GI bleeding is extensively reviewed in the references.²⁻⁵ In brief, pharmacologic therapy can assist in reducing GI hemorrhage via the vasoconstrictors, nonselective beta-blockers, and vasodilators that are listed in Table 92-4.

An important concurrent consideration for the situation of GI bleeding is that end organ perfusion is often limited not only to hypovolemia but also possibly by myocardial ischemia. Furthermore, the untoward consequences of a further reduction in perfusion, by whatever etiology, may further deteriorate the compromised hepatic function in a cirrhotic patient.

Therapeutic considerations and diagnostic maneuvers in an unstable patient should also be coupled with simultaneous therapeutic interventions in the critical care setting. Importantly, because the treatment modalities available will figure prominently in the algorithm for the proper care of upper GI bleeding in the setting of portal hypertension,

TABLE 92-3 Sensitivity and Specificity of Various Diagnostic Modalities³

| | SENSITIVITY | SPECIFICITY |
|----------------------|-------------|-------------|
| Upper endoscopy | 93-100 | 30-100 |
| CT angiography | 86 | 95 |
| Catheter angiography | 42-86 | 100 |
| Radionuclide imaging | ** | ** |

TABLE 92-4 Medications Used in the Setting of Upper GI Bleeding to Achieve Hemostasis

| DRUG CLASS | MECHANISM OF ACTION | EXAMPLES |
|-----------------------------|--|--|
| Splanchnic vasoconstrictors | Produce splanchnic vasoconstriction and reduce portal venous inflow | Vasopressin Terlipressin Somatostatin Vaptreotide |
| Nonselective beta blockers | Reduce hepatic venous pressure gradient via systemic hypotensive effect | Propranolol |
| Venodilators | Decrease intrahepatic and/or portocollateral resistance | Isosorbide mononitrate |
| Antifibrinolytic agents | Reduce the degradation of fibrin by slowing the conversion of plasminogen to plasmin—supporting clot formation | Tranexamic acid |

it is critical to involve interventional radiology early during treatment. Below is a chart that provides a brief algorithm for each diagnostic entity (Fig. 92-2).

Beyond the control of the hemorrhage, the overriding goal involves decompressive strategies to treat the underlying etiology of the hemorrhage. The TIPS procedure is on a continuum of the therapeutic maneuvers that eventually include complex surgical shunts to decompress portal pressure. As experience grows with the procedure and the safety margins increase, TIPS has become a mainline approach to primary portal decompression. As with any portal decompression procedure, a reduction in total hepatic blood flow with an associated reduction in hepatic function is always a major concern. Indications, contraindications, and complications of the TIPS procedure are considered in Table 92-5.

In acute variceal hemorrhage, efforts must be directed primarily at the control of hemorrhage. Conditions may exist that favor surgical portosystemic decompression over a TIPS placement. Portal vein thrombosis with a patent supermesenteric vein, known tumor within the liver in the path of a TIPS, and a technically unfavorable anatomy are common examples of when a surgical intervention is a preferred option. A mesocaval shunt is a good choice to create nonselective portosystemic decompression and control bleeding. The operative management of patients with the coagulopathy and severe portal hypertension should involve a surgeon experienced in a liver transplantation and hepatobiliary surgery.

Antibiotic therapy and proton pump inhibitors (PPI) are important adjuncts in cirrhotic patients with acute upper GI bleeding as they are at a high risk of developing severe bacterial infections (e.g., spontaneous bacterial peritonitis). The use of short-term prophylactic antibiotics (e.g., ceftriaxone) in patients with liver disease and GI hemorrhage has been a show to decrease the rate of bacterial infection and to improve patient survival. A Cochrane collaboration meta-analysis of 2223 subjects assessed the use of PPI in the setting of upper GI bleeding

in cirrhotic patients. Although there was no statistically significant difference in the outcomes of rebleeding, need for surgery, or mortality, those receiving up-front high-dose PPI therapies had a significantly reduced rates of high-risk stigmata identified at endoscopy and thus reduced the need for intervention at the time of endoscopy.³

In summary, portal hypertension can be associated with bleeding and can be a distinct challenge in the critical care environment. As we recommended earlier, the ultimate goal should be toward a definitive therapy. Commensurate with the magnitude of the hemorrhage, it is stressed that simultaneous activation of multidisciplinary diagnostic and therapeutic strategies will facilitate the best patient outcome. In the cirrhotic patient, liver transplantation is often the only definitive treatment. Efforts to preserve candidacy should be at the forefront of the critical care team's thinking as ultimately this strategy may be required for the life-saving outcome.

ASCITES

Another frequent consequence of portal hypertension is the development of ascites. Although it is not usually immediately life-threatening, it can significantly complicate the management of the intensive care unit (ICU) patient. The risk of developing ascites is 6% at 10 years with cirrhosis.

The differential diagnosis of ascites is usually clarified to the calculation of an albumin ascites gradient. A gradient of greater than 1.1 is consistent with portal hypertension, congestive heart failure (CHF), or Budd-Chiari syndrome. A gradient of less than 1.1 is consistent with carcinomatosis, tuberculosis, pancreatitis, serositis, or nephrosis. In portal hypertension associated with cirrhosis, systemic and splanchnic circulation is vasodilated, but renal blood flow is compromised and renal cortical blood flow is shunted to the medullary region of the kidney. These changes lead to a gradual increase in renal sodium and water retention. Thus, ascites contributes to a confusing physiologic state in which patients have excess body sodium but an even greater excess of free water and thus serum hyponatremia. Renal physiology acts as if the patient is intravascularly depleted and alterations in aldosterone metabolism simultaneously add to the sodium retention. Once the pressure of ascites increases in the abdominal compartment, it further compromises renal blood flow due to venous compression. All this creates a vicious cycle that complicates this syndrome. The mainstay of medical management of ascites is a reduction of sodium balance using dietary sodium restriction, free water restriction, and diuretics. Loop diuretics such as furosemide will interfere with sodium reabsorption while potassium-sparing diuretics can further increase sodium excretion, renal functioning permitting. Monitoring the serum albumin levels and giving albumin replacement when the level is below three are advised strategies to enhance control of ascites, as it may assist in increasing oncotic pressure. Newer medical strategies that may be considered for the control of ascites include midodrine, terlipressin, and vasopressin V2 receptor antagonists. Midodrine is an alpha adrenergic receptor agonist that results in an increase in mean arterial pressure in cirrhosis. Terlipressin is a vasopressin analog that acts on the V1 receptor in the splanchnic vasculature to cause splanchnic vasoconstriction, therefore decreasing splanchnic inflow and lowering the portal pressure. These improvements in systemic hemodynamics have been successfully used in the treatment of HRS in cirrhosis. Vasopressin V2 receptor antagonists (vaptans) are agents that compete with vasopressin for attachment onto the V2 receptors at the renal collecting duct to inhibit water reabsorption at that site, thereby inducing an aquaresis and reduced serum water content. There has been evidence that vaptans are also able to reduce the extent of ascites in cirrhotic patients.⁷

In the ICU setting, the baseline therapies for ascites in the cirrhotic patient can create acute alterations and electrolyte abnormalities associated with acute compromised hepatocellular function and acute renal injury. Therefore, it is not uncommon that medical management of ascites must give way to acute mechanical management, such as paracentesis or a TIPS procedure. Each of these procedures must

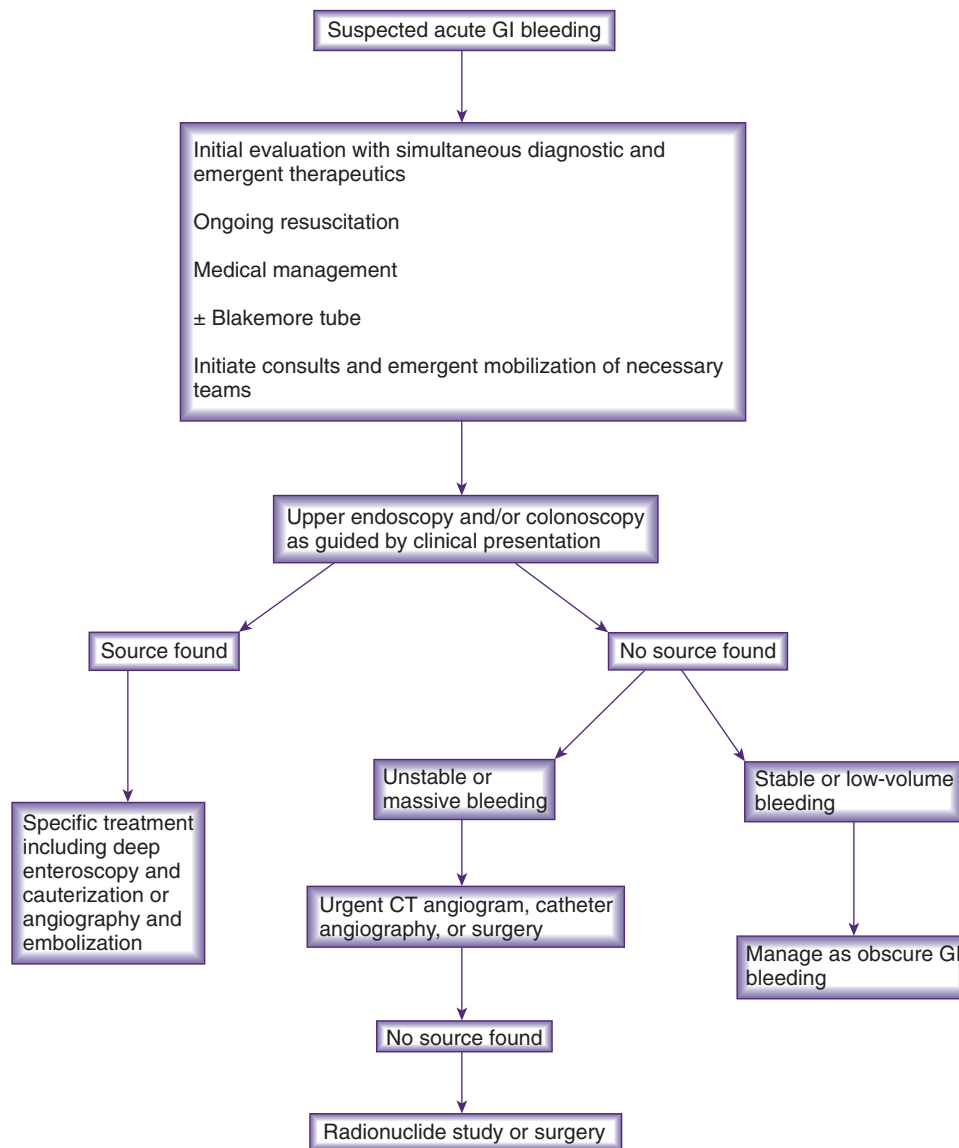


FIGURE 92-2 ■ The proper care of upper gastrointestinal bleeding in the setting of portal hypertension. The algorithm shows each diagnostic entity.

be correlated with the risk-benefit ratio associated with their complications.

As with all complications of portal hypertension, the goal of management is often to create an opportunity window for orthotopic liver transplantation.

■ HEPATIC HYDROTHORAX

Hepatic hydrothorax is defined as a significant pleural effusion greater than 500 mL, associated with cirrhosis and no primary cardiac or pulmonary disease. Pleural effusion is a result of either the increased formation of pleural fluid or decreased absorption of hepatic hydrothorax in which large volumes of fluid from the abdomen are transferred to the pleural space. The defects in the diaphragm are usually associated with the lymphatic fenestra but may also be due to larger defects, such as an iatrogenic injury to the diaphragm. Hepatic hydrothorax occurs most commonly on the right side and is associated with the bare area of the right triangular ligament. The negative pressure of the thoracic cavity favors a unidirectional flow of ascites from the abdomen to the chest. Once a hepatic hydrothorax occurs, it rarely

subsides and thus is considered an agonal finding associated with the end-stage liver disease. Based on the data presented involving 77 patients by Badillo et al. in 2014, patients with hepatic hydrothorax may have worsened outcomes than would be predicted by their MELD score alone. The patients in this study met the criteria of a known diagnosis of cirrhosis, pleural effusion, and pleural fluid consistent with the known characteristics of hepatic hydrothorax and not of an infection, malignancy, or other etiologies. The data suggest that some patients with hepatic hydrothorax die from complications arising from their pulmonary disease rather than from liver failure. The overall outcome of the patients was poor, with approximately half of the patients dying within one year of presentation. Patients who underwent TIPS procedure or liver transplantation had substantially longer periods of survival (Table 92-6).⁸

The diagnosis of hepatic hydrothorax is based on medical history, physical exam, pleural fluid analysis, and radiographic imaging. Pleural effusions associated with ascites are consistent with abdominal ascites and thus are, transudative. The cell count is low, and the total protein concentration is less than 2.5 g/dL. Typically, the serum to pleural fluid albumin gradient is greater than 1.1 g/dL, similar to the high serum to

TABLE 92-5 Indications, Contraindications, and Complications of the TIPS procedure⁶

| INDICATIONS | RELATIVE CONTRAINDICATIONS | CONTRAINDICATIONS | ACUTE COMPLICATIONS | CHRONIC COMPLICATIONS |
|---------------------|--|--|---|--|
| Upper GI bleeding | Pulmonary hypertension | Right-sided heart failure | Neck hematoma | Congestive heart failure |
| Ascites | Severe liver failure | Biliary tract obstruction | Arrhythmia | Portal vein thrombosis |
| Hepatic hydrothorax | Portal vein thrombosis Multiple hepatic cysts | Uncontrolled infection Chronic recurrent disabling hepatic encephalopathy Hepatocellular carcinoma involving hepatic veins | Stent displacement Hemolysis Bilhemia Hepatic vein obstruction Shunt thrombosis Hemoperitoneum Hemobilia Liver ischemia Cardiac failure Sepsis | Progressive liver failure Chronic recurrent encephalopathy Stent dysfunction TIPSitis |

TABLE 92-6 Comparison of Treatment Modalities⁸

| TREATMENT MODALITY | NO (%), N = 77 | AGE, YEARS (MEAN) | FEMALE % | INITIAL MELD (MEAN, RANGE) | CHILD-PUGH SCORE (N = 74) | ASCITES SIZE | DEATH (NO, %) (N = 44) | DAYS FROM PRESENTATION UNTIL DEATH OR END OF STUDY |
|--------------------|----------------|-------------------|-------------|----------------------------|---------------------------|--|------------------------|--|
| Medical management | 64/77 (83%) | 52 | 23/64 (36%) | 16 (4-46) | A = 1 B = 31 | None: 6 Small: 34 Moderate: 16 Large: 8 | 40/64 (63%) | 321 ± 463 |
| TIPS | 8/77 (10%) | 56 | 5/8 (63%) | 12 (7-28) | A = 0 B = 5 C = 2 | None: 1 Small: 3 Moderate: 3 Large: 1 | 4/8 (50%) | 845 ± 407 |
| Transplant | 5/77 (7%) | 54 | 0 | 21 (10-40) | A = 1 B = 1 C = 1 | Large: 1 | 0 | 1896 ± 1752 |

ascites fluid albumin gradient seen in cirrhotic ascites. It should be noted that the hepatic hydrothorax can also be associated with more complex fluid collections in the chest (such as empyema), which may be spontaneous in nature or associated with prior infections of the pleural space. The etiology of empyema in the setting of hepatic hydrothorax is not completely understood.

The primary reason hepatic hydrothorax represents such a difficult treatment dilemma is the risk of converting the hydrothorax to an empyema with iatrogenic manipulation. Repeated thoracentesis should always be preferred over a chest tube. This is because the chest tube removal may be difficult to achieve, and the risk of contamination with leaving it in place is very high. Generally, no more than 2 L of pleural fluid should be removed to avoid pulmonary edema from lung expansion. Therefore, controlling the ascites becomes a very high priority for controlling the hepatic hydrothorax. The principles of managing the hepatic hydrothorax are similar to those presented in the ascites section but are more acute. Lung collapse associated with a substantial hepatic hydrothorax puts the patient at a high risk for a parenchymal lung infection.

Whereas thoracentesis is the preferred method over pigtail or chest tube thoracostomy, empyema may still result. This, of course, is catastrophic in the setting of end-stage liver disease. Ultimately, as in many of the complications of portal hypertension, a liver transplant is the only successful therapy since hepatic hydrothorax represents severe decompensation and, thus, is appropriately considered an agonal finding.

HEPATORENAL SECTION

HRS is defined as a functional renal failure in patients with liver failure and portal hypertension. The clinical scenario is usually one of acutely decompensated chronic liver failure and cirrhosis or in the setting of acute liver failure. The profound changes in renal physiology associated with liver failure are quite predictable, and thus renal dysfunction associated with changes in creatinine clearance are incorporated into the MELD (model for end-stage liver disease) score that is used for liver transplant allocation.

In this syndrome, the kidneys are morphologically intact; however, there are functional abnormalities resulting from renal cortical medullary blood flow derangements, which in turn can cause increases in afferent arteriolar resistance in the renal cortex. This results in renal cortical hypoperfusion and excessive sodium absorption in the tubular medullary areas of the kidney. Aldosterone metabolism and alterations in the renin-angiotensin axis, as well as multiple mechanisms that support vasoconstriction, further exacerbate the pathophysiology. Furthermore, systemic peripheral vascular resistance and splanchnic vasodilation associated with the shunting of the cirrhotic state result in lower mean arterial pressure and gross reduction in renal perfusion.

There are two types of HRSs: (1) type I reflects a more rapid change in renal function; and (2) type II occurs more slowly and is associated with a more insidious decline in hepatocellular function. In type I HRS, serum creatinine doubles over a 2-week interval and is usually greater

than 2.5. In type II HRS, the serum creatinine does not exceed 1.3 and may not have changed but may be associated with mild oliguria. The median survival is 2 weeks and 6 months for type I and type II HRS, respectively. Although there is no single test to definitively diagnose HRS, it should be suspected with a creatinine clearance less than 40 mL per minute, oliguria less than 500 mL per day, urine sodium less than 10 mEq, and serum sodium at less than 130 mEq with urine osmolality being greater than the plasma.

The prevalence of HRS in patients with ascites and cirrhosis is 18% and 39% at 1 and 5 years, respectively. In light of the above changes in pathophysiology, it is not surprising that patients who present with ascites can also have such complications such as hemorrhage, hyponatremia, and worsening encephalopathy. Precipitating factors associated with acute HRS include bacterial infections (57%), hemorrhage (36%), and therapeutic paracentesis with hypovolemia (7%).⁹

The treatment of HRS begins with the elimination of any factors that might be compromising hepatocellular function, such as systemic infection or GI bleeding. All medications should be reviewed for their risk-benefit ratio as it relates to exacerbation of renal toxicity. Vasoconstrictors may be of a transient benefit as well as beta-blockers to reduce splanchnic vasoconstriction. The TIPS procedure also may be useful as it will improve renal function and cirrhosis by decreasing sympathetic tone and thus increasing renal blood flow. In the sense that HRS is a complication of portal hypertension, the underlying cause of liver dysfunction is always best treated with liver transplantation in otherwise qualified candidates.

LIVER TRANSPLANT

As has been emphasized in this chapter, liver transplantation is the ultimate tool to treat portal hypertension. This procedure not only treats portal hypertension but also the source of portal hypertension, liver cirrhosis, as well. Without the option of liver transplantation, 5-year survival of patients with Child C cirrhosis and variceal bleeding is approximately 25%, whereas the 5-year survival after a liver transplant is as high as 75%.⁹ With too many listed patients waiting for too few deceased liver donors, not all patients who qualify for a liver transplant will receive a liver. The indication, listing, and timing of a transplant are complex and must be conducted by a complete liver transplant team. The etiology of liver disease, medical and surgical history, and

social circumstances are all part of the evaluation process. Upon listing, the patient will have a MELD score listed in UNOS DonorNet. It is a dynamic score based on a complex equation using lab values of INR, total bilirubin, and serum creatinine. The score is truncated at 40. There are share systems in place by region. Additionally, there is a discussion of incorporating serum sodium into the MELD score to achieve the fairest allocation of livers to the sickest patients first. The ability to assess when these severely ill patients are ready for a liver transplant is difficult. Contraindications to liver transplantation include active infection, extrahepatic malignancy, or a new malignancy. Other factors that may warrant ICU admission are not necessarily contraindications. Of course, the primary focus of critical care management for a listed transplant patient is to optimize the patient for transplantation.

KEY POINTS

1. Portal hypertension is defined as the presence of a raised portocaval pressure gradient that leads to many subsequent physiologic abnormalities.
2. Gastrointestinal bleeding is the most life-threatening complication of portal hypertension, and its treatment requires expedited multidisciplinary assessment and treatment.
3. Ascites, hepatic hydrothorax, hepatorenal syndrome, and hepatic encephalopathy are other complications of portal hypertension that require prompt recognition and expert medical and sometimes therapeutic intervention.
4. In cases in which liver disease, or even more important, cirrhosis, is involved, the complications of portal hypertension and a critical illness of the patient will be magnified.
5. Liver transplant should always be an underlying consideration and the potential goal for those with liver cirrhosis and portal hypertension as this will provide the ultimate and best treatment.

■ References for this chapter can be found at expertconsult.com.

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An association between advanced liver disease, ascites, and renal failure described in 1861 was named *hepatorenal syndrome* (HRS) by Helvig and Schutz in 1932.¹ HRS is a functional form of renal failure without renal histologic changes.² HRS is characterized by intense renal vasoconstriction, impaired renal perfusion, and low glomerular filtration rate (GFR) in the setting of splanchnic and systemic vasodilation.³ Among advanced cirrhotics, the incidence of HRS is 18% within 1 year and up to 40% at 5 years.^{4,5} The variability in the incidence is related to the degree of liver dysfunction, with higher Model for End-stage Liver Disease (MELD) scores portending an increased risk. HRS heralds a poor prognosis, with nearly half of the patients with HRS type 1 (HRS-1) dying within 2 weeks.^{4,6}

RENAL DYSFUNCTION IN CIRRHOSIS

Renal dysfunction in the setting of cirrhosis is common and is associated with adverse outcomes.^{7,8} The MELD system was implemented in 2002 to prioritize patients for liver transplantation with renal dysfunction weighted heavily. This has led to an increase in the number of patients with renal dysfunction undergoing liver transplantation.⁹ While HRS is the focus of this chapter; there may be other causes of acute kidney injury (AKI) in patients with cirrhosis. Common causes of prerenal AKI include the use of diuretics, lactulose, and hypovolemia. Intrinsic etiologies of AKI include glomerulonephritis, acute interstitial nephritis, and acute tubular necrosis.¹⁰ The etiology of renal disease is independently associated with prognosis, with HRS having the lowest 3-month probability of survival.¹¹

Several consensus definitions of AKI have been formulated. In 2004, the Acute Dialysis Quality Initiative (ADQI) group proposed the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria, which categorized renal dysfunction into grades of increasing severity based on urine output and changes in serum creatinine.¹² Given that even small increases in serum creatinine can reflect kidney injury and adverse outcomes, the Acute Kidney Injury Network (AKIN) criteria were proposed in 2007 (Fig. 93-1).¹³ AKI defined by the RIFLE criteria is predictive of adverse outcomes in patients with cirrhosis.^{14,15} The 8th International Consensus Conference of the ADQI group agreed to apply the modified RIFLE criteria to define AKI in patients with cirrhosis, irrespective of the cause of AKI.¹⁶ At this time, it is unclear whether AKIN or classical HRS criteria better predict prognosis.^{17,18,19} There is evidence that smaller increases in serum creatinine are associated with poor outcomes.²⁰ Patients with the same pathophysiologic derangements of HRS who do not meet criteria may also benefit from treatment.

PATHOGENESIS OF HRS

Low blood pressure, a very low GFR (<40 mL/min), as well as an increase in plasma levels of renin, norepinephrine, and antidiuretic hormone characterize HRS.² The increase in shear stress in the splanchnic vasculature is a result of portal hypertension leading to the overproduction of nitric oxide and other vasodilators.²¹ Other factors contributing to splanchnic vasodilation include increased bacterial translocation, mesenteric angiogenesis, and hyporesponsiveness of the splanchnic vasculature to vasoconstrictors.²²

Sodium retention, impaired free-water excretion, and decreased renal perfusion and glomerular GFR are the main abnormalities in

HRS and are progressive. The first abnormality is the reduced ability to excrete sodium secondary to mineralocorticoid effects. As the disease progresses, patients are unable to excrete the sodium ingested in their diet, and ascites develops. When renal sodium avidity is extremely high, the plasma renin activity and the plasma concentrations of aldosterone and norepinephrine are elevated.^{23,24} Circulatory dysfunction is greater at this stage, with increased activity of the sympathetic nervous and the renin-angiotensin systems.

Renal perfusion and GFR are dependent on increased renal production of prostaglandins. These lipid mediators are vasodilators that antagonize the vasoconstricting actions of angiotensin II and norepinephrine. A syndrome indistinguishable from HRS can be produced in patients with cirrhosis, ascites, and increased plasma renin activity if prostaglandin synthesis is inhibited by nonsteroidal antiinflammatory drugs.^{24,25}

Peripheral arterial vasodilation has been implicated in HRS but primarily affects the splanchnic arterial vascular bed. Doppler ultrasonography studies demonstrate vasoconstriction in renal, brachial, femoral, and cerebral beds.^{26,27} Several endogenous vasodilators have been implicated in splanchnic vasodilation, including nitric oxide, carbon monoxide, glucagon, prostacyclin, and endogenous opiates.²⁸⁻³⁰

End-stage liver disease is associated with reduced systolic and diastolic response to stress, enlarged cardiac chambers, and repolarization changes, termed *cirrhotic cardiomyopathy*.³¹ The development of HRS has been associated with a lower arterial pressure, a marked decrease in cardiac output, and increases in plasma renin activity and plasma norepinephrine³² (Fig. 93-2).

DIAGNOSIS

In 2006, the International Ascites Club updated the diagnostic criteria for HRS,^{33,34} requiring a serum creatinine greater than 1.5 mg/dL in the absence of other potential causes of renal failure (Table 93-1).³⁵ However, it is possible to develop HRS superimposed on kidney injury of other etiologies.¹⁶ The first step in the diagnosis of HRS is a demonstration of elevated creatinine, which greatly underestimates the GFR in advanced cirrhosis.^{2,36} Similarly, urea is synthesized by the liver, and urea synthesis may be reduced as a consequence of hepatic insufficiency.^{37,38} Many patients may not meet the diagnostic criteria for HRS yet have significant renal injury similar to HRS.³⁹

CLINICAL TYPES

HRS is classified into two types according to the severity and form of presentation of renal failure.³⁴ HRS-1 is characterized by severe and rapidly progressive renal failure and defined by doubling of the serum creatinine concentration to 2.5 mg/dL in less than 2 weeks. HRS-1 is often precipitated by an infection, hemorrhage, paracentesis, surgery, or acute hepatitis. The association of HRS and spontaneous bacterial peritonitis (SBP) has been carefully investigated.⁴⁰⁻⁴² HRS-1 develops in approximately 30% of patients with SBP despite rapid and successful treatment. Patients with an intense systemic inflammatory response and high cytokine levels in plasma and ascitic fluid are especially prone to develop HRS-1 after infection. HRS-1 has a 2-week median survival.

HRS-2 is characterized by a more moderate and steady decrease in renal function, with a serum creatinine >1.5 mg/dL that fails to satisfy

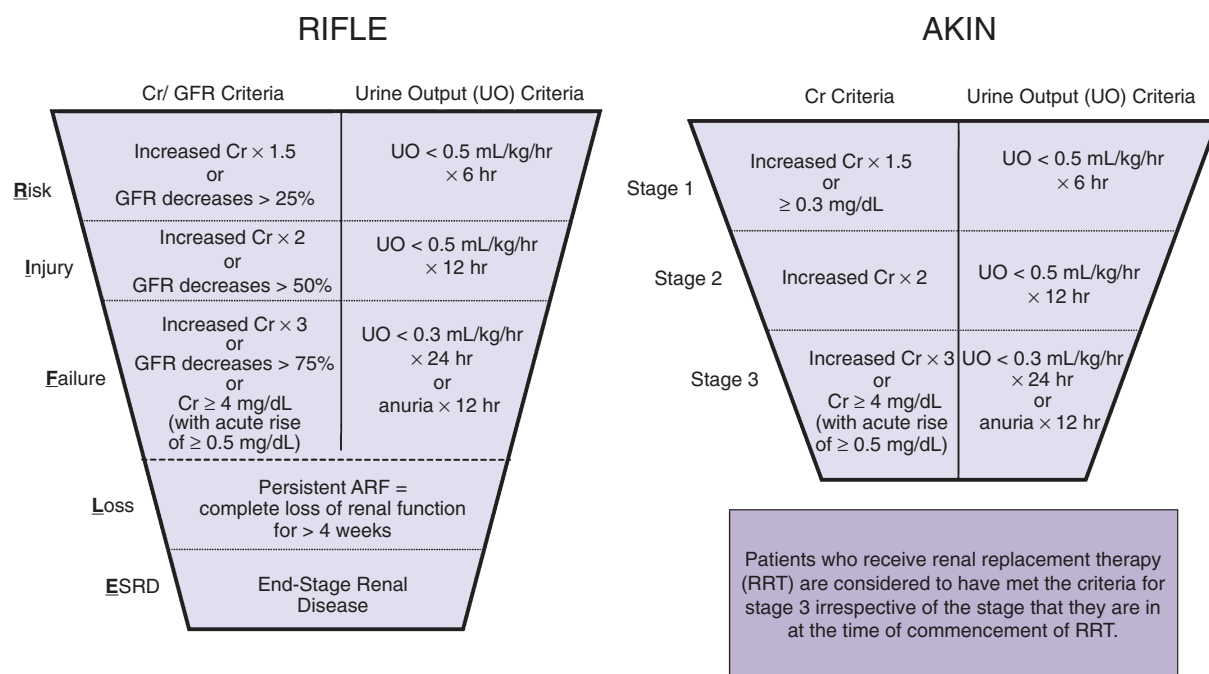


FIGURE 93-1 ■ The RIFLE and AKIN classifications for acute kidney injury. AKIN, Acute Kidney Injury Network; RIFLE, risk, injury, failure, loss of kidney function, and end-stage kidney disease. (From Critical Care 2009, 13:211. doi:10.1186/cc7759; and found on the website <http://www.ccforum.com/content/13/3/211>.)

the diagnostic criteria of HRS-1. The dominant clinical feature is severe ascites with poor or no response to diuretics. Patients with HRS-2 are especially predisposed to develop HRS-1 after precipitating events.⁴⁰⁻⁴² The median survival of patients with HRS-2 is 6 months, which is worse than patients with nonazotemic cirrhosis with ascites.

TREATMENT

Goals of therapy include improvement of liver function as in the recovery of alcoholic hepatitis, treatment of decompensated hepatitis B,⁴³ or medical therapy including pharmacotherapeutics and renal replacement therapy (RRT) as a bridge to either liver transplantation or simultaneous liver-kidney transplantation (SLK). To date, no single therapeutic agent has been found to permanently reverse HRS. Dopamine, fenoldopam, endothelin antagonists, natriuretic peptides, and angiotensin-converting enzyme inhibitors have been shown to either have no benefit or worsen the outcome of HRS.⁴⁴

Liver Transplantation

Liver transplantation is the treatment of choice for HRS.⁴⁵⁻⁴⁹ Immediately after transplantation, further impairment in GFR may be observed with the need for RRT.⁴⁵ Delay in the administration of nephrotoxic medications for 48 to 72 hours after transplantation may be considered.⁵⁰ GFR improves by 1 to 2 months postoperatively, but a moderate level of renal dysfunction persists and is more marked than in patients without HRS.³⁴ The hemodynamic and neurohormonal abnormalities associated with HRS usually resolve within the first month. However, not all patients exhibit renal recovery. Predictors of an HRS-1 reversal following liver transplantation are younger age, lack of chronic kidney disease (CKD), shorter durations of HRS and pretransplant dialysis, and lower preoperative creatinine.⁵¹ There is heterogeneity in the results of studies examining renal recovery post transplant, with results ranging from 58% to 100%.^{52,53}

Patients with HRS, who undergo transplantation have more complications, longer intensive care unit stay, and higher in-hospital

mortality rates.⁴⁵⁻⁴⁹ The 3-year probability of survival is 60%,⁴⁵⁻⁴⁹ which is only slightly less than that for liver transplant recipients without HRS.

SLK

SLK transplant is an option for patients at risk for nonrecovery. SLK should be used only for those who have irreversible kidney injury.^{54,55} At this time, however, renal recovery remains difficult to predict. The Organ Procurement and Transplantation Network (OPTN) liver and intestine committee and kidney committee proposed listing criteria for SLK candidate selection and allocation. Limitations include the definition of AKI, GFR determination, and timing of initiation and duration of dialysis.³⁹ Whereas some studies suggest that patients on RRT for more than 8 to 12 weeks have improved survival with SLK compared to liver transplant alone, there is significant variability.^{55,56,57} The consensus panel suggested liver transplantation alone in patients with HRS for less than 4 weeks.

Volume Expansion and Vasoconstrictors

Vasoconstrictors and volume expansion to increase splanchnic vasoconstriction and improve circulating volume may be the most promising medical approach for HRS. Over the past decade, many small studies have evaluated vasoconstrictors with and without a volume expander.

Volume administration, particularly with albumin, is an important tenet of therapy, with several studies showing that vasopressors alone are not as effective. It is important to avoid fluid overload. Assessment of intravascular volume is challenging, with physical exam findings or static measurements of filling pressures having poor accuracy in predicting a response to a fluid bolus.⁵⁸ The choice of fluid remains controversial,⁵⁹ although a consensus panel recommended albumin. The recommended albumin dose is 1 g of albumin/kg for 2 days, up to a maximum of 100 g/d followed by 20 to 40 g/d.³⁹ "Chloride liberal" fluid administration may be associated with AKI in critically

therapy increased the probability of reversal. Treatment with terlipressin and albumin may be associated with a survival benefit when including studies other than just placebo control studies.⁶⁴

The dose ranges used vary from 1 to 2 mg every 4 to 6 hours. Incremental increases in dosing while monitoring creatinine have been proposed.⁶⁷ A maximal dose of 12 mg/d with minimum duration of 3 to 5 days has been proposed.⁶² There are variable data on the rates of recurrence after discontinuation of therapy, ranging from 5.3% to 50%.^{69,44,62}

α -adrenergic agonists also have been used to augment renal perfusion. Duvoux⁷⁰ treated 12 patients with HRS-1 with intravenous (IV) albumin and norepinephrine. A significant improvement in serum creatinine was observed in 10 patients. Two RCTs compared norepinephrine to terlipressin.^{71,72} In the first study, reversal of HRS occurred in 70% of the patients in the norepinephrine group versus 83% in the terlipressin group. In the second study, norepinephrine was effective in increasing MAP, urine output, and decreasing creatinine. A recent meta-analysis found that norepinephrine is as effective as terlipressin when used in conjunction with albumin and that it appears to be associated with fewer adverse events.⁷³ Until recently, there has been scant evidence in the treatment of HRS-2. A recent RCT by Ghosh found that both terlipressin and norepinephrine are safe and effective with response rates of 74%.⁷⁴

Treatment with norepinephrine is limited to inpatient settings. Angeli⁷⁵ used oral midodrine, a α -adrenergic agonist, IV albumin, and subcutaneous octreotide in five patients with HRS-1. In all cases, there was a dramatic improvement in renal perfusion, GFR, serum blood urea nitrogen, creatinine, and sodium. Esrailian⁷⁶ retrospectively evaluated 60 patients, comparing midodrine plus octreotide to untreated controls. Patients in the treatment arm had an improvement in renal function and increased survival. In a prospective observational study with historical controls, Skagen et al.⁷⁷ studied midodrine and octreotide in patients with HRS-1 and HRS-2. Treatment was associated with an improvement in GFR and an increase in median survival. Studies of monotherapy of octreotide have not shown a benefit over placebo. The combination of midodrine plus octreotide is a promising regimen for HRS-2 as outpatients.

Recent research has focused on identifying predictors of treatment efficacy with vasoconstrictors. A change in MAP during treatment was the sole independent predictor of patient survival.⁷⁸ An increase in MAP of more than 10 mm Hg was associated with better overall survival with no further improvement despite higher targets. A treat to the target concept by the use of a specific MAP goal may potentially guide management.

In summary, these studies show the following:

1. HRS-1 can be reversible with IV albumin and vasoconstrictors.
2. Both components of the treatment are important.
3. Infusion of vasoconstrictors is associated with ischemic complications.
4. There is a delay between improvement in circulatory function and an increase in GFR.
5. Reversal of HRS improves survival, with a significant number surviving to transplantation.

Transjugular Intrahepatic Portosystemic Shunt

Decreasing portal pressure by portosystemic anastomosis to improve the circulatory compromise of cirrhosis has been targeted as a treatment for HRS. Case reports show that HRS can be reversed after a surgical portosystemic shunt.^{79,80}

Transjugular intrahepatic portosystemic shunt (TIPS) in the management of HRS-1 has been evaluated in small-scale studies and may

be of benefit in conjunction with vasopressors.⁸¹⁻⁸³ In one study of patients with HRS-1 who were not candidates for transplantation, it was found that the survival rates at 3, 6, and 12 months after TIPS were 54%, 50%, and 20%, respectively.⁸¹ TIPS may be beneficial in patients with HRS-2 with refractory ascites, with improvements in renal function without improved survival.⁸⁴ A more recent meta-analysis by Salerno, however, found TIPS significantly improved transplant-free survival of patients with cirrhosis and refractory ascites. Further research is needed to define the role of TIPS in the treatment of HRS.⁸⁵

Other Therapeutic Methods

Hemodialysis and arteriovenous or venovenous hemofiltration are a frequent bridge to liver transplantation or for treating an acute but reversible decompensation.⁸⁶ Continuous RRT is often selected in hemodynamically unstable patients, but there are no published studies that allow for evidence-based guidelines on one modality over the other.⁸⁷ Given that the prognosis of HRS-1 is poor without transplantation, strong consideration should be had for withholding RRT in patients who are not liver transplant candidates. These decisions should be made within the context of the patient's goals of care and involve shared decision making.

Noncell-based extracorporeal support systems are available that perform detoxifying functions of the liver. One such noncell-based support system uses an albumin-containing dialysate that is recirculated and perfused through charcoal and anion-exchanger columns. This modality has been shown to improve hemodynamics and reduce plasma renin in patients with HRS-1.^{88,89} In a small series of patients, improved survival was reported.⁹⁰ Modalities such as the Prometheus system and single-pass albumin dialysis have been used in a few patients with some success.^{91,92} However, further studies are needed in this area.

PREVENTION

Preventing precipitating factors, such as infections and acute alcoholic hepatitis, may decrease the incidence of HRS-1. Three randomized controlled studies enrolling a large series of patients have shown that HRS can be prevented in specific clinical settings. In the first study,⁹³ albumin together with cefotaxime was compared to cefotaxime alone in patients with SBP. Treatment with albumin markedly reduced the incidence of impaired circulatory function and the occurrence of HRS-1. The second study showed that oral prophylaxis using norfloxacin decreased the 1-year probability of developing SBP and HRS-1 and improved survival.⁹⁴ In a third study,⁹⁴ administration of the tumor necrosis factor synthesis inhibitor pentoxifylline to patients with severe acute alcoholic hepatitis reduced the occurrence of HRS (8% vs. 35%) and hospital mortality (24% vs. 46%).

CONCLUSION

The pathophysiology of HRS is characterized by intense vasoconstriction with splanchnic arterial vasodilation. HRS-1 is characterized by rapid and progressive deterioration of circulatory and renal function. It often develops following a precipitating event and carries a very poor prognosis (median survival rate <2 weeks). HRS-2 is characterized by steady deterioration of circulatory and renal function with refractory ascites. Patients with HRS-2 have a median survival of 6 months. The administration of albumin plus a vasoconstrictor is an effective treatment for HRS. These approaches may improve survival and may serve as a bridge to liver transplantation, which is the treatment of choice for these patients.

KEY POINTS

1. Portal hypertension leads to the production of vasodilators causing splanchnic vasodilation. This leads to activation of the renin-angiotensin-aldosterone system as well as the sympathetic nervous system, which causes renal vasoconstriction. Decreased renal perfusion due to an imbalance between extremely high vasoconstrictor tone and the decreased production of renal vasodilators leads to HRS.
2. Criteria of the International Ascites Club define HRS (see [Table 93-1](#)) as levels of creatinine above 1.5 mg/dL in the absence of other potential causes of renal failure.
3. HRS is classified into two types:
 - a. Type 1: severe and rapidly progressive renal failure, usually following a precipitating event, with a median survival of 2 weeks.
 - b. Type 2: moderate and steady development of renal failure, clinically characterized by refractory ascites, with a median survival of 6 months.
4. Liver transplantation is the treatment of choice for HRS. The recovery of renal function neurohumoral physiology may take 1 month.
5. The 3-year probability of survival in transplanted patients with HRS is 60%.
6. HRS-1 may be reversible after treatment with intravenous albumin and vasoconstrictors.
7. Successful prevention of HRS has been achieved in the setting of spontaneous bacterial peritonitis and acute alcoholic hepatitis.

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DEFINITION

Hepatopulmonary syndrome (HPS) is defined by abnormal oxygen exchange in association with intrapulmonary vascular dilatation (IPVD) in patients with liver disease.¹ The presence of another cardiopulmonary disease that alters gas exchange does not exclude this diagnosis.²⁻⁵ HPS is most commonly associated with cirrhosis¹ and portal hypertension, but neither of these is required.⁶ The correlation between the degree of liver dysfunction and the presence^{7,8} and severity^{3,4,7,9,10} of this syndrome is debated.

CLINICAL FEATURES

HPS usually presents as dyspnea^{6,11} in patients who are already known to have liver disease. HPS-induced shortness of breath often is relieved when the patient is lying down (platypnea).^{11,12} There are no consistently noted physical examination findings.^{6,13} Hypoxia is often worse in the standing position (orthodeoxia),¹² and it generally can be corrected with sufficient supplemental oxygen.^{1,3,4,10,14}

PATHOPHYSIOLOGY

Dilated precapillary vessels and pleural-based arteriovenous (AV) connections are noted at autopsy in cases of HPS.¹⁵ Current thinking suggests that these abnormal vessels develop due to an excess of pulmonary vasodilators,¹ which cause hypoxia through ventilation/perfusion (V/Q) mismatching, AV shunting, and the limitation of oxygen diffusion to red blood cells (RBCs) in the center of the vessel.¹⁵⁻¹⁷ The hyperdynamic circulation, which is characteristic of cirrhosis, exacerbates this problem by decreasing RBC transit time through the pulmonary capillaries, further limiting oxygen diffusion.^{15,17} Orthodeoxia is due to a worsening of V/Q mismatch and AV shunting in the standing position.¹⁸

Nitric oxide (NO) has been implicated as a key vasodilator in HPS. Exhaled NO levels are elevated in patients with cirrhosis compared to healthy controls and in HPS patients compared to cirrhotic patients without HPS. NO levels correlate with the severity of cirrhosis and gas exchange abnormalities.¹⁹ In rat models of HPS induced by common bile duct ligation (CBDL), increased levels of endothelial²⁰ and inducible NO synthase (eNOS and iNOS) have been observed, and the administration of a NO synthase inhibitor prevents the development of pulmonary vasodilation and HPS.²¹

Excess eNOS, located in the pulmonary arteries and capillaries, is associated with impaired vasoconstriction. Levels of this enzyme correlate with the degree of gas exchange abnormalities.²⁰ CBDL rats demonstrate increased hepatic production of endothelin-1 (ET-1)²² and increased vascular expression of the endothelin-B receptor (ET-B)²³ in proportion to the severity of gas exchange abnormalities.^{22,24} Interaction between the ET-1 and the ET-B receptor is believed to be the trigger for increased eNOS expression. This theory is supported by data that show a reduction in eNOS expression and an improvement in HPS when CBDL animals are treated with ET-B receptor antagonists.²⁴

iNOS is expressed in macrophages found in the lungs of CBDL rats,²¹ while treatment with norfloxacin is associated with a reduction in the rate of gram-negative bacterial translocation, accumulation of pulmonary macrophages, production of iNOS, and severity of HPS.²⁵

Pulmonary macrophages in CBDL rats also express elevated levels of heme-oxygenase-1 (HO-1), an enzyme that catalyzes the formation of the vasodilating gas and carbon monoxide (CO).²⁶ Increased levels of carboxyhemoglobin (COHb) have been observed in rat²⁶ and human²⁷ subjects with HPS, and treatment with an HO-1 inhibitor normalizes COHb levels and partially alleviates HPS in CBDL rats.²⁶ These data suggest that CO also contributes to pulmonary vasodilation in HPS.

Tumor necrosis factor alpha (TNF- α) rises in CBDL rats in association with ET-1 and endotoxin levels, and it has been proposed to influence the accumulation of the iNOS and HO-1-producing pulmonary macrophages.²⁸ Administration of pentoxifylline, a phosphodiesterase inhibitor that suppresses the production of TNF- α , is associated with a reduction in pulmonary macrophage accumulation, ET-B receptor and eNOS expression, and the severity of HPS.²⁹

More recently, ET-1 and ET-B receptor activation have been shown to increase pulmonary intravascular monocyte adherence through the monocyte chemokine, fractalkine.^{30,31} Fractalkine promotes angiogenesis directly and through monocyte secretion of vascular endothelial growth factor-A.³¹ Angiogenesis is emerging as an important feature in experimental models of HPS and may provide new therapeutic targets, as well as explain the delay in the resolution of hypoxia in patients post-transplantation.

DIAGNOSIS

HPS should be considered in any patient with liver disease and dyspnea or hypoxia. Evaluation begins with arterial blood gas (ABG), with the patient seated, resting, and breathing room air.^{6,17} Further evaluation is recommended when the PaO₂ is less than 80 mm Hg or the alveolar-arterial oxygen gradient (A-a gradient) is 15 mm Hg or greater (≥ 20 mm Hg for patients over age 64 years).¹⁷

HPS diagnosis requires the presence of ABG changes that cannot be fully explained by comorbid cardiopulmonary disease. Conditions frequently coexisting with cirrhosis that may influence gas exchange include chronic obstructive pulmonary disease, congestive heart failure, restrictive lung disease due to ascites or hepatic hydrothorax, α_1 -antitrypsin deficiency, and portopulmonary hypertension (distinguished from HPS by its increased pulmonary artery pressure and vascular resistance).³² Patients should have a chest x-ray (CXR) and pulmonary function tests¹² to assess for pulmonary disease. Of note, increased markings at the lung base on CXR^{1,6,8} and the reduced diffusion capacity for CO (DLCO)^{3,4,7,13,18} are common findings in HPS and in isolation, do not exclude the diagnosis. An echocardiogram evaluates cardiac function, often concurrently with IPVD assessment (see later discussion).

When a gas exchange abnormality is present and not fully explained by another cardiopulmonary disease, the patient should be evaluated for the presence of IPVDs. Contrast-enhanced echocardiography (CEE) is commonly used for this purpose as it is widely available and it permits concurrent evaluation for cardiac causes of abnormal gas exchange.¹² Agitated saline is used as a contrast media which creates a stream of microbubbles after injection. In healthy subjects, these microbubbles opacify the right heart only as they are filtered through the pulmonary capillary bed due to their size (greater than 15 μ m in diameter).^{9,33} Intracardiac shunts can be distinguished from

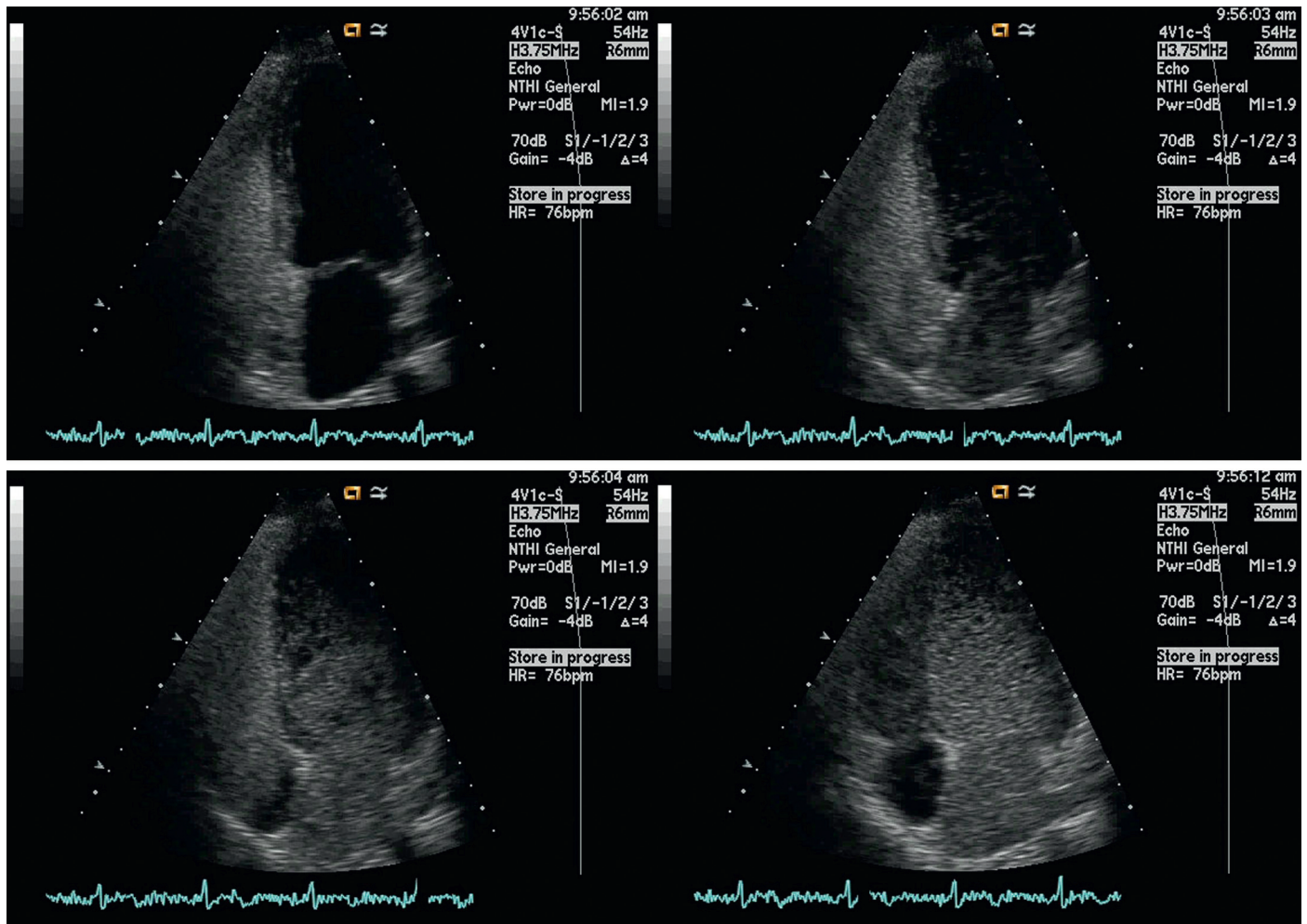


FIGURE 94-1 ■ Photos of contrast-enhanced echocardiography. Top left: Agitated saline enters the right ventricle. Top right: Saline enters the left atrium posteriorly. Bottom left: Saline density is equal in the right and left ventricles. Bottom right: Saline density in the left ventricle exceeds the right ventricle after multiple cardiac cycles. (Photos courtesy of Karl Q. Schwarz, MD. University of Rochester Medical Center, Rochester, NY.)

intrapulmonary shunts based on the number of cardiac cycles required for agitated saline to pass from the right to the left atrium in the apical four-chamber view (Fig. 94-1). In general, contrast appears in the left atrium within three cycles in intracardiac shunts while it takes 4-6 cycles in intrapulmonary shunts.^{9,33} CEE is highly sensitive for evaluation of IPVDs³⁴ and may document them in up to 82% of patients tested.³³ Patients with a positive CEE have a greater incidence of dyspnea³⁵ and abnormal CXRs,^{9,35} as well as more severe cirrhosis^{9,33,35} and gas exchange abnormalities.^{9,35} However, many patients with IPVDs demonstrated by CEE do not have gas exchange abnormalities,^{5,8,13,33,35} and so this test is not specific for HPS.³⁴

Technetium-99m-labeled macroaggregated albumin (MAA) perfusion lung scanning is an alternative test for IPVDs. It is expensive, requires radiation exposure,¹³ and cannot document the site of shunting. However, it can provide a quantitative shunt fraction^{13,17,34} that correlates directly with the A-a gradient^{3,10,14} and inversely with the room air PaO₂ and oxygen saturation.^{3,10,14,36} Perfusion scanning is less sensitive than CEE for IPVD detection but more specific.^{5,10,36} These test characteristics have enabled CEE to be advocated as the first line for evaluating patients with liver disease and abnormal gas exchange.^{5,10,17} If CEE is positive but the relative contributions of other cardiopulmonary disease and HPS are not clear, perfusion lung scanning can determine if HPS is present.^{5,10,12,17}

PREVALENCE

The reported prevalence of HPS varies greatly depending on which diagnostic criteria are used. Using currently recommended criteria, (elevated A-a gradient and positive CEE) 8%-33% of patients being evaluated for liver transplant have HPS.^{8,9,37}

PROGNOSIS

In the absence of liver transplantation, patients with HPS have a poorer functional status, reduced self-reported quality of life,⁸ and a worse survival^{7,8,38} than non-HPS controls matched for severity of liver disease. HPS patients who die during follow-up have been noted to have greater room air PaO₂ reductions, A-a gradient elevations, and shunt fractions than those who survive,^{3,7,38} but this is not a universal finding.⁸ Without a transplant, HPS patients demonstrate progressive hypoxemia.³⁸ Despite this, death is usually due to complications of liver disease^{7,17,38} rather than primary respiratory failure.³⁸

THERAPY

Liver transplantation is the only definitive therapy for HPS and should be considered when patients are symptomatic or have a

$\text{PaO}_2 \leq 60$ mm Hg.^{6,17} Multiple therapies have been tried for HPS without clear efficacy, including inhibitors of NO,³⁹⁻⁴¹ antibiotics,⁴² pentoxifylline,^{29,43,44} mycophenolate mofetil,⁴⁵ transjugular intrahepatic portosystemic shunt,^{12,46} and pulmonary angiography with embolization of dilated capillaries⁴⁷ or AV communications.⁴⁸ Oxygen therapy also has been recommended, although clinical benefit has not been confirmed.^{1,6,11,12,17,37}

Owing to the increased mortality associated with HPS and the lack of other effective therapies, the United Network for Organ Sharing (UNOS) has adjusted organ allocation algorithms to prioritize patients with HPS and a $\text{PaO}_2 \leq 60$ mm Hg.^{49,50} Compared to earlier case series

showing increased posttransplant mortality in HPS,¹⁴ patients who receive these model for end-stage liver disease (MELD) exception points have better pretransplant survival than those without HPS and similar posttransplant outcomes.^{49,50} Also in contrast to prior reports, the largest single-center HPS transplant study found no difference in posttransplant outcomes in patients with very severe hypoxia ($\text{PaO}_2 < 50$ mm Hg),⁵⁰ while an analysis of the UNOS database demonstrated increased mortality in patients with a $\text{PaO}_2 \leq 44$ mm Hg.⁴⁹ Among those patients who survive the perioperative period, improvement in or resolution of HPS is noted in the majority of cases, although the amelioration of symptoms may require a year or more to occur.^{4,14,38}

KEY POINTS

1. Hepatopulmonary syndrome (HPS) consists of a triad of liver disease, abnormal pulmonary gas exchange, and intrapulmonary vascular dilatation. It most commonly presents as dyspnea or hypoxia in patients already known to have liver disease.
2. HPS is believed to result from excessive pulmonary vasodilation. Pulmonary vasodilatation leads to hypoxia through ventilation/perfusion mismatching, arteriovenous shunting, and limitations to oxygen diffusion.
3. Diagnosis of HPS requires a seated, room air, arterial blood gas to document abnormal gas exchange, as well as confirmation of an intrapulmonary shunt using echo or lung perfusion scanning. Prevalence of HPS is thought to be 8%-33% in patients undergoing evaluation for liver transplantation.
4. Patients with liver disease and HPS have an increased risk of death relative to patients with liver disease alone. Liver transplantation is the only effective therapy and improves or resolves HPS in most cases. Transplant evaluation should be pursued in patients with HPS who are symptomatic or have a seated room air PaO_2 less than 60 mm Hg.

■ References for this chapter can be found at expertconsult.com.

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Hepatic encephalopathy encompasses a spectrum of neuropsychiatric abnormalities that occur in patients with liver disease in the absence of other brain disease.^{1,2} The spectrum includes personality changes, impaired mental function, motor abnormalities (i.e., asterixis, tremors, hyperventilation, hyperactive reflexes), and altered consciousness. A consensus panel of experts has proposed the classification of hepatic encephalopathy into *type A*, associated with acute liver failure; *type B*, associated with portosystemic bypass without intrinsic liver disease; and *type C*, associated with chronic liver disease.³

The encephalopathy accompanying acute liver failure (*type A*) is commonly associated with cerebral edema and increased intracranial pressure (ICP), exhibits an abrupt onset with a short prodrome and rapid progression, and often ends with the death of the patient.^{4,5} Patients sequentially experience drowsiness, delirium, agitation or convulsions, decerebrate rigidity, unresponsiveness, and deep coma within a comparatively short period of time, usually hours to days. Irreversible neurologic damage may occur as a result of brain ischemia or herniation. Patients who develop coma in the setting of acute liver failure have a grave prognosis; fewer than 20% survive without hepatic transplantation.⁶

In patients with chronic liver disease, encephalopathy (*type C*) develops insidiously and is often heralded by a change in mental or behavioral status. Encephalopathy may be episodic, persistent, or minimal and subclinical.³ Episodes are sporadic, characterized by exacerbations and remissions, and are generally precipitated by inciting events.¹⁻² Although the initial manifestation of portosystemic encephalopathy (PSE) is usually a subtle change in mentation, neurologic dysfunction may progress and be classified according to confusion, lethargy, and even coma (Table 95-1). Neurologic signs vary and fluctuate but usually include asterixis, hyperreflexia, clonus, and an extensor plantar response. Causes of PSE may not always be apparent but should always be investigated (Box 95-1). In some patients, minimal encephalopathy may not be clinically obvious but only detectable by psychometric testing. By these tests, about two-thirds of cirrhotic patients with portal hypertension have unsuspected minimal hepatic encephalopathy.⁷⁻⁹ Patients who undergo portosystemic shunt or bypass procedures, either surgical or transjugular intrahepatic portosystemic shunt (TIPS), often develop encephalopathy (*type B*) which is similar to the encephalopathy experienced by patients with chronic liver disease.

■ GENERAL PRINCIPLES

No single abnormality of hepatic or neurologic metabolism adequately explains all of the clinical, biochemical, physiologic, or experimental findings of encephalopathy occurring in patients or animal models.^{1-2,5} Abnormalities of multiple neurotransmitters including glutamate, γ -aminobutyric acid (GABA), dopamine, serotonin, and opioids have been described, as well as increased plasma levels of a wide array of potential neurotoxins (ammonia [NH_3], GABA, short-chain fatty acids, and methanethiols).^{10,11} Regardless of the mechanism(s) of hepatic encephalopathy, marked changes in central nervous system (CNS) glial cells are noted on neuropathologic examination in patients with hepatic encephalopathy. Encephalopathy associated with acute liver failure is typically characterized by astrocytic swelling, whereas

encephalopathy from chronic liver disease is characterized by Alzheimer type II astrocytosis.¹¹

Cerebral Blood Flow

In acute liver failure, the brain is potentially subject to hypoxic injury due to complications such as systemic arterial hypotension, respiratory failure, and a reduction in cerebral blood flow that accompanies cerebral edema and intracranial hypertension. Therapy is often directed at optimal oxygenation, maintenance of cerebral perfusion pressure (goal >40 mm Hg), and reduction of ICP (goal <20 mm Hg).^{4,7} Clinical data suggest that cerebral blood flow is relatively low initially but subsequently increases with increasing blood concentrations of NH_3 .¹²⁻¹⁵ Paradoxically, increases in cerebral blood flow may aggravate cerebral edema and worsen neurologic damage.

Cerebral Glucose and Oxygen Metabolism

Brain energy metabolism is unique in that glucose is the only substrate under normal physiologic conditions, and its uptake and utilization by the brain are independent of insulin.¹⁶⁻²⁰ Ammonia accumulation during hepatic failure in humans or in experimental models of hyperammonemia is associated with altered cerebral glucose metabolism. In early acute liver failure, prior to the onset of intracranial hypertension, cerebral glucose metabolism and oxygen consumption are proportionately diminished.¹⁶ There is no evidence of cerebral hypoxia, implying that reduced glucose and oxygen utilization reflects a diminished metabolic demand by the brain at this early stage. Thus, prior to the development of intracranial hypertension, cerebral glucose and oxygen metabolism are reduced, but these changes are consistent with normal aerobic metabolism and physiologic regulation. After the development of intracranial hypertension, oxygen metabolism remains reduced but measurements of cerebral glucose utilization vary from reduced rates to increased rates, and glycolysis may be accelerated.^{17,18,20} These findings suggest that the progression of acute liver failure and development of intracranial hypertension are associated with relative cerebral hypoxia and a switch to anaerobic metabolism.

Ammonia Hypothesis

The *ammonia hypothesis* states that the major mechanism of hepatic encephalopathy is excessive accumulation of NH_3 , which induces neuronal metabolic derangements and also promotes astrocytic swelling.²¹ In addition, NH_3 perturbs cerebral nitric oxide metabolism, which can mediate some of these effects.²² Blood NH_3 originates mainly from four sources: intrahepatic deamination of amino acids, extrahepatic metabolism of nucleotides, gut metabolism of glutamine, and bacterial degradation of intestinal protein and urea.²³ More than 50% of blood NH_3 is derived from the latter source.

NH_3 is normally metabolized by the liver to either urea or glutamine by the actions of carbamoyl-phosphate synthetase I and glutamine synthetase, respectively. Patients with hepatic failure have impaired NH_3 metabolism related to a reduction in liver metabolism and an increase in portosystemic shunting. As a result, an elevation in blood NH_3 concentration is a characteristic feature of severely impaired hepatic function. Certain clinical and experimental

TABLE 95-1

Stages of Encephalopathy in Chronic Liver Disease (West Haven Criteria)

| STAGE | CLINICAL SIGNS |
|-----------|---|
| Stage I | Mental slowness, euphoria or anxiety, shortened attention span, impaired calculating ability |
| Stage II | Lethargy or apathy, inappropriate behavior, personality change, more obvious problems with calculations |
| Stage III | Lethargic, somnolent, marked confusion and disorientation, but responds to verbal stimuli |
| Stage IV | Coma, patient may or may not respond to noxious stimuli |

Patients with chronic liver disease rarely, if ever, demonstrate cerebral edema, regardless of the stage of encephalopathy.

BOX 95-1

Clinical Events Precipitating Hepatic Encephalopathy in Patients with Cirrhosis

Gastrointestinal hemorrhage
 Infection (including spontaneous bacterial peritonitis)
 Sepsis
 Dehydration
 Imbalance of electrolytes or acid-base
 Renal failure
 Drugs, toxins, medications (especially sedative-hypnotics or narcotics)
 Illicit substances
 Alcohol
 Dietary indiscretion (excessive protein intake)

observations link the increase in blood, particularly arterial, NH_3 concentration to hepatic encephalopathy.^{10,11,24,25} Hyperammonemia and elevated concentrations of NH_3 within the cerebrospinal fluid (CSF) are features of acute and chronic hepatic encephalopathy, Reye syndrome, deficiencies of urea cycle enzymes, and sodium valproate toxicity. In patients with cirrhosis or portosystemic shunts, ingestion of NH_3 -generating substances (proteins, amino acids, urea, ammonium salts) may precipitate encephalopathy. In animal models, chronic administration of ammonium salts results in Alzheimer type II astrocytosis, a change indistinguishable from that observed in patients with chronic hepatic encephalopathy.¹¹

Further support for the ammonia hypothesis originates from the clinical benefits of several medications. Production of NH_3 from the intestine is reduced by orally administered nonabsorbable antibiotics such as rifaximin and neomycin, as well as nonabsorbable disaccharides including lactulose, lactitol, and lactose (in lactase-deficient patients). These treatments lower plasma NH_3 concentration and improve subjective and objective measures of encephalopathy.

Other clinical and experimental observations refute the link between NH_3 and hepatic encephalopathy. Blood levels of NH_3 are elevated in patients with cirrhosis regardless of the presence or absence of encephalopathy. Furthermore, some patients with hepatic encephalopathy have normal blood levels of NH_3 . The grade of hepatic encephalopathy does not correlate with the blood concentration of NH_3 . Seizures and hyperexcitability are commonly observed in animal models of NH_3 intoxication and in human congenital hyperammonemia but are rarely observed in patients with chronic hepatic encephalopathy.

Other Potential Hypotheses for Hepatic Encephalopathy

The glutamine-glutamatergic neurotransmitter system has been implicated in the pathogenesis of hepatic encephalopathy because the

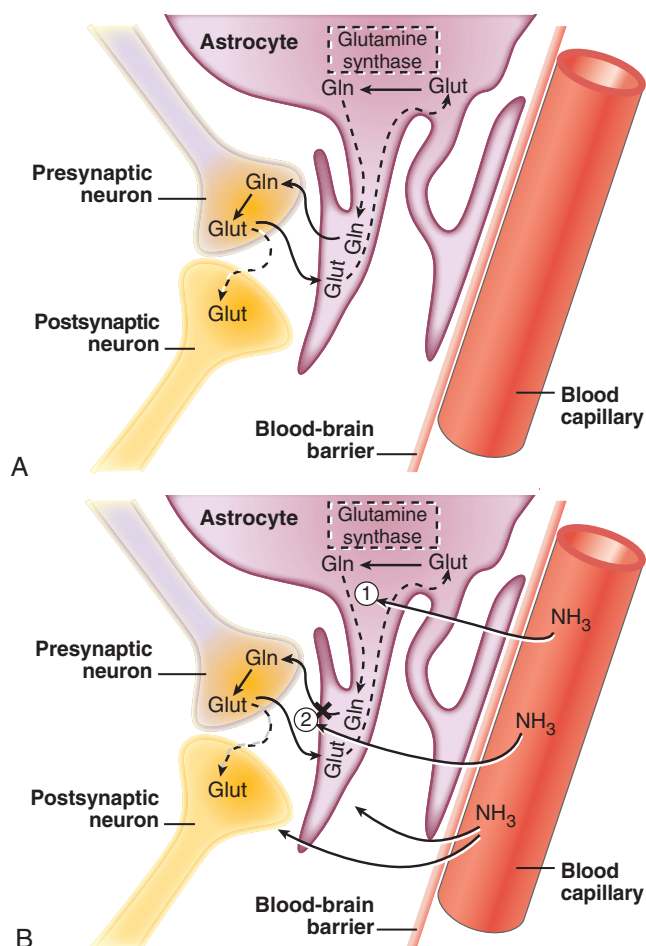


FIGURE 95-1 ■ (A) Glutamine forms predominantly in the astrocyte, is pumped out, and taken up by presynaptic neurons where it is converted to glutamate. Nerve stimulation releases glutamate from the presynaptic neuron to serve as an excitatory neurotransmitter. Astrocytes avidly take up glutamate from the synaptic cleft to abolish neuronal stimulation. (B) Ammonia freely diffuses across the blood-brain barrier and stimulates formation of glutamine by the astrocyte via the action of glutamine synthetase (1). Ammonia also blocks the export of glutamine from the astrocyte at the synaptic cleft (2). The net effect of these two actions is increased concentration of glutamine within astrocytes, which promotes astrocyte swelling.

glutamatergic excitatory neurotransmitter system in the CNS is markedly altered in patients with both acute and chronic liver disease and in animal models of hepatic encephalopathy.^{6,21,22} CNS astrocytes are a major regulatory cell in the glutamatergic system and are responsible for the termination of glutamate-induced excitation.¹¹ When glutamate is taken up by the astrocyte, it is metabolized to glutamine via the action of glutamine synthetase, which utilizes blood-derived NH_3 (Fig. 95-1). The hyperammonemia of liver failure favors the formation of glutamine but also impairs the release of glutamine from the astrocyte. The accumulation of osmotically active glutamine in the astrocyte is associated with cell swelling and can lead to accumulation of glutamate in the extracellular fluid. Clinically, levels of glutamine and glutamate increase in CSF fluid during hyperammonemic states, and CSF concentrations of glutamine correlate loosely with the stage of encephalopathy.

The γ -aminobutyric acid (GABA)-benzodiazepine receptor hypothesis is another important mechanism that likely plays a role in hepatic encephalopathy. GABA is an inhibitory neurotransmitter found throughout the CNS.²⁶ The *GABA hypothesis* states that an excess of

GABA or increased sensitivity of GABA receptors to neurosteroids is responsible for hepatic encephalopathy.^{26,27} GABA originates from the intestine, and plasma levels increase in hepatic failure due to inadequate hepatic extraction. During acute liver failure, the blood-brain barrier (BBB) becomes more permeable and increased amounts of GABA enter the CNS. Once in the brain, GABA binds to its receptor to produce neuroinhibition and clinical encephalopathy. A key component to understanding the relationship of GABA and benzodiazepines was the recognition that the GABA receptor was tightly linked to and modulated by the benzodiazepine receptor.²⁷⁻³¹ The *GABA hypothesis* predicts that benzodiazepines would increase the severity of hepatic encephalopathy and that benzodiazepine antagonists such as flumazenil might ameliorate hepatic encephalopathy. Clinical experience suggests that cirrhotic patients, especially those with encephalopathy, are particularly sensitive to the amnesic and sedative effects of benzodiazepines. In our experience, use of benzodiazepines and other sedative/hypnotics is a common cause of exacerbations of hepatic encephalopathy. Recent studies have demonstrated that patients with hepatic encephalopathy have increased plasma levels of benzodiazepines or “natural” benzodiazepine-like compounds that may act as “false neurotransmitters.”^{32,33}

Previously Studied Agents Associated With Hepatic Encephalopathy

Numerous clinical studies have found alterations in levels of other agents or pathways in patients with hepatic encephalopathy. These agents or pathways include the dopaminergic and serotonergic systems, taurine, methanethiols, short-chain fatty acids, manganese, and zinc. However, conclusive evidence to support or refute their association with hepatic encephalopathy is lacking, and clinical and bench research of these agents as causative or therapeutic targets has been abandoned for over a decade.

ENCEPHALOPATHY IN THE SETTING OF ACUTE LIVER FAILURE

Definition

Acute liver failure, also referred to as *fulminant hepatic failure*, is defined by the development of coagulopathy (prothrombin time [PT] >20 seconds prolonged with an international normalized ratio [INR] >1.5) and hepatic encephalopathy in a patient with acute hepatitis who lacks underlying chronic liver disease (except in Wilson's disease).³⁴⁻³⁷ Patients with acute liver failure usually have extreme elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with the initial injury (e.g., 1000 to 5000 IU/L), are often jaundiced, and exhibit constitutional symptoms. They are at risk of encephalopathy, although most recover uneventfully. Progressive hepatic encephalopathy is a poor prognostic sign and signals the need for hepatic transplantation.

Prognosis

A major determinant of prognosis is the level of encephalopathy (see Table 95-1). Patients with acute liver failure who have progressed to higher stages of encephalopathy (i.e., stage III or IV) have the worst prognosis. The King's College Criteria or Glasgow Coma Scale are useful in assessing the need for transplantation.^{36,38} Cerebral edema on computed tomography (CT) scan of the brain is a late feature of progressive encephalopathy (Fig. 95-2). Additional clinical features that indicate a poor prognosis include metabolic acidosis, renal failure, severe jaundice, or markedly prolonged prothrombin time.³⁸⁻⁴¹

General Clinical Management

Once recognized, patients with acute liver injury and encephalopathy should be transferred to a center with expertise in managing acute liver



FIGURE 95-2 ■ Magnetic resonance image (MRI) of a T₁-weighted sagittal view of the brain demonstrating hyperintensity of the globus pallidus (whitish area indicated by arrow) that may be related to manganese deposition.

failure so that liver transplantation can be offered if indicated. Further recommendations on intensive care management of the patient with acute liver failure is beyond the scope of this chapter but is addressed elsewhere (see Chapter 96).

USE OF INTRACRANIAL PRESSURE MONITORING

Advantages

The use of intracranial pressure (ICP) monitoring in the management of high-grade encephalopathy (i.e., stage III or IV) in acute liver failure remains controversial. Several studies advocate ICP monitoring for its ability to provide important prognostic information about neurologic recovery after hepatic transplantation and in managing intracranial hypertension (ICH) while awaiting liver transplantation.⁴² Therefore, ICP monitoring could be considered for patients with high-grade encephalopathy who are on the transplant wait list. Also, centers could consider ICP monitoring in nontransplant candidates if there is a reasonable likelihood of spontaneous recovery, such as in acetaminophen-induced acute liver failure. In addition to helping with the management of ICH, ICP monitoring assists with close monitoring during the crucial perioperative period of liver transplantation, since it has been found that there is a transient increase in ICP that can last for about 12 hours postoperatively after dissection of the native liver and reperfusion of the graft.³⁷

Disadvantages

However, the use of ICP monitoring may lead to severe complications such as intracranial hemorrhage in these already critically ill patients with coagulopathy. In addition, several nonrandomized studies have failed to demonstrate an improvement in survival with the use of ICP monitoring.⁴² One prospective study of 92 patients with acute liver failure, high-grade encephalopathy, and ICP monitoring found a 10.3% rate of intracranial hemorrhage that likely contributed to the death of two patients.⁴² However, nearly half of the cases of intracranial bleeding were incidental radiographic findings without clinical consequence. Regardless of ICP monitor usage, 30-day survival post transplant was approximately 85%. Other reports confirm that bleeding complications

from the placement of ICP monitoring devices in patients with acute liver failure are mostly mild and without clinical significance.^{42,43} One study demonstrated the effectiveness of recombinant factor VIIa in preventing intracranial bleeding in 11 patients with acute liver failure who required ICP monitoring.⁴⁴ Overall, use of ICP monitoring remains controversial, but experts agree that these devices should not be used in patients with mild hepatic encephalopathy (i.e., stage I or II) or in patients with evidence of cerebral herniation, hypotension, or imminent death.

MANAGEMENT OF ENCEPHALOPATHY AND INTRACRANIAL HYPERTENSION

Encephalopathy is a hallmark of acute liver failure. The encephalopathy of acute hepatic failure is related to both metabolic factors, such as progressive elevation in blood NH_3 concentration, and cerebral edema. Progressively worsening encephalopathy is an ominous clinical feature in acute liver failure; development of grade III or IV encephalopathy may herald the death of the patient due to cerebral edema, increased ICP, and central herniation of the brain. Efforts to control the encephalopathy of acute liver failure are directed at preventing or resolving cerebral edema (Box 95-2).^{42,45-48} Because emerging evidence suggests that NH_3 may play a role in the development of cerebral edema, we recommend that administration of protein should be limited to less than 40 g/day in adults, and lactulose (20-40 g/day in divided doses) should be administered enterally to purge the bowel. However, one

must exercise caution when using lactulose in the setting of acute liver failure; dosing should be monitored carefully and adjusted to avoid excessive diarrhea, alterations in electrolytes, and volume depletion. If oral (PO) lactulose is given simultaneously with intravenous (IV) mannitol, marked deficits of free water can develop, inducing severe hyponatremia. Although one recent study suggested that infusion of hypertonic (3%) saline to maintain serum sodium concentration between 145 and 155 mEq/L is beneficial,⁴⁹ rapid shifts in sodium concentration have been associated with central pontine myelinolysis. Further discussion of hypertonic saline is provided later in this chapter. Administration of terlipressin or vasopressin may worsen intracranial hypertension and should be avoided.⁵⁰

Reversal of coagulopathy prior to placement of ICP transducers is recommended but exact targets (INR < 1.5 to 1.9) vary from center to center. Caution should be used as reversal of coagulopathy may be difficult and require large volumes of fresh frozen plasma (FFP), potentially contributing to volume overload and worsening of cerebral edema. Recombinant human factor VIIa infusion (40 $\mu\text{g/kg}$ bolus, repeated as needed every 4 hours to correct INR) may be preferred over FFP in this setting for limiting volume infusion and rapidly correcting the PT/INR.

Hepatic glycogen, the main storage supply of glucose, is depleted early in the course of acute liver failure predisposing to severe, potentially life-threatening hypoglycemia and worsening of cerebral energy metabolism. All patients with acute liver failure should be treated with glucose infusions, and blood glucose concentration must be monitored frequently.

Second-Line Therapies for Treatment of Mannitol-Refractory Intracranial Hypertension

Hypothermia in Acute Liver Failure

Therapeutic hypothermia or intentional reduction of core body temperatures has been increasingly used to treat hypoxic brain injury after cardiac arrest. Animal models of acute liver failure suggest that hypothermia may be effective in the prevention of cerebral edema.^{51,52} Several case series suggest that therapeutic hypothermia may have some efficacy in patients awaiting liver transplantation.^{19,53-55} However, a multicenter retrospective cohort study from the U.S. Acute Liver Failure Study Group revealed that hypothermia (body temperature target 32°C to 35°C) improved 21-day overall and transplant-free survival in only a subset of young (<25 years) patients with acetaminophen (APAP)-associated acute liver failure and high-grade encephalopathy, but not for the entire cohort of 97 patients.⁵⁶ Based on this analysis, physicians must wait for a prospective trial to further elucidate the use of hypothermia in this clinical setting.

Hypertonic Saline in Acute Liver Failure

Another possible method for treating refractory ICH during acute liver failure is the use of hypertonic saline. There has been great concern about the use of hypertonic saline because of the potential consequence of osmotic shifts across the BBB. However, a presumed advantage of hypertonic saline for the treatment of ICH is a higher osmotic reflection coefficient across the BBB.⁵⁷⁻⁵⁹ Thus, hypertonic saline could potentially lead to reduction in cerebral edema, lower ICPs, and improved perfusion by developing a higher osmotic gradient in the cerebral vascular compartment. In a randomized placebo-controlled study, Murphy et al. studied the effect of hypertonic saline infusion on the induction of hyponatremia in patients with ICP, and clinical outcomes among ICU patients with acute liver failure.⁶⁰ Fifteen patients were treated with 30% hypertonic saline (5-20 mL/hour) to maintain serum sodium levels between 145 and 155 mmol/L. After 24 to 72 hours, ICP reduction was significantly greater in the treatment group compared to the standard care group. However, high osmolar loads and continuous hemofiltration were required, and mortality was similar between both treatment and standard care groups. The use of hypertonic saline in the management of ICH in acute liver failure warrants further investigation, but its use is accepted as prophylactic

BOX 95-2

Measures Used to Monitor and Control Cerebral Edema Due to Acute Liver Failure

- Correction of metabolic abnormalities.
 - Electrolytes (Na, K, Cl, HCO_3).
 - Acid-base (if patient is on mechanical ventilation, induce mild respiratory alkalosis).
 - Glucose (maintenance intravenous glucose infusion).
- Avoid overtransfusion or overhydration.
 - Carefully match intake and output once patient is euvolemic.
 - Daily weight.
 - Avoid use of blood products unless indicated for ongoing bleeding and correction of coagulopathy or to maintain hemostasis when intracranial monitor has been placed. In the latter circumstance, the patient may require diuresis to avoid an excess in intravascular volume, especially from plasma.
- Institute dialysis in patients in renal failure.
 - Continuous arteriovenous or venovenous hemodialysis is preferred over standard hemodialysis.
 - Avoid severe volume shifts, stabilize blood pressure, maintain euvolemia, correct electrolyte and acid-base abnormalities.
- Mechanical ventilation (worsening encephalopathy, >grade II).
 - Main indication in liver failure is airway protection to prevent aspiration pneumonia.
 - Induce mild respiratory alkalosis (pH 7.45-7.50, Pco_2 20-30 mm Hg).
 - Elevate head of bed 15-30 degrees.
 - Use sedation to avoid having the patient "fight the endotracheal (ET) tube."
- Consider placement of intracranial pressure (ICP) monitor in the epidural space.
 - Should be considered when patients evolve from stage II (agitated confusion) to stage III (stuporous) encephalopathy.
 - Maintain adequate platelet count (>60,000) with platelet transfusions and INR < 1.5 with fresh frozen plasma if necessary.
 - Mannitol is used to control ICP in patients with intact renal function or in those on dialysis. Mannitol is given in 0.5-1 g/kg doses. Serum electrolytes, glucose, and osmolality should be checked every 4-6 hours. If ICP is elevated, osmolality < 310, and Na < 145, then give mannitol. Mannitol should be withheld if the patient has excessive serum osmolality or significant hyponatremia.

therapy by societal guidelines for patients with the highest risk of developing cerebral edema.⁶¹

Other Options for Refractory ICH

Other potential therapies that can be considered in acute liver failure patients with refractory ICH include barbiturates such as pentobarbital or thiopental and indomethacin. By inducing a comatose state and reducing cerebral edema, pentobarbital (3–5 mg/kg IV load, then 1–3 mg/kg/hour infusion) or thiopental (5–10 mg/kg load, then 3–5 mg/kg/hour infusion) have been shown to have some benefit in refractory ICH.^{62,63} However, severe side effects such as arterial hypotension, hypokalemia, and prolonged coma limit their use and often necessitate the coadministration of vasopressors in order to maintain cerebral perfusion pressure above 50 mm Hg. Indomethacin (dosed at 25 mg IV over 1 minute) also has the potential to cause an acute decrease in ICP and an acute increase in cerebral perfusion pressure (CPP) by causing cerebral vasoconstriction but has not been validated in a trial. Therefore, these medications may play a role as second- or third-line options for patients with persistent refractory ICH.^{64–66}

Experimental Therapies

Several other methods have been tested in acute liver failure: exchange blood transfusion, plasmapheresis, cross-circulation with human and baboon donors, hemoperfusion through isolated human or animal livers, hemodialysis (conventional and polyacrylonitrile), and column hemoperfusion (microencapsulated charcoal, albumin-covered Amberlite XAD-7 resin). Since none of these techniques has been demonstrated to improve survival, their use in the management of acute liver failure is not currently recommended.

Promising strategies that have been investigated in the management of patients with high-grade encephalopathy in the setting of acute liver failure include an extracorporeal liver assist device based on albumin dialysis (MARS). However, its use did not yield clear survival benefit.⁶⁷ Bioartificial liver (BAL) machines have also emerged as a potential therapeutic intervention. To date, there has only been one large randomized multicenter trial of the use of BAL in acute liver failure, and it did not conclude a survival benefit.⁶⁸ Finally, the use of human hepatocyte transplantation in the setting of acute liver failure as a bridge to transplantation is in persistent development.^{69,70}

Liver Transplantation

Liver transplantation is the only treatment that has been proven to improve survival in patients with acute liver failure and high-grade encephalopathy.^{6,71} Survival without transplantation is 10% to 20%. Survival increases to 60% to 80% with liver transplantation. In the largest series of living donor liver transplants for acute liver failure, Lee et al. report patient survival as 82.3% at 5 years after transplantation.⁷² These results are similar to those of cadaveric transplantation for acute liver failure and also demonstrate the durability of living donor allografts.

At some stage cerebral edema becomes irreversible and patients, despite transplantation, will experience brain death or massive irreversible brain injury.^{73,74} Risk of irreversible neurologic injury is greatest in those with CPP less than 40 mm Hg for more than 4 hours. Lesser increases in ICP may be associated with neurologic injury, but usually cerebral edema resolves in the posttransplant period, and complete or partial neurologic recovery may be expected. In most cases of acute liver failure, all the manifestations of neurologic illness (cerebral edema, encephalopathy, and coma) reverse without sequelae following successful hepatic transplantation. One complication, central pontine myelinolysis, may occur in the absence of cerebral edema and may be related to fluctuations in plasma sodium during resuscitative measures in the ICU, such as IV fluids, transfusions, antibiotics, sedatives, narcotics, invasive procedures, and ventilatory support. Despite the

serious nature of central pontine myelinolysis, significant neurologic recovery can occur.

ENCEPHALOPATHY IN THE SETTING OF CHRONIC LIVER DISEASE

Patients with cirrhosis of any cause and chronic PSE may present with a host of neuropsychiatric symptoms, ranging from subtle changes in mental status to coma. Fetor hepaticus (a peculiar odor to the breath in people with severe liver disease) is common but not invariable. Asterixis, the “flapping tremor,” is due to involuntary intermittent relaxation of sustained motor activity but is less specific than fetor hepaticus for hepatic encephalopathy and is usually only present during the late stages of encephalopathy. Although reported, cerebral edema rarely occurs in patients with encephalopathy in the setting of chronic liver disease. As the patient recovers from hepatic encephalopathy, asterixis and other manifestations of encephalopathy resolve.

Risk Factors and Precipitating Events: Implications for Diagnostic Testing and Treatment

Flares of chronic encephalopathy may occur spontaneously without an identifiable precipitant in patients with very severe hepatic impairment and/or extensive portosystemic shunting. However, in the majority of cases, acute worsening of chronic encephalopathy is precipitated by one or more of a number of common events.

Gastrointestinal Hemorrhage

Hemodynamically significant gastrointestinal (GI) hemorrhage is a major precipitant of hepatic encephalopathy. Delivery of a large protein load to the GI tract via hemorrhage stimulates bacterial metabolism of luminal blood and release of NH_3 , GABA, and other chemicals or compounds that may inhibit neurotransmission. Poor hepatic function or shunting of portal blood via portosystemic collaterals impairs hepatic clearance and enhances delivery of these molecules to the brain.

Infection

Infection—in particular, sepsis—may precipitate hepatic encephalopathy in patients with chronic liver disease. Spontaneous bacterial peritonitis (SBP) always should be considered in the differential diagnosis of patients with ascites and new-onset encephalopathy. Fever may be absent, and clinical signs (abdominal pain, ileus) are lacking. SBP is presumptively diagnosed if the absolute neutrophil count in ascitic fluid exceeds 250 cells/mL. Patients with cirrhosis and malnutrition are susceptible to infections due to reduced leukocyte migration, decreased serum bactericidal activity, depressed white cell mobilization, and impaired phagocytosis. Infection increases protein catabolism, releasing aromatic amino acids that may contribute to the encephalopathy.

Medications (Sedatives)

There are no safe sedatives for administration in cirrhotic patients who have hepatic encephalopathy. Because liver metabolism is usually severely impaired in these patients, the clearance of benzodiazepines, barbiturates, chlorpromazine, morphine, and opioid derivatives such as methadone, meperidine, and codeine are reduced. With repeated dosing, all these compounds tend to accumulate in cirrhotic patients, increasing the degree and prolonging the duration of sedation.

Renal Failure

A common precipitant of hepatic encephalopathy is excessive diuresis, resulting in relative depletion of intravascular volume and prerenal azotemia. Factors contributing to the encephalopathy include electrolyte imbalances, disordered acid-base metabolism, reduced fluid volume, and impaired renal clearance of metabolites, drugs, and toxins.

Fluid, Electrolyte, and Acid-Base Imbalance

Hepatic encephalopathy may be precipitated by dehydration, hypokalemia, and alkalosis. Metabolic alkalosis promotes an increase in levels of nonionic NH_3 , which diffuses very rapidly into the CNS. Diffusion of NH_3 into the brain and enhanced glutamine production may precipitate encephalopathy due to either astrocyte swelling and dysfunction or impairment of glutamatergic neurotransmission. With hepatic impairment, the kidneys produce glucose from branched-chain amino acids (gluconeogenesis) in an attempt to maintain peripheral energy supply. This process results in decreased circulating levels of branched-chain amino acids and an increase in circulating levels of the relatively more toxic aromatic amino acids, which may diffuse into the brain.

Surgical Shunt Procedure or TIPS

Hepatic encephalopathy is a common complication of portal diversion following surgical portosystemic shunts or TIPS.⁷⁵ Predictors of post-shunt encephalopathy include preshunt encephalopathy, severe liver disease (Child-Pugh score >10 or Model-for-End-Stage-Liver-Disease [MELD] score >16), renal failure, and elderly age. The mechanisms of hepatic encephalopathy after placement of a portosystemic shunt include lack of compensatory dilatation of the hepatic artery, lack of perfusion of the liver via the portal vein, and reduction in hepatocyte function. Clinically apparent encephalopathy after placement of a shunt usually responds to medical treatment. In rare circumstances, narrowing of the shunt with a flow-reducing stent or occlusion of the shunt may be necessary to control encephalopathy.⁷⁶

Portosystemic Shunting from Collaterals

In cases of refractory encephalopathy, patients should undergo contrast-enhanced abdominal imaging to visualize the presence of prominent portosystemic collateral vessels. If large collaterals are seen, selected patients may benefit from embolization of these collaterals.^{77,78}

Noncompliance with Therapy

One of the most common factors precipitating encephalopathy is noncompliance with prescribed outpatient medical treatments (e.g., lactulose). A careful history, focusing on adherence to medical therapy, is necessary in the evaluation of encephalopathic patients.

Diagnosis

The diagnosis of PSE is based upon clinical suspicion in patients with chronic liver disease, and the impression is confirmed by resolution following medical therapy. Occasionally it may be necessary to employ additional testing to confirm a diagnosis of PSE. Additional testing is particularly useful when encephalopathy is the primary clinical manifestation of otherwise unsuspected liver disease or if the manifestations of encephalopathy are predominantly a change in behavior or an unusual neurologic syndrome (seizures, focal neurologic deficits). Rarely, cerebral edema complicates chronic liver disease.⁷⁹

Plasma Ammonia

An elevated blood NH_3 level is common in cirrhotic patients, especially those with encephalopathy. Some studies have demonstrated a correlation between blood NH_3 levels and the presence and grade of encephalopathy, while others have not. In general, blood NH_3 levels might be useful as a marker of liver disease but are of little diagnostic or clinical value in managing the cirrhotic patient with hepatic encephalopathy.

Electroencephalography

Electroencephalographic (EEG) abnormalities are relatively nonspecific in hepatic encephalopathy. Two findings have some specificity as regards hepatic encephalopathy: reduced brainstem auditory-evoked potentials and diminished visual-evoked potentials. In various studies, the percentage of encephalopathic cirrhotics with EEG abnormalities is highly variable, ranging from 14% to 78% of patients.

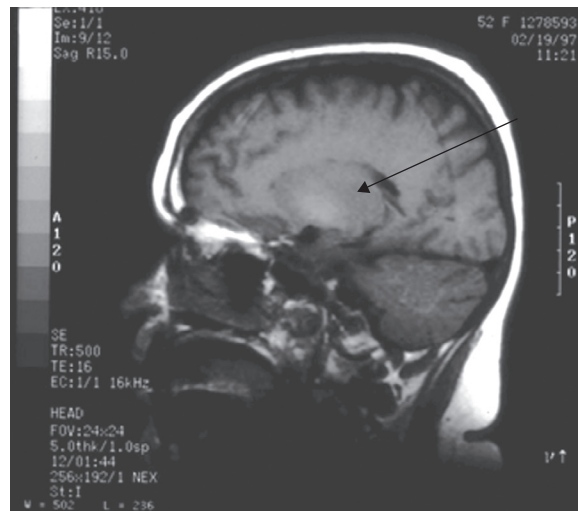


FIGURE 95-3 ■ Computed tomographic (CT) scan of the brain of a patient with acute liver failure, stage IV hepatic coma, and cerebral edema. Note the diminished sulci and lack of distinction between white and gray matter. This patient's cerebral edema resolved with medical management, and she subsequently underwent transplantation. She achieved complete neurologic recovery post transplant.

Radiologic Imaging

Standard CT scans or nuclear brain scans exhibit little or no specific distinguishing features, although loss of cortical volume may be common in patients with Laënnec's cirrhosis and chronic encephalopathy. CT may be used to document cerebral edema or to exclude CNS complications such as tumor, infection, or hemorrhage. Magnetic resonance imaging (MRI) studies have revealed a few features relatively unique to hepatic encephalopathy. One feature, hyperintensity on T_1 -weighted images of the globus pallidus (see Fig. 95-3), correlates with (extrapyramidal) motor disorders and excess accumulation of manganese.

Neuropsychiatric Testing

In general, neuropsychiatric testing is used primarily to monitor efficacy of treatment. A battery of tests is employed to distinguish hepatic encephalopathy and organic brain syndrome from other causes of encephalopathy and underlying psychiatric disease. These tests are itemized in Table 95-2. Poor performance on number connection tests correlates reasonably well with severity of encephalopathy and Child-Pugh and/or MELD classifications.

Therapeutic Options

Past thoughts on the treatment of hepatic encephalopathy included a protein-restricted diet of 40 grams or less per day.^{80,81} However, cirrhotic patients often develop severe muscle wasting; thus, in patients with advanced disease, unnecessary protein restriction might further worsen the poor nutritional state. Therefore, hepatologists currently avoid the use of protein restriction in the management of chronic hepatic encephalopathy.

Lactulose

The mainstay of therapy in the treatment of hepatic encephalopathy is lactulose, a nonabsorbable disaccharide that is fermented by bacteria in the intestine to yield acetic, butyric, propionic, and lactic acids.⁸¹⁻⁸³ The fermentation of lactulose produces an acidic milieu that alters the composition of gut bacterial flora, lowers colonic pH, and produces an osmotic diarrhea. Each of these effects may be responsible for the ameliorative effects of lactulose on hepatic encephalopathy. Changing

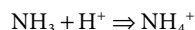
TABLE 95-2 Neuropsychiatric Tests Used to Evaluate Hepatic Encephalopathy

| CEREBRAL FUNCTION | TEST |
|-----------------------------|---|
| Learning and delayed recall | Story Memory Test Figure Memory Test |
| Concentration | Digit Vigilance Test |
| Fine motor coordination | Grooved Pegboard |
| Sequential procedures | Trail Making Test |
| Problem solving | Wisconsin Card Sorting Test |
| Attention | WAIS-R* Digit Symbol Subtest |
| Vocabulary | WAIS-R Vocabulary Subtest |
| Verbal fluency skills | Controlled Oral Word Association Animal Naming |
| Auditory comprehension | Complex Material |
| Visual-spatial analysis | WAIS-R Block Design Subtest |
| Psychological function | MMPI-2† |

*WAIS-R, Wechsler Adult Intelligence Scale-Revised.

†MMPI-2, Minnesota Multiphasic Personality Inventory.

the composition of the bacterial flora may alter the metabolism of fecal contents and reduce the production of toxins, NH_3 , and methanethiols that are responsible for encephalopathy. The acidic luminal milieu creates an environment capable of trapping NH_3 :



Ammonia is neutral and freely diffuses across the mucosal barrier of the colon, where it can enter the portal circulation for delivery to the rest of the body. In contrast, the ammonium ion (NH_4^+) produced from the reaction of NH_3 with hydrogen ions is ionized, highly polar, and unable to diffuse readily across the lipid bilayer of mucosal cells. This ammonium ion is “trapped” in the fecal effluent and eliminated with passage of the bowel movement. In addition to these properties, the breakdown of each molecule of lactulose produces at least four osmotically active particles. Water diffuses into the lumen and down the osmotic gradient, increasing fecal water content, and if enough lactulose is given, a dose-dependent osmotic diarrhea results. The purgative effect of lactulose may also be responsible for altering the composition of colonic bacteria and helping to eliminate toxins and waste that might otherwise accumulate. The usual recommendation is that enough lactulose be given to produce two to three loose, semiformal stools each day. Excessive dosing with lactulose will produce severe diarrhea with large volume losses and electrolyte imbalances and should be avoided.

Rifaximin

Rifaximin is a nonabsorbable antibiotic derivative of rifamycin with broad antimicrobial activity and has become an important adjunct agent along with lactulose for the treatment of hepatic encephalopathy.⁸⁴ In comparison studies of rifaximin with lactulose, patients treated with rifaximin showed greater improvement in the degree of hepatic encephalopathy, had lower NH_3 levels, and had lower PSE index scores.⁸⁴ A randomized controlled trial of 299 patients demonstrated reduction of recurrent hepatic encephalopathy episodes and number of hospitalizations due to hepatic encephalopathy.⁸⁵

Branched-Chain Amino Acids

Early studies demonstrated that cirrhotic patients had an increase in aromatic amino acids and a decrease in branched-chain amino acids in blood samples. Subsequent clinical work suggested that patients with the greatest imbalance in plasma amino acids were more likely to

be encephalopathic and to experience early and higher mortality. For this reason, there have been at least 14 controlled trials of the use of branched-chain amino acids in the treatment of cirrhotic patients with chronic encephalopathy. However, results of these trials have been inconsistent, and separate meta-analyses have yielded opposite conclusions.⁸⁶ A trial of branched-chain amino acids might be considered in patients who develop encephalopathy on standard protein diets and manifest protein-calorie malnutrition.

Benzodiazepine Antagonists

There have been several randomized controlled trials of short-term administration of flumazenil in the treatment of hepatic encephalopathy.⁸⁷⁻⁸⁹ In some studies, flumazenil was superior to placebo in improving the grade of encephalopathy; 30% to 60% of encephalopathic patients improved after administration of flumazenil, and EEG changes paralleled this improvement. In other studies, however, flumazenil was no better than placebo in ameliorating the symptoms of encephalopathy, and EEGs did not improve. Overall, flumazenil has a limited role in the treatment of hepatic encephalopathy.

L-Ornithine-L-Aspartate (LOLA) and Ammonia Scavengers

L-ornithine-L-aspartate (LOLA) is a compound salt that was shown to reduce NH_3 levels by increasing NH_3 disposal through enhanced peripheral metabolism. LOLA increases the activity of hepatic urea cycle enzymes and also increases the rate of glutamine production within skeletal muscle. Although a large randomized controlled study using LOLA in acute liver failure did not find significant changes in survival,⁶² other studies investigated its potential use in hepatic encephalopathy from chronic liver disease. A meta-analysis consisting of three randomized trials and a pool of 212 patients found an overall significant improvement in chronic hepatic encephalopathy symptoms, although lower grade encephalopathic patients had the greatest benefit.⁹⁰

Additional agents (i.e., glycerol phenylbutyrate and ornithine phenylacetate) that were initially developed for ammonia reduction in patients with inborn urea cycle defects are also being tested in clinical trials for the management of chronic hepatic encephalopathy.^{91,92}

Neomycin

Another agent for second-line therapy of chronic hepatic encephalopathy is orally administered neomycin. Neomycin has a limited entrance to the circulation, with the goal of therapy being to alter the bacterial composition of the colonic flora.^{93,94} The main disadvantage is that nephrotoxicity may occur despite its poor absorption. Given the establishment of rifaximin, the use of neomycin has decreased substantially and it is now rarely used. If used in selected cases, it is recommended to give only short courses lasting 2-8 weeks.

Metronidazole

Studies have demonstrated that oral metronidazole (500 mg to 1.5 g/day given for 1 week) was as effective as neomycin or lactulose in controlling encephalopathy.⁹⁴ Others have not observed similar efficacy and have measured little effect of metronidazole on blood NH_3 levels. The advantages of metronidazole are that it does not cause diarrhea. A disadvantage is that many patients complain of epigastric discomfort with its use (leading to poor compliance with long-term treatment) and can develop ototoxicity as well as neurologic side effects that can be irreversible. Maintenance therapy can be expected to cause peripheral neuropathy (already a problem in patients with advanced liver disease), and metronidazole has been reported to cause the “disulfiram reaction” when alcohol is consumed. The physician prescribing metronidazole to cirrhotic patients also should be aware that this drug undergoes extensive hepatic metabolism. Given the establishment of rifaximin, the use of metronidazole for encephalopathy has decreased substantially and it is now rarely used. If used in selected cases, it is recommended to also only give short courses lasting 2-8 weeks to prevent toxicities.

Liver Transplantation

The development of encephalopathy in a patient with chronic liver disease indicates the presence of portosystemic shunting and hepatic dysfunction. The prognosis for patients who develop this complication is grim; one recent study indicated that the 1-year survival rate is 42% and the 3-year survival rate is 23%.⁹⁵ In addition, there are numerous comorbidities in encephalopathic patients, including inability to continue gainful employment, poor function at home, nursing strains on spouse or family, inability to drive a vehicle, and inability to handle personal finances. Although medical therapies can ameliorate the major symptoms of encephalopathy, they are rarely effective enough to return the patient to full function. Often the patient with encephalopathy is at risk of other life-threatening complications of liver disease such as variceal hemorrhage and spontaneous bacterial peritonitis. For all the above reasons, any patient with hepatic encephalopathy should be considered for hepatic transplantation.

CONCLUSION

This chapter has discussed several key issues regarding hepatic encephalopathy, including definitions, clinical syndromes, diagnostic tests, precipitants, prognosis, and outcomes with therapy including hepatic transplantation. The section on pathogenesis defines current knowledge regarding mechanisms of encephalopathy in both acute liver failure and chronic liver disease. The clinician faced with neuropsychiatric syndromes in patients with liver disease must differentiate the nature of the underlying liver disorder (acute liver failure versus chronic liver disease), evaluate diagnostic tests, and institute appropriate therapy. Overall outcomes of patients with encephalopathy depend on the general condition of the patient, severity of underlying liver disease, comorbid conditions, and when in acute liver failure, the

presence of cerebral edema and intracranial hypertension. Liver transplantation, including the option of living donor liver transplantation, may yield favorable outcomes without neurologic sequelae if instituted prior to excessive and prolonged intracranial hypertension in the case of acute liver failure, or prior to multiorgan failure in the case of chronic liver disease.

KEY POINTS

1. Clinical presentation and prognosis of hepatic encephalopathy vary by presence of acute liver failure or chronic liver disease.
2. Patients with high-grade hepatic encephalopathy (stage III or IV) and acute liver failure should urgently be referred to a liver transplant center.
3. The routine use of intracranial pressure monitors in patients with acute liver failure is controversial.
4. Mannitol and hypertonic saline are common therapies for intracranial hypertension in the setting of acute liver failure.
5. Precipitants of hepatic encephalopathy should be assessed with each episode in the setting of chronic liver disease.
6. Lactulose is the mainstay of therapy in patients with hepatic encephalopathy and chronic liver disease.
7. Rifaximin has become an important therapy to prevent recurrent episodes of hepatic encephalopathy in the setting of chronic liver disease.

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Acute liver failure (ALF), also known as *fulminant hepatic failure* (FHF), includes a spectrum of clinical entities characterized by acute liver injury, severe hepatocellular dysfunction, and hepatic encephalopathy. Approximately 2000 people annually in the United States develop FHF, which has a high mortality rate.¹ Loss of hepatocyte function sets in motion multiorgan dysfunction syndrome, with ensuing death even when the liver has begun to recover. Complications of FHF include encephalopathy, cerebral edema, sepsis, acute respiratory distress syndrome (ARDS), hypoglycemia, coagulopathy, gastrointestinal bleeding, pancreatitis, and acute kidney injury (AKI). Acetaminophen toxicity, idiosyncratic drug reactions, and hepatotropic viruses remain the most common causes of FHF in the United States. FHF accounts for 5% to 6% of all liver transplantations, which is currently the only proven and definitive treatment option for patients who are unlikely to recover spontaneously. Unfortunately, many patients die before a suitable organ can be identified. Thus, the dominant medical interventions for ALF in the critical care setting are supportive. Alternative “liver replacement” therapeutic strategies are currently under clinical investigation.

DEFINITIONS

The terms *fulminant hepatic failure* and *acute liver failure* are often used interchangeably. FHF is defined as the presence of encephalopathy (regardless of grade) and coagulopathy (international normalized ratio [INR] > 1.5) within 26 weeks of the appearance of symptoms in patients with no previous history of underlying liver disease. Since the original definition of FHF proposed by Trey and Davidson in 1970, several other classifications have emerged (Box 96-1).²⁻⁶ In the different classifications, the interval between the onset of symptoms or jaundice and the appearance of encephalopathy allows grouping of patients with similar causes, clinical characteristics, and prognosis.

ETIOLOGY

Viral hepatitis remains the most common identifiable cause of FHF in the developing world, whereas acetaminophen toxicity and idiosyncratic drug reactions remain the most frequent apparent causes of FHF in the United States and Europe. Both prognosis and management are determined in part by the underlying etiology of FHF.

Acetaminophen Toxicity

Intentional or accidental acetaminophen overdose is the leading cause of FHF in the United States and accounts for 40% to 50% of cases.⁷ A careful medical history clarifies the quantity ingested; blood levels can be confirmatory but may not be elevated in cases of unintentional overdose. Doses considered nontoxic (<4 g/day in adults) may cause hepatotoxicity if other concurrent factors exist, such as alcohol ingestion, fasting, or malnutrition. Hepatotoxicity usually develops 1 to 2 days after the overdose, and circulating alanine aminotransferase (ALT) levels and INR values peak around day 3. Continued increase of INR after day 3 is associated with a poor prognosis. Although acetaminophen does not traditionally cause kidney injury, there are reports of nephrotoxicity in the case of overdose even in the absence of liver necrosis.⁸

Acetaminophen undergoes phase 1 metabolism by hepatic cytochrome P₄₅₀ 2E1 enzymes to a toxic intermediate compound, *N*-acetyl-*p*-benzoquinone imine (NAPQI), which is rapidly detoxified by hepatic

glutathione into a nontoxic metabolite. Under normal conditions, little NAPQI accumulates. However, in an overdose, owing to a depletion of the glutathione stores, unconjugated NAPQI accumulates, causing hepatocellular necrosis. The amount of liver injury is directly related to the amount of ingested acetaminophen and the amount of NAPQI produced. As a result, the ingested dose does not correlate with the overall prognosis.⁹ Enzyme inducers such as alcohol, antiepileptic drugs, and cigarette smoke can enhance acetaminophen-mediated hepatotoxicity.

Idiosyncratic Drug Reactions

Drug-induced liver damage is a significant cause of death in patients with FHF in Western countries (Box 96-2). The most common implicated drugs are antibiotics (amoxicillin-clavulanate, tetracyclines, and macrolides), antituberculosis drugs (isoniazid, pyrazinamide), anti-convulsants, antidepressants, nonsteroidal antiinflammatory drugs (NSAIDs), and halothane. The diagnosis of drug-induced liver injury should remain a diagnosis of exclusion.¹⁰ Dose, duration, and the hepatic metabolism of the drug all may play roles in the development of drug-induced liver injury. In the setting of FHF secondary to drug toxicity, all nonessential medications should be discontinued as soon as possible in the course.

Most idiosyncratic drug reactions are due to a single agent, but multiple medications can be implicated in some patients. Risk factors include sex, age, obesity, preexisting liver disease, and concurrent use of other hepatotoxic drugs. Most idiosyncratic reactions occur within 4 to 6 weeks after the initiation of treatment, although rare cases have occurred months or years later.

Idiosyncratic hepatic injury is mediated by several mechanisms, including the disruption of intracellular calcium homeostasis, injury to the canalicular transport pumps, such as multidrug resistance-associated protein 3, T cell-mediated immunologic injury, triggering of apoptotic pathways by tumor necrosis factor- α , and the inhibition of mitochondrial beta oxidation.¹¹

Hepatotoxic herbal medicines (kava kava, St. John's wort) and certain dietary supplements are emerging as potential causes in a high proportion of patients with FHF.¹² Mushroom poisoning due to *Amanita phalloides* ingestion is relatively common in Europe, and more sporadic cases occur in the United States. Florid muscarinic effects such as sweating or watery diarrhea occur early on, whereas FHF usually occurs 4 to 8 days after mushroom ingestion. Other toxins (e.g., carbon tetrachloride, yellow phosphorus, aflatoxins) are rare causes of FHF. The role of liver biopsy in the diagnosis of drug-induced liver injury is controversial and can be considered when associated with drugs not commonly implicated in liver injury and to exclude common conditions and assist with prognosis.¹⁰ Treatment with *N*-acetylcysteine (NAC) improves transplant-free survival compared with placebo and may be used in drug-induced liver injury.¹⁴

Viral Hepatitis

Viral hepatitis is an important cause of FHF worldwide. Although the development of FHF due to viral hepatitis is rare (0.2%-0.4% for hepatitis A, 1%-4% for hepatitis B), liver failure can occur because of the worldwide incidence of these viruses. Considerable geographic variation exists with regard to subtype: hepatitis B virus (HBV) is a common cause of FHF in the Far East, whereas hepatitis E virus (HEV) is more common in the Indian subcontinent,¹⁵ and most of the liver

BOX 96-1 Classifications of Acute Liver Failure**TREY AND DAVIDSON²**

Fulminant hepatic failure: development of HE within 8 weeks of onset of symptoms

BRITISH CLASSIFICATION⁶

Acute liver failure (includes only patients with encephalopathy)

Subclassification Depending on the Interval Between the Onset of Jaundice and HE

- Hyperacute liver failure: 0 to 7 days
- Acute liver failure: 8 to 28 days
- Subacute liver failure: 29 to 72 days
- Late-onset acute liver failure: 56 to 182 days

FRENCH CLASSIFICATION³

Acute hepatic failure: a rapidly developing impairment of liver function

Severe acute hepatic failure: prothrombin time or factor V concentration below 50% of normal with or without HE

Subclassification

- Fulminant hepatic failure: HE within 2 weeks of onset of jaundice
- Subfulminant hepatic failure: HE between 3 and 12 weeks of onset of jaundice

INTERNATIONAL ASSOCIATION FOR THE STUDY OF ACUTE LIVER FAILURE⁵

Acute liver failure (occurrence of HE within 4 weeks after onset of symptoms)

Subclassification

- Acute liver failure—hyperacute: within 10 days
- Acute liver failure—fulminant: 10 to 30 days
- Acute liver failure—not otherwise specified
- Subacute liver failure (development of ascites and/or HE from 5 to 24 weeks after onset of symptoms)

HE, hepatic encephalopathy.

transplants due to viral causes in the United States are caused by hepatitis A virus (HAV) and HBV.

HAV is associated with a higher risk of developing FHF if infection is acquired in older adulthood. Thus, vaccination is recommended for adults traveling from developed countries to endemic areas. The relevance of HAV as a cause of FHF in patients with preexisting chronic liver disease has been recognized, and HAV vaccination has been suggested for this high-risk group. Postexposure prophylaxis with immune serum globulin may reduce the incidence of HAV infection but only when administered within 14 days of exposure.

HBV can result in FHF through several mechanisms: acute primary HBV infection, reactivation of HBV in patients with chronic HBV infection, or superinfection with hepatitis D virus (HDV). Acute HBV infection is diagnosed by the detection of immunoglobulin M (IgM) antibodies against hepatitis B core antigen (HbcAg). A substantial number of patients have negative serum hepatitis B surface antigen (HBsAg) and serum HBV DNA. Patients with low or absent levels of HBsAg and HBV DNA typically have a better prognosis and lower rate of recurrence after orthotopic liver transplantation (OLT). FHF after reactivation of chronic hepatitis B has been described mainly in immunosuppressed patients and is usually associated with a subfulminant course and a poor prognosis. Hepatitis C virus infection alone does not typically result in FHE, although cases have been reported.¹⁶

FHF is observed in 2.5% to 6% of HDV cases. Coinfection with HBV and HDV or superinfection by HDV in patients with chronic hepatitis B can also cause FHE. The incidence of coinfection is higher when intravenous (IV) drug abuse is present. Diagnosis of acute infection by HDV is made by the presence of HDV antigen, anti-HDV IgM antibody, or HDV RNA.

Infection by HEV is uncommon in Western countries but can occur in travelers to endemic areas. Pregnant women infected by HEV are more likely to develop FHE. Diagnosis is made by the detection of anti-HEV IgM antibodies.

Other viruses are implicated in the pathogenesis of FHF (Box 96-2).

BOX 96-2 Etiologic Classification of Acute Liver Failure**ACETAMINOPHEN TOXICITY
IDIOSYNCRATIC DRUG
INJURY****Infrequent Agents**

Isoniazid
Valproate
Halothane
Phenytoin
Sulfonamide
Propylthiouracil
Amiodarone
Disulfiram
Dapsone
Bromfenac
Troglitazone
Zidovudine
Lamivudine
Lamotrigine
Gatifloxacin
Methotrexate

Miscellaneous Agents

Ecstasy
Cocaine
Phencyclidine

Rare Agents

Carbamazepine
Ofloxacin
Ketoconazole
Lisinopril
Nicotinic acid
Labetalol
Etoposide
Imipramine
Interferon alfa
Flutamide
Tolcapone
Nefazodone
Oral contraceptives

**Combination Agents With
Enhanced Hepatotoxicity**

Alcohol-acetaminophen
Trimethoprim-sulfamethoxazole
Rifampicin-isoniazid
Amoxicillin-clavulanic acid

VIRAL HEPATITIDES

Hepatitis A, B, C, D, E, G
Human herpesvirus
Cytomegalovirus
Epstein-Barr virus
Herpes simplex virus
Varicella zoster virus
Paramyxovirus
Parvovirus B19
Adenovirus
Togavirus
Parvovirus
SEN virus
TT virus
Yellow fever virus

TOXINS

CCl₄
Amanita phalloides
Yellow phosphorus
Herbal products

VASCULAR

Ischemic
Veno-occlusive disease
Budd-Chiari syndrome
Malignant infiltration
Non-Hodgkin's lymphoma

MISCELLANEOUS

Wilson's disease
Autoimmune hepatitis
Acute fatty liver of pregnancy
Reye syndrome

Other Etiologies

Cardiovascular, metabolic, and other disorders account for 2% to 10% of cases of FHF. Acute liver ischemia secondary to shock states can result in hepatocellular necrosis; however, the prognosis remains good if the primary condition is corrected. The prognosis is worse when FHF is due to other causes such as the acute form of Budd-Chiari syndrome, veno-occlusive disease, or malignancies associated with impaired hepatic blood flow. The first manifestation of Wilson's disease is rarely FHF, although the typical disease course is chronic. Acute fatty liver of pregnancy is rare, occurring in the third trimester of pregnancy, and usually improves with fetal delivery. Other rare causes of FHF are autoimmune hepatitis, non-Hodgkin's lymphoma, heat stroke, or Reye syndrome.

PROGNOSTIC SCORING SYSTEMS

Survival in patients with FHF depends on many factors, including etiology, age, the severity of the liver dysfunction, the degree of liver necrosis, the nature of the complications, and the duration of illness. Patients with grade IV encephalopathy have a higher than 80% mortality rate without OLT. The successful use of OLT in FHF has created a need for early prognostic indicators to select the patients who are the most likely to benefit. Various prognostic scoring systems exist (Box 96-3). Many of these are subject to debate because they equate death with liver transplant, which falsely elevates the positive predictive value of any prognostication method.¹⁷

BOX 96-3**Various Prognostic Criteria Used for Liver Transplantation in Patients with Fulminant Hepatic Failure****KING'S COLLEGE CRITERIA¹⁸****Acetaminophen Overdose**

- Arterial pH < 7.3 (irrespective of grade of encephalopathy)
- or
- PT > 100 s (INR > 6.5) and
- Serum creatinine > 3.4 mg/dL (>300 μmol/L) and
- Patients with grade III and IV hepatic encephalopathy

Non-Acetaminophen-Induced Liver Injury

Acute form (delayed jaundice-encephalopathy <7 days):

- PT > 100 s (INR > 6.5) (irrespective of grade of encephalopathy) or any three of the following variables:
- Aged <10 or >40 years
- Non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions
- Subacute form: delayed encephalopathy >7 days
- Serum bilirubin 17.4 mg/dL (300 μmol/L)
- PT > 50 s

CLICHY CRITERIA¹⁹

- Grade III or IV encephalopathy
- and
- Factor V < 20% in patients <30 years
- or
- Factor V < 30% in patients >30 years

SERUM GC GLOBULIN LEVELS²⁰

Decreasing Gc levels due to dying hepatocytes

SERUM α -FETOPROTEIN LEVELS

Serial increase from day 1 to day 3 has been correlated with survival

LIVER BIOPSY²²

70% necrosis is discriminant of 90% mortality

Gc, plasma group-specific component protein; INR, international normalized ratio; PT, prothrombin time.

For patients with acetaminophen overdose, HAV infection, shock liver, or pregnancy-related ALF, the short-term survival rate without transplantation is over 50%. The short-term transplant-free survival rate is lower (<25%) for patients with FHF of indeterminate cause or FHF caused by other factors such as drugs other than acetaminophen, HBV infection, autoimmune hepatitis, Wilson's disease, Budd-Chiari syndrome, or cancer. The King's College prognostic criteria are the most widely used both in cases of acetaminophen-induced and non-acetaminophen-induced FHF (Box 96-3). These criteria provide a reasonable prediction of the likelihood of death and the need for transplantation in FHF patients.¹⁸

Other approaches include the Clichy criteria,¹⁹ which use factor V assay, factor VIII/V ratio, serial α -fetoprotein levels, and plasma group-specific component protein (Gc globulin) levels.²⁰ Liver volume decreases with the progression of the disease, and its measurement with computed tomography (CT) may help assess the prognosis. Other proposed markers for poor prognosis include serum levels of phosphate above 1.2 mmol/L on day 2 or 3, blood lactate concentration over 3.0 mmol/L, or a Model for End-stage Liver Disease (MELD) score higher than 32.^{21,22} An alternate scoring system, the Acute Liver Failure Study Group index, which is composed of a combination of clinical markers and measurements of the apoptosis biomarker M30, has been shown to better predict outcomes compared with the King's College Criteria or the MELD score.²³

ROLE OF LIVER BIOPSY

Liver biopsy can confirm the suspected cause of FHF and determine the degree of hepatocyte necrosis. Greater than 70% necrosis in a liver biopsy specimen is associated with a 90% mortality rate without transplantation.²⁴ Because coagulopathy precludes safe percutaneous liver

biopsy, the transjugular approach is often preferred. Liver biopsy can help exclude occult malignancy, provide etiologic information, and assess the liver for evidence of regeneration.

PATHOGENESIS AND CLINICAL FEATURES OF ALF

FHF is clinically distinct from chronic hepatic insufficiency, regardless of the etiology. The constellation of symptoms typically involves non-specific symptoms such as malaise and nausea, followed by jaundice, rapid onset of altered mental status, and coma. Altered mentation and a prolonged INR are the hallmarks of the diagnosis. Supportive laboratory findings include high aspartate transaminase/ALT levels, elevated total bilirubin concentration, low serum glucose levels, and arterial blood gas studies showing metabolic acidosis and/or respiratory alkalosis. Patients with subfulminant hepatic failure have a more gradual onset of hepatic insufficiency accompanied by ascites, renal failure, and a very poor prognosis.

The magnitude of the elevation of aminotransferase levels and the rate of decline do not affect the prognosis. When patients spontaneously recover, the serum bilirubin concentration and INR normalize, whereas when the disease progresses, bilirubin levels continue to increase (due to intrahepatic cholestasis), and INR remains prolonged despite declining ALT levels. The high mortality rates associated with FHF are caused by complications such as cerebral edema, renal failure, sepsis, pancreatitis, and cardiopulmonary collapse.

Encephalopathy

Encephalopathy differentiates FHF from acute severe hepatitis. The onset of encephalopathy is often abrupt and, occasionally, may precede the appearance of jaundice. Agitation, delusion, and hyperkinesia are common but short-lived symptoms; coma rapidly ensues. The overall prognosis for those with stable grade I/II encephalopathy is good, whereas the prognosis for patients with grade III/IV encephalopathy is poorer. In cases of acetaminophen overdose, encephalopathy usually occurs on the third or fourth day after ingestion and rapidly progresses to grade IV within 24 to 48 hours.

The pathophysiology of hepatic encephalopathy is likely caused by astrocyte swelling and cerebral edema due to the synergistic effects of excess ammonia and inflammation, although the precise underlying molecular mechanisms are unclear.^{25,26} Newly synthesized glutamine is transported from the cytoplasm into the mitochondria and is metabolized by glutaminase, yielding glutamate and ammonia. The generation of ammonia in the small mitochondrial compartment may reach extremely high levels, leading to the induction of mitochondrial permeability transition, production of free radicals, and potential oxidative damage of the mitochondrial constituents. Elevated serum ammonia concentration is exacerbated by decreased urea synthesis in the injured liver.²⁷ Endogenous substances, false neurotransmitters, short-chain fatty acids, benzodiazepines, and γ -aminobutyric acid are additional factors that can lead to encephalopathy.

The electroencephalogram (EEG) typically shows diffuse slowing of cortical activity and high-amplitude waveforms at 5 to 7 cycles per second. Subclinical seizure activity is often present in patients with grade III or IV encephalopathy, emphasizing the importance of EEG monitoring in these patients. Prophylactic therapy with phenytoin has been shown to reduce both seizure activity and cerebral edema.²⁸

Cerebral Edema

Cerebral edema is estimated to occur in 75% to 80% of patients who progress to grade IV encephalopathy and is the leading cause of death in these patients. The mechanism(s) responsible for cerebral edema are not completely understood but likely include cerebral hyperemia, vasogenic edema due to disruption of the blood-brain barrier, and cytotoxicity due to the osmotic effects of ammonia, glutamine, and other amino acids, as well as the deleterious effects of proinflammatory

cytokines and dysfunction of the sodium-potassium ATPase pump, with loss of autoregulation of the cerebral blood flow.^{29,30}

Intracranial blood flow is markedly reduced in patients with chronic hepatic encephalopathy; the decrease in perfusion appropriately matches the reduction in cerebral metabolic rate (CMR). Patients with FHF often develop either relative or absolute cerebral hyperemia; therefore, perfusion is often not well matched to the reduced CMR present in evolving or established hepatic coma. An early indicator of this pathologic process is either a decrease in the transcranial oxygen content difference (arterial oxygen content – jugular bulb oxygen content) to less than 4 mL/dL or an increase in the systolic blood flow velocity of the middle cerebral artery. Serial transcranial Doppler ultrasonographic monitoring of cerebral blood flow velocity helps in the detection of early cerebral hyperperfusion or hypoperfusion suggestive of impaired cerebral autoregulation.^{31,32} Cerebral ischemia and permanent neurologic sequelae may occur if cerebral perfusion pressure (CPP), calculated as the mean systemic arterial blood pressure minus intracranial pressure (ICP), is not maintained above 40 to 50 mm Hg. CT of the brain often fails to demonstrate cerebral edema in patients with elevated ICP. The late clinical stages of cerebral edema include systemic hypertension, decerebrate rigidity, hyperventilation, pupillary dilation, seizures, and brainstem herniation. An arterial ammonia level above 200 µg/dL in grade III and grade IV encephalopathy is a strong predictor of brain herniation.³³ Full recovery of cerebral function is usually expected following the return of normal liver function; however, permanent brain damage can occur.

Coagulopathy

Severe coagulopathy is typical of FHF due to impaired hepatic synthetic function leading to the inadequate production of coagulation factors. Decreased levels of factors II, V, VII, IX, and X account for the prolongation of prothrombin time and later, activated partial thromboplastin time. In addition to coagulopathy, there also exists a tendency for thrombosis due to a decreased production of anticoagulation factors such as proteins C and S and a decreased clearance of activated coagulation factors by the liver. Disruption of the balance between procoagulant and anticoagulant factors may result in excessive thrombosis and disseminated intravascular coagulation, which can be difficult to confirm with laboratory testing. Coagulopathy is often complicated by thrombocytopenia, with platelet counts below 100,000/µL in two-thirds of patients.

Metabolic Derangements

FHF results in a myriad of metabolic abnormalities. Hypoglycemia is reported in up to 45% of patients with FHF due to the depletion of hepatic glycogen stores and impaired gluconeogenesis, which is often refractory to the infusion of IV dextrose solution. Hepatic insulin resistance and impaired peripheral insulin sensitivity may also be present.³⁴ Lactic acidosis is common in acetaminophen-induced FHF and has a poor prognosis. Hyponatremia, alkalosis, hypokalemia, and hypophosphatemia are also common, and ionized hypocalcemia may indicate concomitant pancreatitis. Acute renal failure is seen in 30% to 70% of patients with ALF due to a combination of factors such as intravascular volume depletion, acute tubular necrosis (ATN), or direct nephrotoxicity from ingested drugs such as acetaminophen or NSAIDs. Adrenal insufficiency has been described in up to 62% of patients with FHF.³⁵

Cardiovascular, Hemodynamic, and Respiratory Complications

Circulatory dysfunction accompanying FHF often mimics sepsis. Typically, patients are hyperdynamic with low systemic vascular resistance due to the proinflammatory effects of circulating endotoxins and cytokines. Patients with hypotension despite adequate volume resuscitation should be started on norepinephrine infusion. Cardiac arrhythmias frequently occur because of electrolyte imbalances as well as increased

circulating levels of catecholamines (from endogenous release or deliberate infusion). Severe peripheral shunting has been observed in FHF and may result from the plugging of small vessels by platelets, interstitial edema, or abnormal vasomotor tone. An abnormal pattern of oxygen supply dependency results in oxygen extraction over a wider than normal range of oxygen delivery, presumably as a compensatory mechanism.

Hyperventilation, hypocapnia, and respiratory alkalosis occur during ALF and may worsen encephalopathy. Arterial hypoxemia is nearly universal and is caused by a combination of intrapulmonary shunting, ventilation/perfusion mismatching, sepsis, aspiration, and ARDS.

Sepsis

FHF is associated with impaired host resistance to and enhanced susceptibility to bacterial and fungal infections. Common infections are aspiration pneumonia and primary bloodstream infections, including fungal infections. The most common microbial pathogens are gram-positive bacteria (*Staphylococcus aureus*, enterococci), enteric gram-negative bacilli (*Escherichia coli*, *Klebsiella* spp.), and *Candida* spp. Diminished hepatic reticuloendothelial function and opsonic activity, defective polymorphonuclear leukocyte function, and impaired cell-mediated and humoral immunity are the major predisposing mechanisms. Periodic surveillance cultures for bacterial and fungal infections are recommended. In one prospective study of 50 patients, 80% had culture-proven infection, with suspected infection in half of the remaining patients.³⁶

MANAGEMENT

Patients with FHF are best cared for in an intensive care unit. Transfer to a liver transplantation center should be considered at the time of admission.

Therapy Directed at the Specific Etiology of FHF

Depending on the suspected etiology, a number of therapies exist that can ameliorate or reverse the degree of liver injury. NAC should be administered to all patients with FHF, regardless of the cause. NAC is a specific antidote for acetaminophen overdose; it replenishes glutathione stores and prevents the development of hepatotoxicity if given within the first 8 to 10 hours after an acute overdose. Administration of NAC within 8 hours is associated with a significantly improved survival rate but may be effective up to 72 hours after acetaminophen ingestion.³⁷ IV NAC is preferred over the enteral route. Although some experts recommend continued treatment until the INR normalizes, prolonged NAC therapy in mice has been shown to impair liver regeneration following acetaminophen poisoning.³⁸

Benefits of NAC on survival, brain edema, hemodynamics, oxygen delivery, and oxygen consumption have been found in patients with established FHF.³⁷ A randomized, controlled trial of NAC by the U.S. Acute Liver Failure Study Group in patients with non-acetaminophen-induced FHF showed an improved transplant-free survival rate.¹⁴ For patients with known acetaminophen overdose within 4 hours of presentation, the administration of activated charcoal prior to starting NAC is recommended.

Hepatitis secondary to HSV may be missed because of its nonspecific presentation and the absence of typical mucocutaneous lesions. Most patients with HSV hepatitis are immunosuppressed hosts. If HSV hepatitis is suspected, treatment with parenteral acyclovir or ganciclovir should be started.

Treatments of other conditions causing FHF vary in terms of success and evidence supporting their use. Wilson's disease can be managed temporarily with plasma exchange, which can remove relatively large amounts of copper in a short period of time. However, plasmapheresis only helps to bridge patients to transplant and carries no survival

benefit. Chelating agents such as penicillamine are ineffective in the setting of FHF due to Wilson's disease. Hemofiltration and albumin dialysis may also be considered as temporizing measures before OLT.^{39,40}

FHF due to autoimmune hepatitis has a variable course, as conventional immunosuppressive therapy with high-dose steroids has been observed to be effective in 20% to 100% of patients with fulminant presentation. These patients should be considered for transplantation even while steroids are being administered.⁴¹ While the exact role of corticosteroids or immunosuppressive agents in the management of FHF due to autoimmune hepatitis has not been well established,⁴² it is recognized that patients who do not respond to treatment after 2 weeks are more likely to die without liver transplantation. Acute fatty liver of pregnancy usually responds to fetal delivery, with improved mortality rates with early delivery. Urgent chemotherapy is indicated for FHF caused by massive infiltration of the liver by lymphoma. Acute Budd-Chiari syndrome may be amenable to thrombolytic therapy or to transjugular intrahepatic portosystemic shunt placement.

Hepatic Encephalopathy

The treatment of encephalopathy is directed at limiting gut ammonia production and the avoidance of aggravating factors such as infection, ileus, obstipation, gastrointestinal hemorrhage, and other central nervous system depressants. Endotracheal intubation for grade III and IV hepatic encephalopathy is usually indicated. Lactulose may be useful in the treatment of patients with grade I or II encephalopathy; however, administration of lactulose does not improve survival in advanced encephalopathy. The efficacy of lactulose in FHF has not been tested in clinical trials. This agent should be used with caution because of the risk of hypernatremia, dehydration due to diarrhea, and the potential for bowel distention. Lactulose by enema remains an option in FHF patients who are unable to tolerate oral or nasogastric administration.

Oral metronidazole, neomycin, and rifaximin directed against ammonia-producing gut flora have been employed. However, metronidazole may be neurotoxic in hepatic failure, and neomycin, although minimally absorbed, can still cause nephrotoxicity and ototoxicity. Rifaximin is effective at decreasing ammonia levels due to hepatic encephalopathy, with good evidence for its use in chronic liver failure, and should be considered as an adjunct to lactulose in treating encephalopathy in FHF. Endogenous benzodiazepine-like substances have been identified in the cerebrospinal fluid of patients with hepatic encephalopathy. Flumazenil, a benzodiazepine receptor antagonist, has been used with some success to provide short-term improvement in patients with hepatic encephalopathy.⁴³ Administration of L-ornithine-L-aspartate in patients with FHF was found to be ineffective at reducing circulating ammonia levels or improving survival and may cause increased seizure activity. L-Ornithine phenylacetate remains a potential temporary agent for the treatment of hepatic encephalopathy while awaiting transplant; however, it has yet to be validated in humans.⁴⁴

Cerebral Edema

The optimal management of cerebral edema requires maintaining the delicate balance between mean arterial pressure and ICP to preserve adequate cerebral perfusion (Box 96-4). Cerebral edema combined with intracranial hypertension is the most common cause of death in patients with FHF whose ICP is above 30 mm Hg. An arterial ammonia level over 200 µg/dL predicts brain herniation.³³ ICP monitoring may help to diagnose intracranial hypertension and guide management, especially in grade III or IV encephalopathy, although its use has not been shown to decrease mortality.^{45,46} ICP should be maintained below 20 mm Hg, and CPP should be maintained above 50 mm Hg, although transplant-free recovery has been reported in acetaminophen-induced FHF patients despite impaired cerebral perfusion for 2 to 72 hours.⁴⁷ Most centers prefer epidural to subdural or intraparenchymal transducers for monitoring ICP because of the lower rates of hemorrhagic and infectious complications.^{45,48} Monitoring

BOX 96-4

Preventive and Therapeutic Interventions for Patients with Cerebral Edema and Intracranial Hypertension

GENERAL MEASURES

Head-of-bed elevation to 30° and maintenance of the patient's neck in a neutral position
Endotracheal intubation for grade III or IV hepatic encephalopathy
Minimize tactile and tracheal stimulation, including airway suctioning
Avoid hypovolemia and hypervolemia
Avoid hypertension
Avoid hypercapnia and hypoxemia
Monitor and maintain ICP < 15 mm Hg
Maintain CPP > 50 mm Hg
Monitor and maintain SvjO₂ between 55% and 85%
Use serial transcranial Doppler monitoring to titrate therapy

MANAGEMENT OF INTRACRANIAL HYPERTENSION

Mannitol boluses, 0.5-1.0 g/kg body weight
Hyperventilation titrated to a PCO₂ of 28-30 mm Hg
Induced moderate hypothermia to 32°C-33°C
Achieve serum sodium levels of 145-155 mEq/L
Induced coma with propofol or pentobarbital titrated to burst suppression of 5-10 cycles/s
CVVH for oliguria and hyperosmolarity (>310 mOsm/L)

OTHER UNPROVEN THERAPIES

Prophylactic phenytoin
Indomethacin, 25 mg intravenous bolus
Plasmapheresis
Total hepatectomy as a bridge to transplant

CPP, cerebral perfusion pressure; CVVH, continuous veno-venous hemofiltration; ICP, intracranial pressure; SvjO₂, jugular bulb oxygen saturation.

jugular bulb oxygen saturation with a reversed jugular bulb venous catheter also can guide interventions to avoid or treat intracranial hypertension. Decreased venous oxygen saturation (<55%) indicates cerebral ischemia, whereas high venous oxygen saturation (>85%) indicates either decreased metabolic demands of the brain or cerebral hyperemia (more commonly the latter).³²

Current recommendations include maintaining the patient's head at midline and a 30-degree upright angle to improve jugular venous outflow. In episodes of intracranial hypertension, a bolus of 0.5 to 1 g/kg of mannitol can be administered IV and repeated until the plasma osmolarity reaches 310 mOsm/L. Patients with oliguria and renal failure may require hemodialysis to avoid hyperosmolarity. Corticosteroids should not be used to control cerebral edema associated with FHF.

Hyperventilation reduces cerebral blood flow by 2% to 3% for every millimeter of mercury reduction in PaCO₂. Moderate hyperventilation (PaCO₂ = 28-30 mm Hg) can be employed to reduce ICP, but not all patients respond to reductions in PaCO₂, and the efficacy of hyperventilation wanes after 48 hours. Excessive cerebral vasoconstriction can be detected as widening of the difference in the cerebral arteriovenous oxygen content. Serial transcranial Doppler studies help detect early changes in cerebral blood flow in response to therapy.³² Induction of mild to moderate hypothermia (core temperature 34°C-35°C), which can be induced with cooling blankets or a special intravascular catheter, has been shown to reduce ICP and cerebral blood flow and improve CPP in patients with FHF awaiting transplant who do not respond to osmotic agents for the management of ICP.⁴⁹ Care must be taken to avoid both cardiac depression and shivering during the induced hypothermia. Induction of a barbiturate coma by administering parenteral sodium pentobarbital, sodium pentothal, or propofol titrated to the appearance of 5 to 10 cycles per second of EEG burst suppression can further reduce both CMR and cerebral blood flow in refractory patients. However, adverse effects such as myocardial depression or arterial hypotension may create the need for inotropic or vasopressor support to preserve CPP in the minimally adequate range. In patients at high risk for cerebral edema with high ammonia levels, grade III/IV encephalopathy, and renal failure despite the use of vasopressors, the use of a

hypertonic saline to induce hyponatremia to maintain a serum sodium concentration of 145–155 mEq/L is recommended.⁵⁰

Indomethacin may be used when cerebral hyperemia is present, as it has been shown to reduce cerebral blood flow and prevent brain edema in experimental models of FHF.⁵¹ Prophylactic infusion of phenytoin has been studied in two controlled studies that reached different conclusions.⁵² Phenytoin in the absence of seizures is not recommended.

Coagulopathy

Despite severe coagulopathy, patients with FHF seldom experience spontaneous hemorrhage. Since the INR is important to the prognostic evaluation, routine use of fresh frozen plasma (FFP) is not recommended unless spontaneous bleeding occurs or an invasive procedure is planned. Administration of FFP does not increase the survival rate and may cause intravascular volume overload and worsen cerebral edema, in addition to the potential risk of developing transfusion-related acute lung injury. Platelets may be transfused before invasive procedures if the platelet count is less than 50,000 cells/ μ L. When evaluation of the patient's mental state is not possible, monitoring coagulation parameters helps clinicians to assess the improvement or worsening of liver function.

AKI

AKI develops in up to 70% of patients with FHF, and the presence of FHF and renal failure has a grave prognosis without renal support. Mechanisms include renal hypoperfusion, ATN due to systemic inflammatory response syndrome (SIRS), hepatorenal syndrome, and direct toxic effects of the etiologic agent responsible for the liver injury (e.g., acetaminophen). The presence of SIRS predicts renal failure in non-acetaminophen-induced FHF.⁵³ Monitoring of serum creatinine and urinary output is essential. Diuretics and “renal dose” dopamine have no protective value in the treatment of acute renal failure and are potentially harmful. Nephrotoxic drugs such as aminoglycosides or radiographic contrast agents should be avoided. Continuous venovenous hemofiltration is preferred over intermittent hemodialysis in order to avoid rapid fluid shifts and abrupt changes in ICP.⁵⁴

Miscellaneous Therapy

Glycemic control is vital in the management of FHF. Constant infusion of glucose is preferable to bolus administration for the maintenance of euglycemia. FHF is a catabolic state, and nutrition should be started soon and adjusted individually to maintain an adequate caloric intake. Enteral nutrition through a nasogastric or nasojejunal tube is preferred to parenteral nutrition. Gastrointestinal prophylaxis is usually indicated.

A high index of suspicion should be maintained for the presence of infection, because fever and leukocytosis are absent in up to 30% of infected patients. Infection must be suspected in the presence of any sudden clinical deterioration, such as worsening encephalopathy or hemodynamic instability, especially when liver function has started to recover.⁵⁵ Microbiological cultures should be obtained from appropriate sites, and empirical antibiotics covering both enteric gram-negative and gram-positive bacteria should be started. Antifungal coverage should be considered, particularly in patients already on broad-spectrum antibacterial coverage with new-onset clinical deterioration. Unless there is high suspicion for bacterial infection, prophylactic antibiotics are not recommended.^{36,56}

Hepatic Replacement Therapies

Liver Transplantation

FHF accounts for about 5% to 10% of liver transplants performed in the United States. OLT, along with advances in critical care support, has dramatically improved the survival rate of FHF. However,

BOX 96-5

Hepatic Replacement Therapeutic Options Available to Patients with Fulminant Hepatic Failure

LIVER TRANSPLANTATION

- Cadaveric transplantation
- Whole liver
- Reduced size liver
- Split liver
- Auxiliary partial or whole liver
- Orthotopic position
- Heterotopic position
- Living-related transplantation
- Left lateral segment
- Left lobe
- Extended left lobe
- Right lobe

ARTIFICIAL LIVER ASSIST DEVICES

- Non-cell-based systems
- Charcoal hemoperfusion
- High-volume plasmapheresis
- Continuous high-frequency hemodiafiltration
- Molecular adsorbent recirculating system
- Cell-based systems (bioartificial liver assist devices)
- Primary porcine hepatocytes
- Human hepatoblastoma cells
- Extracorporeal liver assist device

HEPATOCYTE TRANSPLANTATION

transplantation is high risk, with a lower 1-year survival rate than those transplanted for other causes due to poor clinical condition at the time of the procedure. Contraindications to transplantation include irreversible brain damage, uncontrolled infection, severe pancreatitis, and malignancy. Early identification of patients who are likely to survive without OLT using both the King's College and the Clichy criteria is essential (Box 96-3). Liver biopsy, although not mandatory, can help clinicians decide the need for early transplantation. In general, patients with $\leq 60\%$ necrosis are likely to survive without the need for transplantation, whereas those with $\geq 90\%$ necrosis are unlikely to survive without transplantation.^{18,19} The prognosis without transplantation is less clear for patients in between these boundaries.

Various surgical options exist for liver transplantation in patients with FHF (Box 96-5). The most frequently utilized procedure is cadaveric whole organ transplantation, with the donor organ being placed in the orthotopic position. However, continued efforts are being made to assess ways of expanding the donor pool by using marginal donors, living-donor liver transplantation, cadaveric split-liver transplantation, and various hepatic support systems to prolong survival long enough for the patient to undergo liver transplantation. Therapeutic hepatectomy with temporary portocaval anastomosis in FHF has been reported to stabilize FHF patients until a suitable liver donor organ was procured.^{58,59}

Other Replacement Therapies

The use of artificial and bioartificial liver support devices in FHF has been shown to improve the biochemical and physiologic indices of liver function, although they have not been shown to improve transplant-free or overall survival.⁶⁰ Hepatocyte transplantation has been attempted in patients with FHF to maintain liver function until the regeneration of the native liver occurs or a graft for organ transplantation becomes available. Experimental studies in models of FHF have shown engraftment, function of transplanted hepatocytes, and increased survival.⁶¹ Future trials using this concept are needed.

CONCLUSION

FHF remains a rare but devastating illness with a high mortality rate. The treatment of FHF poses a great challenge to intensive

care clinicians. Early transfer to a transplant center is preferable not only because of the availability of transplantation but also because of the availability of experienced clinicians. A multidisciplinary approach to critical care management is required to address the multitude of organ derangements. Currently, only liver transplantation can radically alter the course of the disease process.

Although transplant surgery including immunosuppressive therapy has considerably advanced over the past decade, this intervention is expensive and is associated with complications related to both the procedure and the need for lifelong immunosuppression. Liver replacement therapies require further validation of their safety and efficacy.

KEY POINTS

1. Fulminant hepatic failure (FHF) is distinguished from severe acute hepatitis by the presence of hepatic encephalopathy. Without liver transplantation, the mortality rate for FHF is 50% to 80%.
2. Acetaminophen overdose remains the dominant cause of FHF in the United States. The hepatotoxic effects of acetaminophen are potentiated by concurrent alcohol ingestion, glycogen depletion, and/or anticonvulsant medication use.
3. The King's College Criteria remain the most widely used prognostic scoring system for FHF; however, failure to fulfil the criteria does not reliably predict survival.
4. The onset of grade III or IV hepatic encephalopathy prognosticates a higher risk for mortality. The onset of grade III or IV encephalopathy is an indication for endotracheal intubation and the performance of diagnostic and therapeutic modalities for intracranial hypertension.
5. Intracranial hypertension is the major cause for early mortality in FHF and is due to cerebral hyperemia, osmotic factors, and derangements of the blood-brain barrier.
6. Cerebral hyperemia can be detected by a decrease in the cerebral arteriovenous oxygen content difference or by transcranial Doppler showing elevated systolic blood flow velocity.
7. Elevated intracranial pressure can be managed with hyperventilation, mannitol administration, mild hypothermia, therapeutic sedation, and other less proven interventions; however, the optimal management of this condition remains unknown.
8. Prophylactic administration of fresh frozen plasma does not improve survival and may aggravate volume overload and cerebral edema.
9. Continuous veno-venous hemofiltration is the preferred method for artificial renal replacement to avoid hemodynamic fluctuations, which can aggravate cerebral hyperperfusion or hypoperfusion.
10. Liver transplantation is the only proven liver replacement therapy to reduce mortality. It remains unproven whether both biological and nonbiological artificial liver replacement therapies can reduce transplant-free mortality.

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Evaluating the patient with a possible acute abdomen in the intensive care unit (ICU) can be challenging. Patients frequently have multiple potential sources of sepsis and are often unable to describe symptoms or localize tenderness on physical examination. In addition, many imaging studies require transporting the patient to the radiology suite, which can be risky. These issues are especially troublesome for patients with potential acute cholecystitis.

Acute cholecystitis, frequently without gallstones, has long been recognized as a complication of surgery or acute critical illness.¹ The pathophysiology of cholecystitis in critically ill patients is different from that in the general population, as at least half of the patients have no gallstones.² Understanding the risk factors and pathogenesis of acute cholecystitis can help increase the index of suspicion and lead to early diagnosis and treatment, which is necessary for good outcomes in the already critically ill patient.

RISK FACTORS AND PATHOPHYSIOLOGY

In the general population, acute cholecystitis is associated with the presence of gallstones, which develop as a result of decreased solubility of cholesterol and bile salts in bile. Risk factors for gallstones include age, female sex, recent pregnancy, positive family history for gallstones, and hemolysis. Patients with gallstones may develop acute cholecystitis at any time. Rarely, acute calculous cholecystitis can occur during hospitalization for other reasons.

Acalculous cholecystitis can occur spontaneously under certain circumstances. In outpatients, risk factors for acalculous cholecystitis include diabetes mellitus, vasculitis, older age, and male sex.³ Acalculous cholecystitis also has been reported in cancer patients and patients with systemic infections. Acute cholecystitis is the most common indication for exploratory laparotomy or laparoscopy in patients with acquired immunodeficiency syndrome.⁴ Most have acalculous disease. Not surprisingly, the mortality rate is high.

In children, the majority of cases of acute cholecystitis are acalculous.⁵ The etiology appears to be dehydration or lymphadenopathy secondary to viral infection. Congenital biliary tract anomalies should also be considered.

Acute cholecystitis has been described in multiple reports as a complication of a variety of surgical procedures,^{6,7} trauma,^{8,9} burns,¹⁰ sepsis,¹¹ cardiovascular diseases, and malignancy.¹² There is also an association between total parenteral nutrition and biliary stasis.^{13,14} The pathophysiology of this association, however, remains unclear.

Theories regarding the pathogenesis of acalculous cholecystitis in critically ill and postoperative patients have evolved over the years. Presumptive causes have included gastrointestinal hypomotility, biliary stasis, and lack of enteral feeding in the postoperative period, leading to increased concentrations of bile salts and cholesterol in bile.¹⁵ The rarely observed acute onset of cholecystitis with refeeding suggests impaction of stones or viscous bile in the cystic duct with gallbladder contractions.

Gallbladder mucosal necrosis, arterial thrombosis, gangrene, and perforation suggest that hypoperfusion may be another critical mechanism for acalculous cholecystitis. Histopathologic studies confirm microvascular changes and ischemic cholecystitis histologically.^{16,17} Hypoperfusion, particularly of the splanchnic circulation, is common in critically ill patients. Etiologic factors include hemorrhage,

dehydration, heart failure, and sepsis. The use of vasopressors can exacerbate the situation. Mechanical ventilation with positive end expiratory pressure can increase hepatic venous pressure and thereby decrease portal perfusion.¹⁸

In addition to hypoperfusion, increased intraluminal pressure may be a critical factor.¹⁹ Biliary stasis secondary to fasting and narcotics may increase intraluminal pressure in the gallbladder. The combination of hypoperfusion and increased intraluminal pressure leads to gallbladder perfusion pressure decrease, wall ischemia, bacterial invasion, and cholecystitis.

The use of parenteral nutrition has also been implicated in the pathogenesis of acalculous cholecystitis. In addition to the effects of fasting, parenteral nutrition can directly decrease bile production, worsening biliary stasis. Biliary sludge can be found in almost all patients on long-term parenteral nutrition.^{14,15} Many go on to form gallstones. Trauma patients also develop sludge over time, which may play a role in the development of cholecystitis, as well as pancreatitis.²⁰

Other suggested etiologies include eosinophilic infiltration of the inflamed gallbladder resulting from a hypersensitivity reaction to antibiotics administered for other reasons²¹ and pigment load from massive transfusions.¹⁸ Neither theory has been substantiated.

INCIDENCE

The incidence of acute cholecystitis in the ICU is difficult to determine, given the great diversity in ICU patient populations and illness severity. Among cardiac surgical patients, acute cholecystitis, half of which is acalculous, is second only to upper gastrointestinal hemorrhage as an indication for abdominal surgery.²² Visceral hypoperfusion related to left ventricular dysfunction has been implicated as an etiologic factor. Early predictors of acute cholecystitis include arterial occlusive disease, low preoperative oxygen delivery, longer cardiopulmonary bypass times, need for surgical reexploration, cardiac arrhythmias, mechanical ventilation for ≥ 3 days, bacteremia, and nosocomial infections.⁶ The common threads among these factors include decreased tissue perfusion and oxygenation, significant surgical trauma with the expected inflammatory response, and perhaps bacterial translocation from the gut lumen. Because of high risk, some have suggested ultrasound screening in patients with complicated courses after cardiovascular surgical procedures.⁷

In the general population of postoperative patients, acute cholecystitis appears to occur with or without gallstones. Mortality is about 30%. Among trauma patients, about 90% of the acute cholecystitis cases are acalculous.^{8,9} The percentage of acute cholecystitis cases that are acalculous has increased significantly over time. Because the incidence of the disease is low but the many risk factors for the disease are common, it is difficult to identify specific groups of ICU patients who might benefit from selective screening for acute cholecystitis.

CLINICAL PRESENTATION

The signs and symptoms of acute cholecystitis do not generally differ between calculous and acalculous disease. Typically, patients with acute cholecystitis present with right upper quadrant or epigastric pain, often associated with ingesting a fatty meal. The pain may radiate to the back. Anorexia, nausea, and vomiting are common findings, as

are fever and chills. If the patient is receiving enteral nutrition, the symptoms may be related to meals or tube feedings.

On examination, the most consistent finding is fever. Focal tenderness in the right upper quadrant or epigastrium is typically found, often with evidence of peritoneal irritation. Rarely, the gallbladder is palpable. There may be abdominal distention and loss of bowel sounds. Jaundice may be present if the patient develops choledocholithiasis, Mirizzi's syndrome (external compression of the common hepatic duct by a stone impacted in the cystic duct), or liver dysfunction from sepsis. In critically ill patients, symptoms and physical examination findings are frequently difficult to assess or absent because of alterations in the patient's mental status and concurrent disease.

The most consistent laboratory finding is a leukocytosis. Circulating levels of liver enzymes and bilirubin are usually normal without choledocholithiasis, Mirizzi syndrome, or sepsis. Clinical findings and laboratory studies are not very sensitive or specific for cholecystitis, even in the general population,²³ and are less so in critically ill patients.

Given that the underlying pathophysiology of cholecystitis in the ICU often involves gallbladder wall ischemia, there is significant risk for rapid progression to gangrene and perforation. Consequently, even though other causes of sepsis in the ICU are more common, one needs to have a low threshold for considering cholecystitis in the differential diagnosis of patients who may have intraabdominal sepsis. Imaging of the gallbladder should be the next step.

IMAGING STUDIES

Ultrasonography is an accurate radiologic test and is usually the first test of choice for acute cholecystitis in the general population and in critically ill patients. In the ICU, the presence or absence of gallstones does not help with the diagnosis. The most useful ultrasonographic findings are thickening of the gallbladder wall and pericholecystic fluid (Fig. 97-1). These findings correlate well with operative findings. False positive findings may occur with sludge, nonshadowing stones, cholesterosis, ascites, hypoalbuminemia, and portal hypertension. Other ultrasonographic findings indicative of acute cholecystitis include the following: the "double wall sign," representing edema of the gallbladder wall; the "halo sign," representing sloughed gallbladder mucosa; intramural gas; distention of the gallbladder; and the "sonographic Murphy's sign," demonstrating point tenderness on physical examination over the gallbladder. The sensitivity of ultrasound for detecting acalculous cholecystitis is 81% to 92%. The specificity is 60% to 96%,²³⁻²⁶ but these results are operator dependent.

One problem in the ICU is that the typical ultrasonographic findings of cholecystitis can be seen in ICU patients without other evidence of cholecystitis. For example, Boland et al. performed ultrasound examinations of the gallbladder twice a week in a variety of ICU patients.²⁴ Half of the patients without calculi developed at least one ultrasonographic finding of acute cholecystitis. Helbich et al. attempted to apply a scoring system to the ultrasonographic findings characteristic of acute cholecystitis, suggesting that patients with several findings should undergo more aggressive diagnostic evaluation and, perhaps, therapeutic interventions.²⁵ In equivocal cases, serial examinations may demonstrate increasing wall thickness, which should increase the suspicion for cholecystitis.²⁶

Scintigraphy of the gallbladder frequently has been used when acute cholecystitis is suspected but findings from other tests such as ultrasound are inconclusive or contradictory. Gallbladder scintigraphy is performed by administering technetium-labeled iminodiacetic acid (IDA). Cholecystitis is diagnosed if the radioactive tracer is visualized in the small bowel without visualization of the gallbladder within 4 hours, suggesting occlusion of the cystic duct (Fig. 97-2). Delayed visualization of the gallbladder may represent chronic cholecystitis. The rate of false positive tests is significant in fasting patients, particularly those receiving parenteral nutrition, as the gallbladder may already be maximally filled. The use of intravenous morphine to increase tone in

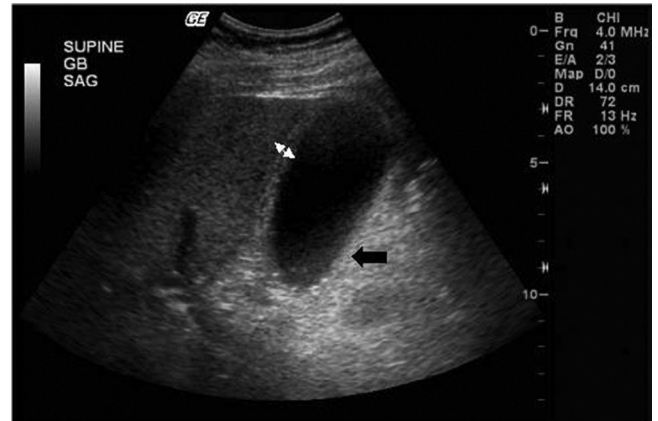


FIGURE 97-1 ■ Ultrasound of the gallbladder demonstrating wall thickening (double arrows) and sludge (black arrow).

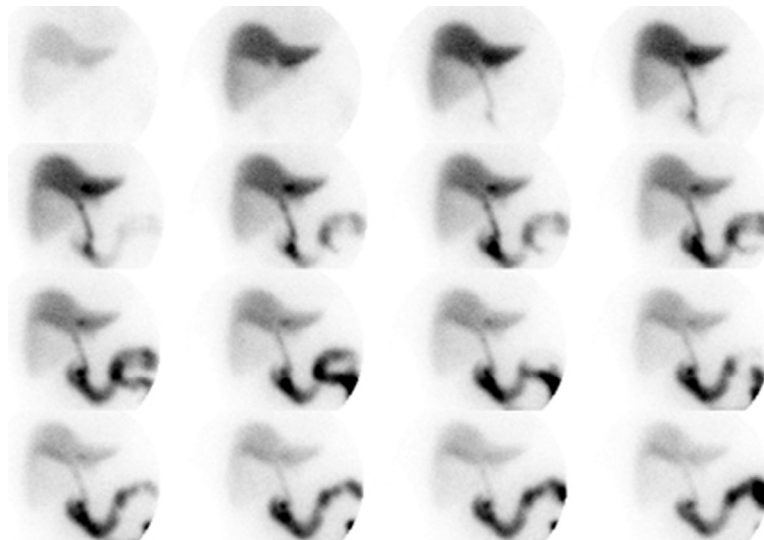


FIGURE 97-2 ■ Scintigraphy of the biliary tree demonstrating concentration of the tracer in the liver followed by flow into the biliary tree and small bowel. The gallbladder is not visualized.

the sphincter of Oddi and thereby increase pressure within the biliary system can decrease the risk of a falsely positive test.²⁷ In patients with severe liver disease, there may be inadequate uptake and excretion of the tracer to provide visualization of the biliary tree. Also, if a patient has had a biliary sphincterotomy, the tracer may pass too quickly through the biliary tree. Overall, the sensitivity of scintigraphy is 91% to 97%, and the specificity is 38% to 99%.²⁷⁻²⁹ Scintigraphy is a useful complement to ultrasonography for early decision making regarding intervention,^{28,29} but all clinical findings should be considered.

Computed tomography (CT) of the abdomen can be used to make the diagnosis of acute cholecystitis.^{30,31} The criteria for a positive study include wall thickness >4 mm, pericholecystic fluid, intramural gas, sloughed mucosa, or subserosal edema without ascites (Fig. 97-3). If intravenous contrast is administered, enhancement of the gallbladder wall may be seen. Although CT may not be as sensitive as the other studies for determining the presence of gallstones or acute cholecystitis, it can help to detect or rule out other causes of an acute abdomen. A great disadvantage of CT for critically ill patients, however, is the need to transport the patient to the scanner. In critically ill patients with suspected cholecystitis, ultrasound remains the first test of choice. Frequently, however, additional studies are necessary.

The differential diagnosis for patients with potential cholecystitis in the ICU includes peptic ulcer disease (particularly perforation), acute pancreatitis, hepatic or subphrenic abscess, pyelonephritis, right lower

lobe pneumonia (although right lower lobe atelectasis is common with a subdiaphragmatic process), and practically any cause of sepsis. The clinical presentation, laboratory studies, and imaging studies all should be considered when making clinical decisions.

To help with confirming the diagnosis of acute cholecystitis, the Tokyo Guidelines for the management of cholecystitis from 2013 (TG13) include specific criteria.³² Patients have suspected cholecystitis if they have signs of local inflammation (right upper quadrant pain, tenderness or mass, or a positive Murphy's sign) and signs of systemic inflammation (fever, elevated C-reactive protein, leukocytosis). The diagnosis is definitive if the patient has positive imaging studies. The severity of cholecystitis is defined as mild (without any of the "moderate" criteria), moderate (white blood cell count >18,000/mm³, palpable tender mass in the right upper quadrant, duration of symptoms >72 hours, or marked local inflammation), and severe (end-organ dysfunction).

MANAGEMENT

The management of a patient with acute cholecystitis involves supportive care, antibiotics, and either drainage or removal of the gallbladder (Fig. 97-4). Even in equivocal cases, drainage of the gallbladder may be appropriate in critically ill patients.

The standard initial medical treatment for acute cholecystitis includes antibiotics, analgesia, and, at least during the early phase, bowel rest. For patients who are septic from cholecystitis, it is appropriate to follow the Surviving Sepsis Campaign guidelines regarding fluid resuscitation, use of vasopressors, and initiation of broad-spectrum antibiotics.³³

Antibiotics for uncomplicated cholecystitis should cover enterococcal species and gram-negative rods, particularly *Escherichia coli* and *Klebsiella* spp.³⁴ Cultures are positive in about half the cases, more so beyond 72 hours after the onset of symptoms. If these patients undergo early cholecystectomy, continuing antibiotic coverage postop may not be necessary. In patients who have more severe illness or have previously received antibiotics, more resistant and unusual organisms are often cultured from gallbladder bile. These organisms can include *Staphylococcus* spp., resistant gram-negative bacilli, anaerobic bacteria, and fungi. Older patients are also more apt to have infected bile with more resistant organisms. In patients with empyema of the gallbladder, Tseng et al. found that bile cultures were positive in 83% of the cases.³⁵ Gram-negative bacteria (e.g., *E. coli*, *K. pneumoniae*, *Morganella morganii*, *Pseudomonas aeruginosa*, and *Salmonella* spp.) were found in 75%, gram-positive bacteria (e.g., *Enterococcus* spp.) in 30%, and obligate anaerobes in 7%. Broader coverage may be required initially until cultures are obtained and coverage can be more tailored, particularly in patients who have been exposed to antibiotics recently or who are immunosuppressed. Local antibiograms can be helpful.



FIGURE 97-3 ■ Computed tomographic study of the abdomen demonstrating thickening of the gallbladder wall with infiltration of the pericholecystic fat (black arrow) and gallstones (white arrow).

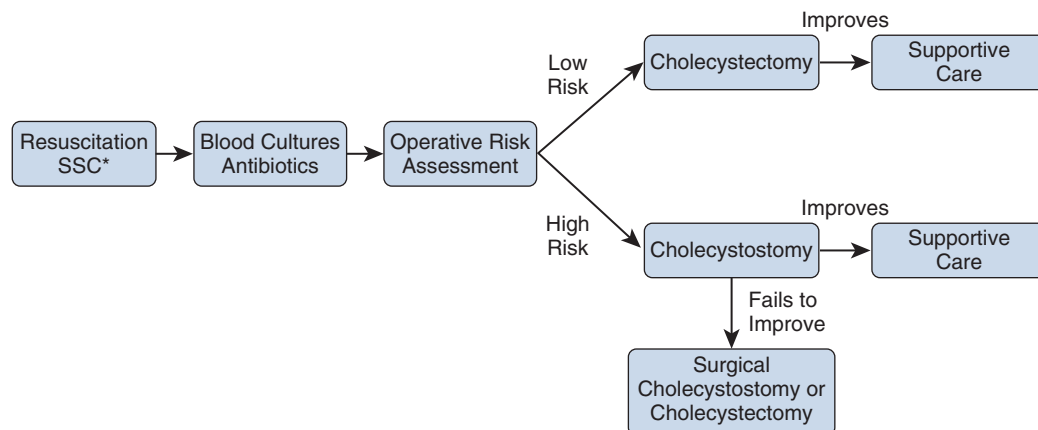


FIGURE 97-4 ■ Management of cholecystitis. *SSC, Surviving Sepsis Campaign.

Nonsteroidal antiinflammatory drugs can be very effective for controlling the pain from cholecystitis. When narcotics are needed, the choice of narcotic analgesic is probably not as important as was once believed. All narcotics can increase the pressure of the sphincter of Oddi, potentially increasing pressure in the biliary tree. Between these agents, there do not seem to be any important differences in pain relief or resolution of symptoms.

The next question is whether to drain or remove the gallbladder acutely. There is a lack of prospective, randomized trials to help clarify this issue. Early surgical consultation is critical. The decision regarding radiographic or surgical intervention must be made with consideration of both the critical care and general surgical issues. If the patient can tolerate transport to the operating room and a general anesthetic, cholecystectomy remains the most definitive therapy, particularly in light of the risk of gallbladder gangrene and perforation. Yacoub et al. have developed a scoring system for risk of gangrenous cholecystitis.³⁶ The 6.5-point scoring system is based upon the findings of age > 45 years (1 point), heart rate > 90 beats/min (1 point), male (2 points), white blood cell count > 13,000/mm³ (1.5 points), and gallbladder wall thickness > 4.5 mm on ultrasound (1 point). Frequently, however, critically ill patients with acute cholecystitis, particularly those with significant respiratory dysfunction or hemodynamic instability, may be too ill for cholecystectomy. With advances in the ease of image-guided drainage, bedside cholecystostomy using ultrasonographic guidance has been performed more commonly.

Image-Directed Drainage

Image-directed cholecystostomy was first used for palliation of obstructive jaundice in 1979.³⁷ The first large series of percutaneous cholecystostomy for acute cholecystitis was reported in 1985.³⁸ Of 114 patients, 113 were treated successfully.

Some physicians have used percutaneous cholecystostomy as a diagnostic and therapeutic maneuver in ICU patients with persistent, unexplained sepsis.³⁹ Many of these patients improved, though few had positive bile cultures. Thus, in critically ill patients without a definitive diagnosis of acute cholecystitis, the role of percutaneous cholecystostomy and bile culture remains unclear. Since the risk of this procedure is low, percutaneous cholecystostomy should be considered when the index of suspicion for acute cholecystitis is high enough in a critically ill patient.

Percutaneous cholecystostomy is contraindicated if the patient has evidence of diffuse peritonitis, suggesting gallbladder perforation. On the other hand, if imaging studies suggest a pericholecystic abscess, concomitant drainage of the abscess or surgical exploration is indicated.

Percutaneous cholecystostomy is performed under ultrasound or CT guidance. A needle is inserted into the gallbladder, usually via a transhepatic approach. The tract is dilated using a standard Seldinger technique. A pigtail catheter is advanced over the wire into the gallbladder. Some use a trocar technique instead. The catheter is then attached to a drainage bag.

Van Sonnenberg et al. reported successful percutaneous cholecystostomies in 125 of 127 patients with a variety of indications for the procedure.⁴⁰ Eleven patients (8.7%) had major complications, including bile peritonitis, bleeding, vagal reactions, hypotension, catheter dislodgment, and acute respiratory distress. Five (3.9%) had minor complications. No deaths were related to the procedure itself. Even in the presence of anticoagulation, the procedure seems to have relatively low risk.⁴¹

Overall mortality for percutaneous cholecystostomy is about 10%, similar to open cholecystectomy.⁴¹⁻⁴⁴ The limiting factor for success of percutaneous drainage is the viability of the gallbladder. Focal ischemia or necrosis is unlikely to improve without cholecystectomy and predisposes the patient to perforation. Cholecystectomy should be considered in patients who do not improve with cholecystostomy.

In many cases, cholecystostomy may provide definitive management without the need for interval cholecystectomy.^{43,44} Atar et al.

reported on a series of 81 patients with sepsis from acute cholecystitis and high anesthetic/surgical risk who underwent percutaneous cholecystostomy.⁴⁴ The procedure was successful in all cases. For patients with acalculous disease, the catheter was removed once the patient's symptoms resolved. This approach differs from the traditional recommendation for keeping the cholecystostomy in place for 6 weeks. Use of a transhepatic approach makes earlier removal safe. These patients did not undergo cholecystectomy. For patients with stones, a cholangiogram was performed. If common duct stones were found, the cholecystostomy access was used to perform a dilatation of the papilla. The stones were then pushed into the duodenum. All survivors with calculous disease underwent interval laparoscopic cholecystectomy.

A novel technique for drainage of the gallbladder involves a transpapillary endoscopic approach.⁴⁵ This approach may be helpful if other indications for endoscopic evaluation or intervention are present. It seems that the intervention is more successful if the ultrasound demonstrates that the gallbladder is not severely distended or thick.⁴⁶ Endoscopic ultrasound can also be used for transgastric or transduodenal placement of a stent into the gallbladder.⁴⁷

Surgical Management

Surgical options include cholecystostomy and cholecystectomy. Surgical cholecystostomy can be accomplished via a small right subcostal incision using local anesthesia or via laparoscopy. This procedure largely has been supplanted by image-guided, percutaneous cholecystostomy.

Cholecystectomy may be advantageous compared to cholecystostomy, since it allows one to examine the entire right upper quadrant for other pathology and to completely drain any fluid collections around the gallbladder. It also alleviates the risk of gallbladder perforation. When cholecystectomy is performed, a laparoscopic approach can usually be attempted, recognizing that one may need to abandon the attempt and proceed with an open procedure because of difficulty with the dissection. The timing of cholecystectomy for acute cholecystitis remains controversial.⁴⁸ On the other hand, if the patient is not responding to nonoperative management, cholecystectomy needs to be considered. If a patient improves after cholecystostomy, it may be beneficial to delay the cholecystectomy for at least 2 weeks.

Bedside laparoscopy can be performed for evaluation of the acute abdomen in critically ill patients. If acute cholecystitis is identified, a cholecystostomy can be performed readily or the patient can be taken to the operating room for a cholecystectomy.^{49,50} If the diagnosis of cholecystitis is excluded, the patient may be spared an unnecessary trip to the operating room.

Summary of Management

Early, supportive care for critically ill patients with cholecystitis should focus on resuscitation of the patient. The next steps are based upon the severity of cholecystitis (see Fig. 97-4). For patients at low risk for an operation, early laparoscopic cholecystectomy is recommended. For patients at high risk, urgent gallbladder drainage is more appropriate. If the patient fails to improve, operative intervention should be considered.

COMPLICATIONS AND OUTCOME

Complications of acute cholecystitis are much more common in critically ill patients than in the general population. Elderly patients are particularly at risk. Among patients with acalculous cholecystitis, gangrene is common.^{8-11,23} Compared to patients without gangrene, those with gangrene are at greater risk of perforation or of failure of percutaneous drainage. Some of these patients have emphysematous cholecystitis (gas in the wall of the gallbladder), a diagnosis that carries an even greater risk of perforation. Emphysema can be identified by plain abdominal radiographs, CT, or ultrasound. In these cases, antibiotics should cover gas-forming anaerobic organisms. Although

percutaneous drainage may be effective, early cholecystectomy is indicated if the patient does not improve promptly.

Perforation of the gallbladder occurs in up to 10% of cases.^{8-11,51} Usually, the resulting fluid collection is localized and amenable to percutaneous drainage. Free perforation also can occur, and when it does, the risk of mortality is markedly increased.⁵² The clinical problem, however, is that preoperative imaging may not demonstrate evidence of perforation.⁵³ The risk of perforation increases with delay in drainage or operation. Cholecystectomy is indicated for free perforation.

Empyema of the gallbladder also greatly increases mortality.⁵⁴ This complication may be amenable to percutaneous drainage, but the risks of failure or perforation are substantial.

The risk of mortality from cholecystitis in the ICU mainly reflects the underlying disease processes and comorbidities. Overall mortality is around 30%.⁸⁻¹¹

PREVENTION

No intervention has been shown conclusively to prevent development of cholecystitis in ICU patients. If the theories regarding the pathophysiologic mechanisms are correct, the incidence of the disease should be reduced by aggressively resuscitating patients with shock, avoiding biliary stasis by implementing early enteral feeding, and minimizing the use of narcotics. Intermittent doses of cholecystokinin or deoxycholic acid have been shown to increase bile flow and, therefore, may decrease the risk of acalculous cholecystitis in patients receiving parenteral nutrition,^{55,56} though studies in ICU patients are needed.

ANNOTATED REFERENCES

Boland G, Lee MJ, Mueller PR. Acute cholecystitis in the intensive care unit. *New Horiz* 1993;1:246-60.

This paper is an extensive review of the pathophysiology, presentation, and management of acute cholecystitis in the intensive care unit.

Helbich TH, Mallek R, Madl C, et al. Sonomorphology of the gallbladder in critically ill patients. Value of a scoring system and follow-up examinations. *Acta Radiol* 1997;38:129-34.

Ultrasound examinations of the gallbladder in patients in the intensive care unit frequently reveal equivocal findings. This group tried to quantify these findings, coupled with serial examinations, to improve the diagnostic accuracy of ultrasonography in this setting.

Hung BT, Traylor KS, Wong CY. Revisiting morphine-augmented hepatobiliary imaging for diagnosing acute cholecystitis: the potential pitfall of high false positive rate. *Abdom Imaging* 2014;39(3):467-71.

The addition of morphine to cholescintigraphy can improve the diagnostic accuracy of this test for diagnosing cholecystitis in critically ill patients.

References for this chapter can be found at expertconsult.com.

SUMMARY

The diagnosis of acute cholecystitis in critically ill patients is difficult because patients frequently do not present with the usual symptoms and signs. Laboratory tests are nonspecific. The best initial radiographic study is ultrasound. Scintigraphy and CT also may be helpful. Management includes antibiotics and bowel rest. Percutaneous cholecystostomy may be preformed in unstable patients, although cholecystectomy remains the most definitive treatment if this intervention can be accomplished safely.

KEY POINTS

1. Critically ill patients frequently do not present with the usual symptoms and signs of cholecystitis.
2. Laboratory tests for cholecystitis are not specific.
3. The best initial imaging study is ultrasound, but scintigraphy or computed tomography may be needed as well.
4. Management begins with antibiotics and bowel rest.
5. While cholecystectomy is the most definitive procedure, image-guided, percutaneous cholecystostomy is indicated for patients too unstable to undergo cholecystectomy.

Atar E, Bachar GN, Berlin S, et al. Percutaneous cholecystostomy in critically ill patients with acute cholecystitis. Complications and late outcome. *Clin Radiol* 2014;69(6):e247-52.

These authors describe a large series of patients who underwent percutaneous cholecystostomy with excellent results.

Yokoe M, Takada T, Strasberg S, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis. *J Hepatobiliary Pancreat Sci* 2013;20(1):35-46.

The Tokyo Guidelines group has published several guidelines for the diagnosis and management of acute cholecystitis. This paper reviews the clinical criteria for making the diagnosis and proposes useful criteria for severity assessment.

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The term *acute pancreatitis* describes a wide spectrum of disease ranging from a mild edematous form of acute pancreatitis to severe acute necrotizing pancreatitis. It is the most common gastrointestinal disease requiring hospitalization in the United States and accounts for annual costs of more than \$2 billion.^{1,2} The mild form of acute pancreatitis is a self-limited disease associated with minimal organ dysfunction; it has a mortality rate of less than 1% and usually resolves in 3 to 4 days. Patients with this form of acute pancreatitis rarely need intensive care unit (ICU) therapy or pancreatic surgery. Although most (80%) patients with acute pancreatitis have mild disease, 10% to 15% develop the systemic inflammatory response syndrome (SIRS) and run a fulminant clinical course leading to pancreatic necrosis and multisystem organ injury.^{3,4} The mortality rate for severe acute pancreatitis is 15% to 30%, whereas the overall mortality rate for all patients presenting with acute pancreatitis is less than 5%.^{3,4}

The first 7 to 14 days of this disease process are characterized by SIRS and resulting end organ dysfunction. Inflammatory mediators are released into the systemic circulation, and patients manifest signs and symptoms of cardiorespiratory and renal failure.⁵ Pancreatic infection is uncommon during this early phase, but bacteremia and pneumonia have been identified at a median of 7 days.⁵ Attempts to modify the course of the disease by instituting therapy with protease inhibitors, octreotide, or platelet-activating factor receptor antagonists have been unsuccessful.^{6,7}

Since the 1980s, the morbidity and mortality associated with acute pancreatitis have decreased substantially. Most cases of pancreatitis that result in patient death are related to infection.⁸ Infection of the necrotic pancreas (and associated tissues) typically develops in the second and third weeks of the disease and is reported to occur in 40% to 70% of patients with pancreatic necrosis.^{5,7,8} Infected necrosis is the most important risk factor for death secondary to necrotizing pancreatitis. Prevention, diagnosis, and optimal treatment of infection in severe acute pancreatitis are crucial for improving outcome for patients with this disease.

This chapter discusses the etiology, pathophysiology, severity and staging, and management of patients with severe acute pancreatitis.

ETIOLOGY AND EPIDEMIOLOGY

Overall rates of hospitalization for acute pancreatitis in the United States have increased to more than 274,000, making it the most common gastrointestinal cause requiring hospitalization.¹ The increasing incidence of acute pancreatitis is believed to be related to increases in alcohol consumption and gallstone disease. Acute pancreatitis is slightly more common in men than in women, with a female-to-male ratio of 1:1.2 to 1:1.5. Hospitalization rates and emergency department visits for patients diagnosed with acute pancreatitis are higher for blacks than for whites. Pancreatitis can occur in any age group, but cases in the very young (<3 years) are likely to be related to a systemic disease such as cystic fibrosis. On the other hand, alcohol-related acute pancreatitis has a peak incidence between 45 and 55 years of age, with a gradual decline thereafter. Biliary pancreatitis is more common in women, and alcohol-related acute pancreatitis is more common in men.

Understanding the etiology of a particular case of pancreatitis is important; evaluation and treatment depend to some extent on the

predisposing disease process. Gallstones are the leading cause of acute pancreatitis in developed countries and account for 35%-40% of all cases.⁹ It is also the most common form of pancreatitis in older patients, probably related to the increased prevalence of cholelithiasis in this age group.

Alcohol abuse typically accounts for about 30% of cases of acute pancreatitis. Infrequent causes of pancreatitis include drug reactions (usually idiosyncratic), pancreatic and ampullary tumors, hypertriglyceridemia, hypercalcemia, choledochal cysts, trauma (including acute pancreatitis after endoscopic retrograde cholangiopancreatography), and infectious or parasitic organisms. Rare causes include bites of certain spiders, scorpions, and the Gila monster lizard. Unidentified causes are termed *idiopathic*.

PATHOGENESIS AND GENETIC SUSCEPTIBILITY

Regardless of the etiology, pancreatitis is an inflammatory process that can initiate SIRS.⁵ The exact intracellular mechanisms initiating and accelerating pancreatitis are not completely understood. Three phenotypic responses occur in the acinar cell in the early phases of acute pancreatitis: (1) changes in secretions, (2) intracellular activation of proteases, and (3) generation of inflammatory mediators.¹⁰ Shortly after an appropriate stimulus, secretions are released from the apical cells into the pancreatic duct. This process entails exocytotic fusion of zymogen granules with the apical plasma membrane; the granules do not fuse with the basolateral membrane. However during acute pancreatitis, there is (1) markedly decreased apical secretion from the acinar cell, (2) disruption of the paracellular barrier in the pancreatic duct with leakage of contents into the paracellular space, and (3) redirection of secretion from zymogen granules to the basolateral regions of the acinar cell. Inappropriate activation of the proteolytic enzyme, trypsin, is thought to be the initial step in the development of acute pancreatitis. Trypsinogen activation is promoted by cationic trypsinogen mutations (PRSS1+), active trypsin, high calcium ion concentration, and low pH. Calcium levels are regulated in part by calcium-sensing receptors (CASR) and dysregulated by ethanol.^{5,11-13} If trypsin is active within the pancreas, inflammation results and this upregulates the serine protease inhibitor Kazal type 1 (SPINK1) gene, which further blocks activation of trypsinogen. Trypsin also activates cells via the trypsin receptor present in acinar and duct cells, known as *protease-activated receptor 2 (PAR-2)* (Fig. 98-1).¹⁴ Trypsin activity in the pancreas is controlled mainly by the pancreatic secretory trypsin inhibitor (PSTI), also called SPINK1.¹⁵ PSTI, a potent natural inhibitor of trypsin, is synthesized in pancreatic acinar cells. When trypsinogen is cleaved to release trypsin in the pancreas, PSTI immediately binds to the enzyme to prevent further activation of additional pancreatic enzymes. PSTI also blocks further activation of pancreatic cells via the trypsin receptor, PAR-2.¹¹

Several additional protective systems prevent pancreatic autodigestion by trypsin, and the genetic expression of these systems may contribute to the risk of developing acute pancreatitis or modulate the severity of the disease when it occurs.^{11,12,15} A mutation in SPINK1, N34S, has been reported in people with familial pancreatitis, in children with idiopathic chronic pancreatitis, and in 2% of the control population.^{11,13} Because these mutations in SPINK1 are much more

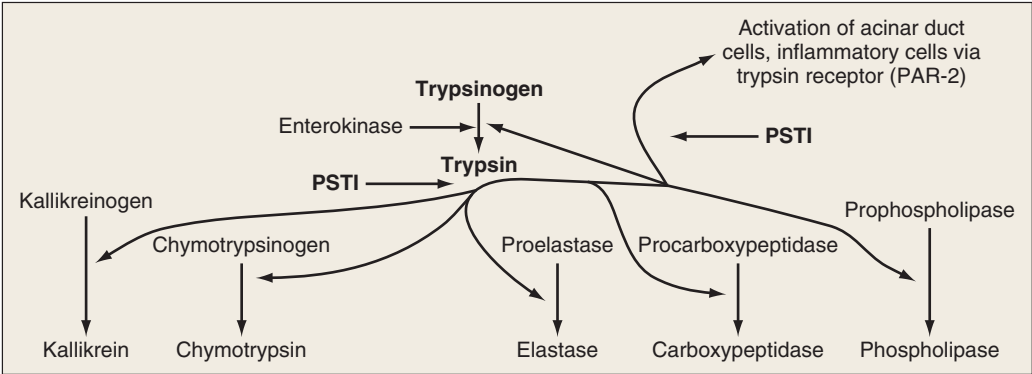


FIGURE 98-1 ■ Activation pathways of proenzymes and protease-activated receptor (PAR)-2 by trypsin. Trypsin activates many digestive proenzymes and inflammatory cells (via PAR-2). Trypsin activity in the pancreas is mainly controlled by pancreatic secretory trypsin inhibitor (PSTI). When trypsinogen is activated into trypsin in the pancreas, PSTI immediately binds to trypsin to prevent further activation of pancreatic enzymes.

common than pancreatitis, this mutation is probably a disease modifier rather than a causative factor of acute pancreatitis.

■ **DIAGNOSIS**

Acute pancreatitis can be diagnosed when a patient presents with acute upper abdominal pain and tenderness, nausea, vomiting, and hyperamylasemia or hyperlipasemia.¹⁶ These signs are nonspecific and can be present in other acute intraabdominal conditions. The Cullen sign and the Grey Turner sign (periumbilical and flank bruising, respectively) are rare and can be present with any cause of retroperitoneal hemorrhage. Although hyperamylasemia is common in patients with acute pancreatitis, normal circulating amylase levels can be present in 10% to 20% of all cases, predominantly in those secondary to hyperlipidemia, acute exacerbations of chronic pancreatitis, and those that present late in the course of the disease.¹⁷ Advantages of serum amylase determination include its technical simplicity, wide availability, and sensitivity. It does, however, have a low specificity. Serum lipase can also be found to be elevated in acute pancreatitis. Its concentration increases within 4 to 8 hours, peaks at 24 hours, and returns to normal after 8 to 14 days.¹⁸ The major advantage of serum lipase determination as a diagnostic test is its excellent sensitivity in acute alcoholic pancreatitis. It is also valuable when patients present to an emergency department days after the onset of the disease, as it remains elevated longer than amylase.¹⁸ Simultaneous estimation of amylase and lipase levels does not improve accuracy of diagnosis of acute pancreatitis.¹⁸

Serum triglyceride levels should be determined when an etiology of pancreatitis is uncertain and lipemic serum is suspected. While it has never been proven, circulating triglyceride levels above 1000 mg/dL (11.3 mmol/L) are believed to trigger pancreatitis.

Trypsinogen-2 can be used for diagnosing acute pancreatitis. It is measured via a urine dipstick assay (urinary trypsinogen-2-UT2), using a threshold of 50 µg/L.¹⁷ It has a reported sensitivity and specificity of 80% and 92%, respectively, at identifying patients with acute pancreatitis.¹⁷

■ **SEVERITY AND SCORING**

Prediction of the severity of the disease at the time of admission can be difficult. Several different prognostic scoring systems with clinical, laboratory, and radiologic criteria have been proposed, yet none of the proposed scoring systems has a high sensitivity, specificity, positive predictive value, or negative likelihood ratio, and frequent clinical assessment is essential for identifying patients with severe disease. Ranson's criteria (Table 98-1),¹⁹ the Imrie²⁰ (Glasgow) score, the Acute Physiologic and Chronic Health Evaluation (APACHE) II and III

| TABLE 98-1 Ranson's Criteria for Patients with Non-Gallstone-Associated Pancreatitis | |
|--|-------------------------------------|
| AT PRESENTATION | DURING INITIAL 48 HOURS |
| Age > 55 years | Hematocrit fall > 10% |
| White blood cell count > 16,000/µL | Blood urea nitrogen > 5 mg/dL |
| Blood glucose > 200 mg/dL | Serum calcium < 8 mg/dL |
| Serum alanine transferase > 250 U/dL | Arterial PO ₂ < 60 mm Hg |
| Serum lactate dehydrogenase > 350 IU | Base deficit > 4 mEq/L |
| | Estimated fluid sequestration > 6 L |

Modified from Blamey SL, Imrie CW, O'Neill J, Gilmour WH, Carter DC. Prognostic factors in acute pancreatitis. *Gut* 1984;25:1340-6.

scores,²¹ the simplified acute physiology score, and Balthazar's computed tomography (CT) index are the most popular scoring systems and are often used to determine the need for admission to an ICU. Ranson's criteria is based on 11 prognostic signs present at presentation and 48 hours later.¹⁹ A meta-analysis of studies using the Ranson criteria reported the following with regard to predicting severe acute pancreatitis (SAP): sensitivity, 74%; specificity, 77%; positive predictive value, 49%; and negative predictive value, 91%. Many institutions routinely utilize the APACHE scoring system for all patients admitted to the ICU.²¹ Patients with SAP and an APACHE II score above 8 have severe disease and are likely to develop organ failure. Key statistical parameters related to APACHE II scores of above 7 and the prediction of SAP are as follows: sensitivity, 65%; specificity, 76%; positive predictive value, 43%; and negative predictive value, 89%. Balthazar's CT index^{22,23} uses both fluid collections and amount of pancreatic necrosis to predict outcomes. An international group of experts concluded that an additional group of patients should be identified: those with moderately severe acute pancreatitis (MSAP).²⁴ In 2012, Talukdar et al. performed a prospective study in which patients were classified as having SAP, MSAP, or mild acute pancreatitis. The MSAP group had intervention rates and hospital stays comparable to those patients with SAP; however, only 12% required ICU care and none of them died, suggesting that this is a separate entity that should be identified early in order to determine prognosis.²⁴

There are several serum biomarkers that have been studied as predictors of the severity of acute pancreatitis. C-reactive protein (CRP) levels above 150 mg/L are associated with pancreatic necrosis

(sensitivity and specificity of 80%); however there is a 48-hour latency period before CRP increases, limiting its utility as an early predictor of disease.²⁵ Procalcitonin levels higher than 3.8 ng/mL can predict pancreatic dysfunction (sensitivity 79%, specificity 93%).²⁶

The scoring systems mentioned help quantify the degree of illness, but it is essential that clinicians identify patients with impending or actual organ failure. Patients with signs of SIRS are especially at risk of further organ dysfunction.

The Atlanta Classification system was initially published in 1993 and grouped pancreatitis into different categories in an attempt to determine severity.²⁷ It was revised in 2012 and groups patients into interstitial edematous pancreatitis and necrotizing pancreatitis: those who have diffuse inflammation of the pancreas and surrounding tissue are considered to have the former, while those with necrotic glands will be grouped as having necrotizing pancreatitis.^{27,28} The Atlanta Classification system also grades presentation into mild acute pancreatitis (no organ failure and no local or systemic complications), moderately severe acute pancreatitis (organ failure that resolves within 48 hours, local or systemic complications without persistent organ failure), and severe acute pancreatitis (persistent organ failure).^{27,28}

IMAGING

Ultrasonography and Endoscopic Ultrasonography

Ultrasonography (US) should be considered as an initial test in all patients with pancreatitis, especially if gallstones or biliary disease is suspected.²⁹ It can be done at the bedside with no sedation, making it an important tool in the evaluation of unstable patients. US is not currently used for grading the severity of pancreatitis or the extent of gland necrosis; however, contrast-enhanced US may change this situation. Contrast-enhanced US has a sensitivity and specificity of 82% and 89%, respectively.²⁹

Endoscopic ultrasonography (EUS) combines ultrasonography and endoscopic evaluation. It is less invasive than endoscopic retrograde cholangiopancreatography (ERCP) and has been shown to be clinically useful in diagnosing acute pancreatitis and choledocholithiasis. EUS may be useful when CT and US fail to show common bile duct stones. EUS may also be useful for selecting patients who might benefit from ERCP and early stone extraction. Petrov et al. reviewed studies of patients randomized to EUS-guided ERCP ($n = 213$) versus ERCP alone ($n = 210$). These authors showed that ERCP could be avoided in 67.1% of patients when EUS failed to identify gallstones.³⁰ The use of EUS significantly reduced the risk of overall complications (relative risk [RR] 0.35, 95% confidence interval [CI] 0.20-0.62) and post-ERCP pancreatitis (RR 0.21, 95% CI 0.06-0.83). One additional advantage of endoscopic ultrasonography is that it can be performed in pregnant women, patients with metallic implants, and patients who are too unstable to be transported out of the ICU.³⁰

Computed Tomography

Contrast-enhanced CT is considered the gold standard for diagnosing pancreatic necrosis and peripancreatic collections and for grading acute pancreatitis.^{22,23} Necrosis is detected by CT as focal or diffuse areas of diminished pancreatic parenchymal contrast enhancement (<50 Hounsfield units). The accuracy of this test is greater than 90%. CT findings of acute pancreatitis include interstitial edema, irregularity of the contour of the pancreas with obliteration of the peripancreatic fat planes, heterogeneous appearance with areas of decreased density within the pancreas, and variable ill-defined fluid collections (Fig. 98-2). The Balthazar index ranges from 0 to 10 and is obtained by adding the points attributed to the extent of the inflammatory process to the volume of pancreatic necrosis. Although CT findings correlate with clinical course and severity of disease in patients with acute pancreatitis, it is not necessary to obtain this study in patients with mild

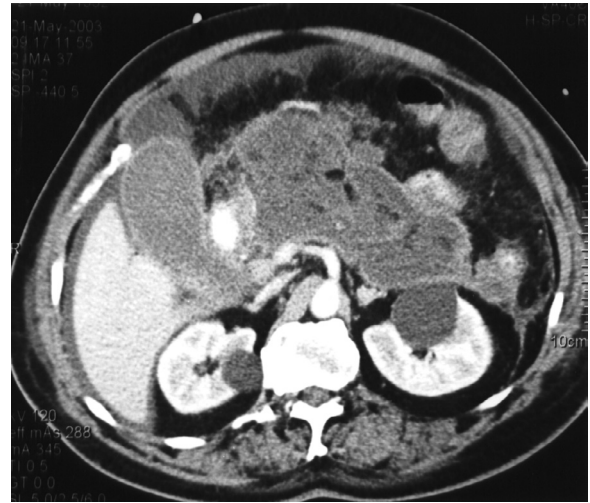


FIGURE 98-2 ■ Computed tomography scan of a patient with severe necrotizing pancreatitis and Balthazar grade E scan; more than 50% necrosis of the gland was seen on previous scans of the gland, giving the patient a Balthazar index of 10.

pancreatitis. Obtaining an early CT scan may cause derangements of pancreatic microcirculation and may lead to contrast nephropathy. Therefore, CT scans before 72 hours of disease should be reserved for patients in which the diagnosis is in doubt.³¹

Endoscopic Retrograde Cholangiopancreatography

ERCP is an effective means of treating common bile duct stones.³² ERCP is not indicated for the management of mild pancreatitis or nonbiliary pancreatitis, and its overall use in patients with acute pancreatitis continues to be debated.³³⁻³⁵ Its main application is in the management of patients with biliary pancreatitis and biliary obstruction or cholangitis. There remains controversy regarding the role of ERCP for the management of patients with biliary pancreatitis but without bile duct obstruction.

Magnetic Resonance Cholangiopancreatography

Magnetic resonance imaging (MRI) and MRCP are noninvasive imaging modalities that are useful for depicting abnormalities of the pancreatic duct and parenchyma. MRI has several advantages over CT: there is no risk from radiation with MRI, it can detect pancreatic duct disruption, and it can help identify the etiology of acute pancreatitis. Without injection of gadolinium, MRI can discriminate between normal pancreatic parenchyma, the presence of edema, and the presence of necrosis, as well as differentiate between solid and liquid fluid collections. MRCP can be performed when ERCP has failed or is not possible, with the disadvantage that the former is just a diagnostic modality and further therapeutic interventions may need to follow.

While contrast-enhanced CT is considered the gold standard, a few studies suggest that MRI compares favorably with contrast-enhanced CT for the diagnosis and grading of severe acute pancreatitis. The major advantage of MRCP for SAP is that MRCP obviates the necessity for the infusion of iodinated contrast media and thereby may lower the risk of acute renal dysfunction in these critically ill patients.^{36,37} Bowel peristalsis, vascular motion artifacts, gastrointestinal air, and the presence of metallic clips can all degrade the quality of images obtained with MRCP. One disadvantage of MRI and MRCP is that acquisition of the image takes longer than with CT.

MANAGEMENT

General Support

Monitoring and Resuscitation

Several publications suggest that patients with SAP should be managed in an ICU, preferably by a specialist team. Resuscitation of intravascular volume is a key component of the initial management, regardless of the etiology and severity of acute pancreatitis. Sequestration of fluid into the extravascular extracellular compartment can lead to loss of as much as a third of plasma volume. Rapid restoration and maintenance of intravascular volume is essential because hypovolemia and shock are probably important factors contributing to the high incidence of acute renal failure among patients with SAP.^{9,16,38–40}

Aggressive fluid resuscitation has been shown to be important in the management of patients with acute pancreatitis, especially during the first 24 hours. Warndorf et al. conducted a retrospective study that associated early resuscitation (one-third of the total 72-hour fluid volume given within 24 hours) with a decrease in SIRS.³⁹ However, excessive inappropriate resuscitation can also lead to significant morbidity and mortality, including respiratory failure and abdominal compartment syndrome (ACS).^{3,40}

Single-organ or multiple-organ dysfunction is common, and monitoring of respiratory and cardiovascular status is essential. Adequate oxygen delivery to tissues and prevention of splanchnic ischemia are essential to prevent further organ injury. Vasoactive agents may be required, but they should be considered only after ensuring adequate resuscitation.

Even when systemic signs of adequate resuscitation are present, local inflammation in the pancreas can continue, leading to ongoing production of cytotoxic mediators. Treatment with protease inhibitors has been successful in experimental models of acute pancreatitis and is used via continuous arterial infusion in Japan.^{41–44} A trial was carried out comparing the administration of no infusions with continuous regional arterial infusions of the protease inhibitor, gabexate mesilate, plus antibiotics.^{43,45,46} Treatment with gabexate mesilate shortened the duration of abdominal pain and duration of SIRS, decreased the length of hospital stay, and decreased circulating levels of several markers of inflammation. Other studies have been unable to replicate these promising results. Yasunaga et al. found no significant differences in mortality (1% vs. 1.2%, $P = 0.789$) or median length of stay (10 days vs. 10 days, $P = 0.160$) between patients treated with and without gabexate mesilate.⁴⁵ A meta-analysis published in 2014 revealed no differences in mortality in patients treated with protease inhibitors when compared to those who did not receive protease inhibitors as part of their treatment.⁴¹

Although there has been significant interest in decreasing cytokine production by administering an anti-TNF antibody and IL-1 receptor antagonists, this approach has not been shown to be beneficial.^{5,47}

Pulmonary Dysfunction

Respiratory dysfunction is a major component of multiple-organ dysfunction syndrome secondary to acute pancreatitis. These patients may develop acute respiratory distress syndrome (ARDS) and require ventilator support. Although the mechanism by which pancreatitis leads to ARDS is not entirely clear, it is believed that pancreatic phospholipase A2 is released into the circulation and it degrades dipalmitoylcholine (a component of surfactant).^{7,48}

Pulmonary Management

Patients with SAP must be monitored closely for hypoxic and/or hypercarbic respiratory failure. Supplemental oxygen is almost uniformly required, and mechanical ventilation is often also required. Noninvasive positive-pressure ventilation (NIPPV) may be used to avoid endotracheal intubation in carefully selected patients. SAP is often associated with marked abdominal distention and diminished functional residual lung capacity on this basis. Management of acute lung injury and

ARDS secondary to SAP is similar to the management of these conditions associated with other primary problems (e.g., sepsis).⁴⁹

Pain Relief

Provision of pain relief to patients with SAP is not only humane but may also improve pulmonary dysfunction. In studies outside the United States, buprenorphine was noted to have a superior effect to procaine and did not exacerbate acute pancreatitis by promoting contraction of the sphincter of Oddi.⁵⁰ In a single trial comparing metamizole and morphine, no difference in analgesia was seen.⁵¹ Although IV narcotics are useful and effective, epidural analgesia with local anesthetics should also be considered.

Specific Support

Nutrition

Traditionally, patients with acute pancreatitis have been managed by providing IV fluids and nutrition, and avoiding enteral feeding to “rest” the inflamed pancreas and prevent stimulation of exocrine function and the release of proteolytic enzymes. Nevertheless, most patients with mild acute pancreatitis can begin oral supplementation within a few days of their presentation and do not require supplemental nutrition.

In the past, the primary approach for providing nutritional support for patients with SAP was total parenteral nutrition (TPN). TPN is expensive, may increase the risk of sepsis or metabolic derangements, and has been associated with alterations in gut barrier function.^{27,52,53} A meta-analysis of several trials of enteral versus parenteral nutrition for patients with SAP revealed that enteral nutrition reduced the frequency of infections, decreased the need for surgery, and shortened length of hospital stay.⁵⁴ Similarly, the Cochrane Group reviewed 8 trials of enteral versus parenteral nutrition and concluded that the relative risk (RR) of death with enteral nutrition was 0.50 (95% CI 0.28–0.91), RR for multiple-organ failure was 0.55 (95% CI 0.37–0.81), RR for systemic infection was 0.39 (95% CI 0.23–0.65), RR for operative interventions was 0.44 (95% CI 0.29–0.67), RR for local septic complications was 0.74 (95% CI 0.40–1.35), and RR for other local complications was 0.70 (95% CI 0.43–1.13). Mean length of hospital stay was reduced by 2.37 days (95% CI 7.18–2.44) in the enteral group.⁵²

If a nasoduodenal or nasojejunal tube is placed, care should be taken if blind manipulation through the duodenum is attempted as the duodenum is often distorted in patients with acute pancreatitis, and the risk of perforation is increased. In a meta-analysis of three randomized controlled trials by Chang et al., a comparison of nasogastric and nasojejunal feeding in patients with pancreatitis was performed. There were no differences in mortality (RR = 0.69, $P = 0.25$), tracheal aspiration (RR = 0.46, $P = 0.20$), diarrhea (RR = 1.43, $P = 0.43$), and exacerbation of pain (RR = 0.94, $P = 0.90$) between the two groups.⁵⁵ This suggests that nasogastric feeding was not inferior to nasojejunal feeding. Supplemental TPN may be valuable when nutritional requirements cannot be achieved using enteral nutrition alone or enteral access cannot be established. Ileus is not an absolute contraindication to enteral feeding, and most patients can tolerate continuous feeding at a slow rate.

Resting energy expenditure varies widely among patients with SAP, depending on the magnitude of the regional inflammatory process and the presence of additional complications, especially infection. Infection can increase energy expenditure by 5% to 20%, but overfeeding should be avoided, nutritional guidelines should be considered, and glucose control should be employed. Although triglyceride levels should be monitored and not be allowed to escalate to levels above normal, administration of lipids is safe and appropriate as there is no proven causal relationship between infusion of exogenous fat and the development of pancreatitis.

The timing of oral refeeding must be based on clinical judgment. Delayed nutrition is associated with increased frequency of infected necrosis/fluid collections, respiratory failure, and a need for ICU hospitalization.⁵⁶

PATHOGENESIS OF PANCREATIC INFECTION AND ANTIBIOTIC PROPHYLAXIS

Microorganisms can gain access to necrotic pancreatic and peripancreatic tissue via several routes, bacterial translocation from the colon being the most likely. Failure of the intestinal barrier permits bacteria and yeast to translocate from the lumen of the gut into ascites, mesenteric lymph, the bloodstream, and the pancreatic phlegmon. The notion that pancreatic infection in acute pancreatitis is due to infection by gut-derived organisms is supported by the observation that most pancreatic infections are monomicrobial and caused by gram-negative bacteria, at least when prophylactic antibiotics have not been administered.^{57–60} Further support for the intestinal origin of pancreatic infection in acute pancreatitis derives from data obtained in a clinical trial of selective decontamination of the gut, wherein enteral administration of poorly absorbed antimicrobial agents was associated with a significant reduction in late mortality, principally owing to decreased incidence of pancreatic gram-negative infection. Microorganisms can also gain access to pancreatic necrosis through hematogenous dissemination from infected central venous catheters, via the biliary tree, or via the pancreatic duct from the lumen of the duodenum.^{61,62}

The wisdom of using prophylactic antibiotics for managing acute pancreatitis has been debated for more than 50 years.^{58,60,63,64} When more than 30% of the gland is necrotic, pancreatic infection occurs in over 30% of patients with acute pancreatitis. Because approximately 80% of deaths due to acute pancreatitis are related to infectious complications, it is important to determine if administration of prophylactic antibiotics can decrease the incidence of local or distant infections or the morbidity and mortality associated with pancreatic necrosis.

There are three trials that are quoted to support the use of antibiotic prophylaxis for acute pancreatitis. The first trial by Pederzoli et al. randomized 74 patients to receive either imipenem or placebo. The secondary rate of pancreatic infection decreased from 30% in the control group to 12% in the imipenem group ($P = 0.10$). There were no beneficial effects on organ failure, mortality, or avoidance of surgery.⁵⁸ The second trial by Sainio et al. randomized 60 patients to receive either cefuroxime or placebo. The infectious complications and mortalities were more common in the group not treated with antibiotic prophylaxis compared with the group treated with cefuroxime (1.8 per patient vs. 1 per patient, $P = 0.10$; 7 vs. 1, $P = 0.03$, respectively).⁶³ Finally, the Luiten et al. trial randomized 102 patients to selective digestive decontamination versus standard therapy. There were 18 deaths among the 52 patients in the control group (35%) and 11 deaths among the 50 patients in the selective digestive decontamination group (22%; $P = 0.048$).⁶⁴

There are other trials that do not support the use of prophylactic antibiotics in the treatment of SAP. Isenmann et al.⁶⁵ compared ciprofloxacin and metronidazole to placebo while Dellinger et al.⁶⁶ did the same with meropenem and placebo. Both studies failed to show a difference in pancreatic infection and mortality rate.

Extrapancreatic infections appear to be lower in patients who receive prophylactic antibiotics. In a study by Hart et al. extrapancreatic infections were decreased when prophylaxis was used (RR 0.51, 95% CI 0.32–0.82).⁶⁷ Xu et al. also concluded that peripancreatic infection (RR 0.69, 95% CI 0.48–0.91) and extrapancreatic infection (RR 0.66, 95% CI 0.48–0.91) were reduced by administration of antibiotics.⁶⁸ In both these studies, there were no differences in mortality between treatment group and placebo group.

Instead of IV antibiotics, the use of probiotics has been considered. In a recent systematic review by Gou et al., 6 trials with a total of 536 patients were analyzed in order to determine if probiotic treatment was beneficial. Probiotics had no significant effect on total infections (RR = 1.09, $P = 0.57$), infection rate (RR = 1.19, $P = 0.47$), operation rate (RR = 1.42, $P = 0.71$), length of stay (RR = 2.45, $P = 0.35$), and mortality (RR = 0.72, $P = 0.25$).⁶⁹

Whether prophylactic antibiotics should be broadly applied for these indications is a controversial topic. One of the most concerning issues with respect to the routine use of prophylactic antibiotics is the change in microbial species over the past decade, with resistant bacterial species and fungal pathogens being commonly identified.^{4,57,70}

Fungal infection in SAP is a risk factor for morbidity and possible mortality. Prophylaxis with any broad-spectrum antibiotic may be associated with increased risk of infection with fungal species or resistant bacteria.⁷¹ If broad-spectrum bacterial agents are used, prophylactic use of an antifungal agent may be warranted. Although prophylactic antimicrobials administered IV or enterally are uniformly used in some institutions, the widespread use of prophylactic antimicrobials cannot be recommended without further data supporting the benefits of use over the apparent increase in antimicrobial resistance being reported in current series.

MANAGEMENT OF PANCREATIC NECROSIS AND ABSCESS

Pancreatic necrosis is defined by the presence of diffuse or focal areas of nonviable pancreatic parenchyma. It can be either sterile or infected. Pancreatic infection occurs in about 10% of all cases of acute pancreatitis but in 30% to 70% of cases with necrosis. Contrast-enhanced CT is currently the gold standard for documenting the presence of nonperfused pancreatic parenchyma. A pancreatic abscess is a circumscribed intraabdominal collection of pus, usually in close proximity to pancreatic necrosis, which arises as a consequence of acute pancreatitis.^{23,72}

Infected pancreatic necrosis should be suspected in patients with acute pancreatitis with clinical signs of sepsis, those who fail to improve with supportive therapy or regress after an initial period of improvement.^{73,74} Patients suspected of having infected pancreatic necrosis should undergo contrast-enhanced CT scan or ultrasound-guided fine-needle aspiration.^{75–77} This approach is a safe and reliable way to differentiate between sterile and infected necrosis. With Gram staining and culture of aspirated material, fine-needle aspiration by ultrasonography has a diagnostic sensitivity of 88% and specificity of 90%.⁷⁸ Because there is a possibility of contamination of sterile necrosis, fine-needle aspiration is indicated only in those patients with signs and symptoms of sepsis, those who fail to improve, and those who worsen after initial clinical improvement. It should not be performed as a matter of routine for patients with SAP who are doing well. Studies have confirmed infection rates of 2.8% to 22% in the first week and 28.8% to 55% in the second to fourth weeks. The timing of fine-needle aspiration should be based on the probability of infection, based on time of onset from the disease and the current clinical condition of the patient. Some authors do not support the practice of needle aspiration of infection because they use prophylactic antibiotics and would not perform an “early” operation based on cultures obtained from a fine-needle aspirate. Rather, they wait 3 to 4 weeks and, if the patient is unwell, operate at that time, whether or not the presence of infection has been proven.⁷⁹

Laboratory Markers of Infected Necrosis

No reliable blood test has been developed to establish the diagnosis of infected necrosis. CRP concentrations greater than 120 mg/L are associated with pancreatic necrosis.²⁵ There is no correlation, however, between the serum CRP level and the presence of infected necrosis. Procalcitonin is a 116-amino acid propeptide of calcitonin that has been shown to be a marker for severe bacterial and fungal infection. In the meta-analysis by Mofidi et al., the sensitivity and specificity of procalcitonin for predicting infected pancreatic necrosis were 0.80 and 0.91, respectively.^{26,73}

Clinicians must pursue the possibility of infected pancreatic necrosis in order to tailor the use of antibiotics and other forms of therapy. While fine-needle aspirates are an invasive modality and can be subject to sampling error, procalcitonin can be obtained noninvasively and is

not altered by antibiotic therapy. Importantly, the clinician must recognize that procalcitonin elevation is a nonspecific marker of potential infection, and if the procalcitonin level is elevated, a systematic search for all potential sites of infection should follow. However, the magnitude of procalcitonin elevation was found to be greatest in patients with intraabdominal infections as compared with respiratory or urinary tract processes.^{25,26}

Indication and Timing of Operative Intervention

Most experts now recommend delaying operation for pancreatic necrosis until infection has been identified.⁸⁰⁻⁸³ An intervention may be delayed until the third or fourth week of ICU care if the patient remains stable. In the past there was some belief that early surgery might improve outcome by removing necrotic tissue and decreasing the stimulus for systemic inflammation, but this notion has now been disproved.⁸⁴ Delaying as long as possible for any sort of invasive débridement has become the most common approach to managing patients with SAP and necrosis as early in the course of the disease, the pancreatic tissue is friable and nonviable tissues are not well demarcated. In addition, viable tissue is usually present, even when the gland grossly appears to be completely necrotic.

Nonoperative management of sterile necrosis is the standard of care according to several published guidelines. In selected cases, patients with extensive necrosis may not improve, and after a prolonged period of observation (6-8 weeks), operative débridement may be warranted.⁸⁴⁻⁸⁷

Operative Procedures

Although there is general agreement that infected necrosis requires drainage, there is no consensus about the best approach to achieve this goal.⁸⁸ All methods aim to remove infected tissue while preserving most of the gland. When a patient is very ill with sepsis, the primary treatment goal is to achieve drainage of infected material. Open necrosectomy has been associated with high rates of complications (34%-95%) and death (11%-39%).^{43,74,84,85,89} Although open treatment of infected pancreatic necrosis is still the most common procedure for débridement, fewer surgeons are using it as the initial treatment modality.

The "step-up approach" consists of percutaneous drainage followed by minimally invasive retroperitoneal necrosectomy, if needed. Patients who received the step-up approach were less likely to develop complications (40% vs. 69%, respectively).⁸³ Additionally, with the step-up approach, there was less organ failure (12% vs. 40%), lower rate of incisional hernia (7% vs. 24%), and lower incidence of new-onset diabetes mellitus (16% vs. 38%). This important trial is unique because it was a randomized study of the surgical care of infected necrosis rather than a case series reported from one or more institutions. The findings from this study also suggest that the step-up approach may be beneficial because of a lower level of surgical trauma and therefore activation of inflammatory mediators.^{74,83} Whether the step-up approach will fully replace open surgical débridement remains uncertain.⁴⁶

Percutaneous drainage of infected necrosis can be achieved in selected patients, especially when the infected material is not too viscous or too loaded with necrotic tissue. Drainage can be achieved via anterior or retroperitoneal approaches and is best achieved using a large-diameter catheter (12-14 F).⁸⁴

In recently reported studies, an endoscopic approach has been used to achieve drainage.^{78,90} Endoscopic ultrasound is used to identify collections through the wall of the stomach. Through serial dilations, the endoscope is advanced into the affected cavity; débridement is then performed with endoscopic instruments. A nasocystic drain is left in place for further irrigation and access.

The advent of minimally invasive techniques now allows for the use of several new approaches in drainage of infected pancreatic material such as video-assisted retroperitoneal drainage (VARD). Using laparoscopic techniques, the retroperitoneum is accessed and laparoscopic instruments are used for débridement of compromised tissue. In hospital, 30-day mortality for this procedure has been reported to be as

low as 2.5%, making it an attractive alternative.^{85,91} While VARD has the potential advantage of eliminating peritoneal contamination, many procedures are commonly needed, and the colon and other abdominal contents cannot be examined or treated if necessary.

Necrosectomy

Conventional resections have been abandoned in the treatment of SAP because of high complication and mortality rates. Necrosectomy removes devitalized tissue from the pancreas and surrounding retroperitoneum and can now be performed by open or less invasive endoscopic or laparoscopic techniques.^{80,90,92} Necrosectomy is designed to remove most of the devitalized tissue without injuring major blood vessels; hemostasis must be carefully obtained before the procedure is completed. Repeated drainage procedures may be necessary.

Additional abdominal complications in patients with acute pancreatitis include concurrent biliary tract problems, stress gastritis and related bleeding, necrosis of the transverse colon, hemorrhage from gastric varices secondary to splenic vein thrombosis, and catastrophic bleeding from ruptured pseudoaneurysms involving the gastroduodenal artery or branches of the superior mesenteric artery. Should massive gastrointestinal bleeding occur, and a gastric or proximal duodenal source is excluded, arteriography should be considered. Necrosis of the transverse colon should be considered in a patient with abdominal tenderness and distention and sepsis. Patients with colonic necrosis are usually dramatically ill. Enterocutaneous fistulas are commonly seen when the open packing technique is used and less commonly when other methods of management are employed.

OUTCOME

With an increasing number of patients surviving SAP, attention has been focused on the quality of life and long-term outcome of surviving patients. This patient population is subject to a wide range of medical problems, including diabetes mellitus, symptoms of polyneuropathy, recurrent pancreatitis, and continual abdominal pain, with endocrine or exocrine dysfunction occurring in the majority of patients.⁹³⁻⁹⁵ Major social problems can also be an issue, especially among patients with alcohol-induced pancreatitis. Chronic pancreatitis and related problems including pseudocysts, splenic vein thrombosis, and mesenteric pseudoaneurysms can occur.

In one study, 35 patients after acute pancreatitis treated with open necrosectomy were evaluated for results on the Short-Form 36 assessment of health-related quality of life. Among this cohort of 35 patients, 32 were employed at the time of their SAP, and 12 patients returned to work within 6 months of discharge. SF-36 scores were above 60% in all patients, and 20 of the 32 patients had a good quality of life (>70%).⁹⁴ Patients with alcoholic pancreatitis had the worst outcomes. In 20 survivors of long-term (>30 days) hospital stay after an episode of SAP, 12 out of 20 experienced morphologic or endocrine sequelae.⁹⁴ Problems noted more than 6 months after discharge from hospital included pancreatic fistulae, stenosis of both the pancreatic and biliary tree, and chronic abdominal pain.

SUMMARY

Acute pancreatitis is a widely variable disease that is usually mild in severity. SAP is a life-threatening disease, however, that can require intensive support, especially during the initial inflammatory period of SIRS, when massive fluid resuscitation and ventilatory, cardiovascular, renal, and nutritional support may be required. In patients with ongoing signs of SIRS beyond the second or third week of disease, progression from SAP with sterile necrosis to infected necrosis should be considered. Fine-needle aspiration should be employed to diagnose pancreatic infection. Débridement of infected pancreatic necrosis is required, but the exact method of surgical débridement is controversial, and a step-up approach to therapy may be best. Although SAP is a life-threatening disease, the overall survival of patients is about 90% at centers with expertise in the management of this complex syndrome.

KEY POINTS

1. Severe acute pancreatitis accounts for 10% to 15% of all patients presenting with pancreatitis and for virtually all the morbidity and mortality associated with the disease.
2. The early phase of severe acute pancreatitis is characterized by systemic inflammatory response syndrome and end organ dysfunction, often requiring intensive support of the cardiopulmonary system. Resuscitation of intravascular volume is an important component of initial management, regardless of the etiology and severity of acute pancreatitis. Sequestration of fluid can lead to loss of as much as one-third of plasma volume.
3. Infected pancreatic necrosis is the most important risk factor for death secondary to necrotizing pancreatitis. Prevention, diagnosis, and treatment of infection in severe acute pancreatitis are crucial.
4. Understanding the cause of severe acute pancreatitis may dictate therapeutic options. A biliary origin should be suspected in female patients older than 40 years of age with a serum alanine aminotransferase level more than three times the upper reference limit.
5. Contrast-enhanced computed tomography (CT) is considered the gold standard for diagnosing pancreatic necrosis and peripancreatic collections and for grading acute pancreatitis. The Balthazar index ranges from 0 to 10 and is calculated by adding the points attributed to the extent of the inflammatory process to the volume of pancreatic necrosis. Although CT findings correlate with clinical course and severity of acute pancreatitis, it is not necessary to obtain this study in patients with mild pancreatitis.
6. Approximately 80% of deaths due to acute pancreatitis are related to infectious complications. Although prophylactic administration of antibiotics is often employed, the quality of evidence supporting this practice is relatively weak. Moreover, problems associated with resistance to antibiotics have been observed in some recent clinical trials. Therefore, prophylactic antibiotics should not be used routinely.
7. Patients with severe necrotizing acute pancreatitis require nutritional supplementation. Enteral nutrition is safe and efficacious and may be best delivered distal to the pylorus. Some patients are so catabolic that enteral and parenteral nutrition may be required to support nutritional needs. Although triglyceride levels should be monitored, lipids can be used for supplementation in most patients.
8. Pancreatic infection should be suspected in three groups of patients: patients who fail to improve, patients who worsen, and patients with initial improvement who regress. A contrast-enhanced CT scan and fine-needle aspiration should be considered to rule out infection.
9. Pancreatic débridement and/or drainage should be performed in patients with infected pancreatic necrosis. The specific approach depends on local considerations, and no single method has been proven to be superior to another.
10. Increasingly, infected pancreatic necrosis is being managed using a more conservative staged or "step-up" approach and less invasive means of drainage in selected patients.

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■ References for this chapter can be found at expertconsult.com.

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Critically ill patients with intraabdominal infection are at high risk for treatment failure and other serious complications. Failure can occur because of inadequate primary source control or the development of secondary complications such as abdominal compartment syndrome or fistula formation. Because there are few controlled studies of the management of patients with intraabdominal infection apart from trials of antibiotic therapy, and fewer still of critically ill patients with peritonitis, recommendations are often based on expert opinion, extrapolation from animal models, and sometimes on clinical data. Adequate and timely resuscitation is crucial for patients with intraabdominal infection to optimize tissue perfusion and oxygenation. Effective resuscitation can mitigate or avoid certain manifestations of intraabdominal infection in critical illness such as ischemic colitis or acute acalculous cholecystitis. Depending on the problem, source control can include drainage of intraabdominal abscesses, débridement of devitalized tissue, closure of perforations, reduction of the burden imposed by bacteria and their toxins, and the administration of appropriate and timely broad-spectrum antimicrobial therapy. Optimal management of these patients also requires understanding of peritoneal host defense, its limitations, relevant microbiology, and the factors that predict adverse outcomes.

■ PATHOGENESIS

Host Defenses

The peritoneal cavity is a complex space lined with mesothelial cells in the visceral and parietal layers. A healthy peritoneal cavity responds rapidly to bacterial contamination. Normally, about 50 to 100 mL of fluid circulates in the peritoneal cavity. The net fluid movement is cephalad toward the diaphragm, facilitated by normal peristalsis, spontaneous diaphragmatic excursions, splanchnic blood flow, and factors that maintain normal membrane permeability of the microcirculation. Conversely, ileus, mechanical ventilation, splanchnic hypoperfusion, and inflammation can disrupt normal fluid movement and cause intra-peritoneal fluid sequestration.

The major intraperitoneal host defense mechanisms include lymphatic clearance of bacteria, phagocytosis of bacteria by immune cells, and mechanical sequestration. Peritoneal macrophages and opsonic proteins circulate to facilitate phagocytosis. Small bacterial inocula in the peritoneal cavity are absorbed by specialized stomata on the undersurface of the diaphragm and are expunged into the thoracic lymphatic channels within a few minutes.¹ The bacteria then pass into the central venous system via diaphragmatic and mediastinal lymphatics, resulting in systemic immunogenicity. When an infectious inoculum is introduced, a brisk inflammatory response ensues to localize the infection, abetted by the omentum and other viscera nearby, leading to abscess formation rather than generalized peritonitis. Intraabdominal abscess formation is a source-containment process; mortality is about one-third lower for patients with abscess than for patients with generalized peritonitis.^{2,3}

Intraabdominal infection stimulates systemic inflammatory responses in addition to local phenomena. Locally, influx and activation of phagocytic cells mediate bacterial killing, impair microvascular integrity, and foster the generation of exudative ascites. Edema of the submesothelial interstitial space to a thickness of 1 mm sequesters

about 1.7 L of fluid in a 70-kg patient. Large volumes of interstitial and free peritoneal fluid can accumulate, resulting in hypovolemia. Whereas intraperitoneal fluid accumulation is detrimental to intraabdominal host defenses, diluting opsonins and impairing neutrophil function, intravenous (IV) fluid administration is imperative for the hypovolemic patient.

Macrophage- and monocyte-derived cytokines have been implicated in the pathophysiology of peritonitis. In gram-negative sepsis, the evident peritoneal tissue damage has been associated with excessive monocyte-derived cytokine release in response to endotoxins.^{4,6} In murine peritonitis model systems, sympathetic neurons regulate monocyte signaling, whereas cyclooxygenase inhibition may attenuate the deleterious effects of cytokines upon gut barrier function.^{7,8}

With inflammatory injury, peritoneal mesothelial cells are denuded, exposing the underlying basement membrane. When platelets and fibrin come into contact with the basement membrane, fibrin polymerization produces a typical exudative “rind” of fibrin and entrapped cells on peritoneal surfaces. Fibrin and apoptotic neutrophils contribute to the formation of adhesions and the walls of abscesses. Normally, the process is self-limiting by up-regulation or activation of fibrinolytic factors such as plasminogen within the first week after mesothelial injury. If the insult is self-limiting, peritoneal repair occurs within 3 to 5 days. Under local hypoxic conditions, the adhesions are invaded by fibroblasts, angiogenesis is stimulated, and the adhesions become tenacious.⁹

Microbiology

Most of the bacteria in the gut are commensal flora that play little if any role in the pathogenesis of intraabdominal infections. It is estimated that as many as 1000 bacterial species are present within the lumen of the healthy human colon. Most of these species are obligate anaerobes. Under normal conditions, the intestinal microbiota support enterocyte and colonocyte function and prevent the overgrowth of pathogenic species such as *Bacteroides fragilis*, *Escherichia coli*, *Klebsiella* spp., and *Enterobacter* spp. Overgrowth of these potentially pathogenic microbes may occur after treatment with broad-spectrum antibiotics.

The bacterial density within the gut lumen increases along the length of the gastrointestinal tract from the stomach to the colon. When released from a gastrointestinal perforation, the bacteria must proliferate to cause infection, while local host defenses seek to prevent or contain the establishment of infection. Microbial colonization of peritoneal surfaces occurs rapidly after gut perforation due to microbial expression of specific adherence factors. Enterobacteriaceae predominate within the first 4 hours, and the *B. fragilis* group supersedes them within 8 hours. Adherent bacteria are difficult to eradicate by operative peritoneal lavage or mechanical means.¹⁰

Besides adherence factors, bacteria possess several other mechanisms for the expression of virulence. Peptidoglycans and lipoteichoic acid in the cell walls of gram-positive bacteria, especially streptococci and staphylococci, stimulate the host inflammatory response. These organisms can elaborate exotoxins and proteases that cause tissue injury and promote bacterial proliferation. Lipopolysaccharides in the outer cell wall of gram-negative bacteria can interact with many cell types to stimulate an inflammatory response. As bacteria proliferate

and the size of the inoculum increases, acidic bacterial metabolites can impair neutrophil function.¹¹ Larger inocula can render antibiotics such as β -lactams ineffective.¹² Some bacterial species alter their gene expression behaviors via extracellular signaling to maximize survival and proliferation, a phenomenon called the *quorum-sensing effect*,¹³ whereas others may express a virulent phenotype under conditions of metabolic stress.¹⁴

Synergistic interactions, usually among members of the *B. fragilis* group and either facultative gram-negative bacilli or enterococci, can suppress local host defenses and promote bacterial survival and growth.¹ *B. fragilis* produces a capsular polysaccharide antigen that suppresses complement activation and inhibits leukocyte recruitment and function.¹⁵ Anaerobic bacteria produce short-chain fatty acids that can impair the function of neutrophils, and they lower the redox potential of the microenvironment to favor proliferation. Facultative bacteria consume residual oxygen, permitting the survival and proliferation of obligate anaerobes. Aerobic and anaerobic bacteria can enhance the growth of other species by providing nutrients or by producing enzymes that inactivate antibiotics.

In some respects, bacteria have evolved the ability to take advantage of host defenses. As an example, bacterial adherence to colonocytes and bacterial growth are enhanced by physiologic concentrations of norepinephrine, whether secreted as part of the counterregulatory response to stress or exogenously administered.¹⁴

Peritonitis

Peritonitis is classified as primary, secondary, or tertiary. Most critically ill patients with intraabdominal infection have secondary or tertiary peritonitis. The bacterial sources characteristic of these classes of peritonitis are shown in Table 99-1.

Primary, formerly “spontaneous” bacterial peritonitis, develops in the absence of gastrointestinal perforation and rarely causes critical illness. This type of peritonitis, which afflicts adults with hepatic cirrhosis, patients with collagen vascular disease, or children with certain glomerulopathies, is almost always monomicrobial.¹⁶ The typical pathogen is usually an enteric gram-negative bacillus such as *E. coli* or *Klebsiella* spp., although streptococcal infections are also known to occur. Definitive diagnosis is made by paracentesis and fluid culture, and operative treatment is not indicated. The presence of polymicrobial or anaerobic flora confirms a visceral perforation that must be treated, usually with surgical exploration.

Device-associated peritonitis is a variant of primary peritonitis that is also almost always monomicrobial. The majority of cases occur with chronic ambulatory peritoneal dialysis (CAPD) catheters, among which the incidence of peritonitis approaches one episode per year of dialysis.¹⁷ The most common pathogens are *Staphylococcus aureus*, *Pseudomonas* spp. and *Candida* spp. Although rare, recurrent CAPD-related peritonitis due to methicillin-resistant *S. aureus* (MRSA)

has been associated with the emergence of vancomycin-resistant strains after treatment with multiple courses of vancomycin.¹⁸ Recent studies have suggested that the administration of periprocedural IV antibiotics and modern device connection techniques reduce the risk of developing device-associated peritonitis.¹⁹ Treatment consists of prompt catheter removal. A 2014 Cochrane review demonstrated that intraperitoneal glycopeptide antibiotic administration is superior to IV antibiotics for achieving resolution when the pathogen is a gram-positive coccus.²⁰

Secondary peritonitis follows perforation of a hollow gastrointestinal viscus. The majority are community-acquired cases. Appendicitis is the most common cause, and the polymicrobial bacterial flora are typically highly susceptible to antibiotics in North America and Europe, although less so in the developing world. Thorough microbiologic analysis of a carefully collected specimen of purulent peritoneal fluid from a patient with secondary peritonitis yields an average of 5 organisms. *B. fragilis* is the most commonly isolated obligate anaerobe, and *E. coli* is the most commonly isolated facultative organism. Less common isolates include *Enterococcus* spp., *Candida* spp., *Clostridium* spp., and *Pseudomonas aeruginosa*. These uncommon isolates do not need antibiotic therapy if the patient was previously healthy, does not have comorbid conditions that increase the risk of an adverse outcome, and has a community-onset infection.

Timely, effective operative source control, combined with a short course of broad-spectrum antibiotics, is curative in more than 85% of all cases and more than 90% of appendicitis cases.²¹ Laparoscopic peritoneal lavage may offer an alternative treatment for select cases of secondary peritonitis. A recent review demonstrated a mortality rate of 1.7% and success rate of 96% among 231 patients with perforated diverticulitis (mostly Hinchey grade 3) managed primarily with laparoscopic peritoneal lavage,²² but multicenter trials are needed. Most cases of community-acquired peritonitis do not result in severe illness, and they seldom require intensive care, but when they do, the mortality rate can exceed 25%.

Tertiary peritonitis describes recurrent or persistent intraabdominal infection after failure of more than one source control procedure to control the infection.²³⁻²⁵ The flora usually include one or more strains of staphylococci (often MRSA) and *Enterococcus* spp., *Candida* spp., or *Pseudomonas* spp.²⁶⁻²⁸ It is debatable whether tertiary peritonitis represents invasive infection or colonization of the peritoneal cavity in the face of impaired host defenses. Fluid collection is often poorly localized and serosanguineous rather than purulent, suggesting an element of host defense impairment. Cases of tertiary peritonitis are fortunately uncommon, but level I evidence for specific management strategies is lacking.

Adjuvants

Adjuvant substances act to decrease the threshold bacterial inoculum necessary to result in infection. Adjuvants can increase virulence or interfere with host defenses, and they are invariably present in patients with gastrointestinal perforation. Common adjuvants include ascites, blood, fibrin, bile, urine, chyle, pancreatic fluid, and platelets.²⁹ Foreign bodies (e.g., nonabsorbable mesh or sutures) may also act as adjuvants. The principal adjuvant is blood. Hemoglobin, fibrin, and platelets all impair host defenses, and iron is essential for bacterial growth and depresses phagocyte function. Fibrin promotes bacterial trapping and abscess formation and can sequester bacteria from neutrophils. Bile salts impair host defenses and are toxic to neutrophils.³⁰ Further, pancreatic enzymes may be activated by bacteria, producing necrotic tissue that may become infected.

Foreign materials, when acting as adjuvants, serve as the foci of bacterial adherence and sequestration from phagocytes. Foreign material may also elicit inflammation, thereby reducing the minimal inoculum necessary to generate infection. Adjuvant foreign materials include surgical drains, nonabsorbable suture material, fibers from gauze sponges, prostheses such as vascular grafts and mesh, topical hemostatic agents, talc, barium sulfate, necrotic tissue, and feces.

TABLE 99-1

Microbiology of Intraabdominal Infection

| PRIMARY (MONOMICROBIAL) | SECONDARY (POLYMICROBIAL) | TERTIARY (POLYMICROBIAL) |
|---------------------------------|-----------------------------------|---|
| <i>Escherichia coli</i> | <i>Bacteroides fragilis</i> group | <i>Acinetobacter</i> spp. |
| <i>Enterococcus</i> spp. | <i>Clostridium</i> spp. | <i>Enterobacter</i> spp. |
| <i>Klebsiella</i> spp. | <i>E. coli</i> | <i>Enterococcus</i> spp. |
| <i>Streptococcus pneumoniae</i> | <i>Klebsiella</i> spp. | <i>Pseudomonas</i> spp. |
| | Other anaerobes | <i>Staphylococcus</i> spp. <i>Staphylococcus epidermidis</i> <i>Streptococcus</i> spp. <i>Candida</i> spp. |

Barium produces a marked chemical peritonitis and activates coagulation via the intrinsic pathway; the combination of barium and feces can be lethal.

THE AT-RISK PATIENT

Fortunately, most patients with intraabdominal infection do not require care in an intensive care unit (ICU). In a population-based study of hospital discharges for peritonitis, severe sepsis developed in only 11% of cases (Table 99-2) but increased the mortality risk by 19-fold.² Similarly, only about 15% of patients enrolled in clinical trials of antimicrobial therapy for secondary peritonitis have an Acute Physiology and Chronic Health Evaluation (APACHE) II score above 15 points.³¹

Some patients with community-acquired secondary peritonitis develop critical illness due to delayed presentation, immunosuppression, or extremes of age. Most patients with peritonitis suffer critical illness due to a hospital-acquired source (Table 99-3). The leading causes of hospital-acquired peritonitis are gastrointestinal anastomotic dehiscence and splanchnic ischemia due to hypovolemia, distributive shock, atheroembolism, and thromboembolism. Hospital-acquired peritonitis is usually polymicrobial; organisms isolated commonly include *Enterococcus* spp., *Candida* spp., *P. aeruginosa*, and other antibiotic-resistant organisms such as MRSA.^{23,27,28}

Surgical ICUs that care for patients with multiple trauma or following emergency surgery are likely to have more cases of intraabdominal infection than medical ICUs. Surgical patients that require operation for source control or have a postoperative secondary nosocomial infection account for 25% to 40% of patients with severe sepsis. Units with a low prevalence of postoperative secondary peritonitis must be equally vigilant in their surveillance and assessment, because a missed intraabdominal infection is frequently fatal.³²

| TABLE 99-2 Risk Factors for Severe Sepsis in Patients With Intraabdominal Infections | | |
|--|---------------|--------------------------|
| PARAMETER | RELATIVE RISK | 95% CONFIDENCE INTERVALS |
| AGE (YEARS) | | |
| <20 | | 1.0 |
| 20-39 | 1.4 | 0.8-2.5 |
| 40-59 | 3.2 | 1.8-5.6 |
| 60-79 | 4.6 | 2.6-8.0 |
| >79 | 6.5 | 4.7-11.8 |
| SITE | | |
| Appendix | | 1.0 |
| Gallbladder | 2.7 | 1.9-3.8 |
| Colon | 3.9 | 2.6-5.8 |
| Stomach/duodenum | 6.9 | 4.6-10.3 |
| Small bowel | 9.0 | 6.1-13.4 |
| EXTENT | | |
| Localized | | 1.0 |
| Abscess | 1.2 | 0.8-1.8 |
| Diffuse | 1.5 | 1.1-1.9 |
| COMORBIDITIES | | |
| Congestive heart failure | 1.2 | 1.0-1.6 |
| Stroke | 1.8 | 1.2-2.7 |
| Liver dysfunction | 2.0 | 1.4-2.8 |
| Renal dysfunction | 2.0 | 1.4-2.9 |

Data from Anaya and Nathens.²

When patients with intraabdominal infection are critically ill, mortality exceeds 25%. The risk of failure increases with the severity of the illness, inadequate empiric antibiotic therapy, delayed surgical therapy, and failure of source control.^{23,27} Most clinical failures are not associated with multidrug-resistant pathogens; however, some studies have suggested that resistant pathogens cause clinical failure in some cases of postoperative peritonitis.^{33,34}

SPECTRUM OF DISEASE CAUSING CRITICAL ILLNESS

Abscess of Solid Organs

Although abscesses of solid organs are rare, failure to diagnose them properly may result in death. Most cases arise as a complication of a community-acquired infection, but on occasion, they can result from complications of medical care. The liver is affected most commonly, followed by the spleen and the kidney.

Pyogenic liver abscess is most often the result of ascending biliary infection (cholangitis) or portal bacteremia that complicates an enteric infection (typically colonic diverticulitis). The most common causative organisms include *Klebsiella* spp., *E. coli*, and *Enterococcus* spp. *K. pneumoniae* has surpassed *E. coli* as the most common bacterial isolate in pyogenic liver abscess.³⁵ Systemic bacteremia may also cause liver abscesses and may entail dental abscess (viridans streptococci) or vascular catheters (*S. aureus*, *C. albicans*, and others). Devitalized liver from trauma, angioembolization, and ablation of neoplasms are at particular risk of infection.

Antibiotic therapy for liver abscesses is obligatory and should be tailored to the source of origin. A treatment course of more than 14 days may be necessary. Amebic liver abscesses are treated primarily with metronidazole. A recent Cochrane review determined the quality of the literature as being insufficient to conclude whether percutaneous aspiration improves outcomes for amebic abscesses.³⁶ Among pyogenic liver abscesses, if the size and location of the abscess permit, percutaneous drainage should be attempted.^{35,37,38} Operative drainage may be required for abscesses that cannot be drained percutaneously. A 2013 study of 85 patients with pyogenic liver abscesses found treatment failure in 40% of patients who underwent percutaneous drainage, compared with 11% who underwent laparoscopic drainage procedures.³⁹ Recently, endoscopic ultrasound-guided liver abscess drainage has

| TABLE 99-3 Clinical Factors Predicting High-Risk Intraabdominal Infection |
|---|
| Shock |
| Advanced age |
| Acute Physiology and Chronic Health Evaluation (APACHE) II score >15 |
| Isolation of enterococci |
| Impaired consciousness |
| Inadequate empirical antibiotics |
| Poor nutritional status |
| Cardiovascular disease |
| Inability to achieve source control |
| Immunosuppression |
| Hypoalbuminemia |
| Thrombocytopenia |
| Diffuse versus localized peritonitis |
| Symptoms lasting more than 24 h before definitive intervention |
| Subsequent nosocomial infection |
| Protein C concentration below 66% of normal |
| Hospitalization >48 h |
| Malignancy |
| Postoperative infection |
| Recent antibiotic therapy |
| Residence in skilled nursing care or long-term care facility |

Data from Pieracci et al.²¹ and Solomkin et al.²⁷

been described and may represent an alternative route of access to drain pyogenic liver abscesses.⁴⁰ Overall mortality rates for liver abscesses approach 25% and are higher for patients with multiple abscesses that are too small to drain (i.e., miliary abscesses).⁴¹

Splenic abscesses are uncommon and usually result from hematogenous or local contamination. Hematologic sources include endocarditis, urinary tract infection, pneumonia, osteomyelitis, otitis, mastoiditis, and pelvic infection. Systemic disorders such as hemoglobinopathies or sickle cell disease can cause splenic infarction. Devitalized splenic tissue resulting from trauma, infarction, or embolization can become infected and produce a splenic abscess.⁴² Splenic abscesses have been reported with other systemic infections, including typhoid fever, paratyphoid fever, malaria, and candidiasis. Additionally, adjacent infections of the pancreas, retroperitoneum, subdiaphragmatic spaces, and diverticulitis may extend directly into the splenic parenchyma.

S. aureus is the most common pathogen in splenic abscesses, whereas gram-negative organisms are relatively unusual. Anaerobic infections (e.g., *Clostridium perfringens*) have also been described. Empiric antibiotic therapy should address all likely pathogens. Percutaneous drainage can be attempted if conditions are favorable, but splenectomy and drainage usually comprise definitive therapy. The overall rate of mortality for splenic abscess is approximately 20%.

Despite the frequency of “urosepsis,” true abscesses of the kidney are uncommon as compared with hepatic or splenic abscesses. Ascending infection from the lower urinary tract is the usual source; therefore, any common urinary tract pathogen (*E. coli*, *Klebsiella* spp., *Enterococcus* spp., *S. aureus*) can be causative. Initial treatment should thus include broad-spectrum antibiotics until microbiologic speciation and susceptibility profiles become available. Surgical drainage may be required for patients with recurrent sepsis, or for those who do not respond to antibiotic therapy.

Acute Acalculous Cholecystitis

In contrast to gallstone-related cholecystitis, the etiology of acute acalculous cholecystitis is gallbladder ischemia with secondary infection of the organ.⁴³ Acute acalculous cholecystitis may complicate several conditions that produce splanchnic hypoperfusion. Risk factors in medical patients include congestive heart failure, diabetes mellitus, abdominal vasculitis, and malignant disease (including after bone marrow transplantation). Acalculous cholecystitis is more common in surgical patients and can occur following burns, trauma, cardiopulmonary bypass, biliary instrumentation, and emergency aortic surgery.⁴³

The diagnosis of acute acalculous cholecystitis can be challenging, and a high index of suspicion is required. Prompt diagnosis and therapy are necessary, as necrosis of the gallbladder occurs in 30% of patients, and gallbladder perforation occurs in 4%. Fever and hyperbilirubinemia are common associated findings.⁴⁴ Serum transaminase and alkaline phosphatase concentrations may also be elevated. When signs and symptoms can be localized to the right upper quadrant, the differential diagnosis includes gastroduodenal perforation, acute pancreatitis, right colon ischemia, and acute hepatitis.

Gallbladder wall thickness greater than 3.5 mm and the presence of pericholecystic fluid by bedside ultrasonography are sufficient to diagnose acute acalculous cholecystitis. Computed tomography (CT) is equally accurate and can be utilized when physical examination findings are equivocal and the patient is stable for transport. Hepatobiliary scintigraphy (HIDA) has a poor positive predictive value for acalculous cholecystitis, as patients generally do not receive sufficient alimentary stimuli for gallbladder contraction. Administration of morphine sulfate, which increases biliary hydrostatic pressure, can promote the filling of the gallbladder and increase the diagnostic accuracy of hepatobiliary scintigraphy.⁴⁵

Percutaneous cholecystostomy is the treatment of choice for acute acalculous cholecystitis in the critically ill patient. Success rates exceed 90% for the control of acute acalculous cholecystitis, although the

overall mortality rate remains about 30%. Percutaneous cholecystostomy fails most commonly due to malposition of the drainage catheter, uncontrolled gallbladder perforation, or another diagnosis. If a cholecystostomy tube study confirms the absence of gallstones once the patient has recovered, the drain can be removed. Interval cholecystectomy is unnecessary if the drain is removable.

Ischemic Colitis and Enteritis

Intestinal ischemia is a dangerous and relatively common complication of critical illness that can progress within hours to gangrene, perforation, and generalized peritonitis.⁴⁶ The splanchnic circulation is especially vulnerable to low cardiac output, particularly when the cardiac index is less than 2 L/min/m². Most cases are caused by nonocclusive ischemia, often a sequela of hypovolemia, shock, and the administration of vasopressors. A number of other causes have been identified. Acquired deficiencies of protein C or S are characterized by hypercoagulability that has been associated with mesenteric arterial and venous thrombosis. Chronic atrial fibrillation or dilated cardiomyopathy can lead to mesenteric arterial thromboembolism. Arteriography may result in cholesterol embolization from dislodgment of atherosclerotic plaques. Intestinal ischemia must also be considered in patients with partial or proximal bowel obstructions, as manifestations may not be obvious under these conditions.

The pattern of injury with intestinal ischemia varies with the mechanism, the presence of heart disease, and the status of the collateral circulation via the celiac and inferior mesenteric arteries. Large thrombi usually occlude the superior mesenteric artery at a narrow point just distal to the origin of the middle colic artery. The first 30 to 45 cm of the small bowel and the left colon may be spared. Smaller emboli may result in patchy intestinal necrosis and are more likely to affect the small bowel and ascending colon (Fig. 99-1). Nonocclusive ischemia classically occurs in watershed areas of the mesenteric circulation where collateral vessels bridge two arterial distributions. Although any segment of intestine can be affected by nonocclusive ischemia, the cecum (farthest from the inferior mesenteric artery collaterals) and the splenic flexure (watershed of the superior and inferior



FIGURE 99-1 ■ Computed tomography after the administration of oral and intravenous contrast in a patient with embolic occlusion of the superior mesenteric artery and patchy ischemia of the small bowel and right colon (arrows). Bowel ischemia is evident from the marked thickening of the intestinal wall.

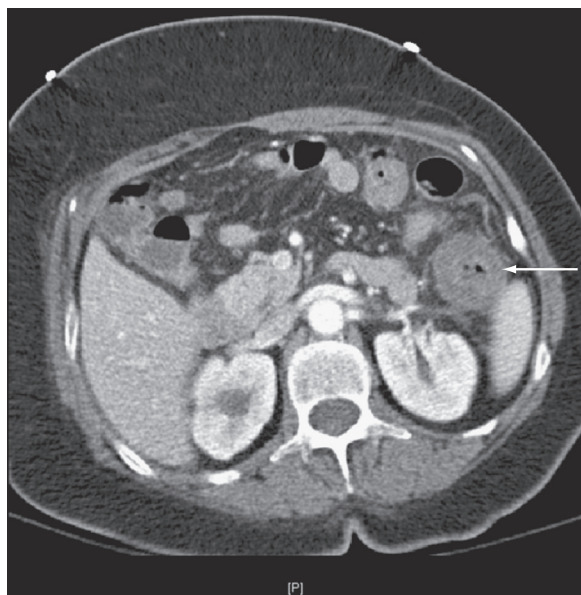


FIGURE 99-2 ■ Computed tomography with oral and intravenous contrast in a patient with nonocclusive mesenteric ischemia of the colon at the splenic flexure (arrow). Ischemia of the colon is evident from the marked thickening of the colon wall.

mesenteric arteries) are most likely to be affected (Fig. 99-2). The left colon is particularly vulnerable after abdominal aortic operations, especially when the inferior mesenteric artery has been ligated during the procedure.

Patients with acute intestinal ischemia are often profoundly ill and will die without prompt intervention. As the blood supply to the mucosa is more vulnerable than to the seromuscular layers, transmural necrosis represents late-stage disease. Patients can develop severe sepsis or septic shock before transmural gangrene or perforation. The diagnosis is often challenging due to the protean manifestations of the syndrome and potential for ischemia at any point of the gastrointestinal tract from the ligament of Treitz to the mid-rectum.

Among communicative patients, severe pain that is disproportionate to tenderness by palpation is the diagnostic hallmark. Among intubated, sedated patients, the clinical features can be subtle. Abdominal distention, hypovolemia, hemoconcentration, unexplained and refractory metabolic acidosis, or occult rectal bleeding may be among the only signs. Hematochezia following abdominal aortic surgery or resuscitation from shock is strongly suggestive of colon ischemia.

Given the propensity for left colon involvement, lower endoscopy at the bedside is usually the first diagnostic modality, but a number of pitfalls should be recognized. Flexible sigmoidoscopy is simple and safe but may miss ischemia at or proximal to the splenic flexure; accordingly, colonoscopy is preferred (Fig. 99-3). Endoscopy visualizes only the mucosa and can underestimate the extent of the disease. CT and CT angiography are increasingly useful diagnostically and have largely supplanted the use of formal arteriography (Fig. 99-4).

Bedside diagnostic laparoscopy represents a technique that can be used to identify intraabdominal pathology in the ICU setting, but reports to date are anecdotal. Laparoscopy should be considered when transferring the patient to radiology or the operating room is considered unsafe or when routine radiologic examinations are inconclusive.^{47,48} Diagnostic testing should be foregone entirely in favor of immediate laparotomy if signs of peritonitis are present.

Surgical therapy is individualized based on the location and extent of the intestinal compromise and the physiologic state of the patient. Infarcted bowels are resected, but bowels of questionable viability may be left for re-inspection at a second-look laparotomy 12 to 48 hours later, particularly if a massive enterectomy would otherwise be needed.

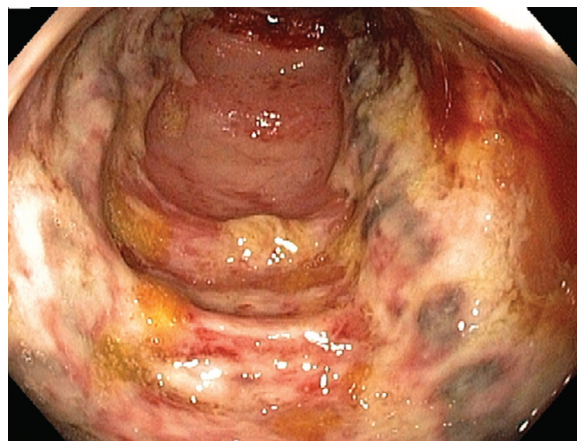


FIGURE 99-3 ■ Colonoscopy is the preferred modality to assess for colonic ischemia but visualizes the mucosa only and may underestimate the extent of the disease.

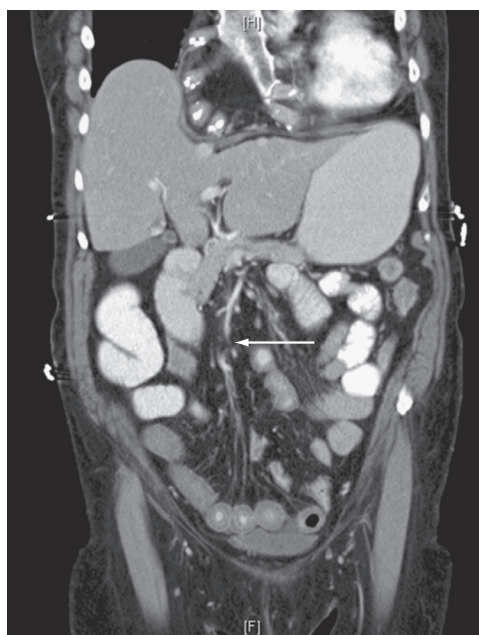


FIGURE 99-4 ■ Computed tomography after administration of oral and intravenous contrast in a patient with an embolism to the superior mesenteric artery and ischemia of the small bowel and right colon. The arrow points to the embolus in the superior mesenteric artery.

Anastomosis can be performed in stable patients without peritonitis or deferred in unstable patients by leaving the occluded ends of the bowel in temporary discontinuity until the second-look procedure. Creation of a temporary ostomy is a third option, although this is performed with decreasing frequency. If a second-look procedure is unnecessary, the abdominal fascia can be closed. If reoperation is planned or if bowel edema and distention are such that definitive closure would risk the development of intraabdominal hypertension or abdominal compartment syndrome, damage-control principles are utilized, and a temporary abdominal wall closure is performed. Methods for temporary closure include closure of the skin only or closure with absorbable mesh, biologic material, or plastic sheeting, usually in conjunction with a negative-pressure wound therapy system.⁴⁹ Expert reviews of surgical literature have concluded that negative-pressure wound therapy systems achieve superior outcomes when compared with alternative temporary closure techniques.⁵⁰⁻⁵²

The wide spectrum of disease in patients with intestinal ischemia makes mortality estimates difficult, but the condition is highly morbid. Acute colon ischemia following repair of a ruptured abdominal aortic aneurysm has a mortality risk as high as 80%.

Clostridium difficile Colitis

The incidence and severity of *C. difficile* infections (CDI) are increasing. CDI remains the most common nosocomial gastrointestinal infection, and it carries substantial morbidity and mortality. Early diagnosis and treatment are essential for a favorable outcome. A highly virulent strain, PCR ribotype 027, has been associated with recent outbreaks in North America and Europe. It is characterized by depressed toxin production and a higher risk of mortality relative to other strains.⁵³ Patients in the ICU are at increased risk for CDI, and in these patients, the disease is more frequent, more severe, more refractory to medical therapy, and subject to higher rates of relapse.⁵⁴ In one study, among patients with CDI requiring ICU admission, emergency total abdominal colectomy was needed in 25%. Diverting loop ileostomy, intraoperative colonic lavage, and postoperative enterostomal vancomycin administration allow successful preservation of the colon in up to 93% of patients with severe complicated CDI in the absence of necrosis or perforation.⁵⁵ Other risk factors for CDI include preoperative antibiotic use, uremia, burns, chronic obstructive pulmonary disease, cancer, abdominal surgery, cesarean section, antiperistaltic medications, proton-pump inhibitors, ICU stay, prolonged hospital stay, chemotherapy, and postpyloric tube feeding.^{53,54}

Clinical examination of patients with CDI may not reveal notable findings of peritonitis unless megacolon or perforation has developed. CT can demonstrate typical findings of colonic wall thickening, dilation, and the so-called *accordion sign* (thickened haustral folds and trapped contrast material, ascites, or pericolic stranding; Fig. 99-5). Identification of the organism by polymerase chain reaction detection of bacterial DNA and endoscopy are useful diagnostic adjuncts, but definitive management in patients with evidence of refractory fulminant colitis should not be delayed for these tests. Routine cases of CDI are treated with oral or IV metronidazole. Severe disease is treated with oral vancomycin, which achieves high intraluminal concentrations owing to the lack of absorption across the gut mucosa.

Fulminant CDI with perforation, toxic megacolon, severe ileus, hypotension, or refractory sepsis occurs in approximately 3% to 8% of

patients. Patients who have a history of inflammatory bowel disease, recent surgery, prior treatment with IV immunoglobulin (Ig) or a vasopressor, leukocytosis, or increased blood lactate concentration should have early surgical consultation. Mortality is notably decreased in patients who have no more than 6 days of medical treatment prior to operation, which supports early total abdominal colectomy for appropriate patients.⁵³⁻⁵⁷

Acute Pancreatitis

Gallstone disease and alcohol consumption account for about 80% of cases of pancreatitis. Trauma, upper abdominal surgery, and cardiopulmonary bypass account for the remainder. Approximately 85% of cases are self-limiting and have a good prognosis. The remaining 15% of cases account for most of the morbidity and all of the mortality. Infection is the most common complication and can lead to multiple organ dysfunction syndrome and death. Mortality risk is associated with large IV fluid requirement, acidosis, and hypocalcemia.⁵⁸ Antibiotic prophylaxis is ineffective and not recommended.

Pancreatic infections include infected pseudocysts, discrete pancreatic abscesses, or infected pancreatic necrosis. The last is a poorly localized process that affects the retroperitoneal fat as well as the pancreas itself. Infection can develop as early as 5 days after the onset of acute pancreatitis, with the peak incidence at day 14. Almost any common organism can cause infection, including staphylococci, enteric gram-negative bacilli, obligate anaerobes, *P. aeruginosa*, and *Candida* spp. Assuming appropriate microbial susceptibility, imipenem-cilastatin, meropenem, doripenem, or a fluoroquinolone plus metronidazole are recommended empiric antimicrobial agents.⁵⁹ Kinetic studies of drug accumulation in normal pancreas or pancreatic fluid suggest adequate pancreatic concentrations are achieved by fluoroquinolones, carbapenems, metronidazole, and fluconazole, whereas aminoglycosides are ineffective.⁶⁰

Many aspects of the prevention and management of pancreatic infection are controversial, including the role of antibiotic prophylaxis, diagnostic methods, and techniques and the timing of the surgical drainage and debridement. Antibiotic prophylaxis of severe pancreatitis with imipenem-cilastatin or meropenem is ineffective and has been associated with an increased risk of fungal infection.⁶¹ Regardless of the severity of the illness, all patients with pancreatitis should undergo ultrasonography to evaluate for gallstones. Pancreatic protocol CT is the best study to define anatomic severity and infection. The study should be performed with contrast infusion and thin (1-mm) cuts through the region of the pancreas to assess for viability and the presence of devitalized tissues (Fig. 99-6). When peripancreatic infection is suspected, CT-guided aspiration should be performed to obtain material for culture.

Source control is essential for patients with established pancreatic infection. Newer techniques with acceptable outcomes and lower morbidity have begun to replace traditional open drainage and surgical necrosectomy. These techniques include minimally invasive endoscopic, radiologic, and laparoscopic approaches. Endoscopic ultrasonography as a guide to drainage and laparoscopic pancreatic necrosectomy has demonstrated success in managing pancreatic necrosis (Fig. 99-7).^{62,63} The results from the Dutch Pancreatitis Study Group demonstrated a significant reduction in major complications (new-onset multiple organ dysfunction syndrome, incisional hernias, and new-onset diabetes mellitus) following a “step-up” approach for managing infected pancreatic necrosis. This approach consists of percutaneous drainage, followed by minimally invasive retroperitoneal necrosectomy, if necessary.⁶⁴ Improvements in resuscitation and operative management of the infectious complications of pancreatitis have reduced the mortality rate to about 20%, about one-half that of the previous era.

Operation for patients with pancreatic necrosis and organ dysfunction without infection is a matter of debate. Current opinion favors a conservative approach with aggressive critical care support, reserving operation for confirmed walled-off infections.⁶⁵ This strategy is meant

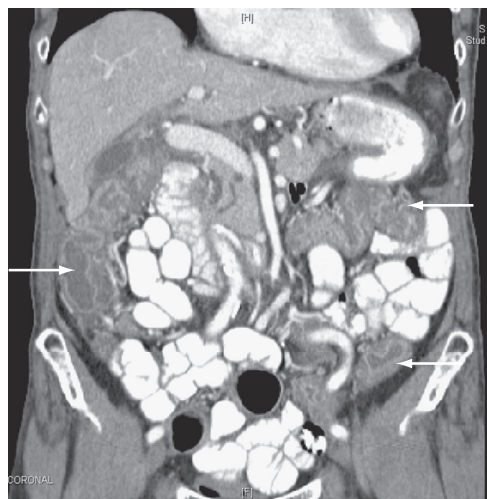


FIGURE 99-5 ■ Computed tomography with oral and intravenous contrast in a patient with *Clostridium difficile* colitis. Typical findings include colonic wall thickening (arrows), dilation, and accordion sign (thickened haustral fold and trapped contrast material, ascites, and pericolic stranding).

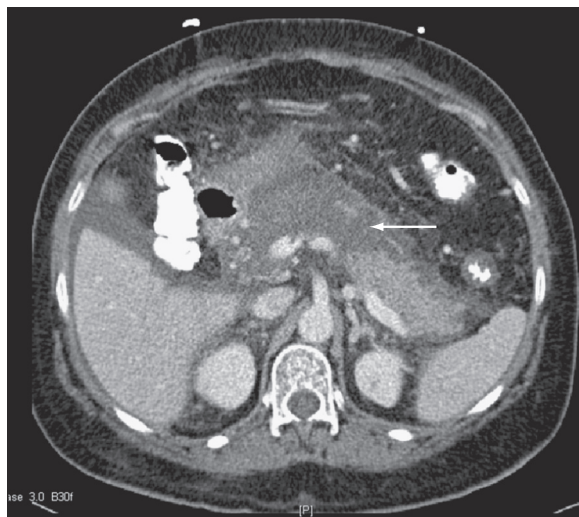


FIGURE 99-6 ■ Computed tomography with oral and intravenous contrast in a patient with severe acute pancreatitis. The borders of the pancreas are indistinct from the surrounding marked inflammation. The hypodense area in the body of the pancreas is an area of pancreatic necrosis (arrow). Study should be performed with contrast infusion and thin cuts through the region of the pancreas.

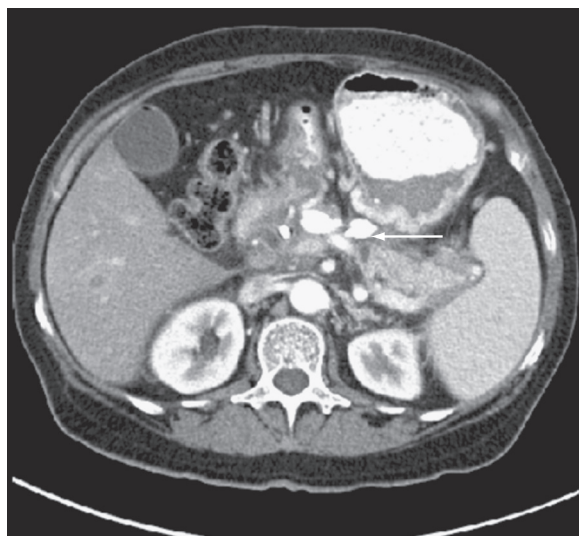


FIGURE 99-7 ■ Interval computed tomography in the same patient as in Fig. 99-6, with pancreatic necrosis and pseudocyst formation. Significant resolution was observed after internal endoscopic drainage, with two stents functioning as a cystogastrostomy (arrow).

to minimize the complications associated with difficult and potentially morbid procedures, including hemorrhage, intestinal fistulas, multiple reoperations, open abdomen management, and abdominal wall hernias.

■ DIAGNOSIS

Diagnosis of intraabdominal infection in critically ill patients can be challenging. Medical history is often unobtainable, and altered mental status can mask the physical findings. At times, the only clue may be unexplained signs of sepsis or organ dysfunction. Radiologic testing is diagnostic in most patients.

Although good-quality plain abdominal radiographs are difficult to obtain at the bedside, pneumoperitoneum (Fig. 99-8), intestinal obstruction, or signs of intestinal ischemia may be found.



FIGURE 99-8 ■ Pneumoperitoneum (crescent-shaped lucency) is evident under the right hemidiaphragm on an upright chest radiograph of a patient with perforated sigmoid diverticulitis. The crescent-shaped lucency under the left hemidiaphragm is a stomach bubble.

Pneumoperitoneum can be an innocuous finding in mechanically ventilated patients and for as long as 7 days after open abdominal operations.^{66,67} Plain radiography can be augmented by water-soluble contrast injection of drains, fistulas, or sinuses to define the anatomy of complex infections or monitor resolution after drainage. Ultrasonography can be performed at the bedside and provides excellent visualization of the biliary tree.

Ultrasonography can also detect abscesses, particularly in the pelvis when transvaginal or transrectal probes are used and can be used to guide percutaneous drainage procedures. Visceral blood flow is assessed with the addition of color Doppler flow analysis. Unfortunately, ultrasonography is operator dependent. Visualization is limited in the presence of bowel gas, and dressings, stomas, and drains can impede the positioning of the probe.

CT with oral and IV contrast is the primary radiologic imaging study for the abdomen and pelvis.⁶⁸⁻⁷⁰ CT signs of intraabdominal infection include extraluminal gas (Fig. 99-9), free fluid, contrast extravasation, fat stranding, and the presence of a contrast-enhancing rim that is characteristic of abscess (Fig. 99-10). CT is now the test of choice for the diagnosis of intestinal obstruction. Intramural gas may be identified when mesenteric ischemia is present; occasionally, a thrombus is seen in a visceral vessel (Fig. 99-4). In the absence of generalized peritonitis or disruption of visceral structures, CT-guided percutaneous drainage is the treatment of choice for abscesses and intraabdominal fluid collections.^{37,38,70}

Although CT is an excellent diagnostic modality, obtaining an adequate study in critically ill patients can be problematic. When patients are unstable hemodynamically or dependent on a high level of mechanical ventilator support, transport out of the ICU may be risky.⁷¹ Iodinated contrast agents may precipitate acute kidney injury or aggravate chronic kidney disease. If the need for CT is anticipated 24 hours in advance, hydration and sodium loading may limit the risk of contrast-induced nephropathy.⁷²

Other radiologic modalities used commonly in elective evaluations have limited value in critical illness. Radionuclide imaging and magnetic resonance are used rarely for ICU patients with intraabdominal infection.

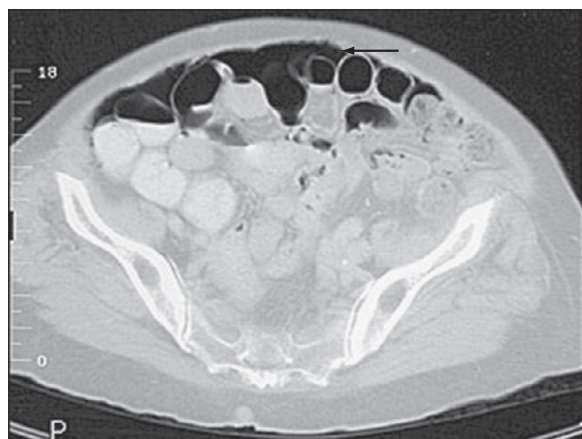


FIGURE 99-9 ■ Computed tomography with oral and intravenous contrast in a patient with pneumoperitoneum from a perforated viscus. Multiple pockets of extraluminal gas are evident (arrow), particularly anterior to the loops of the small bowel.



FIGURE 99-10 ■ Computed tomography with oral and intravenous contrast material in a patient with a large pelvic abscess. The abscess cavity demonstrates classic rim enhancement of the abscess wall (arrow). Percutaneous drainage should be performed under image guidance.

■ PRINCIPLES OF MANAGEMENT

Source Control

Source control for complicated intraabdominal infections remains the most important component of successful treatment. Consensus guidelines aim to implement source control interventions within the first 6 hours of management.^{73,74}

The elements of definitive source control include the removal of infected or nonviable material, closure or control of perforations, and the reduction of peritoneal contamination by bacteria and toxins. Multiple staged operative procedures may be needed. Failure to obtain adequate source control reportedly occurs in 10% to 25% of cases of intraabdominal infection, depending on the severity and complexity of the infection.^{23,74}

Abscess

Abscesses are characterized by local acidosis, low oxygen tension, poor antibiotic penetration, and impaired leukocyte function. Studies

of diverticular disease have reported that abscesses smaller than 3 cm in diameter are likely to resolve with antibiotics alone.⁷⁵ Source control with percutaneous drainage is the treatment of choice for most abscesses, provided adequate drainage is possible and no débridement or repair of anatomic structures is necessary.^{18,73} Percutaneous decompression of abscesses is successful and results in rapid clinical improvement in 85% of cases.^{37,38} Formal operative intervention should be performed without delay if clinical improvement does not occur promptly following drainage.

Peritoneal Toilet

Once source control has been achieved, additional intraoperative measures, including irrigation with fluid or antibiotic solutions and débridement of peritoneal surfaces, are ineffective and may be deleterious.⁷⁶⁻⁷⁸ Bacteria adhere to mesothelial cells on the serosal surfaces in peritonitis, rendering them resistant to removal by passive irrigation.⁷⁸⁻⁸⁰ A prospective trial demonstrated identical rates of intraabdominal abscess among 220 patients treated with suction alone or peritoneal irrigation and suction during appendectomy for perforated appendicitis (18.3% vs. 19.1%; $P = 1.0$).⁸¹ Moreover, animal studies suggest that irrigation fluids disseminate infection by hindering the normal immunologic function of the peritoneum. It has been shown that irrigation with antibiotic solutions confers no benefit if parenteral antibiotics are administered⁹; however, a meta-analysis has also shown that pooled mortality is three-fold higher when saline solution is used rather than antibiotic solution for peritoneal lavage.⁷⁶ High-volume lavage and pulse irrigation used in feculent or purulent peritonitis may be of benefit but may also increase the risk of fistula formation.⁷⁸⁻⁸⁰ Closed suction drains do not prevent recurrent fluid collections and are ineffective at draining the peritoneal cavity.

The Open Abdomen

Open abdomen management techniques are employed in select patients with diffuse peritonitis, inadequate primary source control, intestinal ischemia and discontinuity, abdominal compartment syndrome, or necrotizing infections of the anterior abdominal wall.^{82,83} Open abdomen is a component of the damage-control tactics used in unstable patients with massive trauma. In cases of peritonitis, goals of damage control include the assessment and reassessment of intestinal viability, decompression of the abdomen, and access for peritoneal toilet. The disadvantages of open abdomen management include fluid and protein loss, ileus, fistula formation, and ventral herniation. Neither planned re-laparotomy nor open abdomen management offer survival benefits as compared with repeat laparotomy on demand.⁸⁴

Many variations in open abdomen techniques have been reported. Most often, a negative-pressure wound therapy system is utilized with a fenestrated, nonadherent material to cover the bowel, suction drains to aspirate superficial fluid, and an airtight adherent outer drape to maintain negative pressure and to prevent evisceration until adhesions form (Figs. 99-11 and 99-12). Nasogastric and urinary catheter decompression are maintained, and early enteral nutrition has been shown to provide a benefit to recovery.⁸⁵ At re-exploration, the abdomen is lavaged and loculated fluid collections are evacuated. After achieving resuscitation and adequate source control, aggressive diuresis should be initiated to reverse edema and facilitate closure of the abdomen. In a substantial percentage of patients, the fascia cannot be closed primarily. In these cases, healing by secondary intention is allowed to occur, and ventral hernias are repaired electively with absorbable mesh, biologic grafts, and skin grafts as necessary, but no earlier than 3 to 6 months after the acute episode, when all acute problems have resolved.

Antibiotic Therapy

Optimal antibiotic therapy for intraabdominal infection requires an agent or combination of agents active against gut-derived facultative enteric gram-negative bacilli and obligate anaerobes.^{18,21} The initial

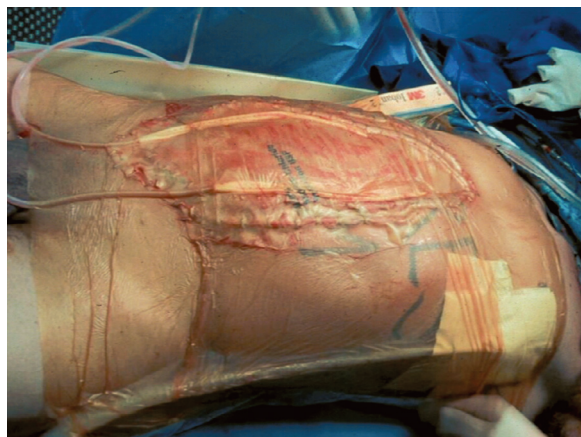


FIGURE 99-11 ■ Open abdomen management of abdominal compartment syndrome. The sterile saline bag was sewn to the skin edges. Closed suction drains were placed to limit fluid accumulation, and occlusive dressing was applied to cover the abdominal wall. (Courtesy Brian J. Kimbrell, MD.)



FIGURE 99-12 ■ Open abdomen management of abdominal compartment syndrome using a VAC system. The bowel is covered with omentum if possible. Nonadherent dressing is layered under a VAC sponge, or a smaller pore sponge is used against the viscera. Negative pressure is applied to the wound closure to drain fluid, facilitate closure, and prevent evisceration. VAC, vacuum-assisted closure. (Courtesy Brian J. Kimbrell, MD.)

antibiotic therapy should be empiric and broad spectrum, as the source is not always known.

A 2005 Cochrane review of 40 studies with 5094 patients comparing 16 different antibiotic regimens for empiric first-line therapy demonstrated equivalent efficacy and made no specific recommendations based on class I evidence.³⁰ Given this equivalence (Table 99-4), the selection of an antibiotic regimen should be based on considerations of cost, availability, ease of administration, susceptibilities, and the risk of toxicity, including allergy to β -lactam agents.^{18,86}

Evidence-based guidelines for the selection of antimicrobial therapy for high-risk patients with intraabdominal infections have been formulated by the Surgical Infection Society and the Infectious Diseases Society of America.¹⁸ The most commonly accepted empiric treatment regimens for complicated intraabdominal infections include extended spectrum β -lactam/ β -lactamase agents such as piperacillin-tazobactam, carbapenems such as imipenem-cilastatin, meropenem, and ertapenem, or a third- or fourth-generation cephalosporin plus metronidazole.

TABLE 99-4

**Antimicrobial Agent Regimens
for Therapy of Serious
Intraabdominal Infections**

SINGLE AGENTS

β -Lactam/-Lactamase Inhibitor Combinations

- Ampicillin/sulbactam
- Piperacillin/tazobactam
- Ticarcillin/clavulanic acid

Carbapenems

- Imipenem-cilastatin
- Meropenem
- Ertapenem
- Doripenem

Cephalosporins

- Cefotetan
- Cefoxitin

Fluoroquinolones

- Moxifloxacin

Glycylcyclines

- Tigecycline

COMBINATION AGENTS

Aminoglycoside Plus an Antianaerobic Agent

- Amikacin, gentamicin, netilmicin, or tobramycin plus clindamycin or metronidazole

Aztreonam Plus Clindamycin

- Combination of aztreonam plus metronidazole is devoid of coverage against gram-positive cocci

Fluoroquinolone Plus Metronidazole

- Ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin

Third- or Fourth-Generation Cephalosporin Plus an Antianaerobic Agent

Data from Solomkin et al.²⁷ and Mazuski et al.²⁸

In hospital-acquired peritonitis, local antimicrobial resistance patterns should be considered. Although mortality appears to be higher when *Enterococcus* spp. are isolated from polymicrobial intraabdominal infections, there is no evidence that anti-enterococcal therapy improves outcomes.^{18,33,87} Combination therapy directed against a specific pathogen (e.g., double-drug coverage of *P. aeruginosa*) has no demonstrated benefit in sepsis and can worsen outcomes, especially leading to acute kidney injury. Newer agents, including tigecycline, ceftolazone-tazobactam, and moxifloxacin, are also equivalent in their ability to treat complicated intraabdominal infections and provide additional options in dealing with evolving bacterial resistance patterns.⁸⁸⁻⁹³

Fungal species are common components of the normal intestinal flora, and fungi are common isolates from peritoneal fluid during operations for perforated viscera. Antifungal treatment in an otherwise immunocompetent patient has not been found to improve survival.⁹⁴ Because fungal colonization usually precedes invasive infection in surgical patients, some experts advocate systemic antifungal treatment when fungal species are recovered from peritoneal fluid.^{18,94,95} Empiric antifungal therapy is warranted when fungi are isolated from two or more normally sterile sites, from the bloodstream of critically ill patients with fungal abscesses, and in immunosuppressed patients.^{2,3,18,95} In critically ill patients, initial antifungal therapy with an echinocandin (caspofungin, micafungin, and anidulafungin) is recommended over treatment with a triazole.^{18,94}

Shorter courses of antimicrobial therapy and modification of agents according to susceptibility analysis are safe in patients with adequate source control. This treatment strategy limits intraabdominal infections caused by multidrug-resistant pathogens.⁹⁶⁻¹⁰⁰ A 4-day course of

antibiotic therapy, extended until resolution of physiologic disturbances, is sufficient for the treatment of abdominal sepsis following a procedure for source control.¹⁰⁰ In hospital-acquired peritonitis, the duration of therapy is less definitive and is based upon clinical parameters such as fever, abdominal pain, leukocytosis, and the return of gastrointestinal function. Persistent sepsis should raise the possibility of inadequate source control, other nosocomial infections, or tertiary peritonitis. Broadening the antibiotic coverage or extending the duration of therapy are inappropriate strategies. Rather, sources of ongoing infection should be identified by a complete diagnostic reevaluation with physical examination, cultures, and imaging.

The concept of deescalation, where targeted narrower spectrum agents replace empiric broad-spectrum antibiotics once susceptibilities are obtained, is safe and should help to reduce the risk of the emergence of antibiotic-resistant isolates. Whereas evidence-based recommendations are unequivocal, compliance with deescalation is poor.⁹⁸ When intestinal function returns, oral antibiotics with good bioavailability can be administered to complete the course of therapy.^{18,101}

The role of antibiotics for tertiary peritonitis is poorly defined. There is little proven benefit to empiric antibiotics, and most bacterial isolates tend to be resistant to standard regimens. Empiric coverage of isolated *Enterococcus* spp. and *Candida* spp. has been well studied and is without clear benefit. Such coverage is recommended for complicated nosocomial infections in immunosuppressed patients, critically ill patients, and patients with valvular heart disease or implanted prosthetic materials.¹⁸ Antibiotics for tertiary peritonitis should be narrow spectrum and should be administered briefly. Anaerobic coverage is probably unnecessary.

COMPLICATIONS

The complications of failed source control include abscess formation, anastomotic dehiscence, surgical site infections, recurrent or persistent peritonitis, fistula formation, sepsis, and multiple organ dysfunction syndrome, which is the leading cause of death. Although an abscess, anastomotic dehiscence, and fistula formation are attributed most commonly to the failure of source control procedures, persistent peritonitis and sepsis often are attributed to the failure of host defenses.

Enterocutaneous Fistula

Enterocutaneous fistula formation is a dreaded complication of peritoneal inflammation and bowel injury. More than 80% of fistulas occur postoperatively, whereas fistulas that arise primarily from infection or irradiated bowel are rare.^{101,102} A fistula may be an occult source of

sepsis before drainage to the skin makes the diagnosis obvious. A fistula can contain an abscess cavity along its tract or exist internally as a connection between two intraabdominal structures.

When a fistula develops, initial care should be supportive. Therapy is directed at appropriate antibiotic therapy if signs of secondary infection are present, along with bowel rest, skin care, and parenteral nutritional support. Administration of octreotide may reduce fistula output, minimize fluid, electrolyte, and protein losses, and facilitate closure.^{103,104} Spontaneous closure with nonoperative therapy occurs in 30% to 50% of fistulas, usually within 3 to 4 weeks.¹⁰²

MORTALITY

Management of peritonitis and intraabdominal infection has improved substantially over the past century; however, mortality remains about 25% for critically ill patients.³ Age and the severity of illness at the time of presentation are more important predictors of mortality than the site of infection within the abdomen.³ Failure of an initial procedure for source control is more likely to result in death than infection caused by a multidrug-resistant pathogen.

Early recognition of organ dysfunction as a sign of persistent intraabdominal infection offers an opportunity to intervene while the process is still reversible.^{105,106} The key elements of management to minimize mortality include early recognition of the problem, rapid resuscitation, sufficient and timely source control procedures, and administration of appropriate broad-spectrum antibiotics.

Administration of glucocorticoids in patients with septic shock does not improve survival or prevent sepsis and increases the risk of superinfection.¹⁰⁷ Judicious transfusion of red blood cell concentrates may be of benefit as an adjunct in sepsis; however, additional data are needed for confirmation.¹⁰⁸ The concept of meticulous blood glucose control in the management of critically ill patients with sepsis has been controversial. Recent studies of medical patients indicate that this practice increases the rates of complications and mortality and should be avoided; however, there is evidence of benefit for critically ill surgical patients.¹⁰⁹⁻¹¹² Although drotrecogin alfa (activated) therapy showed promise in early studies, the PROWESS-SHOCK Study Group determined in 2012 that it does not improve early or late mortality among patients treated for septic shock.¹¹³ Polymyxin B hemoperfusion has been shown to improve outcomes in preliminary studies in Japan and Europe.^{114,115} Other adjunctive therapies of potential promise include IV IgM and IgA, recombinant thrombomodulin, interleukin-7, and thymosin $\alpha 1$.^{115,22} Further studies are under way to develop point-of-care testing for biomarkers that may predict individual responses to therapies tailored to the various manifestations of peritonitis and septic shock.¹¹⁶

KEY POINTS

1. Critically ill patients with intraabdominal infection are at high risk of treatment failure.
2. Adequate and timely resuscitation ensure tissue perfusion and oxygenation and can prevent the life-threatening complications associated with splanchnic hypoperfusion.
3. Source control must also be adequate and timely and should include débridement of devitalized tissue, closure of perforations, drainage of infected collections, reduction of bacterial and toxin burden, and the use of appropriate broad-spectrum antimicrobial therapy.
4. Acute acalculous cholecystitis is an ischemic process and is only secondarily an infection. Its diagnosis is challenging, and a high index of suspicion is required.
5. Intestinal ischemia is a dangerous and relatively common complication of critical illness, which can progress within hours to gangrene, perforation, and generalized peritonitis.
6. Early diagnosis and treatment, including operative intervention where appropriate, are essential to decrease the high mortality associated with fulminant colitis caused by *Clostridium difficile*.
7. Computed tomography is the primary radiologic modality for imaging the abdomen and pelvis in critically ill patients.
8. Percutaneous decompression of intraabdominal abscesses is successful in about 85% of cases and often can be definitive treatment. Patients who do not improve promptly following percutaneous drainage should undergo formal operative intervention without delay.

Continued

KEY POINTS—cont'd

9. Optimal antibiotic therapy for secondary peritonitis requires an agent or combination therapy active against both aerobic gram-negative bacilli and anaerobes. High-risk patients with nosocomial intraabdominal infections should be treated with broader spectrum empirical regimens, including selective use of agents effective against resistant gram-negative organisms, enterococcal species, and *Candida* species.
10. Shorter courses of antimicrobial therapy and the modification of agents once susceptibilities are available are safe in patients with adequate source control and decrease the risk of infections caused by multidrug-resistant pathogens.
11. Complications associated with inadequate source control include abscess formation, anastomotic dehiscence, surgical site infection, recurrent or persistent (secondary or tertiary) peritonitis, fistula formation, abdominal compartment syndrome, sepsis, and multiple organ dysfunction syndrome.
12. Neither planned re-laparotomy nor open abdomen techniques offer survival benefits when compared with on-demand re-laparotomy in achieving adequate source control.
13. Multiple organ dysfunction syndrome is present in virtually every patient who dies from intraabdominal infection.

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Obstructions of the small bowel can be classified into two categories: nonmechanical and mechanical. Nonmechanical obstruction (e.g., ileus, pseudo-obstruction) is defined as a disturbance in motility preventing luminal contents to pass with coordinated peristalsis. Mechanical obstruction is the inability for contents to move forward due to luminal obstruction. Further classification is based on the presence of vascular compromise and ischemia.

Functional obstruction (ileus) has an annual incidence of 20%,¹ while mechanical obstruction has an annual incidence of 2% to 9%, or roughly 1 in 3000.² Nearly 70% of small bowel obstructions are due to adhesions from previous surgery.³ Risk factors for the development of adhesions include pelvic surgery, emergency laparotomy, peritonitis, penetrating trauma or prior bowel obstruction (i.e., stricture or luminal narrowing, anastomosis). Other causes of obstruction are neoplastic (20%) and hernia (10%), with the remaining cases occurring from volvulus, inflammatory changes, or other causes (gallstone ileus, trauma, external mass effect, endometriosis, foreign body).⁴

In a recent review of 87 studies including 110,076 patients, the incidence of adhesive small bowel obstruction (aSBO) following abdominal surgery is 2.4%.⁵ Reviewing patient data collected over 10 years, aSBO accounts for greater than 300,000 annual hospital admissions, which translates into roughly 850,000 inpatient days, with a total cost exceeding \$1.3 billion annually.⁶ A nationwide inpatient sample study performed in 2009 enrolled 27,046 patients with aSBO and demonstrated that a delay in surgery for patients with a complete obstruction due to adhesive disease is associated with an increased length of stay and increased mortality. A delay of 4 days is associated with a 64% increased risk of finding nonviable bowel at time of exploration and a fourfold increase in overall mortality.⁷ This statistic highlights the importance of early recognition and diagnosis of a complete obstruction to facilitate early surgical intervention (<72 hours). The idea of early surgical therapy for aSBO is substantiated by another review of 9297 patients from the NSQIP database from 2005 to 2011.⁸ Keenan et al.⁷ observed that patients who underwent surgery after 3 days had an increased overall 30-day morbidity and those who waited more than 4 days had an increased overall length of stay. Thus, the World Society of Emergency Surgery set guidelines in 2013 for the management of aSBO recommending that nonoperative management should not exceed 3 days due to the increase in mortality.⁹

Multiple surgical studies have investigated the various methods to aid in early diagnosis of complete obstruction, either by clinical or radiographic criteria. The goal of early recognition is to decrease delay to definitive surgical treatment and to reduce additional morbidity and mortality.

■ DIAGNOSIS

Diagnosis of a small bowel obstruction or ileus is based on a combination of patient history and imaging. The main objective in the diagnosis of a bowel obstruction is to differentiate between a functional ileus and a mechanical obstruction. Once a mechanical obstruction is identified, further classification of patients with partial versus complete bowel obstruction is based on a combination of clinical exam, physiologic status, and imaging.

Symptoms include intermittent cramping abdominal pain, progressing to constant pain, nausea, vomiting, distention, and obstipation. Ileus and pseudo-obstruction are generally associated with an additional clinical diagnosis such as recent infection (pneumonia

or urinary tract infection), electrolyte imbalance, or a recent surgical procedure. Laparotomy, orthopedic, and vascular procedures are often associated with prolonged ileus or colonic inertia. Plain films frequently display air fluid levels and dilation of the small bowel with decreased or no air in the colon and rectum. Unfortunately, these signs are present only 20% of the time.¹⁰

Computerized tomography (CT) scan may be more specific and sensitive for the detection of ileus versus small bowel obstruction and will give suggestions of vascular compromise. A transition from a dilated loop to a decompressed segment is the most common finding in bowel obstruction. This transition point is absent with an ileus or pseudo-obstruction. Signs associated with vascular ischemia are thickened bowel walls (>3 mm) or bowel wall edema, portal venous gas, ascites, and decreased enhancement of bowel wall.¹¹ Target or swirl signs suggest volvulus or internal hernia, which can lead to strangulation. CT scan may also be able to identify other potential causes of small bowel obstruction such as hernia or neoplastic processes. Overall, the sensitivity in diagnosis of obstruction with CT scan is 94%, with a specificity of 96%; the sensitivity of plain films is approximately 50% to 70%.¹¹

Differentiation between a partial or complete obstruction is difficult. In a recent study of aSBO, resuscitated patients underwent initial CT scan with intravenous contrast to determine the presence of vascular compromise; those with signs on imaging were directed into the surgery cohort. PO contrast was not used initially to reduce risk of aspiration and to improve diagnostic efficacy with future contrast studies. Those patients with signs and symptoms consistent with aSBO without peritonitis or CT evidence of ischemia were placed in the nonsurgery cohort.¹² Those with symptoms of peritonitis, suspicion of ischemic bowel, with abdominal tenderness, fever, tachycardia, leukocytosis, or metabolic acidosis received urgent surgical intervention after adequate resuscitation without additional diagnostics.¹²

Patients in the nonsurgery group with clinical signs of obstruction and without vascular compromise on CT were observed with serial exams and monitored for resolution of obstruction. Once physiologically improved, an osmotically active oral contrast was administered, and serial films were obtained to monitor for resolution of partial obstruction or identification of complete obstruction.¹³

A recent review combining resuscitation, bowel decompression, and administration of an oral contrast agent found a positive predictive value of 99% for nonsurgical resolution if contrast reached the colon within 24 hours.¹⁴ Lack of contrast in the colon at 24 hours was consistent with a diagnosis of complete obstruction and an indication for operative intervention. The administration of contrast can be both diagnostic for complete obstruction, therapeutic time to resolution, and overall hospital length of stay.¹⁴

■ TREATMENT

Treatment arms differ based on the diagnosis of pseudo, partial, or complete obstruction. Morbidity and mortality are directly affected when definitive treatment of a mechanical obstruction is delayed.¹⁴ Ileus and pseudo obstruction are treated primarily by treating the underlying cause. Correction of electrolyte abnormalities and treatment for infectious etiology result in resolution the majority of the time. Stool softeners and motility agents should be used with caution and in a monitored setting when conservative measures have not resulted in resolution. Pseudo-obstruction is more complex and requires confirmation that an

obstruction is absent. An aggressive bowel regimen with enemas and direct decompression is often necessary. Pharmacologic agents such as neostigmine can be used to promote colonic motility if medical contraindications and mechanical obstruction are absent.

The treatment pathway for mechanical obstruction depends on the clinical picture of the patient. [Figure 100-1](#) depicts an algorithm for managing the patient presenting with symptoms of aSBO.¹² Nonsurgical management is appropriate for patients with a partial obstruction or those without signs suggestive of strangulation or closed loop obstruction. Management involves isotonic fluid resuscitation, bowel decompression, and serial examination. When physiologically stable, the use of an oral contrast challenge may further guide therapy. Frequent abdominal exams are necessary as a clinical change or progression to ischemia mandates operative intervention, as does failure to pass Gastrografin at 24 hours. Those with concerns for strangulation based on CT scan or those with physical exam evidence of peritonitis should receive resuscitation and gastric decompression prior to prompt surgical therapy. The presence of complete obstruction at any time requires operative correction when physiologically stable.

The World Society of Emergency Surgery and EAST practice guidelines¹⁵ both advocate for definitive therapy of complete obstruction within 72 hours of presentation. The presence of contrast within the colon had 96% sensitivity, 98% specificity, 99% positive predictive value and 90% negative predictive value for successful resolution of bowel in cases suggestive of partial obstruction.¹⁶

The objective of surgical intervention is relief of obstruction and assessment of bowel viability. Assessment may include the use of Doppler signals or injection of fluorescein and Wood lamp

examination with the possibility of a second exploration if indicated or if further resuscitation is required. Evaluation of the entire bowel is essential to rule out multiple transition points.

Limited evidence in the medical literature addresses the types of surgical interventions. The use of laparoscopy may be appropriate in select patients. The advantages include earlier return of bowel function, fewer wound complications, lower narcotic use, decreased length of stay, and decreased development of postoperative adhesions.⁹ A national inpatient sample of 6165 patients found a significant decrease in postoperative complications, hospital length of stay, and overall costs of aSBO managed with laparoscopic adhesiolysis.¹⁷ The conditions favoring the use of laparoscopy are mild distention, proximal obstruction, and anticipated single band obstruction based on a clinical history of recent pelvic surgery.¹⁸

Currently, there are no controlled prospective studies to support or refute the use of antibiotics or long-tube decompression devices in the management of small bowel obstruction.¹⁸ Therefore, the use of nasal gastric decompression and isotonic fluid hydration remains the standard of care.

Roughly 80% of those presenting with partial small bowel obstruction have improvement in symptoms and resolution with conservative management alone.¹⁸ Those treated conservatively will have a recurrence rate approaching 20% to 40% within the first year, while early surgical therapy has been shown to reduce recurrence to 6% to 12%.²

Surgical intervention carries its own risks of morbidity, including the formation of fistulas and adhesions, wound infections, and development of a short gut from multiple small bowel resections. A surgical technique with minimal tissue injury and the use of commercially available adhesion barriers (Seprafilm, Interceed, and Adept) may decrease the formation of adhesions; however, there is currently insufficient data to support their global use.

Certain populations present with bowel obstructions not previously mentioned that warrant special consideration. For instance, patients with inflammatory bowel disease (Crohn's) will have higher rates of conservative therapy, incorporating the use of steroids and immune modulation if without infection.¹⁸ Another special case is the trauma patient with an intramural hematoma involving the duodenum, where management requires parenteral nutrition and proximal decompression. Stricture formation necessitating surgical revision or reconstruction rarely occurs.¹⁸

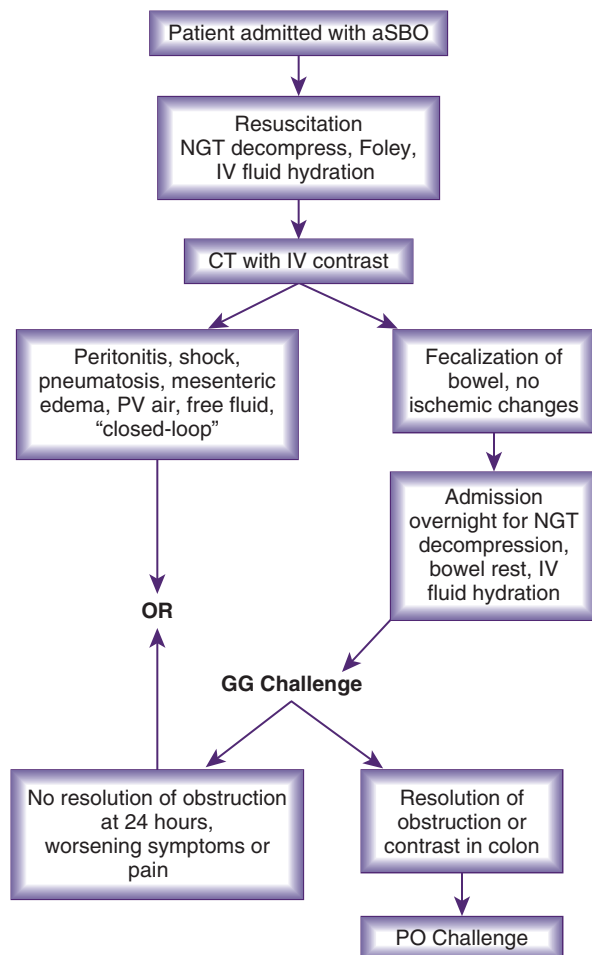


FIGURE 100-1 ■ Patient admitted with adhesive small bowel obstruction.

KEY POINTS

1. CT scan has 98% sensitivity for identification of small bowel obstruction and detecting presence of strangulation.
2. Patients with signs and symptoms of peritonitis (fever, tachycardia, metabolic acidosis, and continuous pain) should undergo early urgent surgical therapy.
3. Patients without peritonitis may be conservatively managed with hydration, bowel decompression, and oral contrast challenge.
4. Administration of oral contrast is both diagnostic and therapeutic for adhesive small bowel obstruction, especially in partial obstruction.
5. Failure to pass contrast into the colon within 24 hours of administration demonstrates complete obstruction, and use of a surgical approach is appropriate.
6. Increased morbidity and mortality are associated with bowel resection and strangulation if surgical therapy is delayed for more than 72 hours.
7. Synthetic materials to prevent adhesion formation are of limited utility.

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Acute megacolon refers to a syndrome defined by abnormal colonic distention in the absence of mechanical obstruction. Megacolon may be a manifestation of Ogilvie's syndrome or toxic megacolon. The sequelae of these disorders result in diffuse colonic dysmotility. Ogilvie's syndrome is an eponym for acute colonic pseudo-obstruction.^{1,2} Critical illness-related colonic ileus (CIRCI) is characterized by constipation for several days without marked colonic distention and may herald the development of Ogilvie's syndrome.³ Ogilvie's syndrome is believed to be a functional disturbance of colonic motility and is often observed in hospitalized patients as a result of hemodynamic, metabolic, pharmacologic, inflammatory or postoperative conditions.⁴ In toxic megacolon, the distention is caused by severe colitis and is associated with systemic manifestations or toxicity. Although usually attributed to inflammatory bowel disease (IBD), most notably ulcerative colitis, toxic megacolon may manifest in the critically ill as a complication of severe infectious colitis, most frequently caused by *Clostridium difficile*. Both Ogilvie's syndrome and toxic megacolon are medical emergencies that, if left untreated, result in intestinal barrier failure, colonic ischemia, perforation, and multiple organ dysfunction. This chapter focuses on toxic megacolon and Ogilvie's syndrome in critically ill patients admitted to intensive care units (ICUs) and provides management and prevention strategies for each disease process.

CLINICAL FEATURES

Ogilvie's Syndrome or Acute Colonic Pseudo-obstruction

The clinical features of Ogilvie's syndrome include abdominal distention with or without abdominal pain in hospitalized or institutionalized patients with serious underlying medical and surgical conditions.^{2,5,6} Patients usually present with constipation; however, passage of flatus or stool is reported in up to 40% of patients.² Bowel sounds may be normal, diminished, or hyperdynamic. Leukocytosis and fever are more common in patients with ischemia or perforation but also occur in those who have not developed these complications. According to Laplace's Law, the pressure required to stretch the walls of a hollow viscus decreases in inverse proportion to the diameter.⁷ Therefore, progressive colonic distention causes the highest tension in the wall of the cecum and is thus most likely to be the site of perforation. The risk of cecal perforation increases sharply when the cecal diameter is greater than 12 cm and when this distention has been present for longer than 6 days.⁸ A diameter of 9 to 12 cm has been suggested as a sign of impending perforation.^{2,4} If the diagnosis and treatment are delayed, progressive distention may cause peritoneal signs, abdominal compartment syndrome, respiratory compromise, sepsis, ischemia, perforation, multiple organ failure, and death.

Toxic Megacolon

Toxic megacolon is the late, life-threatening complication of inflammatory or infectious colitis. Patients present with fever, leukocytosis, abdominal distention and tenderness, with or without signs of local or generalized peritonitis. Both IBD and infectious colitis classically present with diarrhea, but constipation may herald the onset of megacolon, delaying diagnosis. In addition to these findings, patients may

present with dehydration, altered consciousness, electrolyte disturbances, hypoalbuminemia, and hypotension. In severe cases, septic shock and multiple organ failure may ensue.^{9,10} Factors that may trigger or predispose to the development of toxic megacolon have been identified; these include severe hypokalemia, discontinuation or rapid tapering of corticosteroids, sulfasalazine, or mesalazine, use of antidiarrheal agents, and use of antidepressants.¹¹ Barium enema and colonoscopy may cause worsening distention that further impairs colonic blood supply, leading to increased transmural bacterial translocation, and should be avoided.

PATHOGENESIS OF ACUTE MEGACOLON

Colonic Ileus and Ogilvie's Syndrome

The pathophysiology of Ogilvie's syndrome is not fully understood. The current literature suggests an imbalance in the autonomic regulation of the colonic motor function, leading to excessive parasympathetic suppression and sympathetic stimulation. This results in an aperistaltic colon.^{12,13} In addition to autonomic dysregulation, neurotransmitters (e.g., substance P and vasoactive intestinal polypeptide [VIP]), inflammatory mediators (e.g., tumor necrosis factor [TNF], interleukin 1 [IL-1]), metabolic derangements, and pharmacologic interventions also play crucial roles in the development of Ogilvie's syndrome.¹⁴

Postoperative motility disturbances are inevitable after abdominal surgery and result from a complex interaction of neurogenic and inflammatory mechanisms. The extent of parasympathetic suppression and sympathetic activation depends on the amount of surgical stimulation, as demonstrated by Bueno et al. in experimental studies in dogs.¹⁵ Surgical manipulation triggers two different, distinct phases of postoperative ileus. The first or early phase is neurally mediated and is activated during and immediately following surgery. During this phase, intestinal manipulation initiates the release of norepinephrine via the sympathetic nerves from the spinal cord, as well as nitric oxide (NO) and VIP release via vagal nerve stimulation, abolishing the motility of the entire gastrointestinal (GI) tract.^{16,17} This phase ceases once the abdomen is closed. The second, long-lasting phase of postoperative ileus involves the inflammation of the intestinal muscularis. During this phase, activation of peritoneal mast cells triggers the release of vasoactive and proinflammatory substances such as histamine and proteases, which recruit leukocytes and temporarily increase mucosal permeability. This allows luminal bacteria or bacterial products to enter the lymphatics. This likely represents the key event that triggers the next stage of the inflammatory cascade, which is activation of the resident macrophages. Once activated, the resident macrophages release cytokines such as TNF and cause the subsequent up-regulation of inducible NO synthetase and cyclooxygenase-2, further blunting the contractile response of the inflamed tissues.¹⁸ In addition, *in vivo* animal studies have demonstrated that endogenous opioids released peripherally can modulate GI motor and secretory functions.¹⁹ Opioid receptors are stimulated by endogenous opioids, which are secreted locally upon stress. Once activated, they inhibit acetylcholine release from motor neurons and promote transmitter release from inhibitory neurons.²⁰ In addition to stimulation by endogenous opioids, exogenous opioids, commonly used for analgesia, also act upon peripheral opioid receptors in the GI tract, inhibiting GI motility.

CIRCI may be related to circulating bacteria or bacterial products and/or proinflammatory cytokines, following a similar mechanism as previously described. Colonic ileus also has been associated with ischemia-reperfusion injury, causing energy deficit, *functio laesa*, and oxidant-mediated tissue damage. Finally, distal colonic distention induces inhibition of proximal colonic motility, the so-called colocolonic reflex, thereby perpetuating a vicious cycle.²¹

■ PREDISPOSING FACTORS

Ogilvie's Syndrome

Acute colonic pseudo-obstruction was first described by Sir William Heneage Ogilvie in two patients who had retroperitoneal tumors invading the celiac plexus, which led him to suggest sympathetic deprivation as the etiology of the massive distention.⁵ The vast majority of patients presenting with Ogilvie's syndrome have the syndrome in association with a predisposing factor. Clinical factors predisposing to Ogilvie's syndrome are summarized in [Box 101-1](#).^{1,2,6} In a large retrospective series of 400 patients, Vanek et al. reported that the most common predisposing conditions associated with Ogilvie's syndrome were nonoperative trauma (11%), infections (10%), and cardiac disease (10%).⁶ Although nonsurgical factors predisposing to Ogilvie's syndrome are common, surgical operations remain the most common cause of this syndrome. Of these operations, Ogilvie's syndrome is

most likely to occur after obstetric/gynecologic, abdominal/pelvic, trauma, orthopedic/spine, and cardiac procedures. These procedures account for 50% to 60% of all Ogilvie's cases.²² Exogenous catecholamines have dose-dependent effects on intestinal motility; low doses promote and high doses suppress motility. α -Adrenergic agonists and dopamine are stronger inhibitors of acetylcholine release than β -adrenergic agents. Dopamine, in addition to inhibiting upper GI motility, also inhibits distal colonic motility. Antipsychotic agents such as clozapine, haloperidol, and olanzapine have been associated with life-threatening forms of Ogilvie's syndrome.²³ One explanation of these GI side effects is the antimuscarinic properties of these drugs. Opioids suppress GI motility through activation of μ -opioid receptors, which inhibit the release of acetylcholine from the myenteric plexus. The outcome of this interaction is the decreased levels of cyclic adenosine monophosphate (AMP) and calcium, with a reduction in the excitatory neurotransmitter release that ultimately leads to decreased peristalsis.^{12,20} Opioid agonists inhibit GI wall motility, impair reabsorption of fluid from the lumen, and also impair relaxation of the internal anal sphincter.²⁴ Additional predisposing factors such as severe metabolic derangements, sepsis, GI infections, and spinal cord injuries have also been implicated in the development of Ogilvie's syndrome.

Toxic Megacolon

Acute toxic megacolon was originally described in 1950 as a complication of IBD. The incidence of toxic megacolon in IBD has substantially decreased with the advances in the management of severe colitis. Over the course of the past decade, the list of etiologic factors has been expanded by a vast array of inflammatory and infectious conditions; bacterial colitides such as *C. difficile*, *Staphylococcus* spp., *Salmonella* spp., *Shigella* spp., and *Campylobacter* spp., as well as viral (e.g., cytomegalovirus, human immunodeficiency virus, and herpesvirus) and parasitic (*Entamoeba*) infections have all been associated with toxic megacolon.^{25,26} However, the most common cause of acute toxic megacolon in the critically ill is pseudomembranous colitis caused by *C. difficile*. While many conditions have been associated with the development of toxic megacolon, its precise pathophysiology is not fully understood. The causes of toxic megacolon are summarized in [Box 101-2](#).

C. difficile Infection

C. difficile is a gram-positive, spore-forming, toxin-producing, anaerobic rod bacterium. Less than 5% of the healthy adult population is colonized with this bacterium.²⁷ An estimated 30% of hospitalized patients become colonized with *C. difficile*, although most of these patients remain asymptomatic. Pathogenic strains produce two major exotoxins: toxin A (enterotoxin/Tcd A) and toxin B (cytotoxin/Tcd B).²⁸ Purified toxin A possesses potent enterotoxic and proinflammatory activities. Toxin B has been previously reported to

BOX 101-1

Clinical Factors Predisposing to Ogilvie's Syndrome or Acute Colonic Pseudo-obstruction

CARDIOVASCULAR

- Heart failure, stroke
- Gut ischemia

CRITICAL ILLNESS

- Severe sepsis
- Acute pancreatitis
- Shock or hypoxemia

POSTOPERATIVE STATE OR TRAUMA

- Intestinal manipulation
- Peritonitis
- Immobility and dehydration
- Vertebral, pelvic, or hip fracture/surgery
- Retroperitoneal hematoma

METABOLIC FACTORS

- Hypokalemia and hyperglycemia
- Hypothyroidism, diabetes mellitus
- Liver or renal failure
- Amyloidosis

DRUGS

- α -Adrenergic agonists, dopamine¹⁸
- Clonidine and dexmedetomidine³⁶
- Opioids
- Anticholinergics, calcium channel antagonists
- Antipsychotics^{39,40}
- Antidepressants
- High-dose phosphodiesterase inhibitors

GASTROINTESTINAL INFECTIONS

- Cytomegalovirus, herpes zoster
- Tuberculosis

NEUROLOGIC

- Transsection of the spinal cord
- Low spinal cord disease
- Parkinson's disease

OBSTETRIC

- Cesarean section
- Normal delivery

BOX 101-2

Disorders Associated With Toxic Megacolon

INFLAMMATORY BOWEL DISEASE

- Ulcerative colitis
- Crohn's disease

INFECTIOUS COLITIS

- *Salmonella*, *Shigella*, amebic colitis
- *Clostridium difficile*
- Cytomegalovirus colitis
- HIV infection

CANCER CHEMOTHERAPY

ISCHEMIA

HIV, human immunodeficiency virus.

BOX 101-3**Factors Associated With Colonization and Subsequent Infection With *Clostridium difficile*****DISRUPTION OF INDIGENOUS MICROFLORA**

- Antibiotics suppressing indigenous microflora
- Cancer chemotherapeutics with antimicrobial activity
- Preoperative bowel preparation

OPPORTUNITY OF INFECTION

- Prolonged hospital stay

MICROBIAL FACTORS

- Toxigenicity and adhesion

DIMINISHED GASTROINTESTINAL DEFENSE

- Reduced or suppressed gastric acid secretion
- Parenteral nutrition
- Postpyloric enteral nutrition
- Gastrointestinal surgery

ANTIBODY RESPONSE OF THE HOST**POOR UNDERLYING CONDITION**

- Old age
- Cancer
- Renal insufficiency
- Long-term use of corticosteroids
- Bedridden state

exhibit no enterotoxic activities; however, recent studies have described enterotoxic and proinflammatory activities in human intestinal xenografts in mice.²⁹ It has been postulated that toxins A and B act synergistically to activate cell-signaling molecules, including transcription factor, nuclear factor- κ B, and mitogen-activated protein kinases in monocytes, leading to the production and release of proinflammatory cytokines. Toxin A leads to an increased secretion of fluid within the digestive tract, mucosal inflammation, and structural damage. Toxin B, in most cases, is responsible for the major problems associated with infection and is estimated to have 10 times more impact on the GI tract than toxin A.³⁰ Recently, a hypervirulent strain has been identified. This strain, referred to as *NAP1/BI/027*, is responsible for outbreaks of highly virulent pathogens. A deletion in this strain's *tcdC* gene, which is a negative regulator of toxin production, causes the production of both toxins A and B to increase by 16- to 23-fold.^{27,31} This strain is also more resistant to fluoroquinolones, has hypersporulation capacity, and produces an additional toxin, toxin C. This hypersporulation capacity potentially accounts for the enhanced transmission in hospitals compared with previous strains.

Colonial proliferation of *C. difficile* is thought to occur when the bacterial environment has been altered by current or previous exposure to antibiotics.²⁷ Historically, antibiotics such as clindamycin, cephalosporins, and certain penicillins were most commonly associated with *C. difficile* colitis. More recently, fluoroquinolones have been implicated as a more common cause of this infection. The risk of being infected with this organism increases with prolonged hospital stay and institutionalization, and the organism may be spread by nosocomial transmission. It has been postulated that susceptibility is further increased with the concurrent use of gastric acid-inhibiting drugs, which can facilitate increased survival of the *C. difficile* spores. A complete list of factors associated with *C. difficile* infection (CDI) can be found in [Box 101-3](#).

DIAGNOSIS OF ACUTE MEGACOLON

The diagnosis of acute megacolon is suggested by the clinical presentation. A thorough history and physical exam should be obtained for all patients with acute abdominal distention and may help identify the underlying cause ([Boxes 101-2 and 101-3](#)). Mild cases typically present with abdominal pain and cramping, constipation or diarrhea, and low-grade fever. More severe cases may present with significant abdominal



FIGURE 101-1 ■ Plain abdominal radiograph of patient with respiratory insufficiency due to severe emphysema and Ogilvie's syndrome 10 days after dynamic hip screw implantation for femoral fracture. Dilatation is most pronounced in cecum and ascending colon. Gas and fecal pattern in distal colon is normal. Patient was successfully treated with intravenous neostigmine.

tenderness and signs of systemic inflammation, such as fever, leukocytosis, and electrolyte abnormalities. Plain abdominal radiography is essential in the diagnostic workup, which can show varying degrees of colonic dilation. Dilation is most pronounced in the cecum, ascending colon, and right transverse colon. The cecal diameter may range from 6 to 20 cm. "Cutoffs" are common at the splenic flexure and descending colon ([Fig. 101-1](#)), and dilation of the left colon may also occur ([Fig. 101-2](#)). The distribution of colonic dilation may be caused by different origins of the proximal and distal parasympathetic nerve supply of the colon. Air/fluid levels may be seen in the small bowel, indicating a paralytic ileus. The differential diagnosis of acute colon distention in a critically ill patient should include mechanical obstruction, infectious colitis with toxic megacolon, and Ogilvie's syndrome. Prompt evaluation of a patient with acute megacolon should involve excluding mechanical obstruction and other causes of toxic megacolon such as *C. difficile* colitis and assessment for signs of peritonitis or perforation, which indicates a surgical emergency. Mechanical obstruction is excluded if air is visible in all colonic segments, including the rectosigmoid junction. If the diagnosis is in question, mechanical obstruction can be excluded by performing a water-soluble contrast enema or computed tomography (CT) scan. The water-soluble contrast medium creates an osmotic effect and may be therapeutic in decompressing the colon. On contrast enema, the colonic haustral and mucosal pattern is maintained in Ogilvie's syndrome, whereas the pattern is disturbed or lost in toxic megacolon. Pneumatosis of the bowel wall or free intraperitoneal air on CT scan indicates the need for urgent surgical consultation.

If toxic megacolon is suspected, fresh stools should be submitted for laboratory culture and the stools should be screened for the presence of toxigenic *C. difficile*. Commercially available nucleic acid

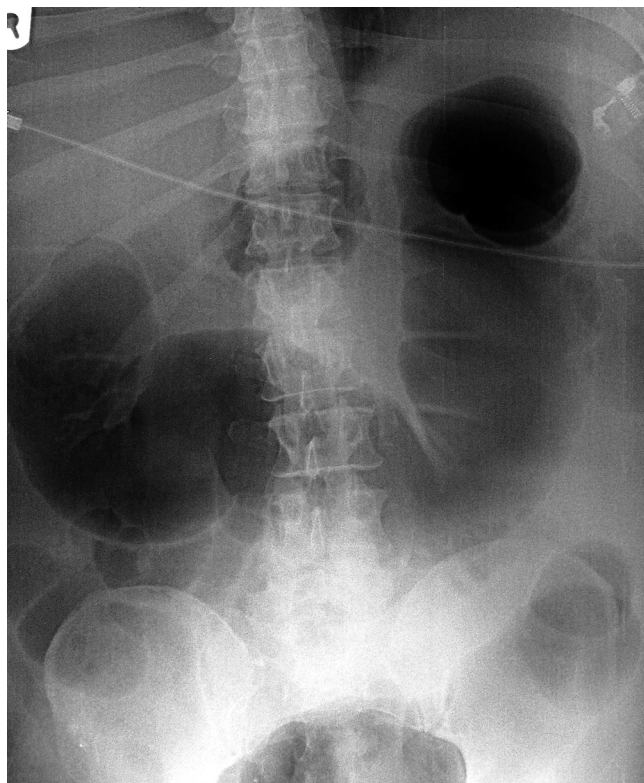


FIGURE 101-2 ■ Plain abdominal radiograph of a patient with Ogilvie's syndrome 11 days after surgery for a ruptured aneurysm of the abdominal aorta. Dilatation (probably due to ischemia) is present in both the right and left colon. The syndrome was resolved with vasodilators and intravenous neostigmine.

amplification tests (NAAT) such as PCR for the rapid detection of CDI are inexpensive, highly sensitive, and allow results to be available within hours. These tests should only be utilized in patients with documented diarrhea. An alternative method for the detection of CDI requires a two-step procedure. The patient should first be screened for the presence of glutamate dehydrogenase (GDH), an enzyme produced by *C. difficile* in relatively large amounts compared with toxins A and B. Although GDH testing is sensitive, it is not as specific for CDI, because this enzyme is produced by both toxigenic and nontoxigenic organisms. GDH-negative specimens require no further testing. GDH-positive specimens must undergo additional screening either by NAAT or by toxins A and B enzyme immunoassay (EIA) testing followed by NAAT if the EIA results are discordant.³² The final results take 2 to 5 days. After an initial negative result, repeat testing within 48 hours should be discouraged, as conversion to a positive result occurs in less than 5% of patients.³³ Studies have shown that both toxin A and B EIA and toxigenic cultures may remain positive for as long as 30 days in patients who have resolution of symptoms. Therefore, "test for cure" studies may complicate clinical care, resulting in unnecessary prolongation of treatment, and therefore should not be performed. Surveillance cultures of feces are advocated to detect other pathogens such as enterotoxin-producing *Clostridium perfringens*, *Staphylococcus aureus*, and *Klebsiella oxytoca*. Blood cultures should be obtained from any patient presenting with toxic megacolon.

Limited endoscopy (e.g., flexible sigmoidoscopy) with biopsy may be valuable in differentiating etiologic causes; however, full colonoscopy bears the high risk of perforation and is therefore contraindicated. IBD is characterized by diffusely abnormal crypt structure, whereas normal crypt architecture is seen in bacterial colitis. Mild cases of *C. difficile* colitis are associated with nonspecific findings of colitis, such as friability of the mucosal surface. In severe cases, focal ulcerations

BOX 101-4

Strategies to Prevent Ogilvie's Syndrome in the Critically Ill

- Early resuscitation of the circulation
- Minimizing prolonged infusion of high doses of α -adrenergic drugs
- Minimizing the use of dopamine
- Minimizing the prolonged use of opioids
- Use of thoracic epidural anesthesia
- Minimally invasive or laparoscopic surgery
- Selective decontamination of the digestive tract
- Avoiding antibiotics that disrupt the growth of anaerobic fecal bacteria
- Early oral or enteral feeding
- Avoidance of proton-pump inhibitors
- Early mobilization and ambulation
- Promoting timely defecation

covered by purulent material or pseudomembranes interspersed with normal intervening mucosa may be seen. While pathognomonic for CDI, these lesions are not uniformly present and may not be present throughout the entire colon.

MANAGEMENT

Ogilvie's Syndrome

Medical Management

An essential concept to the management of Ogilvie's syndrome is prevention. Many hemodynamic, surgical, and metabolic derangements have been implicated in the development of Ogilvie's syndrome. Strategies to prevent Ogilvie's syndrome in the critically ill are highlighted in [Box 101-4](#). Life-threatening complications may occur if treatment is delayed. Supportive therapy is the preferred initial management and should be instituted in all patients. Concomitantly, conditions that impair colonic motility must be corrected. Patients should be made *nil per os* and intravenous fluids administered to restore euvolemia. Nasogastric decompression should be initiated in patients with concomitant paralytic ileus. Electrolyte and metabolic abnormalities, including phosphorous, magnesium, calcium, and thyroid functions, should be corrected via parenteral administration. Blood cultures and empirical antibiotics should be administered if sepsis is clinically suspected. Offending medication use, such as opioids, anticholinergic agents, norepinephrine, and dopamine, should be minimized or discontinued if possible. Optimal body positioning, such as prone positioning with the hips elevated on pillows or the knee-chest position with the hips held high, often aids in spontaneous evacuation of flatus.^{2,5} These positions should be alternated with the right and left lateral decubitus positions regularly, when feasible. The use of a rectal tube may also aid in decompression. Serial abdominal examinations, assessing for signs of peritonitis or free perforation, should be performed, and plain abdominal radiographs should be obtained every 12 hours. Osmotic laxatives lead to increased gas formation in the colon and should be avoided.³⁴ The reported success of conservative management is variable, with rates from 20% to 92%.³⁵ Deterioration or non-resolution of symptoms despite maximal medical therapy within 48 to 72 hours of initiating therapy should prompt reconsideration of the management plan.

If these measures are ineffective, intravenous neostigmine is the drug of choice. Neostigmine is an anticholinesterase parasympathomimetic agent commonly used for postoperative reversal of nondepolarizing neuromuscular blockade and in the treatment of myasthenia gravis. Parasympathetic stimulation can result in bradycardia, asystole, hypotension, bronchospasm, and hypersalivation. Close observation and monitoring with telemetry in a controlled setting are warranted. In a double-blind, randomized placebo-controlled trial of 21 patients with a cecal diameter of at least 10 cm, despite 24 hours of conservative therapy, 10 out of 11 patients randomized to receive an infusion of

2 mg neostigmine had prompt colonic decompression, and one responded after subsequent retreatment.³⁶ None of the 10 patients randomized to placebo experienced resolution, but all 7 in whom neostigmine was openly administered subsequently responded. In a double-blind, placebo-controlled prospective study in critically ill ventilated patients with CIRCI, continuous infusion of neostigmine at 0.4 to 0.8 mg/h resulted in defecation in 80% of the patients, with no reported adverse events.³ Contraindications to the use of neostigmine include mechanical obstruction, the presence of ischemia or perforation, pregnancy, uncontrolled cardiac arrhythmias, severe active bronchospasm, and renal insufficiency.^{2,3} Unfortunately, relapse of Ogilvie's syndrome after the initial response to medical therapy occurs in 40% of patients, and more invasive therapies may then be required.³⁷

Surgical Management

Once medical management has failed, endoscopic decompression is the initial invasive procedure of choice for patients with marked cecal distention (>10 cm) of significant duration (>3–4 days), not improving after 24 to 48 hours of supportive therapy, and who have contraindications to or fail neostigmine treatment.⁴ Colonoscopy is performed without bowel preparation, thus further complicating the procedure. Liberal use of air insufflation should be avoided as it may lead to perforation. Advancing the scope to the level of the proximal hepatic flexure is usually sufficient to obtain adequate decompression.⁷ Gas should be aspirated and the viability of the mucosa assessed during slow withdrawal of the scope. If signs of ischemia are present, the procedure should be aborted. Successful decompression has been achieved in 70% to 80% of patients; however, the recurrence rates are as high as 50%.^{2,38} To increase the therapeutic benefit, decompression tube placement at the time of colonoscopy may reduce recurrence, but controlled trials with this intervention are not available.

Surgical management is rarely necessary and should be reserved for patients who have failed pharmacologic and endoscopic management or those who have clinical signs of colonic ischemia or perforation. Surgical options include a venting stoma (cecostomy) or colectomy. Ogilvie's syndrome is one of the few conditions where cecostomy is indicated. Tube cecostomy should only be performed in patients without evidence of ischemia or perforation. It can be performed laparoscopically or through a limited right lower quadrant incision. A large Foley catheter is left in place for 2 to 3 weeks to allow venting of the colon. Cecostomy can be performed under local anesthesia. In cases of ischemia or perforation, laparotomy is indicated. Segmental or subtotal resection may be performed as dictated by the extent of colon involvement. In the event that a colectomy is needed, an end stoma and mucous fistula should be performed and anastomosis avoided.

Toxic Megacolon

Medical Management

The initial goal of treatment is to reduce the severity of colitis so as to restore normal colonic motility and decrease the likelihood of perforation.²⁵ Patients should be monitored closely in an ICU, with frequent examinations to assess for clinical deterioration. A surgical consultation should be obtained on admission, although medical treatment is successful in about 50% of patients. Initially, complete blood counts, electrolyte panels, and serial plain abdominal films should be reviewed every 12 hours until clinical improvement has been observed. Conditions impairing colonic motility must be corrected (Box 101-1). In general, patients will require adequate resuscitation, electrolyte and vitamin replacement, early optimization of circulation, and, if necessary, mechanical ventilation. A nasogastric tube should be placed to decompress the GI tract. Early total parenteral nutrition has shown no survival benefit and should be reserved for patients who have evidence of severe malnutrition in the absence of bacteremia, especially if they are likely to undergo surgery. However, enteral nutrition should be initiated as soon as possible and tolerance closely monitored. Antimotility agents should be discontinued, and antiperistaltic agents for diarrhea are absolutely contraindicated.

Systemic antibiotics, administered empirically, are necessary to reduce septic complications and peritonitis. Empirical antibiotics should cover both gram-negative and anaerobic species, as guided by local susceptibility patterns and fecal surveillance cultures. It is important to select antibiotics that least inhibit the indigenous colonic flora, and in the case of *C. difficile*, the offending antibiotic should be discontinued. Deescalation of antibiotics should ensue, without delay, once the final microbiological data are obtained.

Patients with toxic megacolon caused by IBD should be treated with high-dose intravenous corticosteroids. Steroid treatment should be started immediately and should not be delayed pending microbiological results. Most authors recommend hydrocortisone 100 mg or equivalent every 6 hours or by continuous infusion. Steroid use should be reevaluated on a regular basis and discontinued once an exclusively infectious etiology of toxic megacolon has been established.

In patients with toxic megacolon due to severe *C. difficile* colitis, the first step is to stop the offending antibiotic and to give vancomycin 125 mg orally, four times a day.³² Treatment should not be delayed while awaiting microbiological confirmation of CDI. Findings suggestive of severe, complicated CDI include admission to ICU, hypotension with or without required use of vasopressors, fever $\geq 38.5^{\circ}\text{C}$, mental status changes, white blood cell count $\geq 35,000$ or <2000 cells/mm³, serum lactate levels >2.2 mmol/L, or evidence of end organ failure. If any of these findings are present, the vancomycin dosing should be increased to 500 mg orally four times a day with the addition of metronidazole 500 mg intravenously every 8 hours. Vancomycin retention enemas (vancomycin 500 mg in 500 mL saline per rectum four times a day) should also be administered.³²

Surgical Management

Patients unresponsive to medical treatment should undergo prompt surgical resection. Surgical intervention should be considered if a patient has progressive signs of organ failure despite optimal medical therapy, CT scan findings suggestive of worsening disease, or signs of peritonitis or perforation. However, because of the lack of prospective randomized studies, it is difficult to identify the optimal point for surgical intervention in patients with severe, fulminant CDI, and the mortality rate ranges from 35% to 80%.³⁹ Subtotal colectomy with end ileostomy is considered the procedure of choice when urgent or emergent surgery is required. More recently, Neal et al. published their experience with an alternative surgical approach comprising diverting loop ileostomy and colonic lavage.⁴⁰ In this technique, an ileostomy is created and intraoperative colonic lavage is performed with a warmed polyethylene glycol solution via the ileostomy. Postoperatively, the patients received antegrade vancomycin flushes (500 mg in 500 mL lactated Ringer's solution) every 8 hours for 10 days. Mortality was reduced from 50% to 19% among the patients treated using this novel technique. There is not currently enough data to support the routine use of this procedure; however, it remains an alternative approach for the treatment of fulminant *C. difficile* colitis.

SUMMARY

Ogilvie's syndrome manifests with massive dilation of the colon in the absence of mechanical obstruction. Evaluation involves exclusion of mechanical obstruction, cessation of offending agents, and selective use of neostigmine and colonic decompression. With appropriate management, colonic pseudo-obstruction usually resolves within several days. Toxic megacolon is a diagnosis based on clinical signs of systemic toxicity in combination with radiographic evidence of colonic dilation. The goal of treatment is to reduce the effects of colonic inflammation and prevent perforation. Timely treatment with broad-spectrum antibiotics combined with cessation of the causative agents helps to minimize the morbidity associated with this disease process. Surgery should be reserved for those patients who fail to respond to medical management or show signs of ischemia or perforation. A high index of suspicion and early recognition of both Ogilvie's syndrome and toxic megacolon are crucial to optimal management.

KEY POINTS

1. Ogilvie's syndrome, or acute colonic pseudo-obstruction, is a syndrome of massive colonic dilation in the absence of mechanical obstruction that develops in critically ill patients with serious underlying medical and surgical conditions.
2. Conservative therapy is the initial preferred management.
3. Numerous contributory metabolic, infectious, and pharmacologic factors are associated with Ogilvie's syndrome. These factors should be identified and corrected early on in treatment.
4. Neostigmine is effective in the majority of cases of Ogilvie's syndrome. Colonic decompression may be required.
5. Toxic megacolon is a syndrome of nonobstructive colonic dilation associated with systemic toxicity.
6. Empiric antibiotics with gram-negative and anaerobic coverage should be initiated early on in the course of treatment.
7. Surgical intervention should be reserved for those patients who fail optimal medical management or show clinical signs of colonic ischemia or perforation.

■ References for this chapter can be found at expertconsult.com.

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Five percent to 15% of patients in intensive care units (ICUs) experience acute deterioration in renal function.^{1,2} Renal dysfunction substantially adds to the morbidity and mortality of critically ill patients. Moreover, changes in renal function directly affect drug disposition. Thus, a means to assess renal function is essential for optimal management of patients with critical illness. This chapter reviews selected aspects of renal physiology with an emphasis on measurement of renal function, consequences of altered function, and approaches to improving renal function. The focus is on measurement and optimization of glomerular filtration rate (GFR) and renal blood flow (RBF).

RENAL BLOOD FLOW

Under physiologic conditions, blood flow to the kidneys is 20% of the cardiac output. This high rate of blood flow (1-1.2 L/min) is particularly remarkable because the kidneys make up only 0.5% of the total body weight. The high blood flow rate is due to, at least in part, the unique anatomic arrangement of the renal vasculature, with the interlobar and arcuate vessels offering little resistance to flow. This is because the interlobular arteries originate from the arcuates in a parallel arrangement and because the afferent arterioles also arise in a parallel arrangement from the interlobular vessels. It is this parallel arrangement that accounts for the low resistance in the RBF because the total resistance of n equals parallel paths, each with a resistance R , is R/n^3 . Major resistance vessels in the kidney are the afferent and efferent arterioles that bind the glomerular capillary network. Although total resistance is a function of resistance across each of these vessels, it is a unique feature of the kidney that variations in individual resistances across the afferent and efferent arterioles may lead to alterations in glomerular capillary pressure and, hence, the GFR.³

Despite a wide range of perfusion pressures, under most conditions, the RBF and GFR are relatively constant, a process described as autoregulation. The term *autoregulation* generally refers to the relative constancy of the GFR over a range of perfusion pressures and to the regulation of RBF. Emphasis has been placed on the preglomerular vasculature, mainly the afferent arterioles, as the major site at which renal perfusion is regulated. However, studies also suggest that the larger vessels, such as the interlobular vessels, respond to a variety of vasoactive stimuli and participate in an autoregulatory phenomenon. A variety of hypotheses have been generated to explain the autoregulatory response of the kidney with respect to the RBF. There is evidence to suggest that neural, humoral, or intrarenal factors are involved in the regulation of renal circulation.⁴

The renin-angiotensin pathway has a significant effect on renal hemodynamics. Renin, which is elaborated in the juxtaglomerular cells, is released in response to a decrease in renal perfusion pressure and to altered sodium chloride delivery to the ascending limb and macula densa cells. Increased renin secretion leads to augmented angiotensin II (AII) formation at the local nephron level. AII affects renal vascular resistance through modulation of both afferent and efferent arterioles, with the major effect being on the efferent arterioles.

Renal eicosanoids affect renal hemodynamics. Eicosanoids are biologically active fatty acid products of arachidonic acid and are

synthesized in the kidney in response to a variety of stimuli, with local release and effect on the renal vasculature. Stimulation of the cyclooxygenase pathway and prostaglandin synthetases leads to the formation of endoperoxides (PGG₂ or PGH₂), prostaglandins (PGD₂, PGE₂, PGF_{2α}, or PGI₂), and thromboxane A₂ (TXA₂). Leukotrienes are synthesized through a pathway involving the enzyme lipoxygenase. In the kidney, the major products of arachidonic acid metabolism are PGE₂ and PGI₂ and, to a lesser extent, PGI_{2α}. These compounds have a predominant effect of relaxing renal vascular smooth muscle and lead to vasodilatation, whereas TXA₂ is a vasoconstrictor prostanoid. It is believed that in disease states, endogenous vasodilator prostaglandins have a protective function to maintain renal perfusion and the GFR in response to vasoconstrictor stimuli, including AII and enhanced sympathetic nervous system activity. In contrast, release of vasodilatory prostaglandins is inhibited by nonsteroidal antiinflammatory drugs.

Other vasoactive compounds that affect renal circulation include plasma and glandular kallikreins and kinins and endothelium-derived vasoactive factors, such as nitric oxide and endothelin.⁴ Among the catecholamines, α - and β -adrenergic agonists are known to affect renal vascular tone by causing vasoconstriction and vasodilatation, respectively. In addition, dopamine in low doses leads to renal vasodilatation. Atrial natriuretic peptide and purinergic agents, such as adenosine, also been shown to participate in modulating renal circulation.

The effect of vasoactive mediators on renal circulation is likely to be influenced by changes in salt intake and extracellular fluid (ECF) volume as well as by hydration status. For example, the influence of AII on renal hemodynamics is greater in sodium depletion, which activates the sympathetic nervous system. In response to mild nonhypotensive hemorrhage, renal hemodynamics is relatively well maintained. However, with further reductions in volume associated with more severe hemorrhage, renal ischemia mediated by activation of the renin-angiotensin system, renal efferent adrenergic nerves, and circulating catecholamines may occur.⁴

Modification of dietary protein and amino acid intake may affect renal hemodynamics. Dietary protein intake in excess of 1 g/kg/d has been associated with renal vasodilatation, as have infusions of casein hydrolysates and amino acids.^{5,6} Conversely, chronic consumption of a low-protein diet may be associated with renal vasoconstriction.

Measurement of Renal Blood Flow

The RBF is measured conventionally by the clearance of infused para-aminohippurate (PAH), which is cleared almost totally from the arterial plasma by both filtration and secretion. Thus, its clearance approximates the rate of renal plasma flow (RPF):

$$RPF = U_{PAH} \cdot V / P_{PAH}$$

where U_{PAH} and P_{PAH} refer to urine and plasma PAH concentration, respectively, and V is the urine flow rate in milliliters per minute.

The RBF can be estimated by correction for hematocrit (Hct):

$$RBF = RPF / [1 - Hct]$$

Although available, this test is rarely used in clinical practice. In fact, direct quantitation of the RPF and RBF is rarely indicated outside research studies; however, sometimes it is necessary to document that the kidneys are being perfused. In this case, one of three additional methods may be utilized: (1) selective arteriography, including CT angiography and MR angiography, (2) Doppler ultrasonography, and (3) external radionuclide scanning. Because the latter two methods are noninvasive, they are preferred. With respect to the nuclide study, until recently, scanning was usually performed utilizing ^{125}I -iodohippurate sodium; however, the poor radiologic characteristics of ^{131}I limit its use in renal imaging.⁷ More recent evidence suggests that other agents, such as ^{127}I -orthoiodohippurate and $^{99\text{m}}\text{Tc}$ -L,L-ethylenedicycysteine are superior to ^{125}I -iodohippurate sodium.^{7,8}

Clinical Correlates

Although a significant amount of data has been obtained to indicate a complex relationship between neurocirculatory factors and renal hemodynamics, several points can be made from a clinical perspective. Optimization of cardiac output and ECF volume, including the intravascular space, is essential for the maintenance of renal perfusion. In particular, because the effects of vasoactive compounds such as AII and catecholamines are accentuated in the presence of renal hypoperfusion and volume contraction, attention should be given to the assessment of ECF volume, with correction of any deficits, and to optimize cardiac function. Frequently, pharmacologic agents have been employed to maintain renal perfusion in situations in which this may be compromised. Specifically, there has been widespread use of the so-called low-dose or renal-dose dopamine infusions. This is based on the observation that in low doses ($<3 \mu\text{g/kg/min}$), dopamine leads to renal vasodilatation.⁹ At higher doses, renal vasoconstriction may occur.

The beneficial effects of dopamine infusion have not been documented in patients who exhibit evidence of intravascular volume depletion, and the use of dopamine has been shown to be ineffective beyond a short period of infusion.⁹⁻¹¹ Thus, while infusions of renal-dose dopamine for 24 to 36 hours may be beneficial under the appropriate circumstance, there is no evidence supporting the long-term use of this agent. Furthermore, reports suggest that adverse outcomes are associated with the use of dopamine.¹¹ Continuous infusions of fenoldopam mesylate, a potent dopamine A-1 receptor agonist, have been employed in an attempt to preserve renal function in a variety of clinical settings. A meta-analysis of 16 randomized trials in critically ill patients showed that fenoldopam significantly reduced the risk of acute kidney injury, need for renal replacement therapy, and in-hospital death.¹²

Beyond anecdotal evidence, there are no compelling data to support the use of other potential vasodilator substances such as prostaglandins. Although high-protein feeding and amino acid infusions may increase the RBF by undefined mechanisms, there is no justification in utilizing these therapies solely from a hemodynamic point of view.^{5,6}

■ GLOMERULAR FILTRATION RATE

Of the 500 to 700 mL of plasma delivered per minute to the kidneys (corresponding to an RBF of 1-1.2 L/min), 20% to 25% is filtered. Glomerular filtration is a major function of the kidney and averages approximately 130 mL/min/1.73 m² in normal males and 120 mL/min/1.73 m² in normal females. Estimation or direct assessment of the GFR remains one of the most important measurements of renal function and is widely utilized in clinical practice.

Measurement of Glomerular Filtration Rate

The GFR is classically measured as the clearance of inulin (C_{in}), a fructose polymer with a mean molecular weight of approximately 5 kD. Because this substance is not present endogenously, it must be

given by constant infusion after a loading dose. Inulin is available commercially but is expensive, often difficult to obtain, and cumbersome to utilize. As a result, the C_{in} is rarely used in clinical practice except for research protocols. Although the C_{in} is generally measured chemically, ^3H - and ^{14}C -labeled inulins are also available but are expensive.

Other radiolabeled nuclides have been found to be satisfactory substitutes for inulin and have advantages in the measurement of GFR.^{7,8,13,14} In particular, $^{99\text{m}}\text{Tc}$ -labeled diethylenetriamine pentaacetic acid (DTPA) and ^{125}I - or ^{131}I -labeled iothalamate clearances closely approximate C_{in} .^{15,16} $^{99\text{m}}\text{Tc}$ -DTPA has been utilized and found to give values that correlate closely with the C_{in} in ICU patients.^{17,18} In addition, the clearance of gentamicin has been utilized in a limited fashion to measure GFR.^{19,20} At the present time, it is not common for the GFR to be measured directly. Rather, the GFR is estimated by endogenous creatinine clearance (C_{Cr}) or serum creatinine determination (see later discussion).

The normal values for the GFR obtained previously apply for individuals from teenage years through approximately 35 years. Thereafter, the GFR declines in most individuals. Although this decline was formerly thought to occur at a relatively constant rate of approximately 10 mL/min per decade,²¹⁻²³ more recent data obtained in a longitudinal manner indicate that this reduction is not so predictable.²⁴ In addition, a circadian rhythm for GFR has been described.^{25,26} GFR is maximal in the day, whereas a minimal value during the night has been found in normal individuals. It is not known whether this circadian pattern of GFR occurs in critically ill hospitalized patients.

CREATININE CLEARANCE AND SERUM CREATININE

Creatinine Clearance

The C_{Cr} enjoys widespread use as a reasonable gauge of GFR when great precision is not demanded, which it rarely is in clinical practice. The use of creatinine as a marker of the GFR has the advantage that creatinine is endogenously produced and easily measured by inexpensive methods. Creatinine, like inulin, is freely filtered and absorbed minimally if at all by the tubules. However, creatinine is secreted, and the contribution of secretion to total excretion is greater as the GFR decreases and serum creatinine rises. At GFRs below 40 mL/min, the C_{Cr} exceeds the C_{in} by 50% to 100%.^{15,27} When GFR is significantly depressed and it is deemed important to get a more precise measurement of GFR, one of the previously mentioned methods to estimate the GFR directly might be utilized. Additionally, because the C_{Cr} overestimates the GFR and the clearance of urea underestimates the GFR, the mean value of simultaneously obtained creatinine and urea clearances has been shown to provide a close estimation of the C_{in} when the latter is below 20 mL/min.²⁸

Because cimetidine competes with creatinine for tubular secretion (see later), administration of cimetidine may increase the accuracy of both creatinine clearance in 24-hour collections (when given for several days beforehand) and 4-hour, water-loaded clearances.²⁹⁻³¹ Taking advantage of this effect results in a more accurate estimate of the GFR. Specifically, the C_{Cr} obtained in the presence of cimetidine (400 mg as a priming dose followed by 200 mg every 3 hours) yielded values that closely approximate C_{in} .^{29,30} Volume expansion in humans causes a small rise in the GFR, whereas volume depletion, severe heart failure, hypotension, anesthesia, surgery, trauma, sepsis, and even mild intestinal bleeding without frank hypotension may depress the GFR substantially.

Various methods are available to measure creatinine. Creatinine is frequently measured using the Jaffé alkaline picric acid reaction. Although this method is widely utilized, this reaction also measures other chromogens, which may lead to a false elevation in the estimated serum creatinine (S_{Cr}) measurement. Substances such as acetoacetate (in ketoacidosis), pyruvate, ascorbate, 5-fluorcytosine, certain (but not

all) cephalosporin antibiotics, and very high urate artifactually raise S_{Cr} in normal subjects by 0.5 to 2 mg/dL.³²⁻³⁸ These substances are excreted into the urine but contribute trivially compared with overall urine creatinine (U_{Cr}). Thus, noncreatinine chromogens affect the S_{Cr} but have little effect on the U_{Cr} .

In individuals with normal renal function, the contribution of serum noncreatinine chromogens in raising the S_{Cr} is approximately equal to the contribution of secretion to creatinine excretion, such that the C_{Cr} closely approximates the GFR. As the GFR decreases, the contribution of noncreatinine chromogens to the total measured S_{Cr} becomes less than the secreted moiety, and the C_{Cr} overestimates GFR to a greater extent. Direct enzymatic creatinine measurements are not affected by noncreatinine chromogens. Very high levels of serum glucose (>1000 mg/dL) and 5-flucytosine may interfere with the enzymatic reaction, whereas high levels of bilirubin (>5 mg/dL) affect the autoanalyzer method³⁶ and lead to falsely low S_{Cr} values. It is therefore important to know the method by which a given laboratory measures S_{Cr} . Competing for the same proximal tubular organic base secretory site as creatinine, certain pharmacologic agents may suppress this process and lead to a rise in the S_{Cr} . Trimethoprim, probenecid, and cimetidine, but not ranitidine, are organic bases that inhibit creatinine secretion competitively and can result in a mild elevation in the S_{Cr} , usually 0.5 mg/dL or less.³⁹⁻⁴²

As with all clearance methods, the C_{Cr} is subject to errors that may amount to as much as 10% to 15%. In addition to potential problems in estimating the S_{Cr} and U_{Cr} , errors in timing of urine collection, incomplete collection, and inaccurate measurement of urine volume are other factors that contribute to errors.⁴³ Although 24-hour U_{Cr} clearances have been widely utilized, no specified time period is required for the clearance to be obtained. In fact, shorter collection periods of several hours may be more accurate in patients passing adequate amounts of urine (not oliguric), particularly if the patient is not in a steady state (see later). To reduce errors in volume measurement, one can induce water diuresis in stable subjects before beginning the test,⁴⁴ although this is rarely practical in the ICU setting. Nevertheless, because many ICU patients have indwelling Foley catheters, it should be possible for accurately timed urine collections to be obtained and for the C_{Cr} to be measured with reasonable accuracy.

Serum Creatinine

Because of the practical and technical problems in obtaining estimates of the GFR by clearance methods, renal function is most commonly estimated by following the S_{Cr} in hospitalized patients. Creatinine is formed nonenzymatically from creatine and phosphocreatine in muscle cells and is normally present in the serum at a concentration of 0.8 to 1.4 mg/dL in adults and 0.3 to 0.6 mg/dL in children and pregnant subjects. The measured S_{Cr} depends on the method of measurement, as discussed previously, the GFR, rate of creatinine production, volume of distribution (e.g., S_{Cr} is lower in anasarca), and extent of its tubular secretion and intestinal degradation.³ Because creatinine production is closely related to muscle mass, the S_{Cr} is generally less in females than in males and decreases as muscle mass is lost with aging or debilitating illnesses.

The relationship between the S_{Cr} and C_{Cr} (and hence GFR) can be described by a rectangular hyperbola⁴⁵; however, this relationship applies in the steady state and assumes a constant rate of creatinine production (Fig. 102-1). Thus, a doubling of the S_{Cr} reflects a 50% decrease in C_{Cr} , a four-fold increase in the S_{Cr} , a 75% drop in the GFR, and so on. Because creatinine production may not remain constant, the S_{Cr} may underestimate the decrease in GFR in critically ill patients who have a decrease in muscle mass secondary to an ongoing catabolic state. Moreover, it should be appreciated that the S_{Cr} is an insensitive marker of change early in the course of renal disease. Thus, a 33% fall in the GFR may raise the S_{Cr} from 0.8 to 1.2 mg/dL, a value still within the normal range. If the prior value is not known, this fall in the GFR may go unrecognized.

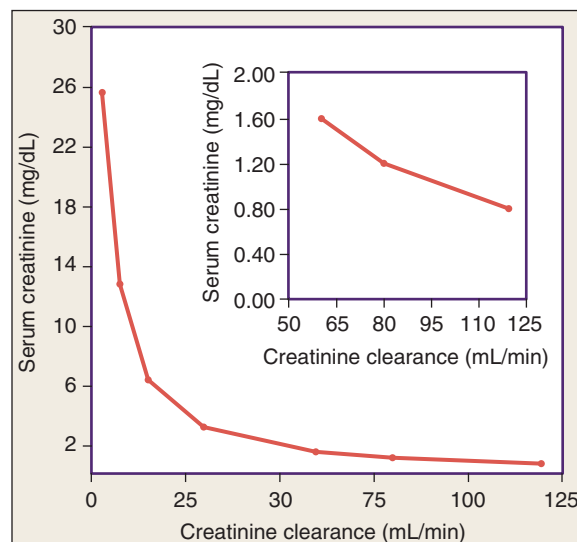


FIGURE 102-1 ■ Relationship between creatinine clearance and serum creatinine. In steady state, serum creatinine should increase twofold for each 50% reduction in creatinine clearance. Inset represents enlarged view of changes in serum creatinine as creatinine clearance decreases from 120 to 60 mL/min. If serum creatinine is 0.8 mg/dL when creatinine clearance is 120 mL/min, creatinine clearance can decrease by 33% such that increased serum creatinine is still within normal range.

The S_{Cr} provides a close estimate of the GFR only in the steady state. With an abrupt decrease in the GFR, as may occur in acute renal failure, creatinine production would be expected to continue unchanged, but because of the decrease in the GFR, creatinine excretion will be impaired. As a result, the S_{Cr} increases until a new steady state is obtained, at which time the amount of creatinine produced equals the amount filtered ($GFR - S_{Cr}$) and excreted ($U_{Cr} - V$). Depending on the extent of damage and decrease in the GFR, it may take several days for a new steady state to be achieved. Therefore, following an insult leading to an abrupt decrease in the GFR, the S_{Cr} rises progressively over the next several days. This should not be interpreted as a new insult each day but rather that a steady state has not yet been obtained. While the S_{Cr} is changing, its absolute value cannot be used as an accurate measure of the decrease in the GFR. If an accurate measurement of the GFR is needed during this time, a short C_{Cr} can be obtained.

Many equations have been developed to estimate the C_{Cr} based on the S_{Cr} without collection of urine.^{45,46} Box 102-1 is a compilation of the more commonly used equations.⁴⁷ These equations generally take into consideration muscle mass (estimated as body weight), sex (males having a higher GFR than females), and age. Aging, hepatic diseases, excessive muscle wasting, severe muscular atrophy or dystrophy, hyperthyroidism, paralysis, and chronic glucocorticoid therapy are associated with reduced creatinine generation.¹⁷ In addition, particularly at low levels of GFR, correction for nonrenal creatinine metabolism is recommended.^{48,49} One of the most commonly utilized equations is that developed by Cockcroft and Gault⁵⁰:

$$C_{Cr} = \frac{(140 - \text{age}) \cdot \text{lean wt in kg}}{72 \cdot S_{Cr}}$$

where age is expressed in years. The preceding expression is used for men. The formula for women is the preceding formula multiplied by 0.85.

BOX 102-1

Common Equations for Estimating Glomerular Filtration Rate or Creatinine Clearance

COCKCROFT-GAULT (C_{Cr} • BSA/1.73 m²)For men: $C_{Cr} = [(140 - \text{age}) \cdot \text{weight (kg)}] / S_{Cr} \cdot 72$ For women: $C_{Cr} = [(140 - \text{age}) \cdot \text{weight (kg)}] / S_{Cr} \cdot 72 \cdot 0.85$ **MDRD (1)** $GFR = 170 \cdot [S_{Cr}]^{-0.999} \cdot [\text{age}]^{-0.176} \cdot [0.762 \text{ if patient is female}] \cdot [1.18 \text{ if patient is black}] \cdot [BUN]^{-0.170} \cdot [Alb]^{0.318}$ **MDRD (2)** $GFR = 186 \cdot [S_{Cr}]^{-1.154} \cdot [\text{age}]^{-0.203} \cdot [0.742 \text{ if patient is female}] \cdot [1.212 \text{ if patient is black}]$ **JELLIFE (1) (C_{Cr} • BSA/1.73 m²)**For men: $(98 - [0.8 \cdot (\text{age} - 20)]) / S_{Cr}$ For women: $(98 - [0.8 \cdot (\text{age} - 20)]) / S_{Cr} \cdot 0.90$ **JELLIFE (2)**For men: $(100 / S_{Cr}) - 12$ For women: $(80 / S_{Cr}) - 7$ **MAWER**For men: $\text{weight} \cdot [29.3 - (0.203 \cdot \text{age})] \cdot [1 - (0.03 \cdot S_{Cr})]$ For women: $\text{weight} \cdot [25.3 - (0.175 \cdot \text{age})] \cdot [1 - (0.03 \cdot S_{Cr})]$ **BJORNSSON**For men: $[27 - (0.173 \cdot \text{age})] \cdot \text{weight} \cdot 0 / S_{Cr}$ For women: $[25 - (0.175 \cdot \text{age})] \cdot \text{weight} \cdot 0.07 / S_{Cr}$ **GATES**For men: $(89.4 \cdot S_{Cr}^{-1.2}) + (55 - \text{age}) \cdot (0.447 \cdot S_{Cr}^{-1.1})$ For women: $(89.4 \cdot S_{Cr}^{-1.2}) + (55 - \text{age}) \cdot (0.447 \cdot S_{Cr}^{-1.1})$ **SALAZAR-CORCORAN**For men: $[137 - \text{age}] \cdot [(0.285 \cdot \text{weight}) + (12.1 \cdot \text{height}^2)] / (51 \cdot S_{Cr})$ For women: $[146 - \text{age}] \cdot [(0.287 \cdot \text{weight}) + (9.74 \cdot \text{height}^2)] / (60 \cdot S_{Cr})$

The reliability of the Cockcroft-Gault equation as a measure of the GFR has been assessed in patients with diabetes, pregnant women with renal disease,⁵¹ obese individuals,⁵² elderly individuals,^{53,54} and African Americans with hypertensive renal disease.⁵⁵ It has also been assessed in critically ill patients.⁵⁶ These studies have indicated that the accuracy of GFR estimates using the Cockcroft-Gault equation is similar to or greater than 24-hour C_{Cr} and that the precision is better. This equation seems to be most accurate for estimating the GFR when the latter is in the range of 10 to 100 mL/min.^{52,55,56} The advantage of this formula is that it is simple and underscores the essential determinants of C_{Cr} .

The Modification of Diet in Renal Disease (MDRD) study equation has gained widespread acceptance by most clinical laboratories, which now routinely report estimated GFRs across populations when serum creatinine testing is ordered.⁵⁷⁻⁵⁹ Its major limitations are imprecision and underestimation of the measured GFR at high GFRs ($GFR > 60 \text{ mL/min/1.73 m}^2$). The MDRD equation is generally more precise than the Cockcroft-Gault equation.⁶⁰

Limitations at higher GFRs prompted a recent modification by the Chronic Kidney Disease Epidemiology Collaboration Research Group.⁶¹ This equation offers improved precision, especially with higher GFRs up to $90 \text{ mL/min/1.73 m}^2$.

CKD-EPI equation for estimated GFR (natural scale):

African Americans:

$$\text{Female } (S_{Cr} \leq 0.7) \text{ GFR} = 166 \cdot (S_{Cr}/0.7)^{-0.329} \cdot (.0993)^{\text{Age}}$$

$$\text{Female } (S_{Cr} > 0.7) \text{ GFR} = 166 \cdot (S_{Cr}/0.7)^{-1.209} \cdot (.0993)^{\text{Age}}$$

$$\text{Male } (S_{Cr} \leq 0.9) \text{ GFR} = 163 \cdot (S_{Cr}/0.9)^{-0.411} \cdot (.0993)^{\text{Age}}$$

$$\text{Male } (S_{Cr} > 0.9) \text{ GFR} = 163 \cdot (S_{Cr}/0.9)^{-1.209} \cdot (.0993)^{\text{Age}}$$

Caucasians or others:

$$\text{Female } (S_{Cr} \leq 0.7) \text{ GFR} = 144 \cdot (S_{Cr}/0.7)^{-0.329} \cdot (.0993)^{\text{Age}}$$

$$\text{Female } (S_{Cr} > 0.7) \text{ GFR} = 144 \cdot (S_{Cr}/0.7)^{-1.209} \cdot (.0993)^{\text{Age}}$$

$$\text{Male } (S_{Cr} \leq 0.9) \text{ GFR} = 141 \cdot (S_{Cr}/0.9)^{-0.411} \cdot (.0993)^{\text{Age}}$$

$$\text{Male } (S_{Cr} > 0.9) \text{ GFR} = 141 \cdot (S_{Cr}/0.9)^{-1.209} \cdot (.0993)^{\text{Age}}$$

Serum Cystatin C

Because of the limitations in utilizing creatinine as a marker for the GFR, there has been an ongoing search for alternative GFR markers. To this end, cystatin C has emerged as a possible candidate biomarker. Cystatin C is a low-molecular-weight protein of 13.3 kDa and is expressed by all nucleated cells. It is cleared by glomerular filtration and metabolized in the kidney. Serum cystatin C levels are minimally affected by demographics such as race and muscle mass. Although initially thought to be an ideal GFR marker, a number of factors may influence cystatin C levels other than GFR. These include hyperthyroidism, malignancy, corticosteroid use, diabetes mellitus, leukocyte count, albumin concentration, and C-reactive protein levels. Despite such limitations, cystatin C use is increasing and analytical methods are standardized. Cystatin C, like creatinine, has been employed in equations that more accurately estimate the GFR. By using both creatinine and cystatin C, even more accuracy in determining the GFR can be obtained, especially in populations with higher baseline levels for GFR. Although the use of these equations has not become routine, cystatin C will likely emerge as an important biomarker for the estimation of GFR.⁶²

Serum Urea Nitrogen

Less accurate as a marker of GFR than the S_{Cr} , serum urea nitrogen (SUN) (or blood urea nitrogen [BUN]) is still used extensively in clinical practice to estimate renal function. Although this was the earliest available indicator of renal function, several other factors should be appreciated regarding the use of this substance. Urea, like creatinine, is freely filtered and is retained in the blood as the GFR falls. However, in contrast to creatinine, urea may be reabsorbed to a significant extent. The excretion of urea tends to be increased with increasing urine flow rates, whereas its excretion is reduced when tubular fluid reabsorption is enhanced. Of greater importance, urea production is more variable than that of creatinine. Produced in the liver, urea increases with high protein intake, amino acid infusions, and hypercatabolic states. In addition, endogenous sources of protein, such as absorbed hemoglobin from gastrointestinal bleeding, may contribute to increased urea synthesis. Even at a constant GFR, SUN may rise in subjects on high protein intake and fall with protein restriction or on refeeding of previously starved, nonhypercatabolic subjects.

Several pharmacologic agents may also affect urea nitrogen formation. Tetracyclines may lead to an increase in SUN by an antianabolic effect without any detectable change in the GFR, whereas glucocorticoids and severe illnesses or trauma do the same by inducing endogenous protein hypercatabolism. Because of the widespread use of hyperalimentation in ICU patients, impairment in renal function is often associated with a marked disproportion in the elevation of SUN compared with S_{Cr} . For this reason, an issue is raised as to whether SUN elevation itself poses an important threat to patients if the GFR is in a range that should not lead to enhanced morbidity by itself. In those circumstances, it is useful to measure the rate of urea appearance (or generation) to estimate whether other factors such as gastrointestinal bleeding, excessive amino acid infusions, and protein administration are contributing to the increase in SUN above that expected by a decrease in the GFR.^{47,48} Urea nitrogen (UN) appearance

can be determined from urine urea nitrogen (UUN), SUN, and body weight as follows:

$$UN = UUN \cdot V + \Delta \text{ body pool UN}$$

where $UUN \cdot V$ is the 24-hour UN excretion, and Δ body pool UN = $0.6 - \text{nonedematous weight (kg)} \cdot \Delta \text{ SUN/day}$.

If the weight is changing^{47,48}:

$$\Delta \text{ body pool UN} = (0.6 \cdot \text{nonedematous weight} \cdot \Delta \text{ SUN}) + (\Delta \text{ weight} \cdot \text{final SUN})$$

Nitrogen balance (BN) is equal to:

$$BN = IN - UN - NUN$$

where IN is the urea nitrogen intake, and NUN is nonurea nitrogen excretions.⁴⁸

NUN, which includes fecal nitrogen, urinary creatinine, uric acid, and unmeasured nitrogen, averages 0.031 g nitrogen/kg/d.⁴⁸ Data obtained from the measurements just described may be quite useful in evaluating the cause of disproportionate elevations in SUN. If a patient is in the steady state (with a stable weight and SUN), $BN = 0$, and IN can be estimated from $UN + NUN$.⁴⁸ Because catabolism, except for severe trauma and burns, is usually 2 to 4 g nitrogen per day, additional conclusions can be drawn if the patient is not in the steady state. For example, if it is known that IN is less than $UN + NUN$, gastrointestinal bleeding with or without excess catabolism would be suggested. Similarly, one can evaluate if an increase in SUN is a reflection of excessive exogenous protein and amino acid administration (usually >1.5 g/kg/d; g UN 0.16 = g protein or amino acids). If the IN is above the UN, such as in severe liver disease, the clinician might more carefully evaluate changes in weight and SUN as well as clearances because the latter may be more severely depressed than initially suspected.

SODIUM BALANCE AND EXTRACELLULAR FLUID VOLUME

Sodium is the primary cation of the ECF, present at a concentration of 140 to 142 mmol/L. The volume of the ECF is approximately 20% of the total body weight and represents one-third of the total body water. Regulation of ECF volume is governed by factors regulating sodium balance and sodium excretion.⁶³

Under physiologic conditions and in the steady state, sodium balance is maintained because the amount of sodium excreted equals that which enters the body by oral and intravenous routes. The excretion of sodium excretion and fraction of filtered sodium that is excreted (FE_{Na}) can be readily determined. Absolute sodium excretion is measured as the product of urine sodium concentration and urine volume:

$$Na^+ \text{ excretion} = (U_{Na} \cdot V)$$

The FE_{Na} can be determined as follows:

$$FE_{Na} = U_{Na} \cdot V / GFR \cdot S_{Na}$$

For practical reasons, the C_{Cr} ($= U_{Cr} \cdot V / S_{Cr}$) is used to estimate the GFR, such that:

$$FE_{Na} = U_{Na} \cdot V / U_{Cr} \cdot V / S_{Cr} \cdot S_{Na}$$

Because V in the numerator and denominator cancels out:

$$FE_{Na} = U_{Na} / S_{Na} \cdot S_{Cr} / U_{Cr}$$

Thus, the FE_{Na} can be calculated from sodium and creatinine determined in a random urine sample and serum (or plasma) simultaneously. The resulting calculation is expressed as a percentage by multiplying by 100. This test is of value in the setting of acute renal failure to aid in distinguishing a prerenal from a renal parenchymal etiology.⁶⁴ It is not usually helpful in aiding in the diagnosis of urinary tract obstruction or in the presence of underlying chronic renal insufficiency. The reason for the difficulty in interpretation in chronic renal insufficiency can be illustrated by the following considerations. At a GFR of 130 mL/min and a dietary sodium intake of 3 g of sodium (130 mmol), an individual in sodium balance will excrete 0.5% of the filtered load ($FE_{Na} = 0.5\%$). For sodium balance to be maintained at lower levels of the GFR with the same sodium intake, the FE_{Na} must be increased progressively. Successive decreases in the GFR by 2 from 130 would result in FE_{Na} of 1%, 2%, 4%, and 8%, respectively. Thus, interpretation of the FE_{Na} in a patient with acute renal failure superimposed on chronic renal insufficiency is problematic unless the prior steady-state FE_{Na} is known, but this is rarely the case.

The fractional excretion of chloride (FE_{Cl}) has been suggested to be more accurate than that of sodium in helping to distinguish prerenal from parenchymal causes of acute renal failure.⁶⁵ This is particularly so in the situation in which acute renal failure occurs with simultaneous metabolic alkalosis. If the urine contains substantial amounts of bicarbonate urinary pH ($U_{pH} > 7$), sodium excretion increases to maintain electroneutrality. Under these circumstances, the FE_{Na} may give misleading information, but the FE_{Cl} can be used to obtain the same information.

Although urinary sodium excretion can be used to help make determinations with respect to the ECF volume under certain circumstances, this may be fraught with potential errors. No laboratory test is available to provide this information. Rather, an astute clinician must rely on bedside evaluation complemented, where appropriate, with measurements of central venous pressure and pulmonary capillary wedge pressure to assist in making determinations with respect to the ECF volume status. For example, a low FE_{Na} (<1%) in the setting of acute renal failure usually indicates a decrease in renal perfusion but does not provide information on the status of the patient's ECF volume. Because a low FE_{Na} can be seen with either ECF volume contraction or severe congestive heart failure, these conditions must be distinguished at the bedside. Moreover, sometimes a low FE_{Na} exists even in the presence of parenchymal renal disease, such as acute glomerulonephritis, severe burns, and radiocontrast nephropathy. Finally, administration of potent diuretic agents can alter the FE_{Na} and may result in misleading interpretations. For this reason, urine samples should be obtained before diuretics are administered. However, it may not be possible to obtain urinary sodium or chloride values while a patient is not receiving diuretics. In this setting, the fractional excretion of urea nitrogen has been employed to distinguish prerenal from renal causes of acute kidney injury. In a well-hydrated individual, the Fe_{UN} is 50% to 65%,⁶⁶ whereas in oliguric prerenal azotemic individual, the Fe_{UN} is below 35%. The use of Fe_{UN} in the setting of acute kidney injury has not attained widespread acceptance owing to variable results in comparative trials.^{66,67}

There is now ample evidence that in a patient in positive sodium balance, diuretic therapy should not be utilized without simultaneously restricting sodium intake, including intravenous saline, if negative sodium balance and reduction in edema fluid are desired.⁶⁸ In general, this requires restriction of dietary sodium intake, usually to less than 2 g of sodium per day (0.88 mmol) if the patient is in an edema-forming state. Although diuresis can be affected even with liberal sodium intake, this requires higher doses of diuretics and more frequent administration of these agents. The coexistence of hyponatremia should not deter clinicians from restricting sodium intake but

rather should cause them to address solute-free water intake as well. Under certain circumstances, obligatory intakes make it difficult to achieve optimal restriction to assist diuresis. That is, with various pharmacologic drips, blood products, and feeding regimens necessary in acutely ill patients in the ICU, restricting sodium intake may become a difficult problem. Under those circumstances, increasing doses of diuretics, including continuous infusions of loop diuretics, may be required.

KEY POINTS

1. Acute deterioration of renal function is common in the ICU and contributes significantly to overall morbidity and mortality.
2. The serum creatinine concentration often underestimates the decrease in GFR and may be abnormal only after marked reductions in GFR.
3. Utilizing equations to estimate renal function should be routine in the ICU.

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Chertow GM, Sayegh MH, Allgren RL, Lazarus JM. Is the administration of dopamine associated with adverse or favorable outcome in acute renal failure? *Am J Med* 1996;101:49–53.

One of the first large, randomized trials exploring the use of low-dose dopamine (<3 µg/kg/min) and high-dose dopamine in ICU patients. The study revealed that there was no evidence that low-dose dopamine improved survival or obviated the need for dialysis, and its use should be discouraged.

Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF III, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–612.

Comprehensive review of the equations used to predict GFR and the presentation of a newly derived equation using large clinical data sets. The CKD-EPI equation is probably the best equation to estimate GFR in the steady state.

Robert S, Zarowitz BJ, Peterson EL, Dumler F. Predictability of creatinine clearance estimates in critically ill patients. *Crit Care Med* 1993;21:1487–1495.

Creatinine clearance, inulin clearance, and estimates of GFR based on the Cockcroft-Gault equation were compared in 20 ICU patients. This study emphasized the inaccuracies of obtaining creatinine

clearances in the ICU setting. The Cockcroft-Gault equation accurately predicted GFR as determined by inulin clearances.

Wilcox CS, Mitch WE, Kelly RA, Skorecki K, Meyer TW, Friedman PA, et al. Response of the kidney to furosemide: I. Effects of salt intake and renal compensation. *J Lab Clin Med* 1983;102:450–458.

Classic study on the pharmacodynamics of furosemide showing the importance of salt intake and homeostatic mechanisms activated by diuretic use.

Wharton WW 3rd, Sondeen JL, McBiles M, Gradwohl SE, Wade CE, Ciceri DP, et al. Measurement of glomerular filtration rate in ICU patients using ^{99m}Tc-DTPA and inulin. *Kidney Int* 1992;42:174–178.

This study in 18 ICU patients compared clearances of inulin, creatinine, and ^{99m}Tc-DTPA to estimated Cockcroft-Gault clearance. The clearance of DTPA correlated best to inulin clearance throughout the entire range of clearances studied. DTPA clearance was also simple and inexpensive to perform in the ICU setting.

■ References for this chapter can be found at expertconsult.com.

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INCIDENCE OF ACUTE KIDNEY INJURY IN THE INTENSIVE CARE UNIT

Using the Risk, Injury, Failure, Loss and End-stage Kidney (RIFLE) or Acute Kidney Injury Network (AKIN) criteria, the incidence of acute kidney injury (AKI) in the intensive care unit (ICU) varies from 20% to 67% depending on the study.¹ AKI requiring renal replacement therapy (RRT) in the ICU has a high mortality rate of over 50%. The commonest cause of AKI in the ICU is septic shock. AKI is a significant problem in ICU patients and carries a high mortality rate and long-term morbidity. A major obstacle to the development of improved management strategies for AKI is the absence of sensitive and specific biomarkers of this clinical entity.² Therapeutic measures are sometimes started late in the course of AKI. The optimum time to start RRT in the ICU is unknown.² Therefore, there is a need to redefine what constitutes AKI in the ICU and to develop accurate biomarkers.³

SERUM CREATININE IN AKI

Serum creatinine (SCr) and blood urea nitrogen (BUN) have typically been used to diagnose AKI. Creatinine is generated in muscles from the nonenzymatic conversion of creatine and phosphocreatine. SCr is not sensitive or specific for the diagnosis of AKI. Interference with the creatinine assay using the Jaffe reaction may give false SCr values.⁴ SCr may change due to nonrenal factors independent of kidney function, e.g., age, gender, race, muscle mass, nutritional status, total parenteral nutrition and infection.^{4,5} SCr may also be altered as a result of renal factors that are independent of kidney function. For example, medications such as trimethoprim, cimetidine, and salicylates alter the tubular secretion of creatinine, leading to changes in SCr independent of the glomerular filtration rate (GFR).^{4,5} In addition, SCr is not sensitive to the loss of kidney reserve as evidenced by the small change in SCr after the loss or donation of a kidney with one normal remaining kidney.⁶ Alterations in SCr may lag several days behind actual changes in GFR.^{5,7}

A biomarker that is released into the blood or urine by the injured kidney and is analogous to troponin release by injured myocardial cells after myocardial ischemia or infarction may be a more sensitive and specific marker of AKI than BUN and SCr. In addition, earlier detection of AKI with a kidney-specific biomarker may result in earlier nephrology consultation, more optimal dosing of antibiotics in ICU patients, avoidance of nephrotoxic agents, and even earlier initiation of RRT.⁸

NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN

Neutrophil gelatinase-associated lipocalin (NGAL) is a small protein expressed in neutrophils and epithelial cells such as renal tubular epithelial cells. NGAL is a component of innate immunity to bacterial infection and is expressed by immune cells, hepatocytes, and renal tubular cells in various disease states.⁹ NGAL is easily detected in the urine, and NGAL protein increases in the kidney and in the urine after ischemic and cisplatin-induced AKI in rats and mice.^{10,11}

NGAL is the most extensively studied biomarker in AKI¹²⁻¹⁶ (Table 103-1). Based on the studies of NGAL as a biomarker of AKI after cardiac surgery, NGAL has been investigated as an early biomarker of

AKI in the ICU. Urine NGAL is an early biomarker of AKI in critically ill children on mechanical ventilation.¹⁷ In 140 pediatric patients, the mean and peak urine NGAL concentrations increased with worsening maximum RIFLE status. Urine NGAL concentrations rose in AKI and 2 days before and after a 50% or greater rise in SCr. Urine NGAL was a good diagnostic marker for AKI, with an area under the receiver operating characteristic (ROC) curve of 0.78. Urine NGAL was also a marker of the persistence of AKI for 48 hours or longer, with an area under the ROC curve of 0.79. However, urine NGAL was not a good marker for AKI severity when it was recorded after a rise in SCr had occurred. In 88 critically ill adults, serum NGAL had a sensitivity of 85% and a specificity of 97% to predict the development of AKI.¹⁸

A multicenter study of serum NGAL was performed in 143 critically ill children with systemic inflammatory response syndrome (SIRS) or septic shock during the first 24 hours of admission to the pediatric ICU.¹⁹ There was a significant difference in the serum NGAL between healthy children, critically ill children with SIRS, and critically ill children with septic shock. Serum NGAL was significantly increased in critically ill children with AKI compared with those without AKI. Thus, serum NGAL is a highly sensitive but nonspecific predictor of AKI in critically ill children with septic shock.

The ability of plasma NGAL (pNGAL) to predict AKI in adult ICU patients was confirmed in another study.²⁰ Using a cut-off of 155 nmol/L, the sensitivity and specificity of pNGAL to predict AKI were 82% and 97%, respectively (area under the ROC curve = 0.92). Of the patients who required RRT, all of them had pNGAL of more than 303 nmol/L. The study concluded that pNGAL at ICU admission was an early biomarker of AKI in adult ICU patients. pNGAL increased 48 hours before RIFLE criteria were observed.²⁰

In another study of pNGAL in the ICU, the influence of sepsis on NGAL was determined. Sixty-five patients admitted to a general ICU with normal SCr were studied.²¹ Data from 27 patients with SIRS, severe sepsis or septic shock without AKI and 18 patients with septic shock and concomitant AKI were analyzed. Peak levels of pNGAL were not significantly different between septic shock patients with and without AKI. Urine NGAL was a good predictor (area under the ROC curve = 0.86), whereas pNGAL was a poor predictor (area under the ROC curve = 0.67) of AKI within the next 12 hours in patients with septic shock. The authors concluded that pNGAL is raised in patients with SIRS, severe sepsis, and septic shock and should be used with caution as a marker of AKI in ICU patients with septic shock. Urine NGAL was more useful for predicting AKI, as the levels were not elevated in septic shock patients without AKI.

The predictive value of urine NGAL, pNGAL, and plasma cystatin C to differentiate among sustained, transient, and absent AKI was compared in 700 ICU patients in a prospective cohort study.²² Urine NGAL was the only biomarker that could significantly differentiate sustained from transient AKI on ICU admission. Urine NGAL performed better than cystatin C for the prediction of sustained AKI. The study concluded that urine NGAL measured on ICU admission can be used to differentiate patients with sustained AKI from patients with transient AKI or without AKI. Combining biomarkers such as pNGAL, urine NGAL, and plasma cystatin C with clinical characteristics adds some value to the predictive model.

In a prospective study of serum NGAL as an outcome-specific biomarker in critically ill patients at the initiation of RRT,²³ serum NGAL was measured in 109 critically ill patients with AKI at the

TABLE 103-1 NGAL as a Biomarker of AKI in the ICU

| SITUATION | N | STUDY | AREA UNDER THE ROC CURVE | REF |
|-----------------------|-----|--|--------------------------|-----|
| Adults | 632 | NGAL measured at ICU admission predicted the development of severe AKI, similar to serum creatinine-derived eGFR. | 0.77-0.88 | 26 |
| Adults | 301 | Plasma NGAL was a good diagnostic marker for AKI development and for RRT use. | 0.78-0.82 | 24 |
| Adults | 109 | NGAL was higher in non-survivors than in survivors. Serum NGAL was a strong independent predictor for 28-day survival. | ND | 23 |
| Adults | 700 | Urine NGAL performed better than cystatin C for the prediction of sustained AKI. | ND | 22 |
| Adults | 88 | Urine NGAL was more useful than serum NGAL in predicting AKI. Urine NGAL levels were not elevated in septic patients without AKI. | 0.86 | 21 |
| Adults | 65 | NGAL at ICU admission was an early biomarker of AKI. | 0.96 | 20 |
| Adults | 88 | Plasma NGAL at ICU admission was an early biomarker of AKI. Plasma NGAL increased 48 hours before RIFLE criteria. | 0.92 | 20 |
| Children | 140 | Urine NGAL increased in AKI patients 2 days before a 50% or greater rise in serum creatinine. | 0.78 | 17 |
| Children | 168 | Serum NGAL increased in AKI patients compared with that in patients without AKI. | | 19 |
| Adults | 88 | Serum NGAL predicted the development of AKI. | 0.96 | 18 |
| Children with sepsis | 143 | A significant difference was found in the serum NGAL between healthy children, critically ill children with SIRS, and critically ill children with septic shock. | | 19 |
| Emergency department | 635 | Elevated urine NGAL in AKI patients was compared to prerenal azotemia, CKD, or normal kidney function. Urine NGAL was highly predictive of clinical outcomes. | 0.948 | 91 |
| Critically ill/Trauma | 31 | Urinary NGAL was a predictor of AKI. | 0.98 | 92 |

AKI, acute kidney injury; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; ND, not determined; NGAL, neutrophil gelatinase-associated lipocalin; RRT, renal replacement therapy; SCr, serum creatinine; SIRS systemic inflammatory response syndrome.

initiation of RRT. There was a significant difference in the serum NGAL between healthy subjects, critically ill patients with SIRS, and critically ill patients with sepsis. Multiple linear regression showed that NGAL levels were independently related to the severity of AKI and the extent of systemic inflammation. NGAL levels were higher in nonsurvivors compared with those in survivors. Serum NGAL was a strong independent predictor for 28-day survival.

The diagnostic accuracy of pNGAL for the early detection of AKI and the need for RRT in an adult ICU was examined in a study of 307 consecutive adult patients admitted to a general medical/surgical ICU.²⁴ pNGAL was a good diagnostic marker for AKI development within the next 48 h (area under the ROC curve = 0.78) and for RRT use (area under the ROC curve = 0.82). Peak pNGAL concentrations increased with worsening AKI severity.

In a prospective observational study, 106 ICU patients were included to determine whether a panel of novel and traditional renal markers is superior to conventional renal markers in predicting RRT requirements.²⁵ Urine NGAL, serum cystatin C, and Acute Physiology and Chronic Health Evaluation (APACHE) II score were significant independent predictors of RRT (urine NGAL: area under the ROC curve = 0.73, serum cystatin C: area under the ROC curve = 0.76, SCr: area under the ROC curve = 0.78, APACHE: area under the ROC curve = 0.73). SCr combined with normalized NGAL and serum cystatin C combined with NGAL were the best predictors for RRT initiation (area under the ROC curve = 0.8). The combination of serum cystatin C and APACHE II score proved to be the best for detecting patients without AKI on ICU entry (area under the ROC curve = 0.78). The study concluded that the combination of a marker of GFR with one of tubular injury was the best predictor of RRT.

The ability of pNGAL and urine NGAL compared with estimated GFR (eGFR) to predict severe AKI was determined in a study of 632 patients on ICU admission.²⁶ The primary outcome measure was the occurrence of AKI based on the RIFLE classification during the first week of ICU stay. pNGAL and urine NGAL values at ICU admission were significantly related to AKI severity. The areas under the ROC curves for pNGAL and urine NGAL were RIFLE category—risk (RIFLE R; 0.77 and 0.80, respectively), RIFLE category—injury (RIFLE I; 0.80 and 0.85, respectively), and RIFLE category—failure (RIFLE F;

0.86 and 0.88, respectively) and were comparable with those of admission eGFR (0.84, 0.87, and 0.92, respectively). Thus, NGAL measured at ICU admission predicts the development of severe AKI similar to SCr-derived eGFR. It was also found that NGAL in combination with eGFR alone or with other clinical parameters has increased predictive ability.

In summary, NGAL appears to be an excellent biomarker of AKI and the need for RRT in some studies. However, there is variation among studies, and conditions such as sepsis, chronic obstructive pulmonary disease (COPD), cardiac dysfunction, age (NGAL seems superior in children), sex, and baseline renal function may affect the sensitivity and specificity of NGAL as a biomarker of AKI in the ICU.²⁷ Thus, there are limits in the interpretation of NGAL in AKI, and NGAL may be increased in sepsis without AKI.²⁸ pNGAL is a marker of severity in patients with severe acute pancreatitis without AKI and may predict the development of multiple organ failure and fatal outcome. Further, pNGAL may be increased in patients with COPD without AKI and is related to COPD severity. Therefore, it has been suggested that pNGAL be used with caution in critically ill patients as a consequence of the confounding factors discussed above.²⁸

In addition, pNGAL and urinary NGAL assays have detected different molecular forms of NGAL, and these various molecular forms have different predictive values as biomarkers of AKI.²⁹

Urine NGAL is an early biomarker of AKI and a predictor of outcomes in critically ill children and adults in the ICU. However, before NGAL is routinely and cost effectively used in the ICU, further work is needed to describe the natural history of AKI and NGAL physiology in the ICU. Future studies should focus on accurate, early identification of AKI and the identification of new therapies.³⁰ Studies of NGAL as a biomarker of AKI in the ICU are summarized in Table 103-1.

■ INTERLEUKIN-18

Interleukin (IL-18) is a proinflammatory cytokine that plays a role in both innate and acquired immune response.³¹⁻³³ In studies in non-ICU patients, urinary IL-18 is an early biomarker of AKI that increases in the urine within 6 hours after AKI in adults and children after cardiopulmonary bypass.³⁴⁻³⁶ Subsequent studies in humans have

TABLE 103-2 Urinary IL-18 as a Biomarker of AKI in the ICU

| SITUATION | N | STUDY | AREA UNDER THE ROC CURVE | REF |
|---------------|------|---|--------------------------|-----|
| Adults on RRT | 101 | A strong correlation was found between serum IL-18 and the hospital mortality of ICU patients with dialysis-dependent AKI. | ND | 40 |
| ARDS adults | 138 | Urinary IL-18 predicted the development of AKI 24 and 48 h later. Urinary IL-18 on the day of initiation of mechanical ventilation was a strong predictor of mortality. | 0.73 | 37 |
| Children | 137 | The peak levels of IL-18 correlated with the severity of AKI. In nonseptic AKI patients, urinary IL-18 increased 2 days prior to serum creatinine. | ND | 38 |
| Infants | 47 | NGAL, IL-18, and cystatin C, but not KIM-1, differentiated patients with good versus poor outcomes in the early postoperative period. | 0.62 | 93 |
| Adults | 451 | Urinary IL-18 did not reliably predict AKI development but did predict poor clinical outcomes. | 0.67 | 39 |
| Adults | 101 | A strong correlation was found between serum IL-18 and the hospital mortality of ICU patients with dialysis-dependent AKI. | ND | 40 |
| Adults | 4512 | IL-18 predicted AKI. | 0.66 | 41 |

ATN, acute tubular necrosis; ICU, intensive care unit; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; ND, not determined; NGAL, neutrophil gelatinase-associated lipocalin; SCr, serum creatinine.

demonstrated that urinary IL-18 is an early predictive biomarker of AKI in the ICU.³⁷ On multivariable analysis, urinary IL-18 values predicted the development of AKI (defined as a 50% increase in SCr) 24 and 48 hours later. On diagnostic performance testing, urinary IL-18 demonstrated an area under the ROC curve of 73% to predict AKI in the next 24 hours. The presence of sepsis in both control and AKI patients did not have a significant effect on urinary IL-18. On multivariate analysis, the urinary IL-18 value on the day of initiation of mechanical ventilation for acute respiratory distress syndrome was a strong predictor of mortality.³⁷ The finding that urinary IL-18 is an early biomarker of AKI in critically ill adults was reproduced in children.³⁸ Urinary IL-18 rises prior to SCr in nonseptic critically ill children, predicts the severity of AKI, and is an independent predictor of mortality.³⁸

The ability of urinary IL-18, measured within 24 hours of ICU admission, to predict AKI, death, and the need for acute dialysis in 451 ICU patients was prospectively investigated.³⁹ Eighty-six patients developed AKI within 48 hours of enrollment and had higher median urinary IL-18 levels than patients without AKI. The area under the ROC curve for urinary IL-18 to predict the subsequent development of AKI within 24 hours was 0.62 and improved modestly to 0.67 in patients whose enrollment eGFR was greater than 75 mL/min. The highest median urinary IL-18 levels were observed in patients with sepsis at enrollment, those receiving acute dialysis, and those who died within 28 days of ascertainment. After adjustment for a priori selected clinical predictors, urinary IL-18 was an independent predictor of a composite outcome of death or acute dialysis within 28 days. The study concluded that urinary IL-18 did not reliably predict AKI development but did predict poor clinical outcomes in a broadly selected critically ill adult population.

A strong correlation was found between serum IL-18 and the hospital mortality of ICU patients with dialysis-dependent AKI.⁴⁰ Serum samples were collected from 101 critically ill patients with AKI at the initiation of RRT in the ICU, and serum cystatin C, NGAL, and IL-18 were measured. The observed overall mortality rate was 56.4%, confirming the high mortality rate of ICU patients requiring RRT. Serum IL-18 and cystatin C concentrations and APACHE III scores determined on the first day of RRT were independent predictors of hospital mortality. The APACHE III score had the best discriminatory power (0.872 ± 0.041 , $P < 0.001$), whereas serum IL-18 had the best Youden index (0.65) and the highest correctness of prediction (83%).

Urinary IL-18 as a biomarker of AKI in various clinical settings was analyzed in a meta-analysis of prospective studies.⁴¹ Subgroup analysis showed that the area under the ROC curve of urinary IL-18 to predict AKI was 0.66 in ICU or coronary care unit patients.

In summary, the proinflammatory cytokine IL-18 is both a mediator and a biomarker of ischemic AKI.^{42,43} Urinary IL-18 increases before SCr in critically ill adults and children in the ICU and is a predictive biomarker of mortality in the ICU. Studies of IL-18 as a biomarker of AKI in the ICU are summarized in Table 103-2.

KIDNEY INJURY MOLECULE-1

KIM-1 is a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain. KIM-1 mRNA and protein are expressed at low levels in normal kidneys but are increased in post-ischemic kidneys.⁴⁴

Urinary KIM-1 and netrin-1 were studied as early biomarkers of septic AKI in the ICU.⁴⁵ One hundred fifty septic patients in the ICU were studied at 0, 1, 3, 6, 24, and 48 hours after ICU admission and compared with non-AKI patients. SCr started to increase at 24 hours after ICU admission. KIM-1 increased significantly by 6 hours, peaked at 24 hours, and remained significantly elevated until 48 hours after ICU admission. Netrin-1 levels increased significantly at 1 hour, peaked at 3 to 6 hours, and remained elevated up to 48 hours after ICU admission in septic AKI patients. Urinary KIM-1 levels at 24 hours and 48 hours were higher in nonsurviving than in surviving AKI patients.⁴⁵

The effect of timing on the predictive values of KIM-1, brush border enzymes, and NGAL measured before the rise of SCr in critically ill, nonseptic patients was determined in adult critically ill patients at four time points prior to the rise in SCr.⁴⁶ Patients with sepsis and/or AKI at ICU entry were excluded.

Both NGAL and KIM-1 concentrations gradually increased until AKI diagnosis. π - and α -glutathione S-transferase (GST) peaked 24 hours before AKI and declined rapidly afterward. The predictive values at 24 hours prior to AKI were modest for π - and α -GST, while the predictive value of NGAL 24 hours before AKI showed an area under the ROC curve of 0.79. KIM-1 was a good discriminator at the time of AKI only (area under the ROC curve = 0.73).⁴⁶

In summary, while KIM-1 is a promising biomarker of AKI in non-ICU patients, KIM-1 remains to be proven as an early biomarker of AKI and prognosis in the ICU. Studies of KIM-1 as a biomarker of AKI in the ICU are summarized in Table 103-3.

TUBULAR ENZYMES

The apical membrane of proximal tubular epithelial cells contains numerous microvilli that form the brush border. The brush border contains enzymes that carry out the specialized functions of the

TABLE 103-3 KIM-1 as a Biomarker of AKI

| SITUATION | N | STUDY | AREA UNDER THE ROC CURVE | REF |
|-----------|-----|---|--------------------------|-----|
| Adults | 150 | KIM-1 increased significantly by 6 hours after ICU admission, peaked at 24 hours, and remained significantly elevated until 48 hours. | ND | 45 |
| Infants | 49 | KIM-1 did not differentiate patients with good versus poor outcomes in the early postoperative period. | ND | 93 |
| Adults | 700 | KIM-1 increased at the time of AKI, not earlier. | 0.73 | 46 |

KIM-1, kidney injury molecule-1.

TABLE 103-4 Tubular Enzymuria as a Biomarker of AKI in the ICU

| SITUATION | N | STUDY | AREA UNDER THE ROC CURVE | REFERENCE |
|---------------|----|--|--------------------------|-----------|
| Adults | 38 | Urinary α -GST levels were increased in sepsis but not in AKI patients. Urinary GST levels at ICU admission were higher in all RIFLE groups than in controls. | ND | 52 |
| ED vs. ICU | 77 | Plasma NGAL diagnosed AKI at all times, GST at 8 to 12 hours post insult. Peak 24-hour urinary NGAL independently predicted 30-day mortality and dialysis. | ND | 51 |
| Adults | 26 | GGT, AP, NAG, and GST but not LDH were higher in the AKI group on admission and were useful in predicting AKI. | 0.845-0.950 | 94 |
| Sepsis adults | 40 | Urinary α -GST and π -GST were elevated early on in all patients with sepsis syndrome but were not predictive of AKI. | ND | 49 |

AP, alkaline phosphatase; DPP, dipeptidyl peptidase IV; γ GT, γ -glutamyl transpeptidase; GGT, gamma-glutamyl transferase; GST, glutathione S-transferase; LAP, leucine aminopeptidase; LDH, lactate dehydrogenase; NAG, N-acetyl-glucosaminidase; NEP, neutral endopeptidase; RBP, retinol-binding protein.

proximal tubule. Intracellular enzymes can be released into the urine during AKI. GST isomers are found in the proximal and distal tubular cells. N-acetyl-glucosaminidase (NAG) is mostly found in the proximal tubules, and alkaline phosphatase (AP) and γ -glutamyl transpeptidase (GGT) are other brush border enzymes.

Nearly 30 years ago, tubular enzymes in the urine were measured as a biomarker of AKI.⁴⁷ Tubular enzymuria may be very sensitive to tubular injury from multiple causes such as tubulointerstitial nephritis and chronic glomerulonephritis.⁴⁸

Urinary α -GST and π -GST were measured at 48 hours after ICU admission in 40 consecutive septic patients.⁴⁹ In this study, urinary π -GST was elevated early on in all patients with sepsis syndrome but was not predictive of AKI as defined by AKIN. GGT, AP, NGAL, cystatin C, KIM-1 and IL-18 were investigated in a prospective observational study of 529 patients in two general ICUs.⁵⁰ On ICU entry, no biomarker had an area under the curve of above 0.7 in the diagnosis or prediction of AKI. NGAL, CysC, and IL-18, but not KIM-1, predicted dialysis (area under the ROC curve over 0.7) and death at 7 days (area under the ROC curve between 0.61 and 0.69). In this study, brush border enzymes did not perform well as biomarkers of AKI.

Biomarker performance on arrival in the emergency department (ED) was compared with subsequent performance in the ICU.⁵¹ Urinary and pNGAL, urinary cystatin C, urinary AP, urinary GGT and GST, and albumin were measured on ED presentation, at 0, 4, 8, and 16 hours and days 2, 4, and 7 in the ICU in patients after cardiac arrest, sustained or profound hypotension, or ruptured abdominal aortic aneurysm. It was concluded that early measurement of biomarkers of AKI in the ED has utility but is not better than measurement later in the ICU. Urinary NGAL best predicted mortality or dialysis compared with other biomarkers.⁵¹

The potential of urinary levels of α -GST and π -GST—markers of proximal and distal renal tubule damage, respectively—for the early diagnosis of AKI in the ICU was investigated in 38 patients.⁵² The urinary α -GST levels were not increased in patients who developed AKI versus those who did not and were elevated early on in all patients with sepsis syndrome.

In summary, the measurement of tubular enzymuria is inexpensive and easy. However, tubular enzymuria may be increased with multiple causes of tubular injury, including acute tubular necrosis, acute rejection, and acute tubulointerstitial nephritis and may be too sensitive for use in the ICU. Studies of tubular enzymes as biomarkers of AKI in the ICU are summarized in Table 103-4.

■ CYSTATIN C

Cystatin C is a 13-kD protein produced by all nucleated cells. It is freely filtered by the glomerulus, completely reabsorbed by the proximal tubules, and is not secreted by the renal tubules.⁵³ Thus, some of the limitations of SCr—for example, the effect of muscle mass, diet, gender, and tubular secretion—may not be a problem with cystatin C. Cystatin C is best measured using an immunonephelometric assay and is a better marker of GFR than SCr.^{48,54,55} Increases in cystatin C occur sooner after changes in kidney function than SCr.⁵⁶ In critically ill patients, serum cystatin C correlated better with GFR than did creatinine and was diagnostically superior to creatinine.⁵⁷ Serum cystatin C and beta-2 microglobulin were found to be better than SCr in the detection of AKI in critically ill children.⁵⁸

Cystatin C rapidly detects AKI in the ICU.⁵⁹ In 442 patients, cystatin C and creatinine were measured on admission to the ICU and then daily for 7 days. Cystatin C predicted sustained AKI with an area under the ROC curve of 0.80. Cystatin C and creatinine were moderately predictive of death or dialysis, with areas under the ROC curves of 0.61 and 0.60, respectively.

The performance of serum cystatin C and SCr as biomarkers of GFR in 47 critically ill patients was compared with GFR.⁶⁰ The areas under the ROC curves to detect a GFR of less than 60 mL/min were 0.799 and 0.942 for SCr and serum cystatin C, respectively. It was concluded that serum cystatin C outperforms SCr for the detection of an impaired GFR in critically ill patients.⁶⁰

The impact of sepsis on the levels of plasma cystatin C in AKI and non-AKI patients was determined.⁶¹ Three hundred twenty-seven ICU patients were divided on the basis of the presence or absence of sepsis

TABLE 103-5 Cystatin C in AKI in the ICU

| SITUATION | N | STUDY | AREA UNDER THE ROC CURVE | REF |
|---------------------|-----|--|--------------------------|-----|
| Adults septic shock | 6 | Serum cystatin C showed limited value in determining the residual renal function in septic patients. | ND | 95 |
| Noncardiac children | 160 | NGAL was most diagnostic of AKI as defined by cystatin C. Combining serum creatinine and serum cystatin C improved the diagnostic performance. | 0.69 | 63 |
| Adults | 151 | Serum and urine cystatin C were poor biomarkers for AKI and RRT in the ICU. | 0.66 | 62 |
| Adults | 327 | Cystatin C or creatinine did not differ significantly between septic and nonseptic patients. Cystatin C predicted a composite outcome. | 0.78-0.80 | 61 |
| Adults | 47 | Serum cystatin C outperformed serum creatinine for the detection of an impaired GFR in critically ill patients. | 0.94 | 60 |
| Adults | 50 | Serum cystatin C correlated better with GFR (creatinine clearance) than serum creatinine. | 0.927 | 57 |
| Adults | 422 | Cystatin C rapidly detected AKI in the ICU and predicted sustained AKI. | 0.80 | 59 |
| Children | 25 | Serum cystatin C and B2M were better than creatinine in the identification of a creatinine clearance of under 80 mL/min. | 0.792-0.851 | 58 |

AKI, acute kidney injury; B2M, beta-2 microglobulin; GFR, glomerular filtration rate; NGAL, neutrophil gelatinase-associated lipocalin; RRT, renal replacement therapy; SCr, serum creatinine.

and AKI. The change in cystatin C or creatinine did not differ significantly between the septic and nonseptic patients with or without AKI. In another study of 150 ICU patients, serum and urine cystatin C were found to be poor biomarkers for AKI and RRT in the ICU.⁶² The area under the ROC curve to predict AKI for serum cystatin C was fair at 2 days before AKI (0.72) and poor at 1 day before AKI (0.62). Serum and urine cystatin C on Day 0 were poor predictors for the need for RRT (area under the ROC curve ≤ 0.66).⁶² Cystatin C was evaluated as an early biomarker of AKI in 160 noncardiac critically ill children.⁶³ NGAL was most diagnostic of AKI as defined by cystatin C (area under the ROC curve = 0.69); further, IL-18 was most diagnostic for AKI as defined by SCr (area under the ROC curve = 0.69).

There are limitations to the use of cystatin C as a marker of GFR. Abnormalities of thyroid function⁶⁴ and glucocorticoid therapy^{65,66} may affect cystatin C independent of kidney function. The levels of C-reactive protein may increase cystatin C levels, and it has been suggested that cystatin C is a marker of inflammation.⁶⁷

In summary, serum cystatin C is at least equal if not superior to SCr as a marker of GFR and is independent of height, gender, age, and muscle mass. Three studies show that serum cystatin C is an early marker of AKI in the ICU, and it does not seem to be influenced by sepsis. Studies of cystatin C as a biomarker of AKI in the ICU are summarized in Table 103-5.

■ CYTOKINES

Both IL-6 and IL-8 are proinflammatory cytokines and have been studied as predictors of AKI. In one clinical trial, 547 patients from the placebo group of the Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) dataset were studied.⁶⁸ Of these 547 patients, 127 (23.2%) developed AKI. Using multivariate Cox regression, the predictors of AKI were log IL-6 and the APACHE II score.

The Program to Improve Care in Acute Renal Disease (PICARD) was a prospective multicenter cohort study designed to examine the natural history and outcomes of critically ill ICU patients with established AKI.⁶⁹ Serum IL-1 β , tumor necrosis factor (TNF)- α , IL-6, IL-8, C-reactive protein, and IL-10 were determined in a subset of 98 patients from the PICARD study at the time of enrollment and then weekly for the duration of their hospital stay. Patients were enrolled into PICARD at the time of their nephrology consultation and thus had established AKI. The proinflammatory cytokines IL-1 β , TNF- α , IL-6, and IL-8 and the antiinflammatory cytokine IL-10 were significantly elevated compared with those in healthy controls. Increased

serum levels of IL-6, IL-8, and IL-10 at baseline were significantly correlated with increased in-hospital mortality in AKI patients. Thus, the cytokine response in patients with AKI is significantly dysregulated. When cytokine values were further adjusted for the severity of illness (APACHE III scores), only IL-6 remained an independent predictor of mortality. Thus, IL-6 may be an important biomarker of outcomes in patients with AKI.

A study examined the relationship between increases in plasma IL-6, IL-8, and IL-10 on outcomes in critically ill ICU patients with AKI.⁷⁰ In this study, plasma IL-6, IL-8, and IL-10 were determined in 103 consecutive critically ill ICU patients with SIRS, with or without AKI.⁷⁰ Plasma cytokines were determined prospectively on the day of admission and 2 days after. Patients with AKI had significantly higher levels of plasma IL-6, IL-8, and IL-10 than patients without AKI.

IL-6 and other proinflammatory markers were studied in 879 patients in the low-tidal-volume versus high-tidal-volume mechanical ventilation study database of the first Acute Respiratory Distress Syndrome Clinical Network (ARDS-net) trial.⁷¹⁻⁷³ AKI was defined by an increase in SCr of at least 50% from baseline. Baseline values of IL-6, IL-8, IL-10, von Willebrand factor, TNF- α , type I and II soluble TNF receptors (sTNF-I and -II), protein C, plasminogen activator inhibitor-1 (PAI-1), surfactant protein-A, surfactant protein-D, and intercellular adhesion molecule-1 were correlated with the development of AKI. After adjustments for demographics, interventions, and the severity of illness, increased levels of IL-6, sTNF-I, sTNF-II, and PAI-1 levels were independently associated with the development of AKI.

In summary, in both patient and animal studies, early AKI is associated with a proinflammatory burst that is characterized by early increases in serum IL-6 and KC/IL-8. Such a proinflammatory burst may also be linked with other complications in the ICU such as acute lung injury.^{74,75} Studies of cytokines as biomarkers of AKI in the ICU are summarized in Table 103-6.

■ LIVER FATTY ACID-BINDING PROTEIN

Fatty acid-binding proteins (FABPs) are a family of carrier proteins for fatty acids and other lipophilic substances including eicosanoids and retinoids. FABPs also transport lipophilic molecules from the outer cell membrane to intracellular receptors such as peroxisome proliferator-activated receptors.

Urinary and serum liver-FABP (L-FABP) were measured in 80 critically ill patients.⁷⁶ Urinary L-FABP levels in patients with septic shock were significantly higher than those in patients with severe sepsis without shock, patients with AKI, or healthy subjects ($P < 0.001$).

TABLE 103-6 Cytokines as Biomarkers of AKI in the ICU

| SITUATION | N | STUDY | AREA UNDER THE ROC CURVE | REF |
|------------------------|-----|---|--------------------------|----------|
| Adults | 879 | Increased levels of IL-6, sTNFR1, sTNFR2, and PAI-1 were independently associated with the development of AKI. | | 71,72,73 |
| Adults | 103 | Patients with AKI had significantly higher levels of plasma IL-6, IL-8, and IL-10 than patients without AKI. | ND | 70 |
| Adults | 98 | IL-1 β , TNF α , IL-6, IL-8, and IL-10 were significantly elevated. Increased serum IL-6, IL-8, and IL-10 at baseline was correlated with increased in-hospital mortality in AKI patients. | ND | 69 |
| Severe sepsis patients | 547 | Increased log plasma IL-6 and APACHE II score were significant risk factors of AKI. | | 68 |
| Septic shock | 537 | Elevated serum TNF-R1 and RII were associated with the development of ARF. TNF-R was an independent predictor of mortality in AKI patients. | | 96 |

ATF3, activating transcription factor 3; ATN, acute tubular necrosis; β 2M, beta-2 microglobulin; CPB, cardiopulmonary bypass; GGT, gamma-glutamyl transferase; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-1 β , interleukin-1 beta; NAG, N-acetyl-glucosaminidase; PAI-1, plasminogen activator inhibitor-1; PKD, polycystic kidney disease; sTNFR1, soluble tumor necrosis factor receptor1; sTNFR2, soluble tumor necrosis factor receptor2; TNF- α , tumor necrosis factor alpha.

TABLE 103-7 L-FABP as a Biomarker of AKI in the ICU

| SITUATION | N | STUDY | AREA UNDER THE ROC CURVE | REF |
|-----------|-----|---|--------------------------|-----|
| Adults | 80 | Urinary L-FABP levels in patients with septic shock were significantly higher than those in patients with severe sepsis without shock, patients with ARF, and healthy subjects. | ND | 76 |
| Adults | 145 | AKI patients had significantly higher levels of urinary NGAL and L-FABP, as well as higher mortality. Urinary L-FABP was an independent predictor for 90-day mortality. | 0.73-0.78 | 77 |
| Adults | 337 | Mortality in AKI patients diagnosed by serum creatinine was increased remarkably when urinary L-FABP and NAG were positive. | 0.75 | 97 |

L-FABP, L-type fatty acid binding protein; NAG, N-acetyl glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin.

Serum L-FABP levels showed no significant differences between patients with septic shock, patients with severe sepsis, patients with AKI, and healthy subjects.

The diagnostic and prognostic abilities of urinary L-FABP in heterogeneous critically ill patients were determined.⁷⁷ Urine NGAL and L-FABP were measured in 145 medical and surgical patients at the time of ICU admission. AKI patients had significantly higher levels of urinary NGAL and L-FABP, as well as higher mortality rates than non-AKI patients. The area under the ROC curve was 0.773 for NGAL and 0.780 for L-FABP for the diagnosis of AKI. On multivariate Cox analysis, urinary L-FABP was an independent predictor for 90-day mortality. Thus, urinary L-FABP is promising both for the diagnosis of AKI and for the prediction of prognosis in heterogeneous ICU patients.⁷⁷ Studies of L-FABP as a biomarker of AKI in the ICU are summarized in Table 103-7.

■ OTHER BIOMARKERS OF AKI

Information on additional biomarkers of AKI is given in Table 103-8. In one study, 340 candidate biomarkers were measured in critically ill ICU patients with sepsis or one or more risk factors for AKI such as hypotension, sepsis, and major trauma. In the initial analysis, the biomarkers were ranked by their ability to predict RIFLE I and F within 12 to 36 h. The two best biomarkers were the cell cycle arrest proteins, urinary insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2), which are both inducers of G1 cell cycle arrest, a key mechanism implicated in AKI.⁷⁸ In the Sapphire validation study, in 728 critically ill patients, the primary endpoint was moderate to severe AKI ([Kidney Disease: Improving Global Outcomes] KDIGO stage 2 to 3) within 12 hours of sample collection.⁷⁸ IGFBP7 and TIMP-2 demonstrated an area under the curve of 0.80 (0.76 and 0.79 alone) for the primary endpoint. Urine concentrations of IGFBP7 and TIMP-2 were significantly superior to all previously described markers of AKI ($P < 0.002$), none of which

achieved an area under the curve of more than 0.72. In the Topaz study, in 420 ICU patients, a predefined cut-off value of IGFBP7 and TIMP-2 was prospectively validated for risk assessment in AKI diagnosed by a clinical adjudication committee.⁷⁹ Critically ill patients with urinary [TIMP-2].[IGFBP7] greater than 0.3 had seven times the risk of AKI compared with critically ill patients with a test result below 0.3. Urinary TIMP-2 and IGFBP7 greater than 0.3 identified patients at risk for imminent AKI. In addition, urinary TIMP-2 and IGFBP7 are associated with adverse long-term outcomes in patients with AKI.⁸⁰ The measurement of TIMP-2 and IGFBP7 has been marketed as “Nephro Check” and has been the first set of biomarkers to be approved by the FDA for the detection of AKI in ICU patients.

CD163 is a scavenger receptor for haptoglobin-hemoglobin complexes that is almost exclusively expressed by monocytes and macrophages and is shed (as soluble [sCD163]) by inflammatory stimuli. In one study, 1657 critically ill patients randomized to “conventional” or “intensive” insulin therapy were compared with healthy controls.⁸¹ On admission, critically ill patients had 1.6-fold higher sCD163 levels than controls ($P < 0.0001$). Long-stay patients (ICU stay >5 days), non-survivors, and patients who developed liver dysfunction or kidney injury had higher baseline sCD163 levels. On multivariable analysis, elevated baseline sCD163 levels were independently associated with ICU mortality, liver dysfunction, and time to discharge from the ICU and hospital. sCD163 further increased during the ICU stay in patients who developed organ dysfunction and in nonsurvivors. This study demonstrated the association of elevated sCD163 with organ dysfunction and adverse outcomes in critically ill patients.⁸¹

The diagnostic value of urine sCD163 for the identification of sepsis, the severity of sepsis, AKI, and prognosis was determined in 60 ICU patients and 20 controls.⁸² There were higher levels of urine sCD163 on the day of ICU admission in the sepsis group compared with the SIRS group. The area under the curve was 0.83, with a sensitivity of 0.83 and a specificity of 0.75 for the sepsis group. The urine sCD163 levels at AKI diagnosis were significantly higher than those

TABLE 103-8 Other Biomarkers of AKI in the ICU

| BIOMARKER | SITUATION | N | STUDY | AREA UNDER THE ROC CURVE | REF |
|------------------------------------|---------------|-----|--|--------------------------|-----|
| Urinary TIMP-2 and IGFBP7 combined | Adults | 728 | Urinary TIMP-2 and IGFBP7 predicted the primary endpoint: moderate to severe AKI (KDIGO stage 2 to 3) within 12 hours of sample collection. | 0.80 | 78 |
| Urinary TIMP-2 and IGFBP7 combined | Adults | 692 | [TIMP-2][IGFBP7] measured early on in the setting of critical illness may identify patients with AKI at increased risk for mortality or receipt of RRT over the next 9 months. | | 80 |
| sCD163 | Adults | 80 | There is a potential value of urine sCD163 levels for identifying sepsis and AKI. | 0.83 | 82 |
| sTREM-1 | Adults | 104 | The sepsis group had higher levels of urine sTREM-1 and APACHE II scores. Urine sTREM-1, SCr, and BUN levels increased at 48 h before AKI. | ND | 84 |
| RBP4 | Adults | 123 | RBP4 was significantly decreased in critically ill patients and was associated with hepatic and renal function, insulin resistance, and acute mortality. | ND | 85 |
| Ang-2 | Adults on RRT | 117 | Ang-2 levels were higher in AKI patients with RIFLE category—injury or failure. Ang-2 was a strong and independent predictor of mortality in dialysis-dependent ICU patients. | ND | 86 |
| Resistin | Adults | 230 | Serum resistin was elevated in sepsis and was associated with renal failure and unfavorable outcomes. | ND | 87 |

Ang-2, angiotensin-2; AOPPs, advanced oxidation protein products; BNP, brain natriuretic hormone; IGFBP7, urine insulin-like growth factor-binding protein 7; ND, not determined; RBP4, retinol-binding protein 4; sCD163, soluble, hemoglobin-scavenging receptor; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; TIMP2, tissue inhibitor of metalloproteinases-2; TREM-1, triggering receptor expressed on myeloid cells 1.

present in the sepsis patients at ICU admission. The study shows the potential value of urine sCD163 levels for identifying sepsis and AKI.⁸²

Triggering receptor expressed on myeloid cells 1 (TREM-1) is an amplifier of the innate immune response. Its soluble form (sTREM-1) acts as a decoy for the natural TREM-1 ligand and dampens its activation. sTREM-1 has received attention as a biomarker of sepsis in the ICU.⁸³ Urine sTREM-1 was evaluated for early sepsis identification, severity and prognosis assessment, and diagnosis of AKI in 104 patients in the ICU.⁸⁴ On the day of admission to the ICU, compared with the SIRS group, the sepsis group exhibited higher urine sTREM-1 levels and APACHE II scores. Urine sTREM-1 was higher in patients with severe sepsis as compared with those with sepsis. Urine sTREM-1 was increased among the nonsurvivors. For the 17 patients with AKI, urine sTREM-1, SCr, and BUN levels at 48 h before AKI diagnosis were higher than those in non-AKI subjects. Urine sTREM-1 was more sensitive than white blood cells, serum C-reactive protein, and serum procalcitonin for the early diagnosis of sepsis and for prognosis. Thus, urine sTREM-1 may also be an early marker of AKI in sepsis patients.⁸⁴

Retinol-binding protein 4 (RBP4) promotes insulin resistance in mice and is systemically elevated in patients with obesity and type 2 diabetes. RBP4 was measured in 123 critically ill patients on admission to a medical ICU and compared with that in 42 healthy nondiabetic controls.⁸⁵ Low serum RBP4 upon admission was an adverse predictor of short-term survival in the ICU but was not associated with overall survival during long-term follow-up.

Endothelial activation has emerged as an early event in the pathogenesis of microcirculatory dysfunction, capillary leakage and multi-organ dysfunction syndrome. Angiotensin-2 (Ang-2), a circulating antagonistic ligand of the endothelial-specific Tie2 receptor, has been identified as a nonredundant gatekeeper of endothelial activation. Ang-2 was examined as an outcome-specific biomarker in 117 critically ill patients requiring RRT in the ICU.⁸⁶ Circulating Ang-2 levels were significantly higher in AKI patients with RIFLE I or F compared with patients with RIFLE R. Elevated levels of circulating Ang-2 correlated with impaired oxygenation, low mean arterial pressure, vasopressor dose and the sequential organ failure assessment (SOFA) score. Ang-2 concentrations were significantly higher in nonsurvivors than in survivors at day 0 and 14 after the initiation of RRT. The study concluded that circulating Ang-2 is a strong and independent predictor of mortality in dialysis-dependent ICU patients.⁸⁶

Resistin is a hormone that is mainly derived from macrophages in humans and from adipose tissue in rodents. Resistin regulates glucose

metabolism and insulin sensitivity. Resistin was prospectively measured on admission to the medical ICU in 170 patients and compared with that in 60 healthy nondiabetic controls.⁸⁷ Serum resistin was significantly elevated in all critical care patients compared with the healthy controls and was also found to be significantly higher in sepsis than in nonsepsis patients. Serum resistin concentrations were closely correlated to inflammatory parameters such as C-reactive protein and cytokines such as IL-6 and TNF- α and were also associated with renal failure and liver synthesis capacity. High resistin levels (>10 ng/mL) were associated with an unfavorable outcome in nonsepsis patients in the ICU and poor overall survival.⁸⁷

In summary, novel biomarkers of AKI in the ICU have recently been identified. These biomarkers include the cell cycle arrest biomarkers (IGFBP7 and TIMP-2), sCD163, urinary sTREM-1, RBP4, advanced oxidation protein products, Ang-2, and resistin.

COMBINATIONS OF AKI BIOMARKERS

The classical biomarker paradigm is that one test detects one disease—for example, troponin for acute myocardial infarction and prostate-specific antigen for prostate cancer. However, AKI is a complex disease with multiple causes, and it is possible that a panel of biomarkers may be necessary.⁸⁸

The diagnostic performance of nine urinary biomarkers of AKI was evaluated in 204 patients with or without AKI, healthy volunteers, patients undergoing cardiac catheterization, and patients admitted to the ICU.⁸⁹ The biomarkers studied were KIM-1, NGAL, IL-18, hepatocyte growth factor (HGF), cystatin C, NAG, vascular endothelial growth factor (VEGF), chemokine interferon-inducible protein 10 (IP-10; CXCL10), and total protein. Using a logistic regression model, the area under the curve (0.94) was greater for the combination of biomarkers than for the individual biomarkers. Age-adjusted levels of urinary KIM-1, NAG, HGF, VEGF, and total protein were significantly higher in patients who died or required RRT compared with those who survived or did not need RRT.

In summary, more than one biomarker may be necessary to obtain sufficient sensitivity and specificity for AKI screening.

CONCLUSION

The clinical application of biomarkers is difficult in critically ill patients because the timing of the renal insult is often unknown,

sepsis may lead to false positives, and the pathophysiology of AKI in sepsis patients is complex and not due only to ischemia and hypotension.⁹⁰ Plasma biomarkers may be an indication of the severity of disease rather than of true AKI.⁹⁰ Finding the ideal biomarker of AKI and prognosis in the ICU is a subject of intense investigation. Problems and prospects related to biomarker investigation in ICU patients have been reviewed in depth.⁹⁰ However, despite the issues mentioned above, there are multiple promising serum and urinary

biomarkers of AKI in the ICU, including urinary levels of IGFBP7, TIMP-2, IL-18, NGAL, KIM-1, cystatin C, and L-FABP, which detect AKI before the rise in SCr and predict the outcome in patients with AKI. Ultimately, disease control studies are necessary to determine the impact of biomarker screening on reducing the burden of disease.

■ References for this chapter can be found at expertconsult.com.

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■ ACID-BASE DISORDERS

Acid-base disorders are common in the intensive care unit (ICU) and can contribute to significant morbidity and mortality. Appropriate management of acid-base disorders in the ICU requires timely recognition of the disorder, accurate interpretation of the disturbance, identification of the cause, and knowledge of the treatment.

Acid-base disorders can be quantified by the physiologic, base-excess, and physiochemical approaches (Stewart method).¹ This chapter focuses on the physiologic approach with the bicarbonate-carbonic acid buffer system.

Normal Acid-Base Homeostasis

On a daily basis, the body's metabolic processes generate 10,000 to 15,000 mEq of volatile acids and 1 to 2 mEq/kg of fixed acids that must be buffered and excreted to maintain the pH within a narrow range of 7.35 to 7.45. Chemical buffers and the pulmonary and renal systems operate interdependently to regulate and maintain acid-base balance. The most important buffer is the bicarbonate-carbonic acid (HCO_3^- - H_2CO_3) system, which acts immediately to buffer the extracellular fluid. The relationship between pH, HCO_3^- , and carbon dioxide (CO_2) is described by the Henderson-Hasselbalch equation:

$$\text{pH} = 6.10 + \log \left(\frac{[\text{HCO}_3^-]}{[0.03 \times \text{PCO}_2]} \right)$$

The number 6.10 represents the dissociation constant for the reaction; 0.03 represents the solubility coefficient of CO_2 in blood. PCO_2 is the partial pressure of CO_2 in the blood.²

Normal acid-base status is maintained by pulmonary excretion of volatile acids and by renal excretion of fixed acids and formation of bicarbonate. In order to maintain acid-base balance, the kidney must reabsorb all of the filtered bicarbonate (about 4000 mEq/day) and excrete the fixed daily acid load. Reabsorption occurs mostly in the proximal tubule (>90%) and, to a lesser degree, in the collecting tubule. Renal excretion of acid is achieved by combining hydrogen ions (H^+) with urinary buffers to be excreted as titratable acids, such as phosphate, urate, and creatinine, or with ammonia to form ammonium.³ The ammonia buffering system is especially important because other buffers are filtered in fixed concentrations and can be depleted by high acid loads; by contrast, tubular cells actively regulate ammonia production in response to changes in acid load.

When acid-base derangements occur, the blood pH is returned toward normal initially by chemical buffering, followed by pulmonary ventilation, and finally by renal regulation of acid-base excretion. The Paco_2 is finely regulated by changes in tidal volume and minute ventilation. A decrease in pH is sensed by arterial chemoreceptors and leads to increases in tidal volume or respiratory rate. Pulmonary regulation occurs over minutes to hours. The kidney controls pH through the regulation of H^+ excretion, bicarbonate reabsorption, and the production of new bicarbonate. Reabsorption of bicarbonate is equivalent to removing free H^+ . Changes in renal acid-base handling occur hours to days after changes in acid-base status.

Acid-Base Pathophysiology

Terminology and Classification

Acid-base disorders occur when a change in the normal value of the blood pH results from abnormal renal or pulmonary function or when an acid or base load overwhelms excretory capacity. *Acidemia* refers to

a decrease in the blood pH below the normal range, while *alkalemia* refers to an increase in the blood pH above the normal range. *Acidosis* is a process that tends to decrease the blood pH and occurs by a fall in the plasma bicarbonate concentration and/or an elevation in Paco_2 . In contrast, *alkalosis* is a process that tends to raise the blood pH through an elevation in the plasma bicarbonate concentration and/or a fall in Paco_2 . Although acidemia cannot be present without acidosis and alkalemia cannot be present without alkalosis, acidosis or alkalosis can exist at any blood pH.

The four primary acid-base disorders are classified as respiratory or metabolic. A respiratory disturbance occurs when acidosis or alkalosis results from a primary change in the Paco_2 . Respiratory acidosis is a disorder that elevates the Paco_2 and reduces the pH; respiratory alkalosis is a disorder that reduces the Paco_2 and elevates the pH. A metabolic disturbance occurs when acidosis or alkalosis results from a primary change in the plasma bicarbonate concentration. Metabolic acidosis is a disorder that reduces the plasma bicarbonate concentration and pH; metabolic alkalosis is a disorder that elevates the plasma bicarbonate concentration and pH. Compensation refers to physiologic respiratory and renal changes by which the body attempts to return the pH toward normal in response to primary acidosis or alkalosis.^{4,5} Compensation does not return the pH back to a completely normal value.

A simple acid-base disorder is a single primary acid-base disorder (respiratory acidosis, respiratory alkalosis, metabolic acidosis, or metabolic alkalosis) with appropriate respiratory or renal compensation for that disorder. A mixed acid-base disorder is characterized as the simultaneous presence of two or more primary acid-base disorders and is frequently encountered in ICU patients. The arterial blood pH will depend on the direction and magnitude of disturbances. Mixed acid-base disorders can be suspected from the patient's history and whenever the measured compensatory values of either bicarbonate or Paco_2 differ significantly from what is expected.

Compensatory Responses

Disturbances in acid-base balance lead to predictable responses that serve to limit the magnitude of change of the blood pH. The expected compensatory responses to primary acid-base disturbances are listed in Table 104-1.^{5,6} The magnitude of the compensatory response is proportional to the severity of the primary acid-base disturbance. The Henderson-Hasselbalch equation shows that pH is determined by the ratio of the plasma HCO_3^- concentration and Pco_2 , not by either value in isolation.⁶ In each acid-base disorder, compensatory renal or respiratory responses act to minimize the change in pH by minimizing alterations in the ratio. Metabolic disorders result in respiratory compensation (change in Paco_2); respiratory acid-base disorders result in metabolic compensation (change in HCO_3^- concentration).

In metabolic acidosis, a low plasma HCO_3^- concentration decreases the pH, stimulating medullary chemoreceptors to increase ventilation and thereby decrease Paco_2 and restore the pH toward normal. In general, for metabolic acidosis, respiratory compensation results in a 1.25-mm Hg decrease in Paco_2 for every 1.0-mEq/L reduction in the plasma HCO_3^- concentration down to a minimum Paco_2 of 10 to 15 mm Hg.⁶ The expected Paco_2 in a simple metabolic acidosis can be calculated by Winters' formula⁷:

$$\text{Paco}_2 = 1.5 \times (\text{HCO}_3^-) + 8 \pm 2$$

This formula may be used in patients with metabolic acidosis to evaluate whether the observed Paco_2 is an appropriate compensatory

TABLE 104-1 Acid-Base Abnormalities and Appropriate Compensatory Responses for Simple Disorders

| PRIMARY ACID-BASE DISORDERS | PRIMARY DEFECT | EFFECT ON pH | COMPENSATORY RESPONSE | EXPECTED RANGE OF COMPENSATION | LIMITS OF COMPENSATION |
|-----------------------------|---|--------------|--|--|--|
| Respiratory acidosis | Alveolar hypoventilation (\uparrow P_{CO_2}) | \downarrow | \uparrow Renal HCO_3^- reabsorption ($HCO_3^- \uparrow$) | Acute: $\Delta[HCO_3^-] = +1$ mEq/L for each $\uparrow \Delta P_{CO_2}$ of 10 mm Hg Chronic: $\Delta[HCO_3^-] = +4$ mEq/L for each $\uparrow \Delta P_{CO_2}$ of 10 mm Hg | $[HCO_3^-] = 38$ mEq/L $[HCO_3^-] = 45$ mEq/L |
| Respiratory alkalosis | Alveolar hyperventilation (\downarrow P_{CO_2}) | \uparrow | \downarrow Renal HCO_3^- reabsorption ($HCO_3^- \downarrow$) | Acute: $\Delta[HCO_3^-] = -2$ mEq/L for each $\downarrow \Delta P_{CO_2}$ of 10 mm Hg Chronic: $\Delta[HCO_3^-] = -5$ mEq/L for each $\downarrow \Delta P_{CO_2}$ of 10 mm Hg | $[HCO_3^-] = 18$ mEq/L $[HCO_3^-] = 15$ mEq/L |
| Metabolic acidosis | Loss of HCO_3^- or gain of H^+ (\downarrow HCO_3^-) | \downarrow | Alveolar hyperventilation to \uparrow pulmonary CO_2 excretion ($\downarrow P_{CO_2}$) | $P_{CO_2} = 1.5[HCO_3^-] + 8 \pm 2$ $P_{CO_2} = \text{last 2 digits of pH} \times 100$ $P_{CO_2} = 15 + [HCO_3^-]$ | $P_{CO_2} = 15$ mm Hg |
| Metabolic alkalosis | Gain of HCO_3^- or loss of H^+ (\uparrow HCO_3^-) | \uparrow | Alveolar hypoventilation to \downarrow pulmonary CO_2 excretion ($\uparrow P_{CO_2}$) | $P_{CO_2} = +0.6$ mm Hg for $\Delta[HCO_3^-]$ of 1 mEq/L. $P_{CO_2} = 15 + [HCO_3^-]$ | $P_{CO_2} = 55$ mm Hg |

Adapted from Bidani A, Tazouzi DM, Heming TA. Regulation of whole body acid-base balance. In: DuBose TD, Hamm LL, editors. Acid base and electrolytes disorders: a companion to Brenner and Rector's the kidney. Philadelphia: Saunders; 2002. p. 1–21.

response or whether there is additional respiratory acidosis (P_{aCO_2} greater than predicted) or respiratory alkalosis (P_{aCO_2} less than predicted).⁵

Respiratory compensation to metabolic alkalosis should raise the P_{CO_2} by about 0.6 to 0.75 mm Hg for every 1-mEq/L increase in the plasma bicarbonate concentration.^{6,7,8} The expected P_{aCO_2} may be estimated by the following formula:

$$P_{aCO_2} = 40 + ([\text{current } HCO_3^-] - 24) \times 0.7$$

In metabolic alkalosis, a high pH induces hypoventilation with a resultant rise in P_{aCO_2} and decrease in pH. However, hypoxemia induced by progressive hypoventilation eventually activates oxygen-sensitive chemoreceptors to stimulate ventilation and generally limits the compensatory pulmonary response to a P_{aCO_2} of <55 mm Hg.⁷

METABOLIC ACIDOSIS

Metabolic acidosis occurs through increased bicarbonate loss, decreased excretion of acid, an imbalance between production and consumption of endogenous acids, or ingestion or intravenous administration of exogenous acidosis. The clinical significance of metabolic acidosis depends on the severity of the disorder. Without appropriate intervention, metabolic acidosis can progress to life-threatening changes in cardiac, neurologic, and metabolic function as listed in Box 104-1.⁹ Metabolic acidosis can be classified as high-anion gap (AG) metabolic acidosis or non-AG (hyperchloremic) metabolic acidosis.

Serum Anion Gap

Calculation of the serum AG is a useful tool in the evaluation of metabolic acidosis. The serum AG represents the difference in the measured cations (mainly sodium) and the measured anions (chloride and bicarbonate). Mathematically, this is represented as follows:

$$AG = Na^+ - (Cl^- + HCO_3^-)$$

Based on the law of electroneutrality, the concentration of cations should be equal to the concentration of anions in the human body. The serum AG appears on laboratory testing because certain cations and anions are not measured on routine laboratory chemistry panels. This can be represented as follows:

$$\begin{aligned} Na^+ + \text{Unmeasured Cations (UC)} \\ = Cl^- + HCO_3^- + \text{Unmeasured Anions (UA)} \end{aligned}$$

BOX 104-1 Systemic Effects of Acidosis

NEUROLOGIC

- Obtundation and coma
- Hyperactivity of sympathetic nervous system
- Decreased cerebral metabolism
- Decreased response to catecholamines

RESPIRATORY

- Increased minute ventilation
- Subjective dyspnea
- Respiratory muscle fatigue

CARDIOVASCULAR

- Decreased contractility of myocardium
- Core vasculature blood pooling (venoconstriction and arterial dilatation)
- Decreased cardiac response to catecholamines
- Tachyarrhythmias

METABOLIC

- Hyperkalemia (inorganic acidemia)
- Hyperphosphatemia
- Increased protein catabolism

Adapted in part from Whitney GM, Szerlip HM. Acid-base disorder in critical care setting. In: DuBose TD, Hamm LL, editors. Acid-base and electrolytes disorders: a companion to Brenner and Rector's the kidney. Philadelphia: Saunders; 2002. p. 165–183.

Therefore:

$$AG = Na^+ - (Cl^- + HCO_3^-) = UA - UC$$

Calcium, magnesium, gamma globulins, and potassium are the major “unmeasured” cations and account for approximately 11 mEq/L under normal conditions (Fig. 104-1). Although potassium is routinely measured in chemistry panels, the concentration of potassium in the blood is relatively small compared with that of sodium, chloride, and bicarbonate, so potassium is not typically included as a “measured” cation in the AG equation. Negatively charged plasma proteins (albumin), sulfates, phosphates, and other organic anions are the major “unmeasured” anions and account for 20 to 24 mEq/L. Thus, the normal AG is about 12 mEq/L (23–11). Under normal circumstances, the serum AG is typically 12 ± 4 mEq/L but can vary depending on the laboratory method used.¹⁰ Therefore, the established normal range provided by the particular laboratory that performs the testing should be used.

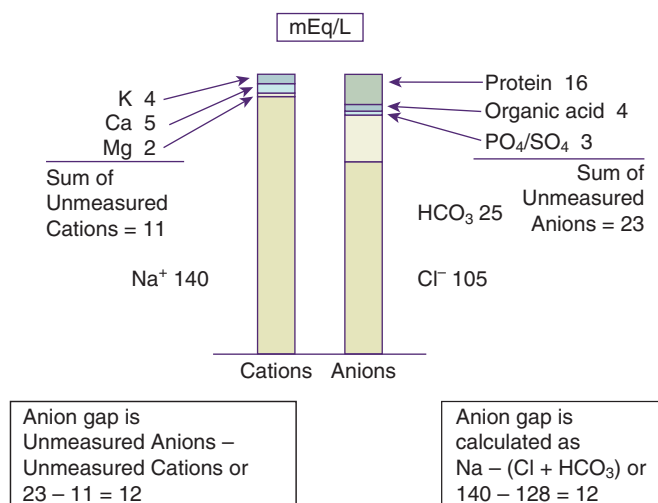


FIGURE 104-1 ■ Components of the serum anion gap.

The AG can be affected by increases or decreases in the UC or UA. The most important contributor to a normal serum AG is albumin, which has a negative charge at a physiologic pH. In patients with hypoalbuminemia, as commonly observed in critical illness, the AG must be corrected for low albumin. For each 1-g/dL fall in the plasma albumin concentration from a normal albumin concentration, the AG falls about 2.5 mEq/L.¹⁰ This can be represented as follows:

$$\text{AG adjusted} = \text{AG} + 2.5 \times (\text{normal albumin} - \text{measured plasma albumin [g/dL]})$$

Other causes of a low AG that may be important to consider for diagnostic and treatment purposes in ICU patients are listed in Table 104-2 and include hypercalcemia, hypermagnesemia, lithium intoxication, hypergammaglobulinemia as occurs in myeloma, and halide (bromide or iodide) intoxication.¹¹

The contributors to serum AG in the normal physiologic state and in high AG and non-AG metabolic acidosis are depicted in Figure 104-2.

■ HIGH-ANION GAP METABOLIC ACIDOSIS

High-AG metabolic acidosis develops from excessive production, ingestion, or retention of a strong acid or a compound metabolized to a strong acid. These include negatively charged acids such as ketones, lactate, sulfates, or metabolites of methanol, ethylene glycol, or salicylate, which accumulate in place of the consumed HCO₃⁻ and cause a high AG. Other causes of an increased AG include hyperalbuminemia or uremia (increased anions) and hypocalcemia or hypomagnesemia (decreased cations)¹¹ (see Table 104-2).

The presence of a significantly elevated AG (AG > 20 mEq/L) always represents metabolic acidosis, regardless of the pH or plasma bicarbonate concentration. Therefore, the serum AG should always be calculated in the ICU setting. In the event of a mixed acid-base disorder with a normal blood pH, a high AG points toward underlying metabolic acidosis, which otherwise may be missed. The common causes of high-AG acidosis in the ICU are lactic acidosis, ketoacidosis, toxin-induced, and renal failure (Box 104-2).

Lactic Acidosis

L-Lactic Acidosis

L-lactic acidosis is among the most frequent causes of elevated AG metabolic acidosis in the ICU and is associated with a high mortality.^{12,13} Lactic acid concentration should be measured directly if lactic acidosis is expected because the serum AG has a sensitivity and

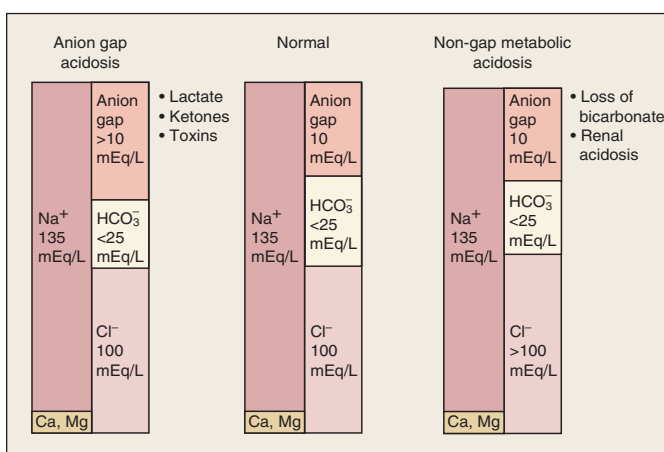


FIGURE 104-2 ■ Contributors to plasma anion gap in normal physiologic state and in metabolic acidosis. (Data from Gamble JL. Chemical anatomy, physiology, and pathology of extracellular fluid. 6th ed. Cambridge: Harvard University Press; 1954; Stewart PA. How to understand acid-base. New York: Elsevier; 1981.)

| Anion Gap in the Diagnosis of Metabolic Acidosis | |
|---|--|
| Anion Gap = Na ⁺ - (Cl ⁻ + HCO ₃ ⁻) = 9 + 3 mEq/L | |
| DECREASED ANION GAP | INCREASED ANION GAP |
| Increased cations (not Na ⁺) ↑ Ca ⁺⁺ , Mg ⁺⁺ ↑ Li ⁺ ↑ IgG Decreased anions: (not Cl ⁻ or HCO ₃ ⁻) Hypoalbuminemia* Acidosis Laboratory error Hyperviscosity Bromism | Increased anions (not Cl ⁻ or HCO ₃ ⁻) ↑ Albumin concentration Alkalosis ↑ Inorganic anions Phosphate Sulfate ↑ Organic anions L-Lactate D-Lactate Ketones Uremic ↑ Exogenously supplied anions Toxins Salicylate Paraldehyde Ethylene glycol Methanol Toluene Pyroglutamic acid ↑ Unidentified anions Uremic Hyperosmolar, nonketotic states Myoglobinuric acute renal failure Decreased cations (not Na ⁺) ↓ Ca ⁺⁺ , Mg ⁺⁺ |

Adapted from Emmett M, Narins RG. Clinical use of the anion gap. *Medicine* 1997;56:38-54; Oh MS, Carroll HJ. The anion gap. *N Engl J Med* 1977;297:814-817; Kraut JA, Madisa NE. Serum anion gap: its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol* 2007;2:162-174.

*Albumin is the major unmeasured anion. A decline in serum albumin of 1.0 g/dL from the normal value of 4.5 g/dL decreases the anion gap by 2.3-2.5 mEq/L. Correction is very important to diagnose anion gap acidosis in the setting of hypoalbuminemia.

specificity of <80% in identifying elevated lactate levels.¹⁴ Thus, a normal AG does not rule out lactic acidosis. Jensen et al. have shown that lactate levels serve as a prognosis indicator that can signal underlying deterioration, prompt more aggressive management, and also help avoid unnecessary treatment when the condition stabilizes.¹⁵ Lactic

BOX 104-2**Clinical Causes of High Anion Gap and Normal Anion Gap Acidosis****HIGH ANION GAP****Ketoacidosis**

Diabetic ketoacidosis (acetoacetate)
Alcoholic (β -hydroxybutyrate)
Starvation

Lactic Acid Acidosis (see Box 104-4)

L-Lactic acid acidosis (types A and B)
D-Lactic acid acidosis
Renal failure: sulfate, phosphate, urate, hippurate

Ingestions (Toxins and Their Metabolites)

Ethylene glycol \rightarrow glycolate, oxalate
Methyl alcohol \rightarrow formate
Salicylate \rightarrow ketones, lactate, salicylate
Paraldehyde \rightarrow organic anions
Toluene \rightarrow hippurate (commonly presents with normal AG)
Propylene glycol \rightarrow lactate
Pyroglutamic acidosis (acetaminophen use) \rightarrow 5-oxoproline

NORMAL ANION GAP**Gastrointestinal Loss of HCO_3^- (Negative Urine Anion Gap)**

Diarrhea
Fistula, external

Renal Loss of HCO_3^- or Failure to Excrete NH_4^+ (Positive Urine Anion Gap)

Proximal renal tubular acidosis (RTA type 2)
Acetazolamide
Classic distal renal tubular acidosis (low serum K^+) RTA type 1
Generalized distal renal tubular defect (high serum K^+) RTA type 4

Miscellaneous

NH_4Cl ingestion
Sulfur ingestion
Dilutional acidosis
Late stages in treatment of diabetic ketoacidosis

Adapted in part from DuBose TD Jr. Acid-base disorders. In: Brenner BM, editor. Brenner and Rector's the kidney. 8th ed. Philadelphia: Saunders; 2008, p. 513–546.

acidosis occurs whenever production of lactate exceeds its utilization. In most cases of clinically significant lactic acidosis, there is evidence of defective utilization as well as increased production, depending on the etiology of lactic acidosis.

Pyruvate is the precursor of lactate and is produced in the cytoplasm from glucose metabolism via glycolysis by the Embden-Meyerhof pathway. Pyruvate normally undergoes oxidative decarboxylation by mitochondrial pyruvate dehydrogenase (PDH) to acetyl-coenzyme A and then ultimately to CO_2 and H_2O . This process results in the synthesis of 36 moles of adenosine triphosphate (ATP) and requires oxidized nicotinamide adenine dinucleotide (NAD^+). Pyruvate can also enter the Cori cycle in the liver and renal cortex and be converted back to glucose. Oxidative phosphorylation, ATP synthesis and reoxidation of NADH are inhibited during hypoxia. This leads to an increased (NADH/NAD^+) ratio, conversion of pyruvate to lactate, and synthesis of two molecules of ATP, rather than the 36 generated via the tricarboxylic acid cycle. The overall result of anaerobic metabolism is increased lactate levels, an elevated lactate/pyruvate ratio, greater glucose utilization, and lower energy production.

Traditionally, lactic acidosis has been categorized as type A or type B acidosis. Type A lactic acidosis is characterized by an impaired mitochondrial oxidative capacity in the setting of tissue hypoxia, while type B lactic acidosis is due to dysregulation of cell metabolism rather than hypoxia (Box 104-3). Most cases of type A lactic acidosis are due to reduced oxygen delivery as a result of reduced tissue perfusion from shock or cardiopulmonary arrest. Other causes are carbon monoxide poisoning and severe anemia. Type B lactic acidosis is classified as type B1 (related to underlying diseases like malignancies or liver disease),

BOX 104-3**Etiologies of Lactic Acidosis****L-LACTIC ACIDOSIS****Conditions Associated with Type a Lactic Acidosis**

Poor tissue perfusion
Shock
Cardiogenic
Hemorrhagic
Septic
Profound hypoxemia

- Severe asthma
- Severe anemia

 Carbon monoxide poisoning

Conditions Associated with Type B Lactic Acidosis

Liver disease
Diabetes mellitus
Catecholamine excess

- Endogenous
- Exogenous

 Thiamine deficiency
Ketoacidosis
Seizure
Malignancy
Intracellular inorganic phosphate depletion
Intravenous (IV) fructose
IV xylose
IV sorbitol
Alcohols metabolized by alcohol dehydrogenase

- Ethanol
- Methanol
- Ethylene glycol
- Propylene glycol

 Mitochondrial toxins

- Salicylate intoxication
- Cyanide poisoning
- 2,4-Dinitrophenol ingestion
- Nonnucleoside antireverse transcriptase drugs

 Metformin
Inborn errors of metabolism
Pyroglutamic acidosis
Kombucha tea

D-LACTIC ACIDOSIS

Short bowel syndrome
Ischemic bowel
Small bowel obstruction

Adapted in part from DuBose TD Jr. Acid-base disorders. In: Brenner BM, editor. Brenner and Rector's the kidney. 8th ed. Philadelphia: Saunders; 2008, p. 513–546.

type B2 (related to the effect of drugs and toxins), and type B3 (associated with inborn errors of metabolism).¹⁶ The most common drugs associated with type B2 lactic acidosis include biguanides, reverse-transcriptase inhibitors, ASA, propofol, and linezolid, among others (see Box 104-3). In critically ill patients, the clinical distinction between type A and B lactic acidosis may not hold; patients can have dysregulation of cellular metabolism as well as hypoxia.¹⁷

Sepsis is a common cause of lactic acidosis in the ICU. The source of lactic acid in sepsis is controversial. Sepsis-induced lactic acidosis has been conventionally classified as type A lactic acidosis due to inadequate oxygen supply and augmented anaerobic metabolism. However, the lack of response to increased oxygen delivery, the absence of tissue hypoxia, and normal tissue ATP levels suggest that lactate formation during sepsis is due to dysregulation of cellular metabolism.^{18,19} Decreased clearance of lactate rather than increased production has been demonstrated in sepsis.²⁰ In addition, increased pyruvate production, decreased PDH activity, regional differences in lactate production, and decreased clearance of lactate have been implicated as possible contributors to lactic acidosis.^{21–23} Decreased muscle PDH activity has been shown in sepsis, and its restoration by dichloroacetate, an activator of PDH, suggesting that lactic acidosis during sepsis is due

to functional inhibition of PDH, with enhanced conversion of pyruvate to lactate.^{24,25}

Treatment of lactic acidosis requires identification and correction of the underlying cause. The therapeutic goal in type A lactic acidosis is restoration of tissue oxygen delivery through hemodynamic and/or respiratory support. The use of sodium bicarbonate in lactic acidosis is controversial and not supported by clinical studies.⁹ Intravenous administration of sodium bicarbonate may increase lactate production, decrease portal vein flow, decrease ionized calcium levels, lower intracellular pH, and worsen cardiac output.^{9,26,27} Bicarbonate increases extracellular pH only if ventilation removes the excess CO₂ generated; otherwise, hypercapnia can lower intracellular pH and impair cellular function.^{9,26,27} Bicarbonate can worsen tissue oxygen delivery if the arterial pH increases more than the intracellular pH, with a leftward shift in the oxyhemoglobin dissociation curve. If tissue hypoxia is present, the use of bicarbonate can stimulate glycolysis mediated by the pH-sensitive rate-limiting enzyme phosphofructokinase and paradoxically increase lactate production.²⁸ Sodium bicarbonate should be administered cautiously when the arterial pH is less than 7.15 since a pH below this value will promote the development of decreased responsiveness to catecholamines, arrhythmias, cardiac depression, and hemodynamic instability.⁹

Alternative buffering agents, such as tris-hydroxymethyl amino-methane (THAM), carbicarb, and dichloroacetate (DCA) have not shown any clinical benefit in patients with lactic acidosis. Carbicarb and DCA are unavailable in the United States. THAM can bind to both CO₂ and metabolic acids. Protonated THAM is excreted by the kidney through glomerular filtration together with bicarbonate or another anion. Thus, THAM can increase the buffering capacity of blood without generating CO₂ but is less effective in patients with anuria. Reported toxicities of THAM include hyperkalemia, hypoglycemia, and respiratory depression.⁹ THAM has not been specifically evaluated as a therapeutic agent for lactic acidosis in clinical trials. Carbicarb, an equimolecular mixture of sodium bicarbonate and sodium carbonate, has a buffering capacity similar to sodium bicarbonate but generates less CO₂. Animal studies have demonstrated inconsistent benefits of carbicarb in lactic acidosis, and one human study comparing the effects of sodium bicarbonate with carbicarb in metabolic acidosis found no benefit.²⁹⁻³¹ DCA stimulates the activity of mitochondrial PDH enzyme complex indirectly through inhibition of the PDH kinase and hence decreases lactate production. Data from animal studies and one placebo-controlled double-blind clinical trial demonstrated that DCA improved acid-base status but not hemodynamics or survival.^{28,32}

Dialysis can be theoretically used to treat lactic acidosis as it provides bicarbonate, removes lactate, prevents decreased ionized calcium, avoids volume overload, and removes drugs associated with lactic acidosis such as metformin.^{9,27} However the same potential risks of worsening lactic acidosis with bicarbonate administration through the dialysate exist. Furthermore, in severe lactic acidosis, the quantity of lactate cleared by dialysis is much less than the quantity of lactate generated. Continuous dialysis modalities are preferred over intermittent dialysis in hemodynamically unstable patients, and it can deliver bicarbonate at a lower rate. Evidence supporting intermittent or continuous dialysis for treatment of lactic acidosis is anecdotal at best, and prospective controlled trials are warranted.²⁷

D-Lactic Acidosis

D-lactic acidosis is an uncommon form of lactic acidosis that occurs in patients with jejunoileal bypass, small bowel resection, or other causes of short bowel syndrome due to bacterial overgrowth. In these patients, abnormally large amounts of glucose and starch are metabolized to D-lactic acid by gram-positive intestinal anaerobes such as *Lactobacilli*.^{33,34} D-lactic acid is then absorbed into the systemic circulation and causes acidemia that tends to persist since D-lactate is not recognized by L-lactate dehydrogenase, the enzyme that converts L-lactate into pyruvate. Patients typically present with recurring episodes of metabolic acidosis following a carbohydrate meal and neuro-

logic abnormalities including confusion, ataxia, slurred speech, and memory loss.³⁵ The diagnosis can be easily missed because the D-isomer responsible for the acidosis is not detected by the standard assay for lactate and requires a special assay for detection. Therapy for D-lactic acidosis includes administration of sodium bicarbonate to correct the acidosis, oral antibiotics to decrease gram-positive anaerobic colonic bacteria, and a low-carbohydrate diet to reduce carbohydrate delivery to the colon. D-lactic acidosis has also been described in patients who have large amounts of propylene glycol and in those with diabetic ketoacidosis (DKA).^{36,37}

Ketoacidosis

Ketoacidosis is a common complication in patients with insulin-dependent diabetes mellitus but can also be seen in chronic alcoholism and starvation (see Box 104-2). It results from the overproduction of ketone bodies, leading to accumulation of ketones in the plasma (ketonemia) and urine (ketonuria).

Diabetic Ketoacidosis

DKA occurs in patients with insulin-dependent diabetes mellitus and results from severe insulin deficiency in the setting of increased metabolic demand, such as from a concurrent infection or myocardial infarction. It can also occur from poor compliance with insulin or missed injections. Insulin deficiency results in decreased glucose uptake, glycogen store depletion, lipolysis, and fatty acid oxidation with increased ketoacid production (acetoacetate and beta-hydroxybutyrate). Symptoms can progress from polydipsia, polyuria, nausea, vomiting, dyspnea, and diffuse abdominal pain to confusion, lethargy, and somnolence. Laboratory findings include hyperglycemia, increased serum AG, ketonemia, ketonuria, and increased plasma osmolality. The diagnosis is established by measuring plasma and urine ketone levels. However, clinicians must be aware that the nitroprusside reaction used in standard plasma and urine tests only measures acetone and acetoacetate levels and not beta-hydroxybutyrate levels, which is the predominant ketone in severe untreated DKA. Therefore, laboratory analysis for ketones may be falsely negative. High plasma glucose levels can cause dilutional hyponatremia since the osmotic effect of hyperglycemia causes the movement of water into the intravascular space. For each 100 mg/dL of glucose over 100 mg/dL, the plasma sodium level is lowered by approximately 1.6 mEq/L. In spite of severely depleted total body potassium from osmotic diuresis, plasma potassium levels are initially elevated or within the normal range from insulin deficiency.^{38,39}

The major goals of treatment are rapid volume expansion, correction of hyperglycemia, correction of acid-base and electrolyte disturbances, and identification and treatment of the precipitating cause such as infection. Adults should initially receive a rapid infusion of 1 L of isotonic saline with repeat boluses as necessary to prevent hemodynamic collapse. When the blood pressure and heart rate have stabilized and the patient is euvolemic, isotonic saline can be switched to 0.45% saline at a slower rate to replace the free water lost by osmotic diuresis. Insulin is typically administered as a 10- to 20-unit intravenous (IV) bolus (0.15 units/kg) followed by an infusion of 5 to 7 units/hour (0.1 unit/kg/hour). Insulin inhibits lipolysis and gluconeogenesis and allows for the conversion of ketones to bicarbonate. If the blood sugar falls below 250 mg/dL, the rate of insulin should be decreased to 0.03 u/kg/hour. Once the AG normalizes, subcutaneous insulin should be administered while the insulin infusion is continued for another 1 to 2 hours. When blood sugar is less than 200 to 250 mg/dL, 5% to 10% dextrose should be added to the fluids. Potassium replacement should be administered at 10 to 20 mEq/hour if the plasma potassium level is less than 5.3 mEq/L and if renal failure is not present. Plasma potassium levels should be measured frequently, and the infusion should be stopped if hyperkalemia occurs. Small amounts of IV sodium bicarbonate should only be administered if the arterial pH is less than 6.9, with frequent monitoring of pH and serum AG. Intravenous phosphate replacement can be given if the initial level is less than

1.0 mg/dL. Plasma phosphorus levels can be high initially due to the transcellular shift of phosphate out of the cell in the setting of acidosis and insulin deficiency.^{38,40}

Hemodialysis-dependent patients with DKA are managed differently. Insulin administration is frequently the only treatment needed for DKA management in these patients. Dialysis patients usually present with signs of extracellular volume expansion rather than volume depletion since osmotic diuresis cannot occur in the absence of kidney function. Therefore, dialysis patients do not require IV fluids unless they have evidence of extracellular fluid loss such as vomiting, diarrhea, or excessive insensible losses. If volume depletion is present, small amounts of isotonic saline should be carefully administered with close monitoring of respiratory and hemodynamic parameters. When volume overload is apparent, immediate hemodialysis is the therapy of choice. Dialysis-dependent patients with DKA should not receive routine potassium supplementation since total body potassium stores may be high and patients are unable to excrete a potassium load. Urgent dialysis is indicated if hyperkalemia is present with electrocardiographic findings. Similarly, significant metabolic acidosis can only be corrected by hemodialysis.⁴⁰

Alcoholic Ketoacidosis

Alcoholic ketoacidosis (AKA) occurs in the setting of chronic alcoholism, recent binge drinking, minimal oral intake, and persistent vomiting. It is characterized by elevated plasma ketone levels, high AG, and normal or only slightly elevated plasma glucose level. Prolonged starvation results in decreased insulin activity, glycogen depletion, increased counterregulatory hormone production, dehydration, and increased lipolysis and fatty acid oxidation with accumulation of ketoacids. The metabolism of ethanol itself promotes ketoacidosis by leading to an accumulation in reduced NADH. Reduced NADH then results in impaired conversion of lactate to pyruvate, preferential conversion of pyruvate to lactate, and a shift toward beta-hydroxybutyrate production. Beta-hydroxybutyrate is the predominant ketone in AKA. The standard nitroprusside test for detecting ketones only detects acetoacetate and may be falsely negative or only minimally positive in AKA, leading to an underestimation of the degree of ketoacidosis.^{41,42}

Patients with AKA frequently present with a mixed acid-base disturbance. They can have elevated AG metabolic acidosis from ketoacidosis and lactate, metabolic alkalosis from persistent vomiting, and chronic respiratory alkalosis from liver disease. Magnesium and phosphate levels may be low due to increased urinary excretion and poor nutrition.

The mainstay of treatment is hydration with 5% dextrose in isotonic saline. Before glucose administration, thiamine should be given to avoid precipitating Wernicke encephalopathy. Carbohydrate and fluid replacement reverse the pathophysiologic derangements that lead to AKA by increasing plasma insulin levels and suppressing the release of glucagon and other counterregulatory hormones. Dextrose stimulates the oxidation of NADH and aids in normalizing the NADH/NAD⁺ ratio. Insulin should be avoided since it can lead to hypoglycemia, especially as the patient's endogenous insulin levels rise with carbohydrate and fluid repletion. Bicarbonate is only recommended if the plasma pH is less than 7.1 and the acidosis is not responding to IV fluids. Hypophosphatemia, hypokalemia, and hypomagnesemia should be corrected. Glucose infusion can exacerbate hypophosphatemia, resulting in rhabdomyolysis if not repleted.⁴³

Starvation Ketoacidosis

Starvation, as mentioned above, results in ketoacidosis due to the increase in counterregulatory hormones and a decrease in insulin level, promoting fatty acid oxidation, gluconeogenesis, and ketone production. However, in comparison to the potentially severe ketoacidosis that develops in uncontrolled diabetes and alcoholic states, ketoacid levels do not typically exceed 10 mEq/L with fasting. This is probably due to the insulin level, which, though lower, is still enough to limit the production of free fatty acids and thus ketoacidosis.^{44,45}

Toxin-Induced

See Boxes 104-2 and 104-3.

Toxic Alcohol Ingestions

Accumulation of the metabolites of methanol, ethylene glycol, diethylene glycol, and propylene glycol cause a high AG and increased plasma osmolal gap. Intoxication should be suspected in any patient who presents with high-AG metabolic acidosis, renal failure, and neurologic findings, and treatment should be initiated early.

The normal range of plasma osmolality is 285 to 290 mOsm/kg. Plasma osmolality can be estimated from the following formula:

$$\text{Calculated Posm} = (2 \times \text{plasma [Na]}) + (\text{glucose, in mg/dL})/18 + (\text{blood urea nitrogen, in mg/dL})/2.8$$

The plasma osmolal gap represents the difference between the measured and calculated plasma osmolality. A difference of higher than 10 mOsm/kg is considered an osmolal gap. Accumulation of the above alcohols will typically produce an osmolal gap of higher than 20 mOsm/kg. Methanol gives rise to the greatest increment in plasma osmolality, followed by ethylene glycol, propylene glycol, and finally diethylene glycol.⁴⁶ The absence of an osmolal gap does not exclude an alcohol-related intoxication. Furthermore, although the plasma osmolal gap may support the diagnosis of ingestion of a toxic alcohol, plasma toxicology screens specifically looking for the toxins are considered as the gold standard.

Other causes of high-AG metabolic acidosis that can be associated with an elevated plasma osmolal gap include lactic acidosis, ketoacidosis, advanced chronic kidney disease (CKD), formaldehyde ingestion, and paraldehyde ingestion. The plasma osmolal gap is usually less pronounced in these disorders (≤ 15 –20 mOsm/kg), and such testing is not typically performed. Substances that can cause an osmolal gap without metabolic acidosis are ethanol, isopropyl alcohol ingestion, infusion of nonconductive glycine, sorbitol or mannitol solutions, severe hyperproteinemia, and severe hyperlipidemia.⁴⁶

Methanol, used as a laboratory and industrial solvent, is commonly found in windshield-wiper fluid, deicing products, gas-line antifreeze, and various paint solvents and thinners. It is metabolized by alcohol dehydrogenase (ADH) to formaldehyde, which is further metabolized by aldehyde dehydrogenase (ALDH) to formic acid. The most common symptoms of methanol intoxication are abdominal pain and visual disturbances, including decreased visual acuity, photophobia, and blurred vision. Formic acid is the main toxic metabolite responsible for retinal, ophthalmic, and neural toxicity. Permanent blindness may occur due to optic nerve atrophy. High-AG metabolic acidosis is due to generation of formic acid and increased production of lactic acid. Lactic acidosis results from impaired cellular respiration by formate or increased generation of NADH during the metabolism of methanol.^{46,47}

Ethylene glycol is typically found in radiator antifreeze as well as various solvents and paint formulations. It is metabolized by ADH to glycoaldehyde, then by ALDH to glycolic acid, which is further metabolized to glyoxylic acid and finally oxalic acid. The metabolites are responsible for neurologic, cardiopulmonary, and renal toxicity. Typically, neurologic abnormalities occur initially, followed by cardiopulmonary dysfunction, and finally renal dysfunction. Neurologic findings include coma, seizures, meningism, external ocular paralysis, and delayed onset of cranial nerve deficits. Cardiopulmonary findings include tachycardia, hyperventilation, and heart failure. Oxalic acid combines with plasma calcium to form calcium oxalate, which leads to hypocalcemia, QTc prolongation, and risk of ventricular arrhythmias. Calcium oxalate crystals precipitate in the renal tubules, causing flank pain, oliguria, and renal failure. Calcium oxalate crystals are present in the urine 4 to 8 hours after ingestion of ethylene glycol. High-AG metabolic acidosis is due to generation of glycolic, glyoxylic, and oxalic acids and increased production of lactic acid. Measurement of plasma ethylene glycol levels can confirm poisoning.^{46,47}

Methanol and ethylene glycol poisoning are treated with fomepizole or ethanol, which inhibits ADH and prevents the formation of toxic

metabolites. Fomepizole (15 mg/kg loading dose, then 10 mg/kg every 12 hours) is preferred over ethanol due to its easier dosing regime and better side effect profile. The indications for antidotal therapy are a plasma concentration of methanol or ethylene glycol higher than 20 mg/dL and two of the following: osmolal gap higher than 10 mOsm/kg, arterial pH lower than 7.3, plasma bicarbonate level lower than 20 mEq/L, and presence of urinary oxalate crystals. Indications for hemodialysis are severe metabolic acidosis (pH < 7.25), visual abnormalities, renal failure, electrolyte abnormalities not responsive to treatment, hemodynamic instability despite ICU treatment, and plasma concentration higher than 50 mg/dL. In ethylene glycol toxicity, pyridoxine and thiamine are administered to increase the metabolism of glycolic and glyoxylic acid to the less toxic metabolites glycine and alpha-hydroxy-beta-ketoadipate. In methanol toxicity, folic acid or folinic acid increases the breakdown of formic acid to CO₂ and water.^{46,47}

Diethylene glycol is present in brake fluid and is used as an illegal adulterant in ethanol spirits or in medication. Diethylene glycol is oxidized by ADH to 2-hydroxyethoxyacetaldehyde and then via ALDH to 2-hydroxyethoxyacetic acid. Acute oliguric and nonoliguric renal failure are frequent. Treatment consists of hemodialysis and fomepizole.⁴⁶

Propylene glycol is a solvent for unstable drugs including benzodiazepines, phenytoin, nitroglycerine, and some topical medications. The majority of intoxications have resulted from excessively large or rapidly infused intravenous injections of propylene glycol-containing medications such as benzodiazepines. Neurologic depression is the primary manifestation of acute propylene glycol poisoning. Metabolic acidosis is attributed to generation of lactic acid during metabolism of propylene glycol. Discontinuation of propylene glycol-containing medication can lead to correction of the acidosis within 24 hours in most patients. In the face of extremely high blood concentrations, hemodialysis is extremely effective in rapidly reducing plasma propylene glycol levels.⁴⁶

Use of isopropyl alcohol is the most common cause of toxic alcohol exposure in the United States; it is found in rubbing alcohol, hand sanitizer gels, and other antiseptic preparations. It is metabolized by ADH to acetone, without production of AG acidosis. Toxicity is mainly limited to gastrointestinal (GI) effects, such as hemorrhagic gastritis and neurologic depression. Isopropyl alcohol is the only toxic alcohol that causes ketosis without acidosis. In comparison to other toxic alcohols, isopropanol intoxication is usually managed supportively. Hemodialysis may increase the rate of elimination of both isopropyl alcohol and acetone and should be considered for patients with deteriorating mental status or hemodynamic instability.⁴⁶

Salicylates

Salicylate toxicity may develop with either acute or chronic exposure to salicylates. Acute and chronic salicylate toxicity is associated with a high mortality if not recognized early and treated. Salicylates are found in over-the-counter medications such as aspirin, bismuth subsalicylate, effervescent antacids, ointments, liniments, and oil of wintergreen (methyl salicylate) as well as in numerous prescription medications. Patients with salicylate toxicity may present with neurologic symptoms (cerebral edema, coma, agitation, tinnitus, or seizures), pulmonary symptoms (hyperventilation/tachypnea or acute lung injury) and GI symptoms (nausea or vomiting). Nausea, vomiting, diaphoresis, and tinnitus are the earliest signs and symptoms of salicylate toxicity. Salicylates stimulate the respiratory center, leading to hyperventilation and respiratory alkalosis. They also uncouple oxidative phosphorylation and interfere with the Krebs cycle, leading to increased lactate production, ketosis, and high-AG metabolic acidosis. Interference with aerobic respiration also causes hypoglycemia, fever, and fluid loss. Adult patients with acute poisoning usually present with mixed respiratory alkalosis and metabolic acidosis but can also present with primary respiratory alkalosis. In children, respiratory alkalosis may be transient, with metabolic acidosis occurring early in the course.⁴⁸

The therapeutic range of salicylates is 10 to 30 mg/dL. Patients become symptomatic at concentrations higher than 40 mg/dL. Levels

higher than 90 to 100 mg/dL usually have serious or life-threatening toxicity. In overdoses, the peak plasma concentration may not occur for 4 to 6 hours. A 6-hour salicylate level higher than 100 mg/dL is considered lethal and is an indication for hemodialysis. Labs should be repeated every 4 to 6 hours until the level falls into the nontoxic range. Renal excretion of salicylic acid depends on urinary pH. Increasing the urine pH to 7.5 prevents reabsorption of salicylic acid from the urine. Since acidosis facilitates transfer of salicylate into tissues, especially in the brain, it must be treated aggressively by raising the blood pH higher than the brain pH, thereby shifting the equilibrium from the tissues to the plasma. Alkalinization with IV sodium bicarbonate is the mainstay of treatment in patients whose plasma pH is not already elevated (>7.5), and care should be taken not to raise plasma pH to inappropriately high levels (>7.55). Hypokalemia occurs commonly in salicylate-poisoned patients and prevents urinary excretion of salicylate unless corrected. Since intoxication can decrease cerebral glucose concentrations despite normal plasma glucose concentrations, adults who are hypoglycemic or have altered mental status, regardless of their plasma glucose concentration, should be treated with supplemental glucose. Indications for hemodialysis include a plasma level higher than 120 mg/dL (acutely) or higher than 100 mg/dL (6 hours post ingestion), refractory acidosis, coma or seizures, noncardiogenic pulmonary edema, volume overload, and renal failure. In chronic overdose, hemodialysis may be required for a symptomatic patient with a plasma salicylate level higher than 60 mg/dL.^{48,49}

Pyroglutamic Acidosis

Accumulation of 5-oxoproline (pyroglutamic acid), an organic acid intermediate of the gamma-glutamyl cycles, is a rare, but underdiagnosed, cause of severe, high-AG metabolic acidosis in adults. The acidemia associated with pyroglutamic acid usually occurs in association with acetaminophen therapy and in the setting of severe sepsis or liver or renal dysfunction. Heterozygosity for glutathione synthase deficiency may also be an underlying risk factor for development. The etiology appears to be a drug-induced reversible inhibition of either glutathione synthetase or 5-oxoprolinase. Diagnosis is made by measuring urinary 5-oxoproline levels to demonstrate the presence of pyroglutamic acid. Treatment with *N*-acetylcysteine to replenish glutathione should be considered.⁵⁰⁻⁵²

Renal Failure

Early CKD is associated with hyperchloremic normal AG metabolic acidosis, while end-stage renal disease (uremia) is associated with elevated AG metabolic acidosis. In early CKD, acid excretion is initially maintained by increased ammonium excretion. When the glomerular filtration rate (GFR) falls below 40 to 50 mL/min, tubular function decreases, leading to retention of H⁺, an increase in the amount of bicarbonate excreted, and metabolic acidosis. To maintain electroneutrality, the kidneys retain chloride with each bicarbonate ion lost, causing hyperchloremic metabolic acidosis. Since glomerular function decreases at a much slower rate than the loss of tubular function, the excretion of sulfate and other organic and inorganic acid anions is not affected as their filtration by the kidney is maintained. The AG remains in normal range due to the continued excretion of organic acids by the kidneys. In advanced CKD, when the GFR falls below 20 mL/min, the capacity of the kidneys to filter the anions of organic acids is significantly diminished, causing retention of phosphates, sulfates, urate, and hippurate anions in the plasma and development of elevated AG metabolic acidosis.^{53,54}

Clinical consequences of chronic metabolic acidosis in CKD include osteopenia, worsening secondary hyperparathyroidism, CKD progression, and increased mortality. Recent clinical trials have suggested that correction or prevention of metabolic acidosis by alkali administration is able to slow progression of CKD. As a result, to prevent CKD progression and bone loss, sodium bicarbonate supplementation (0.5-1 mEq/kg/day) is recommended for patients with CKD having plasma bicarbonate concentrations lower than 22 mEq/L.⁵⁴

BOX 104-4**Differential Diagnosis of Hyperchloremic Metabolic Acidosis****GASTROINTESTINAL BICARBONATE LOSS**

Diarrhea
 External pancreatic or small bowel drainage
 Ureterosigmoidostomy, jejunal loop

Drugs

Calcium chloride (acidifying agent)
 Magnesium sulfate (diarrhea)
 Cholestyramine (bile acid diarrhea)

RENAL ACIDOSIS**Hypokalemic**

Proximal RTA (type 2) (see Box 104-6)
 Distal (classic) RTA (type 1)

Drug-Induced Hypokalemia

Acetazolamide (proximal RTA)
 Amphotericin B (distal RTA)

Hyperkalemic

Generalized distal nephron dysfunction (type 4 RTA) (see Box 104-6)
 Mineralocorticoid deficiency or resistance (pseudohypoaldosteronism type 1)
 PHA-I, PHA-II
 ↓ Na⁺ delivery to distal nephron
 Tubulointerstitial disease
 Ammonium excretion defect

Drug-Induced Hyperkalemia

Potassium-sparing diuretics (amiloride, triamterene, spironolactone)
 Trimethoprim
 Pentamidine
 Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers
 Nonsteroidal antiinflammatory drugs
 Cyclosporine, tacrolimus

Normokalemic

Early renal insufficiency

OTHER

Acid loads (ammonium chloride, hyperalimentation)
 Loss of potential bicarbonate: ketosis with ketone excretion
 Dilution acidosis (rapid saline administration)
 Hippurate
 Cation-exchange resins

Adapted in part from DuBose TD Jr. Acid-base disorders. In: Brenner BM, editor. Brenner and Rector's the kidney, 8th ed. Philadelphia: Saunders; 2008, p. 513–546.

NONANION GAP (HYPERCHLOREMIC) METABOLIC ACIDOSIS

Normal or non-AG metabolic acidosis is also called *hyperchloremic metabolic acidosis* because the kidneys reabsorb chloride instead of bicarbonate, yielding no net change in the serum AG. Hyperchloremic metabolic acidosis may result from impaired renal acid excretion, increased renal or GI bicarbonate loss, H⁺ gain, marked urinary excretion of organic acid anions with replacement with chloride, or administration of chloride-rich solutions during resuscitation (Box 104-4). In impaired renal acid excretion, the absence of sufficient ammonium excretion results in the acid anions being excreted with sodium and potassium. This results in a sodium deficit and avid renal retention of filtered sodium and chloride. The retained chloride replaces the lost bicarbonate. GI or urinary bicarbonate loss leads to a sodium deficit and a reduction in extracellular fluid volume. This stimulates renal retention of sodium and chloride, thereby replacing the lost bicarbonate by the retained chloride.⁵⁵

Urinary Anion Gap

In assessing the cause of hyperchloremic metabolic acidosis, the urine AG (UAG) may be useful in differentiating renal causes from GI

causes. The UAG is calculated as the difference between the measured urine cations (Na⁺ and K⁺) and urine Cl[−]:

$$\text{UAG} = (\text{Na}^+) + (\text{K}^+) - (\text{Cl}^-)$$

In diarrhea and other nonrenal causes of hyperchloremic acidosis, the kidney should attempt to compensate by increasing net acid excretion. The major mechanism for this increase is a marked increase in urinary ammonium excretion. Since urinary ammonium measurements are not readily available, the UAG serves as a surrogate. Under normal circumstances, the sum of the excreted urine sodium and urine potassium is greater than the amount of excreted urine chloride. Therefore, the UAG has a positive value in healthy individuals. In patients with normal AG metabolic acidosis, the excretion of ammonium occurs with chloride, increasing the urine chloride concentration. In such settings, urine chloride usually exceeds the sum of urine sodium and urine potassium, resulting in a negative UAG; the UAG will be negative when ammonium is present and balanced by negatively charged urinary chloride. A negative UAG is consistent with increased ammonium excretion and occurs in patients who develop metabolic acidosis as a result of diarrhea. If there is little ammonium present, the UAG will be zero or positive, similar to that in patients who have hyperchloremic metabolic acidosis associated with impaired ammonium excretion, as seen in renal tubular acidosis (RTA).

There are several limitations to the UAG. The UAG cannot be interpreted accurately in the setting of increased urinary excretion of unmeasured anions. Unmeasured anions may be excreted with sodium or potassium or with ammonium. Examples of unmeasured urinary anions include ketoacids, hippurate, D-lactate, and 5-oxoproline. As a result, the excretion of ammonium with these unmeasured anions will not reduce the UAG, which occurs when ammonium is excreted with chloride. In addition, the excretion of sodium or potassium with unmeasured anions leads to a positive UAG.⁵⁶ The UAG also cannot be interpreted in volume-depleted states with urine sodium levels less than 25 mEq/L due to impaired distal sodium delivery.⁵⁷

The urine osmolal gap (UOG) can overcome some of the limitations of the UAG.⁵⁶ The UOG indirectly assesses urine ammonium concentration by comparing the directly measured urine osmolality to the calculated urine osmolality. The formula for calculating urine osmolality is as follows:

$$\begin{aligned} \text{Calculated urine osmolality (mOsm/kg)} \\ = (2 \times [\text{Na} + \text{K}]) + (\text{urea nitrogen in mg/dL})/2.8 \\ + (\text{glucose in mg/dL})/18 \end{aligned}$$

The UOG is the difference between the directly measured osmolality and the calculated urine osmolality. Besides sodium, potassium, urea, and glucose (if present in the urine), the major urinary solute that contributes to urine osmolality is ammonium. Most of the UOG is, therefore, made up of ammonium in the form of ammonium chloride as well as ammonium excreted with other unmeasured anions. Thus, the UOG detects ammonium excretion regardless of the anion that is excreted along with it. The UOG must be divided by two in order to account for the anion being excreted with ammonium. In the setting of metabolic acidosis, urine ammonium levels should be higher than 200 mEq/L. An ammonium urine concentration of less than 75 mEq/L in a patient with metabolic acidosis indicates impaired renal ammonium excretion and correlates with a UOG of less than 150 mOsm/kg. In the setting of hyperchloremic metabolic acidosis from GI causes such as diarrhea, the UOG should be higher than 400 mOsm/kg.^{55,56}

Renal Tubular Acidosis

RTA is characterized by impaired urinary acidification, resulting in retention of H⁺, reduction in plasma bicarbonate levels, and hyperchloremic normal AG metabolic acidosis. RTA can be classified as proximal (type 2), distal (type 1), and hyperkalemic (type 4). The UAG is usually positive in RTA due to an inability to excrete H⁺. Proximal (type 2) and

BOX 104-5 List of Select Disorders Associated with Renal Tubular Acidosis***RENAL DEFECT IN NET ACID EXCRETION, CLASSIC DISTAL RENAL TUBULAR ACIDOSIS (RTA 1)****Systemic or Tubulointerstitial Disease**

Medullary sponge kidney
 Cryoglobulinemia
 Balkan nephropathy
 Nephrocalcinosis
 Chronic pyelonephritis
 HIV nephropathy
 Renal transplant
 Sjögren syndrome
 Thyroiditis
 Hyperparathyroidism

Drug or Toxin Induced

Ifosfamide
 Amphotericin B
 Foscarnet
 Toluene
 Mercury
 Classic analgesic nephropathy

RENAL DEFECT IN HCO_3^- RECLAMATION, PROXIMAL RENAL TUBULAR ACIDOSIS (RTA 2)**Selective (Unassociated with Fanconi Syndrome)****Idiopathic**

Carbonic anhydrase deficiency or inhibition
 Drugs such as acetazolamide
 Carbonic anhydrase II deficiency with osteopetrosis (Sly syndrome)

Generalized (Associated with Fanconi Syndrome)

Primary: inherited or sporadic
 Genetically transmitted systemic diseases: cystinosis, Lowe syndrome, Wilson syndrome

Dysproteinemic States

Multiple myeloma
 Monoclonal gammopathy

Secondary Hyperparathyroidism with Chronic Hypocalcemia

Vitamin D deficiency or resistance
 Vitamin D dependency

Drugs or Toxins

Ifosfamide
 Lead
 Outdated tetracycline
 Streptozotocin
 Mercury
 Amphotericin B (historic)

Tubulointerstitial Diseases

Sjögren syndrome
 Medullary cystic disease
 Renal transplantation

GENERALIZED DEFECT OF THE DISTAL NEPHRON WITH HYPERKALEMIA (RTA 4)**Mineralocorticoid Deficiency****Primary Aldosterone Deficiency**

Adrenal disease (hemorrhage, destruction, infarction)
 Heparin (low MW or unfractionated)
 Persistent hypotension in critically ill patient
 Renin angiotensin system modulating agents (ACEI, ARB)

Secondary Aldosterone Deficiency (Hyporeninemic Hypoaldosteronism)

Diabetic nephropathy
 HIV disease
 Tubulointerstitial nephropathy
 NSAID use

Renal Tubular Dysfunction (Voltage Defect)**Drugs That Interfere with Na Channel or $\text{Na}^+/\text{K}^+-\text{ATPase}$**

Amiloride
 Pentamidine
 Triamterene
 Trimethoprim
 Cyclosporine
 Tacrolimus

Disorders Associated with Tubulointerstitial Disease

Renal failure
 Lupus nephritis
 Obstructive uropathy
 Renal transplant rejection
 Sickle cell disease

Adapted in part from DuBose TD Jr. Acid-base disorders. In: Brenner BM, editor. Brenner and Rector's the kidney. 8th ed. Philadelphia: Saunders; 2008. p. 513–546.

*See source for complete list of disorders.

distal (type 1) RTA are uncommon disorders. See Boxes 104-4 and 104-5.

Proximal Renal Tubular Acidosis (Type 2)

Proximal RTA is characterized by impaired proximal bicarbonate reabsorption with a lowered threshold for bicarbonate reclamation. This results in renal bicarbonate wasting whenever the bicarbonate concentration exceeds this lowered threshold. Below this threshold, bicarbonate is conserved, and maximal urinary acidification (urine $\text{pH} < 5.5$) occurs. Bicarbonate loss in the urine leads to increased H^+ concentration in the blood and a subsequent reduction in the arterial pH . Because of impaired proximal bicarbonate reabsorption, the distal nephrons become overwhelmed by an increase in bicarbonate delivery and cannot compensate for the loss in proximal function. However, as the plasma bicarbonate level decreases to 15 to 18 mEq/L , the amount of filtered bicarbonate decreases with reduced delivery of bicarbonate to the distal nephrons. At that point, the distal nephrons are able to function, leading to a reduction in bicarbonate loss and appropriate acidification of the urine to a pH less than 5.5. These patients also have hyperaldosteronism from salt wasting due to the defect in proximal reabsorption of filtered bicarbonate. Because of

hyperaldosteronism, urinary potassium wasting and hypokalemia are common.^{55,58}

Proximal RTA is diagnosed by measurement of the urine pH and fractional bicarbonate excretion during bicarbonate infusion. Intravenous sodium bicarbonate is infused at a rate of 0.5 to 1.0 mEq/kg/hour to increase the plasma bicarbonate concentration toward normal (18–20 mEq/L). The urine pH , even if initially acidic, will rise rapidly once the reabsorptive threshold for bicarbonate is exceeded. As a result, the urine pH will increase to higher than 7.5, and the fractional excretion of bicarbonate will exceed 15%.^{55,58}

In adults, proximal RTA is typically secondary to acquired proximal tubular damage such as heavy metal exposure and multiple myeloma, while in children, it is associated with metabolic defects (see Box 104-5). Proximal RTA is often accompanied by other proximal tubular transport defects including renal glycosuria, phosphate wasting, aminoaciduria, and hypouricemia (Fanconi syndrome). Medications such as carbonic anhydrase inhibitors (e.g., acetazolamide) and topiramate can cause proximal RTA by impairing proximal bicarbonate reabsorption without affecting the reabsorption of other proximal tubule solutes. The drugs tenofovir and ifosfamide can cause Fanconi syndrome.⁵⁵

Complications include bone disease due to an increase in bone buffering of excess acid and acquired vitamin D deficiency from decreased calcitriol production. Defects in proximal transport may also result in phosphate wasting and hypophosphatemia, leading to rickets in children and osteomalacia or osteopenia in adults.^{55,58}

Standard treatment is with oral alkali therapy. Since exogenous alkali is rapidly excreted in the urine, considerably higher doses of alkali are required as in comparison to distal and type 4 RTA. About 10 to 15 mEq/kg/day of alkali is typically required to stay ahead of urinary excretion. Potassium citrate is the preferred form of alkali to help with potassium losses. Thiazides are also sometimes used in conjunction with a low-salt diet to reduce the amount of alkali required. Thiazides induce volume contraction and enhance proximal bicarbonate reabsorption.⁵⁸

Classic Distal Renal Tubular Acidosis (Type 1)

Classic distal RTA results from defective H⁺ secretion in the distal tubule. Impaired H⁺ secretion results in an inability to acidify the urine pH beyond 5.5 and reduced net acid excretion. The plasma bicarbonate may fall below 15 mEq/L. Hypokalemia occurs due to urinary potassium wasting from increased potassium secretion by distal tubular cells in the setting of diminished H⁺ secretion. Hypercalciuria, alkaline urine, and low urinary citrate levels promote the precipitation of calcium phosphate stones and nephrocalcinosis. A diagnosis is made by the findings of hypokalemia, normal AG metabolic acidosis, inappropriately high urine pH (>5.5) regardless of the plasma bicarbonate concentration, and a positive UAG.⁵⁸

The most common causes in adults are autoimmune disorders such as Sjögren's syndrome. In children, RTA is most often a primary hereditary condition (see Box 104-5). Drugs such as ifosfamide and amphotericin cause distal RTA in adults and children. Complications include failure to thrive, rickets, and stunting of growth in children and osteomalacia or osteopenia in adults. Patients may otherwise be asymptomatic or may present with symptoms of severe acidosis or hypokalemia.⁵⁸

Adults are generally treated with oral sodium bicarbonate or sodium citrate 1 to 2 mEq/kg/day. Patients with significant hypokalemia, nephrolithiasis, or nephrocalcinosis are treated with potassium citrate or Polycitra (potassium citrate plus sodium citrate).

Hyperkalemic Distal Renal Tubular Acidosis (Type 4)

Hyperkalemic distal RTA is characterized by hyperkalemia and hyperchloremic metabolic acidosis. It can occur in the setting of aldosterone deficiency or resistance or due to a voltage-dependent defect in H⁺ secretion. In aldosterone deficiency or resistance, hyperkalemia is the primary disturbance, suppressing proximal tubular ammonium production and producing metabolic acidosis.⁵⁹ Urinary acidification is intact. The metabolic acidosis seen is generally mild, with the plasma bicarbonate level usually higher than 15 mEq/L. Despite impaired distal H⁺ secretion, the urine pH is generally below 5.5. The ability to acidify the urine in this condition is due to the inadequate amount of ammonia available for buffering of protons since the urinary pH falls in the absence of buffers. The findings of hyperkalemic, normal AG metabolic acidosis with an appropriately low urine pH (<5.5) and positive UAG confirm the diagnosis. The diagnosis is further supported by a bicarbonate fractional excretion of higher than 10% in the setting of bicarbonate infusion.⁵⁸

Hyporeninemic hypoaldosteronism is the most common cause of type 4 RTA in patients with mild to moderate renal insufficiency due to diabetic nephropathy (see Box 104-5). Many drugs can cause type 4 RTA by affecting renin release, aldosterone production, or tubular potassium excretory capacity. Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit renin release. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcineurin inhibitors, and heparin can all reduce aldosterone production. Inhibitors of tubular potassium excretion include spironolactone, eplerenone, triamterene, and amiloride. The tubulointerstitial diseases commonly

associated with type 4 RTA include sickle cell disease and obstructive nephropathy.^{58,59}

Hyperkalemia from aldosterone deficiency or resistance can be diagnosed by measuring the transtubular potassium gradient (TTKG)^{59,60}:

$$\text{TTKG} = \frac{(\text{urine K}^+ \times \text{plasma osmolality})}{(\text{plasma K}^+ \times \text{urine osmolality})}$$

A TTKG higher than 8 indicates that aldosterone is present and that the collecting duct is responsive to it. A TTKG less than 5 in the presence of hyperkalemia indicates aldosterone deficiency or resistance. For the test to be accurate, the urine sodium concentration should be higher than 10 mEq/L and the urine osmolality should be greater than or equal to the plasma osmolality.⁶⁰

Therapy is aimed at reducing the plasma potassium concentration and includes volume expansion, dietary potassium restriction, and potassium-wasting diuretics. Acidosis will usually improve once the hyperkalemic impedance of ammonium production is removed. Any drugs that suppress or block aldosterone should be discontinued. Mineralocorticoid replacement with fludrocortisone will improve hyperkalemia and acidosis but is not appropriate with patients having hypertension or a history of heart failure. These patients are instead treated with a low potassium diet and a loop diuretic.⁵⁹

Gastrointestinal Tract Loss

The secretions of the large and small bowel are mostly alkaline and have a bicarbonate level higher than that in the plasma. Significant loss of lower GI secretions results in non-AG metabolic acidosis (see Box 104-4). Diarrhea is the most common cause of external loss of bicarbonate resulting in non-AG metabolic acidosis. Other causes include external drainage of pancreatic or biliary secretions as from fistulas, ileus secondary to intestinal obstruction, and villous adenomas. Drugs that increase GI bicarbonate loss include calcium chloride, magnesium sulfate, and cholestyramine. Significant bicarbonate loss also occurs in patients who abuse laxatives. Urinary diversions, such as ureterosigmoidostomy or ureteroileostomy, can cause non-AG metabolic acidosis due to absorption of chloride in exchange for bicarbonate across the bowel mucosa. Absorption of urinary ammonium in the sigmoid colon may also contribute to the development of acidosis as metabolism of the ammonium in the liver results in production of H⁺.

Metabolic acidosis and hypokalemia from GI losses increase renal synthesis and ammonia excretion, thereby providing a urinary buffer that increases urine pH despite increased net acid excretion.⁵⁵ The urine pH is higher than 5.5 instead of an acid urine pH as expected with systemic acidosis. Metabolic acidosis due to GI losses with a high urine pH can be differentiated from RTA by calculating the UAG.

Other Causes of Nonanion Gap Acidosis

See Box 104-4.

Expansion of the extracellular-fluid volume with non-bicarbonate-containing solutions, such as isotonic saline, causes metabolic acidosis by diluting the previous existing plasma bicarbonate (dilutional acidosis) and increasing the chloride load. This increased chloride load exceeds the renal capacity to generate equal amounts of HCO₃⁻.^{55,61}

Amino acids in total parenteral nutrition (TPN) are metabolized to HCl, which causes a transient non-AG metabolic acidosis. The decreased pH and decreased HCO₃⁻ stimulate renal reabsorption and generation of HCO₃⁻. Metabolic acidosis occurs if the acid load overrides the ability of the renal tubules to secrete H⁺ and generate ammonia for excretion in the urine, usually a short-lived process.⁵⁹

In prolonged hypercapnia, renal tubules compensate for a prolonged respiratory alkalosis by decreasing reclamation and generation of HCO₃⁻ (which takes 12-24 hours for full affect). If the respiratory alkalosis resolves rapidly, reclamation and generation of HCO₃⁻ will return to normal over 1 to 2 days. During this period a resolving non-AG metabolic acidosis occurs.

In toluene intoxication or the treatment phase of DKA, metabolic acid production is markedly increased. Although ammonium excretion is also increased, the rate of urinary excretion of the acid anions (hippurate and ketoanion, respectively) exceeds the excretion of ammonium. The anions not excreted with ammonium are excreted with sodium and potassium, causing sodium deficits and avid retention of filtered sodium and chloride. The lost bicarbonate is replaced by the retained chloride. In addition, administration of large volumes of isotonic saline for resuscitation in patients with DKA promotes diuresis with continued urinary loss of ketone bodies with sodium as the cation while delivering chloride to replace the lost ketoanions.^{55,59}

METABOLIC ALKALOSIS

Primary metabolic alkalosis is a subset of acid-base disorders characterized by an elevation in blood arterial pH, an increase in plasma HCO_3^- concentration, and a compensatory hypoventilation, resulting in a rise in Paco_2 . It is encountered relatively frequently in clinical practice as a result of loss of H^+ from the GI tract or urine. This disorder is also often accompanied by hypochloremia and hypokalemia.⁶²

In the presence of an increased serum bicarbonate concentration and low serum chloride (Cl^-) concentration, a patient may have either metabolic alkalosis or chronic respiratory acidosis. These disorders can be differentiated by the arterial pH, which is increased (>7.4) in metabolic alkalosis and decreased (<7.4) or normal in chronic respiratory acidosis. In primary metabolic alkalosis, the Paco_2 generally increases approximately 6 to 7.5 mm Hg for every 10 mEq/L increase in HCO_3^- above normal.

Metabolic alkalosis may occur as a simple disorder or, when associated with other disorders like respiratory acidosis, respiratory alkalosis, or metabolic acidosis, as a mixed disorder. An increase in the serum AG may be the only sign that metabolic acidosis coexists with metabolic alkalosis. Clinical examples of a mixed AG acidosis and metabolic alkalosis include patients with both DKA and vomiting, or lactic acidosis with vomiting.⁶³

Pathogenesis

Metabolic alkalosis can result from the loss of H^+ , transcellular H^+ shift, exogenous alkali administration, or contraction alkalosis. These factors may initiate systemic alkalosis, but under normal physiologic circumstances, alkalosis should never develop because the kidney is efficient at removing excess bicarbonate. However, in conditions where kidney function may be compromised, bicarbonate excretion may become impaired. Metabolic alkalosis is typically associated with impairment in kidney function, which is thought to maintain the alkalosis.

In effect, metabolic alkalosis results from impaired bicarbonate elimination from the kidney by its regular mechanisms. An increase in the plasma bicarbonate concentration results from either exogenous HCO_3^- administration or endogenous production. The kidneys will preserve rather than eliminate excess alkali and maintain alkalosis, if either of the following conditions is present: (1) Cl^- deficiency (or extracellular volume contraction), typically accompanied by potassium (K^+) depletion, which reduces effective renal perfusion and glomerular filtration and enhances bicarbonate reabsorption. Alkalosis in this setting can usually be corrected with saline infusion (saline-responsive) and K^+ repletion; or (2) hypokalemia due to a mineralocorticoid excess, which is not responsive to extracellular volume expansion.⁶⁴⁻⁶⁶ This cause of alkalosis is not generally responsive to saline (saline-resistant), and treatment considerations include medications or surgical resection.

The most common factor maintaining metabolic alkalosis is a reduction in extracellular volume (ECV), which leads to a reduction in GFR and a subsequent increase in sodium (Na^+) and HCO_3^- reabsorption. Hypokalemia can both cause and maintain the presence of metabolic alkalosis. Mineralocorticoid excess is another factor that

may trigger metabolic alkalosis, and in those cases, hypokalemia is the factor that maintains the alkalosis.

Metabolic alkalosis associated with a reduction in volume responds well to repletion with normal (0.9%) saline and is known as saline-responsive. However, mineralocorticoid or hypokalemia-induced alkalosis does not generally respond to volume administration and is said to be saline-unresponsive.

Symptoms of Metabolic Alkalosis

The symptoms of metabolic alkalosis vary according to the severity of the underlying acid-base abnormality. Presenting symptoms are often similar to those of hypocalcemia and may include mental confusion, decreased consciousness, seizures, muscle cramping, tetany, paresthesia, cardiac arrhythmias, and dyspnea. Common electrolyte abnormalities associated with alkalosis include hypokalemia and hypophosphatemia.⁶⁷

Extracellular Fluid Volume Contraction, Hypokalemia, and Secondary Hyperaldosteronism

See Box 104-6.

Gastrointestinal Causes

GI hydrogen loss can result from the removal of gastric secretions (vomiting or nasogastric suction) or loss of intestinal secretions (congenital chloridorrhea, villous adenoma, laxative abuse). Loss of H^+ leading to metabolic alkalosis most commonly occurs through the GI tract by vomiting or nasogastric (NG) suction. Gastric fluid contains a high concentration of hydrochloric acid (HCl) and a lower concentration of potassium chloride (KCl). Each mEq of H^+ secreted generates 1 mEq of HCO_3^- , which is then absorbed into the plasma. Under normal physiologic conditions, the increase in plasma HCO_3^- concentration is only transient, as acid secretion into the duodenum stimulates an equal amount of pancreatic HCO_3^- secretion, which neutralizes the acid. However, if gastric fluid is removed by vomiting or NG suction, there is no stimulus for HCO_3^- secretion, since the HCl does not reach the duodenum. The net result is an increase in plasma HCO_3^- and subsequent metabolic alkalosis.

Under normal circumstances, any excess HCO_3^- generated would be excreted by the kidney in the urine, thereby correcting alkalosis. However, vomiting or NG suction also lowers the extracellular fluid compartment and effective circulating volume (ECV). The reduction in ECV leads to decreased GFR and less HCO_3^- filtered, and also stimulates angiotensin and aldosterone production (secondary hyperaldosteronism), leading to increased Na^+ and HCO_3^- reabsorption by the proximal tubules.⁶⁸ Increased Na^+ reabsorption leads to increased HCO_3^- reabsorption, because of the increase in H^+ secretion as Na^+ is exchanged for H^+ by the Na-H^+ transporter at the proximal tubule. Secreted H^+ ions combine with filtered HCO_3^- , causing reabsorption. Aldosterone primarily acts at the distal tubule to increase H^+ and K^+ secretion, resulting in greater acid and K^+ excretion. These processes lead to a hypokalemic metabolic alkalosis. Notably, the near complete reabsorption of HCO_3^- in the setting of reduced ECV leads to the paradoxical finding of an acidic urine, despite the presence of extracellular alkalosis.

Renal Causes

See Box 104-6. Contraction alkalosis occurs when there is a relatively large loss of bodily fluid that does not contain HCO_3^- . In this setting, which is most commonly due to diuretics, the extracellular volume contracts around a fixed amount of HCO_3^- , resulting in a rise in HCO_3^- concentration.⁶⁹ Note that in this situation, total body bicarbonate remains the same despite the concentration change. Chronic diuretic use generates alkalosis by increasing salt delivery to the distal tubule, with resulting stimulation of H^+ and K^+ secretion. Loop and thiazide diuretics may effectively lower extracellular volume without

BOX 104-6 Causes of Metabolic Alkalosis**EXOGENOUS HCO_3^- LOADS**

Acute alkali administration
Milk-alkali syndrome

EFFECTIVE EXTRACELLULAR VOLUME CONTRACTION, NORMOTENSION, HYPOKALEMIA, AND SECONDARY HYPERRENINEMIC HYPERALDOSTERONISM**Gastrointestinal Origin**

Vomiting
Gastric aspiration
Congenital chloridorrhea
Villous adenoma
Combined administration of sodium polystyrene sulfonate (Kayexalate) and aluminum hydroxide)

Renal Origin

Diuretics (especially thiazides and loop diuretics)
Acute
Chronic
Edematous states
Posthypercapnic state
Hypercalcemia-hypoparathyroidism
Recovery from lactic acidosis or ketoacidosis
Nonreabsorbable anions such as penicillin, carbenicillin
 Mg^{++} deficiency
 K^+ depletion
Bartter's syndrome (loss-of-function mutation of Cl^- transport in thick ascending limb of Henle's loop)
Gitelman's syndrome (loss-of-function mutation in Na^+/Cl^- cotransporter)
Carbohydrate refeeding after starvation

EXTRACELLULAR VOLUME EXPANSION, HYPERTENSION, K^+ DEFICIENCY, AND HYPERMINERALOCORTICOIDISM**Associated with High Renin**

Renal artery stenosis
Accelerated hypertension
Renin-secreting tumor
Estrogen therapy

Associated with Low Renin

Primary aldosteronism
Adenoma
Hyperplasia
Carcinoma
Glucocorticoid suppressible

Adrenal Enzymatic Defects

11 β -Hydroxylase deficiency
17 α -Hydroxylase deficiency

Cushing's Syndrome or Disease

Ectopic corticotropin
Adrenal carcinoma
Adrenal adenoma
Primary pituitary

Other

Licorice
Carbenoxolone
Chewer's tobacco
Lydia Pinkham tablets

GAIN-OF-FUNCTION MUTATION OF ENAC WITH EXTRACELLULAR FLUID VOLUME EXPANSION, HYPERTENSION, K^+ DEFICIENCY, AND HYPORENINEMIC HYPERALDOSTERONISM

Liddle's syndrome

Bartter's syndrome is a disorder characterized by impaired Cl^- absorption, which then leads to salt wasting, volume contraction, and activation of the renin-angiotensin system. Five types of Bartter's syndromes have been discovered with four inherited in an autosomal recessive manner.⁷⁰ Bartter's occurs more often in children, and the most common disorder results from a mutation of the gene encoding the bumetanide-sensitive $\text{Na}^+2\text{Cl}^-/\text{K}^+$ cotransporter (*NKCC2* or *BSC1*) on the apical membrane; however, other mutations have been found involving different transporter channels. Elevated prostaglandin levels have been reported with this disorder, likely from volume contraction, hypokalemia, or high angiotensin II levels.⁷¹ These defects lead to contraction of the extracellular volume, hyperreninemic hyperaldosteronism, increased Na^+ delivery to the distal nephron, subsequent with K^+ wasting and alkalosis. The differential diagnosis of Bartter's syndrome includes other causes of extravascular volume contraction, such as emesis, diuretic use, or laxative abuse. Inhibition of the renin-angiotensin-aldosterone system or the prostaglandin-kinin system has been the goal of current treatment, with medications like spironolactone, prostaglandin inhibitors, propranolol, and ACE inhibitors, but the utility of such agents has been limited. K^+ and magnesium (Mg^{++}) repletion are also an important part of therapy.

Gitelman's syndrome, like Bartter's syndrome, is autosomal recessive and may manifest with hypokalemia, volume depletion with secondary hyperreninemic hyperaldosteronism, normotension, or even low blood pressure. Gitelman's differs from Bartter's syndrome in that it occurs more often in adulthood and is characterized by hypocalciuria, hypermagnesuria, hypomagnesemia, similar to the effect of thiazide diuretics. Gitelman's syndrome occurs as the result of missense mutations in the gene *SLC12A3*, responsible for encoding the thiazide-sensitive distal convoluted tubule Na^+/Cl^- cotransporter (*NCCT*).^{70,72} Diminished activity of the Na^+/Cl^- cotransporter leads to calcium reabsorption and hypocalciuria. Reported symptoms include fatigue, cramping, nocturia, and salt craving. Treatment considerations include a sodium and potassium avid diet, with magnesium supplementation. ACE inhibitors have also been advocated for this disorder.

Hypokalemia is a frequent finding in patients with metabolic alkalosis. It is an important contributor to both the development and maintenance of the alkalosis. The underlying causes of metabolic alkalosis (e.g., vomiting, mineralocorticoid excess, diuretic use) induce both H^+ and K^+ loss and thus cause hypokalemia. However, hypokalemia itself can be a primary cause of metabolic alkalosis. Hypokalemia causes metabolic alkalosis by several mechanisms. Initially, hypokalemia causes a transcellular shift, where K^+ leaves and H^+ enters cells, thereby increasing extracellular pH. Hypokalemia also causes a transcellular shift in proximal tubule cells, resulting in intracellular acidosis and ammonium (NH_4^+) production and excretion. Finally, H^+ secretion increases in the proximal and distal tubules with hypokalemia, leading to further HCO_3^- reabsorption. The net effect is an increase in acid excretion.

Magnesium deficiency promotes distal H^+ secretion and acidification of urine by stimulating renin and aldosterone secretion, which result in hypokalemic alkalosis.

Posthypercapnic alkalosis is frequently overlooked as a complication of mechanical ventilation. The normal physiologic response to respiratory acidosis is a compensatory increase in HCO_3^- reabsorption by the kidney, which increases plasma HCO_3^- . Use of mechanical ventilation for this disorder may rapidly lower the Paco_2 ; however, plasma HCO_3^- will remain elevated, resulting in development of metabolic alkalosis.⁷³ The duration of alkalosis in this setting, however, is unclear. Chronic respiratory acidosis is thought to be associated with urine Cl^- loss, leading to hypovolemia and hypochloremia. Repletion of Cl^- and restoration of volume (usually with 0.9% saline) typically corrects this disorder. In posthypercapnic alkalosis, the rapid fall in Paco_2 may also lead to an acute increase in cerebral intracellular pH.^{74,75} Complications including neurologic abnormalities and death have been reported with this effect, and as a result most experts have recommended a gradual reduction in Paco_2 in patients with chronic hypercapnia.

concomitant loss of HCO_3^- , resulting in a net increase in serum HCO_3^- and contraction alkalosis. Alkalosis is then maintained by one of several mechanisms, such as reduction of the extracellular volume, hypokalemia, secondary hyperaldosteronism, or continued effect of the diuretic. Repletion of the extravascular fluid with 0.9% saline will typically improve the alkalosis in this setting.

Extracellular Volume Expansion and Mineralocorticoid Excess

The common causes of metabolic alkalosis maintain the alkalosis by hypovolemia-induced secondary hyperaldosteronism, which leads to increased acid excretion and hypokalemia. Disorders of mineralocorticoid excess, such as Conn's syndrome, Cushing's syndrome, and excess corticosteroid administration, produce a state of hyperaldosteronism, which also leads to hypokalemia and metabolic alkalosis (see Box 104-6).⁷⁶ In these disorders, the extracellular volume increases, and hypertension may result. In these patients, metabolic alkalosis is perpetuated by the effects of hypokalemia, rather than hypovolemia, which leads to increased ammonium production, H^+ secretion, and HCO_3^- reabsorption.

Patients with secondary hyperaldosteronism from reduced arterial blood volume, as observed in conditions like congestive heart failure and cirrhosis, do not usually develop metabolic alkalosis unless treated with diuretics. In these patients, distal sodium delivery is reduced due to the expanded reabsorption of sodium in the proximal tubule. Without high distal sodium delivery, the effect of aldosterone on sodium reabsorption and K^+ and H^+ excretion is diminished. High distal sodium delivery and elevated mineralocorticoid levels may occur together with primary mineralocorticoid secretory disorders or conditions like Liddle's syndrome, which manifest as primary hyperaldosteronism.

Alkali Administration

In normal individuals and under most circumstances, chronic administration of sodium bicarbonate will only slightly alter the systemic pH due to the relatively rapid renal excretion of excess alkali and minimal rise in plasma bicarbonate levels. Alkalosis may occur, however, if large amounts of sodium bicarbonate or any substance metabolized to bicarbonate (like the sodium salts of citrate, acetate, or lactate) are administered more rapidly, such as in the use of sodium bicarbonate to treat lactic acidosis or administration of sodium citrate in the form of massive blood transfusions. Notably, other factors contributing to alkalosis, like hypovolemia, hypokalemia, or renal impairment, will often be present.

Citrate, the anticoagulant used in blood products, is being increasingly used as an anticoagulant for CRRT. Since 1 mmol of trisodium citrate is metabolized to 3 mmol of sodium bicarbonate by the liver, metabolic alkalosis can occur from increased citrate. Metabolic alkalosis from citrate delivery in CRRT can be easily managed by decreasing the citrate infusion rate, increasing citrate and bicarbonate losses by increasing the dialysate/replacement fluid flow rate, or reducing the bicarbonate concentration in the dialysate/replacement fluid.⁷⁷

The milk-alkali syndrome results from the ingestion of large quantities of calcium carbonate, along with vitamin D, and is characterized by hypercalcemia and metabolic alkalosis. Hypercalcemia causes impaired renal function through renal vasoconstriction, renal salt wasting, and volume depletion; the latter is exacerbated by vomiting. Hypovolemia and decreased renal function are responsible for maintaining systemic alkalosis. Alkalosis also increases renal reabsorption of calcium, thereby worsening hypercalcemia.

Diagnosis of Metabolic Alkalosis

When a diagnosis of metabolic alkalosis is established, the etiology can usually be determined from the patient's history. Otherwise, alkalosis is generally due to one of three common causes: (1) emesis; (2) diuretic use; or (3) mineralocorticoid excess. Measurement of the urine chloride concentration usually helps to differentiate among these conditions. When metabolic alkalosis is associated with a reduction in ECV, Na^+ and Cl^- reabsorption are enhanced to replenish extracellular volume. In these setting, urinary Cl^- concentration should be very low, typically less than 25 mEq/L. See Table 104-3 and Figure 104-3.

TABLE 104-3 Diagnosis of Metabolic Alkalosis

| SALINE-RESPONSIVE ALKALOSIS | SALINE-UNRESPONSIVE ALKALOSIS |
|---|-----------------------------------|
| LOW URINARY $[Cl^-]$ | HIGH OR NORMAL URINARY $[Cl^-]$ |
| Normotensive | Hypertensive |
| Vomiting, nasogastric aspiration | Primary aldosteronism |
| Diuretics | Cushing's syndrome |
| Post hypercapnia | Renal artery stenosis |
| Bicarbonate therapy of organic acidosis | Renal failure plus alkali therapy |
| K^+ deficiency | Normotensive |
| Hypertensive | Mg^{++} deficiency |
| Liddle's syndrome | Severe K^+ deficiency |
| | Bartter's syndrome |
| | Gitelman's syndrome |
| | Diuretics |

Urinary Na^+ concentration is not a reliable measure of extracellular volume status in the setting of metabolic alkalosis. If all of the filtered HCO_3^- cannot be reabsorbed, then some will be excreted with Na^+ , and urinary Na^+ may be high. Thus, the volume status may incorrectly appear to be euvolemic or hypervolemic.

If the urinary Cl^- is low, indicating a hypovolemic state, then 0.9% NaCl and water administration to replenish ECV should stop aldosterone production and lead to appropriate excretion of excess HCO_3^- , improvement of hypokalemia, and correction of metabolic alkalosis. These causes of metabolic alkalosis are considered saline-responsive.

Mineralocorticoid excess, by contrast, is associated with increased extracellular volume and occasionally hypertension. Urinary Cl^- will be high, typically when higher than 40 mEq/L. Saline administration in such patients would further expand extracellular volume and worsen hypertension. Alkalosis, which in this setting is primarily due to hypokalemia, would not be corrected. These causes of metabolic alkalosis are considered saline-resistant.

The causes of saline-resistant metabolic alkalosis can be further distinguished according to whether or not hypertension is present. Hypertension tends to occur in mineralocorticoid excess states, while Bartter's and Gitelman's syndromes and exogenous alkali load are associated with normal blood pressure.

Treatment

The goals of the treatment of metabolic alkalosis are to reverse the cause of bicarbonate generation and address those factors that restrict secretion of excess bicarbonate from the kidneys. Diagnostic evaluation of metabolic alkalosis can be aided by measurement of the urine chloride concentration, systemic blood pressure, and the estimated volume status of the patient. Other clinical findings that may assist with the evaluation include vomiting, NG suctioning, or alkali or diuretic use. Reversal of the underlying cause of alkalosis may include controlling emesis, addressing the removal of gastric secretions or lowering the gastric acid content removed, and discontinuing loop or thiazide diuretics. Medications that reduce gastric acid secretion, such as proton pump inhibitors or histamine-2 receptor blockers, have been administered to improve alkalosis in patients with persistent vomiting.^{78,79} Any exogenous source of alkali, like bicarbonate, or substances that metabolize to bicarbonate (like citrate or lactate) should be discontinued as possible. Hypokalemia is common in metabolic alkalosis and should be corrected.

A reduction in renal excretion of excess bicarbonate is required to maintain metabolic alkalosis, so addressing factors that impair renal function and subsequent bicarbonate secretion will help correct

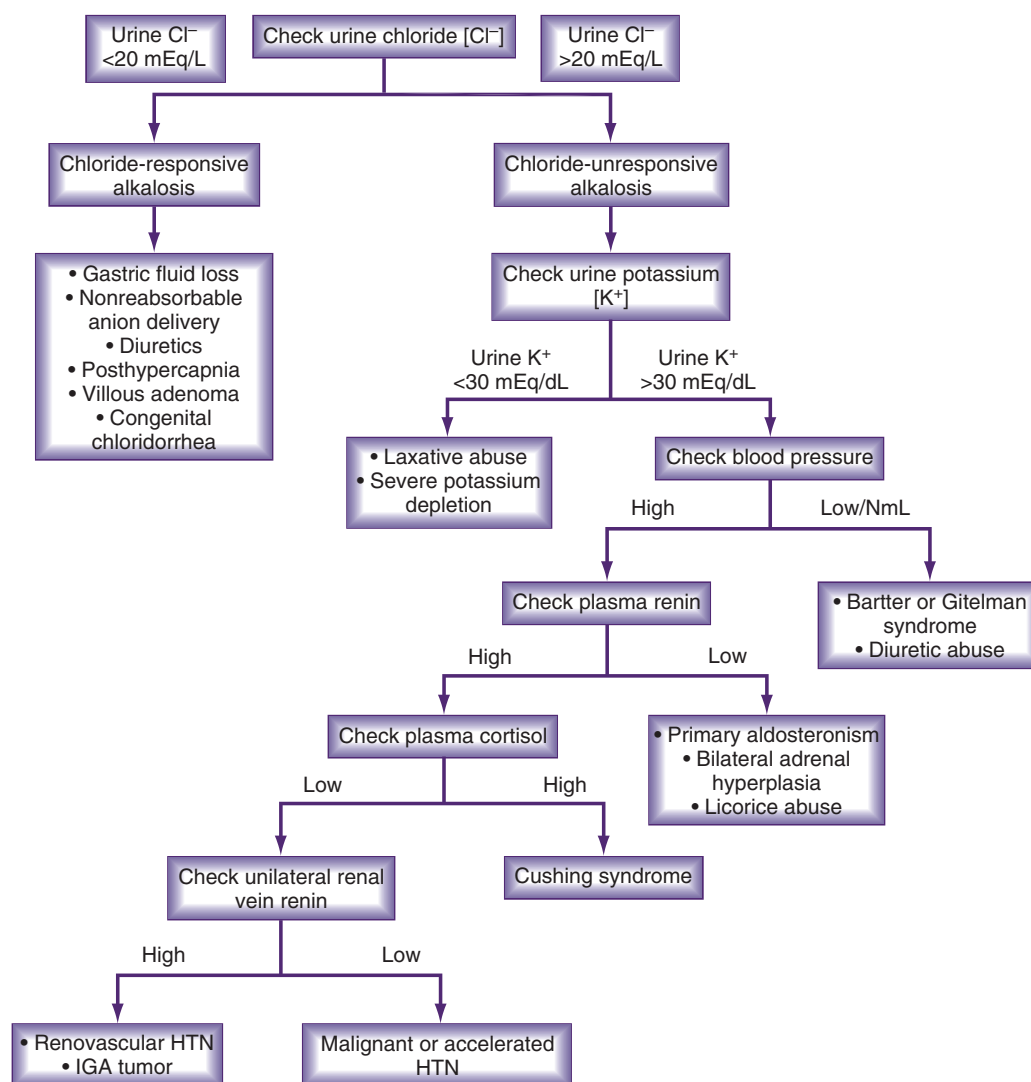


FIGURE 104-3 ■ Workup of metabolic alkalosis. (Data from DuBose TD Jr. Acid-base disorders. In: Brenner BM, editor. Brenner and Rector's the kidney. 8th ed. Philadelphia: Saunders; 2008, p. 513.)

alkalosis. Such conditions include reduced renal function, reduced arterial blood flow, K^+ depletion/hypokalemia, and Cl^- depletion/hypochloremia.

Treatment of metabolic alkalosis can be further divided on the basis of whether it responds to intravascular volume expansion. Patients with volume contraction as the cause of metabolic alkalosis are generally saline-responsive. On the other hand, patients with metabolic alkalosis due to mineralocorticoid excess, hypokalemia, or renal insufficiency are typically saline-resistant.

The treatment of metabolic alkalosis associated with volume contraction consists of volume expansion with 0.9% saline. Reexpansion of intravascular volume and correction of chloride deficiency lower proximal tubular bicarbonate reabsorption, enhance urine bicarbonate excretion, and lower the plasma bicarbonate concentration. Hypokalemia, if present, should be treated with potassium chloride. Metabolic alkalosis due to gastric acid loss, diuretics, and chloride depletion and the posthypercapnic state typically respond to 0.9% saline administration.

Saline-resistant metabolic alkalosis does not improve following administration of 0.9% saline. These patients are generally not volume depleted or chloride deficient as shown by high concentrations of

urinary chloride. In patients with excessive mineralocorticoid production, like in Conn's syndrome, use of spironolactone to inhibit mineralocorticoid activity may be beneficial. Corticosteroid therapy may need to be discontinued, and ACE inhibitors may be helpful due to their potassium-sparing effect and control of hypertension. Surgical or chemical ablation of the adrenal glands may be necessary for definitive management.

Severe hypokalemia increases tubular H^+ excretion, ammonia production, and chloride wasting. Potassium repletion corrects this defect. As potassium wasting is a central finding in mineralocorticoid excess, Bartter's syndrome, and Liddle's syndrome, potassium-sparing diuretics like amiloride or triamterene are used in these patients.

Metabolic alkalosis may be observed in patients with edematous states, including heart failure, nephrotic syndrome, and cirrhosis. This often results from the use of diuretics; however, treatment with 0.9% saline is not usually helpful in these patients. Infusion of saline in this setting will increase fluid retention and edema, and the alkalosis will not be corrected as avid Na reabsorption will reduce excretion of any excess bicarbonate. These patients are often K^+ deficient, and potassium chloride may improve the alkalosis by increasing the serum K^+ concentration. Use of potassium-sparing diuretics like amiloride and/

or aldosterone antagonists like spironolactone for these patients may be indicated.

Renal replacement therapy may be considered to correct metabolic alkalosis in situations where patients fail to respond to conventional therapies like volume expansion or K^+ repletion.⁸⁰ In such instances, dialysis with a lower bicarbonate bath concentration can quickly improve the alkalosis; however, even use of a standard bicarbonate bath concentration can be effective as the patient's serum bicarbonate level is often higher than that of the standard bath concentration. CRRT can also be used to treat metabolic alkalosis, but attention to the CRRT fluid buffer composition is warranted since bases such as bicarbonate, citrate, or lactate may increase the serum bicarbonate concentration at high effluent/ultrafiltration rates.⁸¹

Hydrochloric acid (HCl) for the treatment of metabolic alkalosis is usually reserved for patients with severe symptoms who do not respond to conventional therapy with intravenous fluids and for correction of electrolyte derangement. The arterial pH is usually higher than 7.55, and there may be evidence of seizures, altered sensorium, or cardiovascular complications. Dilute HCl (0.1 N) should be given through a central intravenous catheter, and careful vigilance of catheter integrity and surrounding tissue should be maintained to avoid complications of acid extravasation, which may cause tissue necrosis.^{82,83} Hemolysis can also complicate therapy with HCl. Titration of HCl can be challenging, and the goal of therapy is to lower the arterial pH to approximately 7.5, rather than to normalize the value.

DIAGNOSIS OF ACID-BASE DISORDERS

A systematic approach is necessary for determining which acid-base disorder or disorders are present.⁸⁴ Accurate interpretation of acid-base balance requires simultaneous measurements of arterial pH and plasma electrolytes. The arterial blood gas (ABG) test directly measures arterial pH and P_{aCO_2} . The bicarbonate concentration from the ABG test is calculated using the Henderson-Hasselbalch equation, while the bicarbonate concentration on venous chemistry panel is measured directly as "total CO_2 " with an ion-selective electrode. The calculated value for HCO_3^- reported with the ABG test should be within 2 or 3 mEq/L of the measured HCO_3^- concentration obtained on the electrolyte panel. A discrepancy in the values suggests either the samples were not obtained simultaneously or that a laboratory error has occurred. The cause of acid-base disturbances is determined by examining the pH, P_{aCO_2} , and plasma electrolytes (primarily plasma bicarbonate) in the context of a given clinical situation. Analysis involves identification of the likely dominant acid-base disorder, followed by an assessment of the compensatory response. A stepwise approach to the diagnosis of acid-base disorders follows and is summarized in Box 104-7.^{5,6}

The initial screening for an acid-base disorder entails obtaining a detailed history and performing a physical examination. The history and physical examination usually strongly suggest the acid-base disorder that is present. A history of diuretics or vomiting suggests metabolic alkalosis. A history of diarrhea, alcoholism, or diabetes suggests metabolic acidosis. Stigmata of liver disease on the physical examination may signify the presence of respiratory alkalosis, while findings of volume contraction suggest metabolic alkalosis. Kussmaul respiration is often associated with DKA and severe metabolic acidosis. Medications that can affect acid-base balance (e.g., laxatives, diuretics, topiramate, or metformin) should be considered as well as signs of intoxication that may be associated with acid-base disturbances.

The first step in acid-base analysis is to determine if the patient has acidemia or alkalemia by examining the arterial pH. If acidemia is present then an acidosis must be present; similarly, if alkalemia is present, then alkalosis must be present. The second step is to determine whether the deviation in the pH (acidemia or alkalemia) is due to a primary respiratory or metabolic derangement by examining the P_{aCO_2} and plasma bicarbonate concentration. In acidemia, a low plasma bicarbonate concentration denotes primary metabolic acidosis, while an elevated P_{aCO_2} points to primary respiratory acidosis. Likewise, in

BOX 104-7

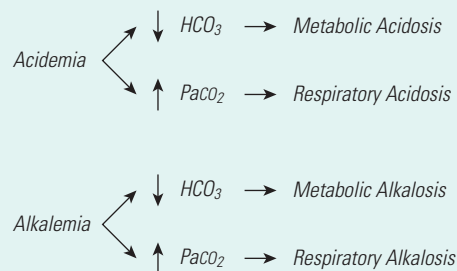
Stepwise Approach to Diagnosing Acid-Base Disorders

INITIAL SCREENING

Consider the clinical setting by obtaining history and physical examination. Obtain arterial blood gases (ABG) and electrolytes simultaneously. Compare bicarbonate on ABG to venous electrolytes to ensure the calculated bicarbonate on ABG is within 2-3 mEq/L of measured bicarbonate on electrolyte panel.

STEPS

1. Examine pH to determine if the patient has acidemia or alkalemia.
2. Look at PCO_2 , HCO_3^- to determine if the primary process is metabolic or respiratory.



3. If a primary respiratory disorder is present in step 2, determine if it is acute or chronic.
4. Calculate the serum anion gap.
 - a. Anion gap = $Na^+ - (Cl^- + HCO_3^-)$
5. If a metabolic disturbance is present from step 2 or high anion gap from step 4, determine if the respiratory system is adequately compensating.
 - a. Expected P_{aCO_2} in acidosis: $P_{aCO_2} = (1.5 \times HCO_3^-) + 8 \pm 2$
 - b. Expected P_{aCO_2} in alkalosis: $P_{aCO_2} = 40 + 0.7 \times (HCO_3^-_{meas} - HCO_3^-_{normal}) \pm 5$
6. If anion gap is elevated, then calculate the Delta Delta Ratio (Δ/Δ) to assess for other simultaneous disorders.
 - a. Δ/Δ compares the change in the anion gap to the change in bicarbonate.
 - b. If ratio is between 1 and 2, then pure elevated anion gap acidosis is present.
 - c. If <1 , then there is a simultaneous normal anion gap acidosis is present.
 - d. If >2 , then there is a simultaneous metabolic alkalosis present or a compensated chronic respiratory acidosis.

alkalemia, an elevated plasma bicarbonate concentration signifies primary metabolic alkalosis, whereas a low P_{aCO_2} is consistent with primary respiratory alkalosis. If a primary respiratory disturbance is present from step 2, the third step is to assess if it is acute or chronic by comparing pH and P_{aCO_2} by the formulas in Table 104-1.⁶ If no primary respiratory disturbance is present, step 3 is skipped.

The fourth step is to calculate the serum AG. If primary metabolic acidosis is present from step 2, the serum AG is used to diagnose high-AG metabolic acidosis. The AG should be adjusted for hypoalbuminemia. Even if metabolic acidosis is not present or the pH and P_{aCO_2} are within normal range, the serum AG should always be calculated since a mixed disorder can exist with a normal pH, P_{aCO_2} , and plasma bicarbonate concentration, which is seen with high-AG metabolic acidosis and concurrent metabolic alkalosis. If a high AG is present, ancillary tests to consider for differentiating the causes include plasma and urine ketones for ketoacidosis, plasma creatinine for renal failure, plasma L-lactate for lactic acidosis, plasma osmolality to calculate an osmolal gap and assess for toxic alcohol ingestions, and urine microscopy for crystals if ethylene glycol is suspected. If the primary metabolic acidosis is non-AG metabolic acidosis (plasma bicarbonate concentration is low without elevated AG), the UAG can help differentiate GI from renal causes.^{85,86}

If a metabolic disturbance is present from step 2 or 4, the fifth step is to determine if the respiratory system is adequately compensating. In metabolic acidosis, Winters' formula should be used to calculate the

expected Paco_2 for the degree of acidosis present. If the measured Paco_2 is higher than the calculated expected Paco_2 , then concomitant respiratory acidosis is present. If the measured Paco_2 is lower than the expected Paco_2 , then respiratory alkalosis is also present. In metabolic alkalosis, the normal respiratory response is less predictable. However, in general, the Paco_2 should be between 40 and 50 mm Hg for appropriate compensation for metabolic alkalosis.⁶

If high-AG metabolic acidosis is present from step 4, the last step is to determine the existence of any concurrent metabolic disturbances (such as non-AG metabolic acidosis or metabolic alkalosis) by comparing the degree of change in the serum AG with the change in the plasma bicarbonate level. This is done to assess the extent of contribution of the AG-producing process to the actual acidosis. This measurement is called Delta Delta Ratio⁸⁴:

$$\text{Delta Delta Ratio} = \Delta\text{AG} / \Delta\text{HCO}_3^- = (\text{AG} - 12) / (24 - \text{HCO}_3^-)$$

If the metabolic disturbance is solely due to an elevated AG, the HCO_3^- should decrease by the same amount that the AG increases. A Delta Delta Ratio between 1 and 2 usually indicates uncomplicated

high-AG metabolic acidosis. A Delta Delta Ratio higher than 2 usually indicates a lesser fall in HCO_3^- than would be expected given the change in the AG and the presence of concurrent metabolic alkalosis. An example of combined AG metabolic acidosis and metabolic alkalosis is volume contraction from vomiting in the setting of DKA. A Delta Delta Ratio less than 1 indicates a greater fall in HCO_3^- levels than would be expected given the increase in the AG and therefore the presence of simultaneous non-AG metabolic acidosis. This might occur when lactic acidosis is superimposed on severe diarrhea. In this situation, the additional fall in HCO_3^- levels is due to further buffering of an acid that does not contribute to the AG.⁸⁴

SUMMARY

Acid-base disorders are common in the ICU and need to be anticipated in all critically ill patients. A clinician must be able to accurately monitor the acid-base status in order to promptly recognize derangements and implement appropriate interventions to prevent life-threatening complications as a result of the disturbance.

KEY POINTS

1. Metabolic and mixed acid-base disorders are common in ICU patients and require early detection with a search for the underlying cause and initiation of appropriate treatment to prevent potentially fatal complications.
2. Metabolic acidosis can be categorized as high or normal anion gap (AG) acidosis. High AG acidosis is frequently due to lactic acidosis, ketoacidosis, toxic ingestions, or renal failure; non-AG acidosis is mostly due to gastrointestinal (GI) or renal bicarbonate loss. Diagnostic tests for differentiating causes of high AG acidosis include plasma and urine ketones, plasma creatinine, plasma L-lactate, plasma osmolality and osmolal gap, and urine microscopy for crystals. The urine AG can help differentiate causes of non-AG acidosis.
3. The serum AG should always be calculated in the ICU since the presence of a significantly elevated serum AG represents metabolic acidosis, irrespective of pH or plasma bicarbonate. The serum AG must be adjusted for hypoalbuminemia.
4. Compensation for primary metabolic acidosis is determined by Winters' formula. The delta-delta gap is calculated to identify a concomitant metabolic disorder.
5. Treatment for metabolic acidosis involves treating the underlying cause. Alkali therapy is often given for non-AG acidosis but is rarely indicated in high AG metabolic acidosis unless the arterial pH is less than 7.15 or for salicylate intoxication.
6. Metabolic alkalosis may be initiated by acid loss or bicarbonate gain and maintained by renal mechanisms associated with bicarbonate resorption, including extracellular fluid volume contraction, chloride depletion, hypokalemia, and elevated mineralocorticoid activity.
7. Metabolic alkalosis is most often caused by volume depletion with upper GI loss of hydrogen chloride (recurrent vomiting or nasogastric suction) or by diuretic use with renal loss of H^+ .
8. The evaluation of metabolic alkalosis begins with measurement of the urine chloride and estimation of the extracellular volume status. Metabolic alkalosis involving the loss or excess secretion of chloride is termed *chloride-responsive*.
9. Compensation for primary metabolic alkalosis is estimated by increase in $\text{Paco}_2 = 0.75 \times \Delta \text{HCO}_3^-$.
10. Treatment for metabolic alkalosis involves treating the underlying cause by administering intravenous 0.9% saline in chloride-responsive metabolic alkalosis and correcting mineralocorticoid excess and primary hyperaldosteronism in patients with a chloride-resistant metabolic alkalosis.

ANNOTATED REFERENCES

- Bonnet F, Bonarek M, Morlat P, et al. Risk factors for lactic acidosis in HIV-infected patients treated with nucleoside reverse-transcriptase inhibitors: a case-control study. *Clin Infect Dis* 2003;36:1324–1328.
- The problem of NRTI-induced lactic acid acidosis in patients with HIV is evaluated by a case-controlled study to determine risk factors. Two factors were identified to be associated with an increased risk of lactic acidosis: (1) creatinine clearance less than 70 mL/min and (2) a low CD4⁺ T-lymphocyte count before inception of therapy. Interestingly, the total cumulative exposure to NRTIs was not associated with an increased risk of lactic acidosis. Therefore, creatinine clearance and CD4⁺ T-lymphocyte count should be monitored in patients infected with HIV and could lead to modifications in antiretroviral therapy to diminish the risk of occurrence of lactic acidosis.
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- Ogedegbe AE, Thomas DL, Diehl AM. Hyperlactatemia syndromes associated with HIV therapy. *Lancet Infect Dis* 2003;3:329–337.
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- Mizock BA, Belyaev S, Mecher C. Unexplained metabolic acidosis in critically ill patients: the role of pyroglutamic acid. *Intensive Care Med* 2004;30:502–505.

This paper identifies an important and recently realized cause of high-AG acidosis in the critical care setting. This is an unsuspecting yet very common setting in which metabolic acidosis due to accumulation of this compound may develop; hence, this information is critical to the clinician when formulating diagnostic and therapeutic plans for high-AG acidosis.

Stacpoole PW, Nagaraja NJ, Hutson AD. Efficacy of dichloroacetate as a lactate-lowering drug. *J Clin Pharmacol* 2003;43:683–691.

■ References for this chapter can be found at expertconsult.com.

This paper by the same senior author who performed the first controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults demonstrates that the maximum lactate-lowering effect of dichloroacetate is dose dependent but independent of time after administration. The study suggests that dichloroacetate could be effective in reducing lactate levels in patients with mild hyperlactatemia. This may be an important observation for ongoing investigation in low-level hyperlactatemia as it applies to a number of clinical circumstances.

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Water is the body's most abundant component. Without ingesting sufficient fresh water, humans can survive for just a few days. Ingested water, plus water produced endogenously, must be appropriately excreted to maintain homeostasis. In the human body, water has many functions: intracellular, intravascular, and extracellular carrier of essential substances; body coolant; lubricant; reactant and product in metabolic reactions; and shock absorber (e.g., CSF surrounding the brain). In critically ill patients, water metabolism and balance present special challenges. Patients are admitted to the intensive care unit (ICU) because of disordered water homeostasis, while it is disturbed by ICU treatments.

Water accounts for 50%-67% of an average person's weight. Because fat has a lower percentage of water and women tend to have more fat, their proportion of water is lower (52%-55%) than that of men (60%). Water percentage is lower in the elderly and obese. A 70-kg man has ~40 L of water: ~25 to 27 L intracellularly, ~7 L extracellularly, and ~4 L intravascularly. Liquid water is the body's most common molecule, although some water is found in hydrated compounds. Hypovolemia and hypervolemia significantly threaten life. Therefore, the body defends fluid volume and osmolarity within very narrow ranges.

■ WATER INGESTION AND PRODUCTION

Water is ingested via the gastrointestinal tract or infused via venous (or interosseous) routes. Water intake is regulated by thirst, although normally humans sufficiently self-regulate their intake so that thirst is only occasionally activated. Thirst is also activated by salty food, hot weather, and exercise. The latter two cause sweating and increased respiratory water loss. Adequate water intake is ~3 L/day for men and ~2.2 L/day for women.

Thirst: Thirst is vital for defending against hypovolemia. Hypovolemic thirst is triggered when body water levels decrease to ~2% to 3%. Hypertonic thirst occurs when osmolality increases to >290 mOsm/kg. Hypotension and hemorrhage also stimulate thirst. Peripheral and central mechanisms detect and react to these physiologic perturbations, leading organisms to seek and ingest appropriate fluids and fluid volumes. Drinking stimulates oral and pharyngeal receptors, thereby providing hypothalamic input to end the thirst sensation. Thirst ends even before plasma tonicity is reduced, likely preventing water over-ingestion. Thirst sensation is so powerful that normal subjects do not become hypernatremic if they have access to water. The inability to find, detect, react, request, or drink water adequately can cause severe illness and even death. The inability to self-regulate water intake—for example, during anesthesia and critical illness—makes patients totally dependent on caregivers to prevent and treat water disorders.

In the elderly, decreased kidney function, physical and cognitive problems, blunted thirst, and polypharmacy increase dehydration risk. There is also reduced renal sodium conservation (altered renal tubular function, greater atrial natriuretic peptide (ANP) secretion, lower renin-angiotensin-aldosterone secretion), decreased renal water excretion (lower renal blood flow, glomerular filtration rate, and distal renal tubular diluting capacity; greater renal passive water reabsorption and ADH secretion), and reduced solute delivery caused by poor nutrition, limiting free water excretion. A water-loss dehydration prevalence of up to 30% is observed in the elderly with concomitant morbidity.¹ A positron emission tomography study revealed

age-associated changes in central nervous system (CNS) satiation patterns in response to hyperosmolarity, which were associated with inadequate hydration.² Paradoxically, elderly patients with worsening heart failure have increased thirst.³

Metabolic Water Production: Water is the principal end product of nutrient oxidation (Table 105-1). Although more water molecules are produced per mole of fat than per mole of glucose (129 vs. 36) per kilocalorie, overall, aerobically oxidized carbohydrates contribute to ~15% more water molecules than lipids.⁴ An increased metabolic rate increases metabolic water production.

Water Loss

Water is lost through many routes but mainly through the kidneys. Urine volume and composition depend on hydration status and the osmole load. Fecal losses are generally small, while sweating can cause large losses.

Renal Function: Renal function, the major mechanism defending against disordered water balance, protects blood osmolarity within a narrow range by altering urine osmolarity over a wide range (50-1200 mOsm). Concentrated urine is formed by creating an osmotic gradient that progressively increases from the corticomedullary border to the tip of the inner medulla.⁵ When the body must rid itself of excess water, urine can be diluted to as low as 50 mOsm.

Aging reduces the maximum urine-concentrating ability. Compared with younger individuals, those aged 60 to 79 years had an ~20% reduction in maximum urine osmolality, an ~50% decrease in the ability to conserve solute, and a 100% increase in minimum urine flow rate.⁶

Insensible Losses: Insensible losses include transepidermal diffusion and evaporation of solute-free water plus evaporative water loss from the respiratory tract. Total insensible losses, ~800 mL/day in unstressed adults, are equally divided between skin and respiratory tract losses. Activity increases respiratory water losses so that active adults can lose up to 50 mL/h. Age reduces transepidermal water losses.⁷ In febrile patients, insensible losses can increase by four- to six-fold.⁸

Respiratory water losses are affected by many factors (see Table 105-1). In normal subjects, mouth breathing resulted in 42% greater water loss compared with nose breathing.⁹ Cold exposure increases the need to humidify and warm inspired gases, thus increasing water losses. Using heat-and-moisture-retaining face masks during sleep reduced these losses.¹⁰ In critically ill patients, rapid spontaneous respiratory rates increase respiratory water losses, while endotracheal tubes bypass the natural warming and humidifying mechanisms, requiring inspiratory gases to be artificially humidified and warmed.

Sweating: Sweating is mainly a mechanism of thermoregulation, although it also occurs in response to psychologic stress (see Table 105-1). Sweating involves the secretion of water-rich liquid by the eccrine glands located throughout the body surface and secretion of protein-, lipid-, and steroid-containing sweat by the apocrine glands found in the axilla, mammary, perineal, and genital areas. Thermoregulatory sweating mainly involves eccrine secretion occurring in response to intrinsic (fever, exercise) and extrinsic stimuli (elevated environmental temperatures). Maximum adult sweat rates can be 2 to 4 L/h during intense exercise.

TABLE 105-1 Water and the Human Body**WATER BALANCE**

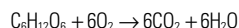
Water balance = (water intake + metabolic water production) – water loss
 ~5%-10% of body water turns over daily
 Total body water (estimate): Children = $0.6 \times (\text{wt, kg})$
 Adult men = $0.6 \times (\text{wt, kg})$
 Adult women = $0.5 \times (\text{wt, kg})$

RECOMMENDED WATER INTAKE

Average energy expenditure (EE) and environmental exposure = 1.0 mL/kcal EE⁴⁰
 Increased activity, sweating, and solute load = 1.5 mL/kcal EE⁴⁰

METABOLIC WATER

Water produced by metabolism (usually oxidation) of endogenous substrates
 Approximately 250-350 mL water/day (3-4 mL/kg/day)
 Example: Glucose oxidation:



Metabolism produces ~110 g water/100 g fat, 41 g water/100 g protein and 55 g water/100 g starch
 ~3 g water released per gram metabolized glycogen

WATER LOSS

Respiratory water loss (250-350 mL water/day) is influenced by temperature and humidity of inspired air.
 Urinary loss depends on water and solute intake
 Insensible losses—skin and respiratory system = 0.7 L/day
 Fecal loss—0.1 L/day
 Sweating—0.1 L/day
 Disease-associated losses—e.g., nasogastric drainage, vomiting, diarrhea

WATER AND HEAT LOSS

Heat exchange = radiation \pm conduction \pm convection (+evaporation)
Heat gain via radiation, conduction, and convection plus endogenous body heat production
Heat loss via radiation, conduction, convection, and evaporation
 Sweat evaporation
 Heat of water vaporization = 580 calories/m at normal skin temperature
 580 calories/g = heat loss to cool down 580 g of water 1°C
 Evaporation rate influenced by
 Water temperature at air-water interface
 Air temperature
 Humidity of surrounding air—higher humidity lowers evaporation rate
 Area of air-water interface
 Water's chemical composition—vaporization rate decreases as salt content increases
 Wind speed
 Sweat that drips or is wiped off does not contribute to cooling
 Burn patients lose much water and heat through evaporation from open wounds. Therefore, they should be treated in warm humid environments and burned areas covered.

Regulation of Water Balance

Regulating water balance involves central and peripheral volume and osmolarity sensors, providing neural input to the brain and other organs, thereby activating a cascade of endocrine and local activity.

Antidiuretic Hormone (ADH)/Arginine Vasopressin (AVP): ADH is a peptide, produced by the neurons of the hypothalamic paraventricular and supraoptic nuclei as a prohormone comprising vasopressin, neurophysin II, and copeptin. Neurons containing osmoreceptors have excitatory synapses with prohormone neurosecretory cells. ADH, bound to the carrier protein neurophysin II, then travels down the pituitary stalk (infundibulum) axons to the posterior pituitary where it is stored and secreted into the circulation.

ADH production and secretion are also stimulated by angiotensin II and decreased blood volume detected by atrial stretch-sensitive low-pressure/vascular volume baroreceptors. A 5% to 10% blood volume decrease is necessary for substantial ADH release. ADH is also secreted when carotid sinus and aortic arch baroreceptors detect a 10% blood pressure drop. Copeptin, the C-terminal fragment of the

prohormone, is more stable than ADH. Copeptin plasma concentrations are often used as an ADH surrogate.

ADH levels increases the water permeability of distal renal tubules and collecting ducts, thus increasing water reabsorption and resulting in greater urine osmolarity and reduced renal water excretion. ADH binds to vasopressin-2 receptors on renal epithelial cells. These G protein-coupled receptors activate adenylyl cyclase, converting ATP to cyclic AMP (cAMP). Increased cAMP increases the transcription of the aquaporin-2 gene, increasing aquaporin-2 in collecting duct cells and triggering the fusion of aquaporin-2 water channels to the apical membranes of distal tubule and collecting duct epithelial cells, allowing water to move down an osmotic gradient into the nephron. Aquaporin-3, located on the opposite side of the nephron, permits water leaving the nephron to be reabsorbed into the blood. ADH also upregulates aquaporin-3.

cAMP also activates protein kinase A, leading to protein phosphorylation (aquaporin-2 and thiazide-sensitive sodium chloride cotransporter) and upregulating expression of urea transporters, thereby increasing urea permeability of the collecting duct. There is also greater sodium absorption across the ascending loop of Henle. These two effects further increase distal tubular and collecting duct water reabsorption.

Renin-Angiotensin-Aldosterone System (RAAS): RAAS is a hormonal system stimulated by changes in renal blood flow. When renal blood flow or blood pressure decrease, juxtaglomerular cells in the renal afferent arterioles activate prorenin, which is cleaved to renin. The latter is secreted into the circulation where it converts angiotensinogen, an α -2-globulin synthesized by the liver, to angiotensin I. Angiotensinogen production is enhanced by estrogen, thyroxine, and glucocorticoids. There is evidence that cytokines (e.g., interferon- γ) also induce angiotensin production, a possible mechanism for maintaining blood pressure during sepsis.¹¹

Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme (ACE). ACE, a glycoprotein found mainly in the lungs and also in endothelial cells and plasma, also breaks down the potent vasodilator bradykinin, providing another mechanism for increasing blood pressure. Angiotensin II, a potent vasoconstrictor, increases blood pressure and decreases renal medullary blood flow and glomerular filtration, while vasoconstricting afferent and efferent arterioles. These changes increase sodium and water reabsorption in the loop of Henle. Hydrogen ion is excreted coupled with bicarbonate reabsorption. Angiotensin II's effects are attributable to its enhancing proximal and distal sodium/hydrogen ion exchanger, basolateral membrane sodium/bicarbonate ion cotransporter, sodium/potassium ion ATPase activity, and distal tubular epithelial sodium channel. Angiotensin II also stimulates posterior pituitary ADH release, further causing water retention.

Angiotensin II's major actions occur via the stimulation of AT-1 receptors located in the kidney, brain, heart, blood vessels, and adrenal cortex. The activated receptor couples to G proteins, activating phospholipase C and generating diacylglycerol and inositol trisphosphate. The latter increases cytosolic Ca^{2+} concentrations, which then activate intracellular kinases such as protein kinase C and tyrosine kinases. The activated AT-1 receptor also inhibits adenylyl cyclase. Angiotensin II also stimulates lower affinity AT-2 receptors, leading to effects opposite those caused by AT-1 receptor stimulation. AT-2 receptors lower blood pressure by increasing nitric oxide production, enhancing sodium excretion, and inhibiting renin production.¹² The latter action is a feedback loop designed to limit further angiotensin II production.

Angiotensin II stimulates adrenal cortical aldosterone synthase, which synthesizes aldosterone from deoxycorticosterone. Aldosterone regulates blood pressure by binding to the mineralocorticoid receptors of the renal distal tubular and collecting duct epithelial cells, thereby increasing expression and activity of ion channels in the distal nephron. By upregulating and activating the basolateral Na-K-ATPase pumps, aldosterone increases renal tubular sodium and water reabsorption plus the excretion of hydrogen ions and potassium, increasing body fluid volume and blood pressure.

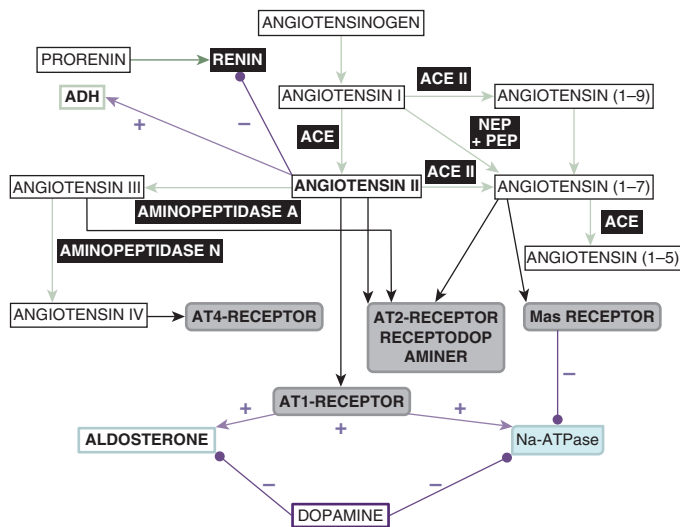


FIGURE 105-1 ■ RAAS system plus its interactions with ADH and dopamine. ADH, antidiuretic hormone; ACE, angiotensin converting enzyme.

The endocrine RAAS system is augmented by an RAAS with intrarenal paracrine, autocrine, and intracrine activity. Angiotensinogen produced intrarenally is converted by local renin to angiotensin I, which is then metabolized by ACE to angiotensin II and by ACE2 to angiotensin I-VII.¹³ Although most local effects are attributed to angiotensin II operating through AT-1 receptors, angiotensin I-VII operating through Mas receptors counteracts many of the effects of angiotensin II/AT-1, leading to diuresis, natriuresis, and renal vasodilation (Fig. 105-1). Other local mediators include angiotensin III (angiotensin II-VIII) working via the AT-1 receptors and angiotensin IV through the AT-4 receptors.¹⁴ Intrarenal angiotensin IV increases cortical blood flow and decreases sodium transport. In addition to the extracellular processing of these mediators, there is evidence that angiotensin II and angiotensin I-7 also exist intracellularly.¹⁵

Natriuretic Factors (Peptides): Natriuretic factors consist of a peptide family involved in water and sodium homeostasis that counteract RAAS effects. ANP, released by atrial myocytes in response to atrial distention secondary to elevated blood volume,¹⁶ is also secreted in response to sympathetic stimulation (α - and β -stimulation), angiotensin II, and endothelin. Cardiac ventricles, brain, adrenal glands, and kidneys (where it also acts as an autocrine/paracrine factor) are additional synthesis sites. ANP decreases circulating water and sodium, reducing atrial distention, and ultimately, lowering blood pressure. Another family member is brain natriuretic peptide (BNP), a peptide so named because it was first identified in porcine brain, although in humans it is mainly released by the heart in response to excessive cardiomyocyte distention. Biologically inactive circulating N-terminal fragments of ANP and BNP prohormones are used as biomarkers.

ANP and BNP increase glomerular filtration rates, reduce sodium and water reabsorption, inhibit renin release, and in proximal tubules, inhibit angiotensin II activity. The natriuretic peptides bind to NPR-A and NPR-B receptors, which are membrane guanylate cyclases that are characterized by a single protein containing both receptor and enzyme that produce cyclic GMP.¹⁷ cGMP targets cGMP-dependent protein kinases, cGMP-gated ion channels, and cGMP-regulated cyclic nucleotide phosphodiesterases. Changes in these enzymes and channels cause vasorelaxation, inhibit medullary collecting duct sodium reabsorption, and increase glomerular filtration rate by dilating afferent and constricting efferent arterioles, leading to greater glomerular capillary hydraulic pressure that enhances ultrafiltration. ANP, more effectively than BNP, stimulates cGMP production. ANP-induced diuresis and natriuresis occur, in part, by V2 receptor-mediated action of ADH in

the collecting ducts. Natriuretic peptide-induced increase in water and sodium excretion protects the body from overhydration. In pathologic conditions, such as congestive heart failure, ANP and BNP are stimulated by atrial overload secondary to the heart's inability to adequately empty.

Dopamine: The importance of dopamine in water homeostasis remains unclear, although renal production is increased by volume expansion, leading to natriuresis and water loss. Dopamine, synthesized in the renal proximal tubule from circulating L-dopa by L-amino acid decarboxylase, increases the glomerular filtration rate and diminishes sodium reabsorption in proximal tubules and collecting ducts. Dopamine, via D1 receptors, stimulates c-AMP generation and via D1/D5 receptor heteromers, stimulates phospholipase C, inhibiting both the Na-K-ATPase pump and sodium/hydrogen ion exchanger-3. D2-like receptors (D2, D3, and D4) also inhibit Na⁺-H⁺ exchanger 3, although the effects of D1 receptors are more dominant. Caveolin-1, a membrane scaffolding protein, helps organize the D1 receptor signaling pathway and intracellular effects.¹⁸ Dopamine also decreases aldosterone secretion¹⁹ and inhibits the antinatriuretic effects of angiotensin II.²⁰ Dopamine is metabolized by the enzymes catechol-O-methyltransferase and monoamine oxidase. Some of the effects of ANP are likely mediated by dopaminergic mechanisms.²⁰

Local renal prostaglandin (PGE-1 and PGE-2) generation is associated with increased basolateral membrane Na-K-ATPase.²¹ The renal nitric oxide/endothelin system appears to be active in collecting ducts. Endothelin-1, operating via the autocrine and paracrine mechanisms, is a diuretic/natriuretic factor inhibiting ADH-mediated osmotic water permeability.

Evaluating Water Balance

There are various ways to evaluate water balance (Table 105-2). In the ICU, water balance is generally assessed using body weight and fluid input-output. However, both methods have limitations.

WATER METABOLISM DISORDERS

Abnormal (hypervolemic or hypovolemic) water balance attributable to various intrinsic and extrinsic etiologies result in ICU admissions when the physiologic derangement endangers survival and/or requires treatment under close monitoring.

Hypervolemic Disorders

Hypervolemic disorders are caused by excessive water ingestion and/or the inability to excrete excess body water.

Water Intoxication: The classic example of abnormal positive water balance is water intoxication (water poisoning or hyperhydration), where an individual consumes very large volumes of water. Such excess water intake overwhelms the kidney's capacity to excrete water (maximum daily renal capacity ~15 L), despite maximal dilution (urine osmolality of ~50 mOsm/L).^{22,23} This situation results in hyponatremia, hypochloridemia, and hypokalemia. Brain edema occurs secondary to the extracellular to intracellular concentration gradient, leading to headache, delirium, seizures, coma, and death. Other symptoms include nausea, vomiting, twitching, and muscle weakness.

Water intoxication (psychogenic polydipsia) is largely observed in psychiatric patients (predominantly in schizophrenia but also in anorexia nervosa). It is hypothesized that schizophrenics who develop water intoxication have impaired hippocampal regulation, resulting in increased ADH secretion in response to psychologic stimuli. Another cause might be the drugs used to treat schizophrenia.²⁴ Forced water intake in children can also lead to water intoxication, as can excessive drinking in marathon runners and military trainees. Excessive water drinking among users of the recreational drug ecstasy (3,4-methylenedioxymethamphetamine) can cause water intoxication.²⁵

TABLE 105-2 Evaluating Water Balance**QUANTIFYING INPUT AND OUTPUT**

Clinical computation

Fluid balance = input (all intravenous and enteral intakes) – output (urine, gi, other drainages)

Often does not include

Intake: Accurate quantification of blood products, irrigation fluids

Output: Diarrhea, fluid lost into linens and bandages, insensible losses (skin, respiratory), sensible losses (sweating due to fever, surface exudation from burns)

BODY WEIGHTFluid balance = Δ body weight

Requires accurate scale and bed tearing

Tare weight = weight of bed without patient but with sheets, pillows, etc.

Net weight (patient weight) = gross weight (total weight) – tare weight

URINE SPECIFIC GRAVITY U_{sg} = density of urine/density of water

Range: 1.003–1.035

Euhydration: 1.010–1.026

High-molecular-weight substances, e.g., glucose, protein, and radiographic contrast, can increase $U_{sg} > 1.035$.**SERUM AND PLASMA OSMOLALITY/OSMOLARITY**

Osmolality = osmoles of solute/liter solution

Osmolality = osmoles of solute/kilogram solvent

Urine and plasma osmolalities should be measured but can be estimated

Calculated serum osmolality (when using SI units [mmol/L])

Calculated serum osmolality = $2(\text{Na}^+) + 2(\text{K}^+) + \text{glucose} + \text{urea}$

OR

Calculated serum osmolality = $2(\text{Na}^+) + \text{glucose} + \text{urea}$ Calculated serum osmolality (when Na^+ is mEq/L and glucose and BUN are [mg/dL])Calculated serum osmolality = $2[\text{Na}^+] + [\text{glucose}]/18 + [\text{BUN}]/2$ Normal serum osmolality: 275–290 mOsm/kg. 295–300 mOsm/kg indicates impending dehydration; >300 mOsm/kg indicates dehydration.

Urine: specific gravity vs. osmolality

Unlike specific gravity, osmolality is unaffected by the number and size of particles in solution. Urine containing glucose and/or protein will have a specific gravity $>$ osmolality. $U_{sg} = 1.020$ – 1.030 corresponds to osmolality of 800–1200 mOsm/kg H_2O $U_{sg} = 1.005$ is an osmolality <100 mOsm/kg H_2O

Normal kidneys can concentrate urine to an osmolality 4 times greater than serum and dilute urine to 25% of serum osmolality.

ELECTROLYTE-FREE WATER CLEARANCEElectrolyte-free water clearance ($T^e_{\text{H}_2\text{O}}$) – amount of water in urine free of solutes $T^e_{\text{H}_2\text{O}} = V [(U_{\text{Na}} + U_{\text{K}})/P_{\text{Na}}] - 1$ V = total urine volume U_{Na} = urine (Na^+) U_{K} = urine (K^+) P_{Na} = plasma (Na^+)Positive $T^e_{\text{H}_2\text{O}}$ – water is being excreted (e.g., causing hypernatremia)Negative $T^e_{\text{H}_2\text{O}}$ – water is being reabsorbed (e.g., causing hyponatremia)**FREE WATER DEFICIT**

In hypernatremia, estimated free water deficit

Water deficit = $\text{TBW} * \{(\text{serum } [\text{Na}]/140) - 1\}$ TBW = estimated total body water: men – $0.6 * \text{Wt}$ (kg); women – $0.5 * \text{Wt}$ (kg). In the elderly and those significantly dehydrated: men – $0.5 * \text{Wt}$ (kg); women – $0.4 * \text{Wt}$ (kg)

This estimate does not account for ongoing water (i.e., insensible, urine, gastrointestinal tract) or iso-osmotic fluid (i.e., osmotic diuresis, diarrhea) losses that continue to contribute to water deficit.

BIOELECTRIC IMPEDANCE

Noninvasive method used to estimate total body water based on the assumption that only body water conducts electricity while fat, which has little water content, restricts the flow of current.

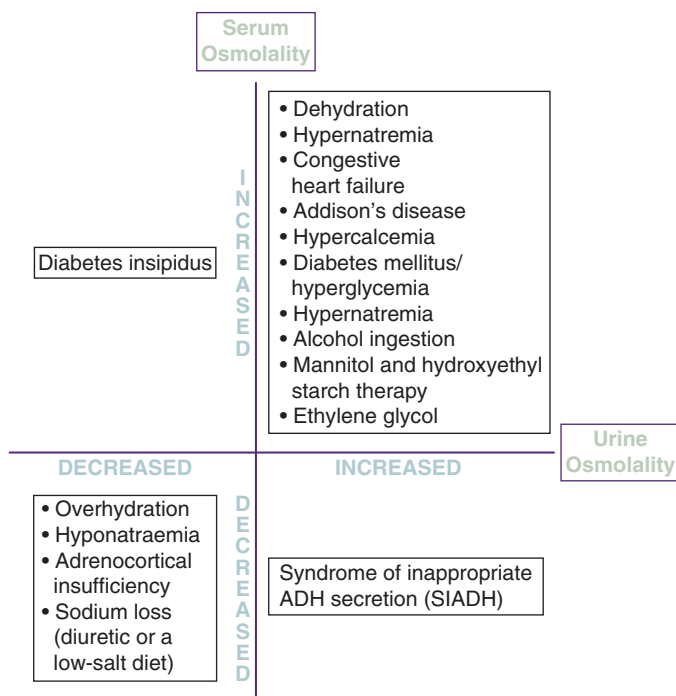
Iatrogenic causes of water intoxication include excessive, rapid water ingestion before pelvic ultrasound examinations and transurethral resection of the prostate syndrome. The latter occurs when a large volume of nonconducting (electricity) water plus glycine irrigation solution is absorbed through the prostatic veins and sinuses. The amino acid glycine is rapidly metabolized, causing water overload, hyposmolality, and hyponatremia. The introduction of bipolar cautery, which does not disperse electric current, permits using electrolyte-containing irrigation solutions (e.g., normal saline), thereby preventing hyposmolality and hyponatremia but not fluid overload. The absorption of water–glycine distention medium during operative hysteroscopy can also lead to intravascular volume overload and water intoxication.

Treatment of water intoxication involves water restriction and loop diuretics. Hypertonic saline is rarely required and should only be considered in cases of severe hyponatremia. Too rapid a correction of hyponatremia can result in central pontine myelinosis.

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH): SIADH causes hyponatremia and hyposmolality because of impaired water excretion secondary to inappropriate, continued secretion, or action of ADH despite normal or increased plasma volume. ADH promotes water reabsorption without affecting sodium reabsorption, leading to dilutional hyponatremia because of water excess rather than sodium deficiency.

Excessive water reabsorption activates volume receptors causing the secretion of natriuretic peptides and natriuresis. Eventually, a steady state is reached with urinary sodium excretion matching sodium intake. Therefore, only when water intake exceeds the reduced urine output does hyponatremia develop. Importantly, hyponatremia does not occur with severely restricted water intake. In addition to inappropriate ADH secretion, SIADH may include inappropriate thirst sensation, leading to water intake in excess of free water excretion. This increased water intake helps maintain hyponatremia.

SIADH includes hyponatremia, inappropriately elevated urine osmolality (>100 mOsm/kg), and reduced serum osmolality in a euvolemic patient (Fig. 105-2). SIADH should be considered when these findings occur in the setting of otherwise normal cardiac, renal,

**FIGURE 105-2** ■ Relationships between plasma and urine osmolality.

adrenal, hepatic, and thyroid function; absence of diuretic therapy; and absence of other factors that stimulate ADH secretion such as hypotension, severe pain, nausea and stress.

Impaired ADH regulation in SIADH:

- Type A—erratic, unregulated ADH release unrelated to plasma osmolality
- Type B—modest, constant ADH secretion
- Type C—(“reset osmostat”)—downward resetting of the osmostat. Plasma sodium concentrations regulated at a lower level and continue to fall without therapy
- Type D—normal osmoregulation. ADH secretion varies appropriately with the plasma osmolality, but urine is concentrated even if ADH release is suppressed (e.g., vasopressin receptor is constitutively activated, production of antidiuretic compound other than ADH, postreceptor defect in transferring aquaporin-2 water channels).

Classification of SIADH etiology:

- CNS disorders (e.g., stroke, hemorrhage, infection, inflammation, trauma, neurosurgery, acute intermittent porphyria). Must differentiate SIADH from cerebral salt wasting (ADH secretion is secondary to reduced extracellular fluid volume)
- Ectopic (paraneoplastic) ADH production by tumors (small cell lung carcinoma in 75% of cases)
- Pulmonary diseases (pneumonia, asthma, atelectasis, pneumothorax)
- Drugs that mimic ADH, stimulate ADH release, potentiate ADH effects, or have unclear mechanisms (e.g., exogenous ADH analogs, SSRIs, phenothiazines, tricyclics, carbamazepine, cyclophosphamide, vincristine)
- Postoperative (likely mediated by pain afferents), transsphenoidal surgery
- Symptomatic HIV infection
- Hereditary/genetic—(e.g., gain-of-function mutation of arginine vasopressin receptor type 2—nephrogenic syndrome of inappropriate antidiuresis—causing constitutive receptor activation)
 - Aging
 - Unknown origin/idiopathic

Acute treatment includes water restriction and treating the underlying cause. In severe symptomatic cases associated with neurologic complications, hypertonic saline is administered to gradually correct hyponatremia. Loop diuretics can be useful by aiding water excretion. However, too rapid correction of serum sodium concentrations, especially in asymptomatic patients, can result in neurologic impairment from central pontine myelinolysis. Another complication of aggressive sodium correction is severe hypernatremia.

Pharmacologic treatment for SIADH includes vasopressin receptor antagonists (vaptans), which competitively bind to V-2 receptors. An advantage of these agents is their ability to reduce the need for severe fluid restriction, while correcting hyponatremia within a short time. During the initial 24 hours of administration, it is critical to prevent overly rapid correction of hyponatremia. Discontinuing vaptan therapy for more than 5 to 6 days requires monitoring for hyponatremic relapse. Therefore, it is prudent to taper the vaptan dose while restricting fluid intake. Side effects include thirst, polydipsia, and urinary frequency. Vaptans are ineffective in inappropriate antidiuresis caused by constitutive activating mutations of V-2 receptors.

Another treatment for SIADH is demeclocycline, a macrolide antibiotic, which induces nephrogenic diabetes insipidus by reducing adenylate cyclase expression, cAMP generation, AQP2 gene transcription, and AQP2 abundance in the renal medulla. Its frequent side effects include nausea and skin photosensitivity. In addition, oral urea is used to induce osmotic diuresis, which increases water excretion.

Cerebral (Renal) Salt-Wasting Syndrome (CSW): CSW is the extracellular volume depletion caused by abnormal sodium transport in patients with intracranial disease (and other conditions) and normal adrenal and thyroid function. CSW usually develops in the week following brain insult. Its duration is usually brief (2-4 weeks) but can last for several months. Both SIADH and CSW present with low serum

osmolality, elevated urine osmolality, and high urinary sodium concentrations. The basic difference is that in CSW, there is hypovolemia, while in SIADH, there is euvoolemia or mild hypervolemia. Urinary sodium concentrations are elevated in SIADH and CSW (>40 mEq/L). However, urinary sodium excretion (urinary sodium concentration [mEq/L] \times urinary volume [L/24 h]) is much higher than sodium intake in CSW but usually equals sodium intake in SIADH. Therefore, net sodium balance is negative in CSW. Failure to distinguish CSW from SIADH in hyponatremic brain-injured patients can lead to inappropriate therapy with fluid restriction.

In CRW, excessive sodium is lost in the proximal tubule, leading to reduced effective circulating volume. The two proposed mechanisms are the excessive secretion of natriuretic peptides (BNP and CNP) and the loss of renal sympathetic stimulation. Both the mechanisms reduce proximal and possibly distal sodium transport. The ensuing hypovolemia leads to baroreceptor activation increasing ADH secretion and water conservation in an attempt to return to a euvolemic state. In contrast, SIADH is due to an inappropriate euvolemic increase in ADH secretion. Depressed sympathetic drive and increased BNP concentrations are also associated with decreased renin and aldosterone concentrations, further inhibiting sodium retention.

The decreased serum sodium concentration associated with CRW reduces serum osmolality, and a tonicity gradient develops across the blood-brain barrier, causing or exacerbating cerebral edema. Symptoms include lethargy, agitation, headache, altered consciousness, seizures, and coma. Treatment involves correcting intravascular volume depletion and hyponatremia, plus replacing persistent urinary sodium loss with intravenous normal or hypertonic saline solutions. Saline infusion corrects the hypovolemia, removing a potent stimulus for ADH secretion, increasing free water excretion, and correcting the hyponatremia. There are reports of favorable responses to mineralocorticoid therapy. Once the patient is stabilized, enteral salt supplementation should be considered.

Hepatic Cirrhosis: Regardless of etiology (alcoholic, chronic hepatitis, autoimmune, genetic, cryptogenic), cirrhosis involves the loss of normal hepatic architecture and irreversible liver damage. Cirrhosis changes splanchnic circulation, causing mechanical obstruction to the portal flow and portal hypertension. Ascites occurs when portal pressures of >12 mm Hg cause intrahepatic sinusoidal hypertension. If portal pressure decreases to <12 mm Hg (e.g., after portosystemic shunt) ascites usually disappears. Presinusoidal portal hypertension (e.g., portal vein thrombosis) does not cause ascites in the absence of another predisposing factor.

In addition to the mechanical obstruction to portal flow, cirrhosis is associated with an increased portal venous inflow secondary to splanchnic arterial vasodilation and the opening of portosystemic collaterals. The latter, because of increased circulating vasodilators, such as nitric oxide and prostacyclin, reduces systemic vascular resistance and arterial pressure. Cardiac output increases in compensation. This hyperdynamic pattern can be found in cirrhotic patients even before ascites develops. In response to cirrhosis-associated vasodilation, endogenous vasoconstrictors and sodium-retaining neurohumoral mechanisms activate (RAAS, sympathetic nervous system, ADH) in an attempt to normalize perfusion pressure. The net effect is sodium and water retention. However, cirrhotics are effectively intravascularly volume depleted despite increased extracellular sodium stores, plasma volume, and cardiac output. As the disease progresses, solute-free water excretion is increasingly impaired because of the increased ADH secretion. Reduced water excretion plus ascites accumulation adds to total body fluid overload. The intravascular depletion leads to further “compensation,” including nonosmotic ADH secretion, worsening excess water retention, hypoosmolality, and dilutional hyponatremia. Nonosmotic ADH secretion is mediated via atrial, ventricular, aortic arch, and carotid sinus baroreceptors, which stimulate hypothalamic ADH release. This ADH secretion is paradoxical because serum osmolality is low. The net result is enhanced sodium and water retention, which attempts to correct the depleted circulatory volume. Sodium retention occurs despite increased total body

extracellular sodium concentrations. Hyponatremia severity correlates with worsening survival.

Other factors implicated in the development of hyponatremia and associated with cirrhosis include decreased renal PGE₂ production and slower ADH metabolism. Resistance to the natriuretic action of ANP may play a role in sodium retention. Renal perfusion in cirrhosis with ascites depends on a delicate equilibrium between the degree of stimulation of vasoconstrictor systems (sympathetic nervous system, RAAS) and the activity of intrarenal vasodilator compounds, (prostaglandins and nitric oxide). Imbalance between systemic vasoconstriction and local renal vasodilation can result in progressive renal failure (hepatorenal syndrome).

Stressed States: Exudation of protein-rich intravascular fluid from plasma to the extracellular space is the hallmark of stressed states (sepsis, pancreatitis, burns), resulting in relative intravascular hypovolemia. Such exudation leads to sequelae, including acute respiratory distress syndrome, diffuse edema, and abdominal compartment syndromes. Plasma ADH and aldosterone are usually increased during the initial phase of septic shock and burns and decrease later in the course. Extravascular fluid shifts diminish as the patient convalesces. The greater the fluid accumulation, the greater are morbidity and mortality. There is currently no direct treatment for this condition.

The endothelium tightly controls intravascular fluid exchange from the circulation to the tissues. Dysfunction of this barrier causes fluid exudation and edema. Various mechanisms appear involved in increasing membrane permeability. The main function of vascular endothelial (VE)-cadherin, a cell adhesion molecule localized to endothelial cell junctions, is regulating and forming a homophilic calcium-dependent bond with a twin on an adjacent cell. The cytoplasmic domain of VE-cadherin is bound to catenins, which attach to the cytoskeletal structure. When endothelial cells are exposed to permeability factors, they contract via myosin-actin crossbridge cycling, resulting in the dissociation of vascular endothelial cadherin from its adjacent homolog, forming interendothelial gaps. Permeability factors include proinflammatory cytokines (TNF, IL-6, IL-8, interferon- γ , IL-1 β), nuclear transcription factors (HMGB1, high-mobility group box1), transforming growth factor, and vascular endothelial growth factor (VEGF). These factors likely operate through the MyD88-ARNO-ARF6-signaling axis while also diminishing VE-cadherin expression.²⁶ VE-cadherin is internalized by VEGF-induced signaling through VEGF receptors and undergoes tyrosine phosphorylation leading to greater vascular endothelial cell detachment and transendothelial permeability. Matrix metalloproteases (e.g., MMP-9, gelatinase b) have been implicated as degrading interendothelial adherens junction proteins. An associated mechanism is activation of Rho-A GTPase, which increases actomyosin contractility, inducing intercellular junction breakdown and enhancing permeability.²⁷

Hypovolemic Disorders

Diabetes Insipidus (DI): DI, polyuria (defined as a urine output exceeding 3 L/day in adults and 2 L/m² in children) caused by plasma ADH deficiency or renal resistance to ADH's effects, is characterized by the failure to appropriately concentrate urine.

In the absence of ADH (<0.5 pg/mL), renal collecting duct membranes become impermeable to water (fewer aquaporin-2 water channels), thereby allowing the formation of dilute filtrate in proximal nephrons. This results in the excretion of relatively large urine volumes of low osmolality (≤ 100 mOsm/kg), causing hypovolemia and even hypotension. These stimulate hypothalamic osmoregulators, encouraging water intake via thirst. With normal thirst and access to water, fluid intake increases to compensate for most of the water loss. Consequently, even in the complete absence of vasopressin, urine output and fluid intake increase in parallel, maintaining plasma osmolality within the normal range. Severe dehydration and hypernatremia occur when access to water or intravenous fluids is lacking or there is coexisting thirst deficiency.

The most common cause of DI is inadequate neurohypophyseal ADH secretion, resulting in partial or complete central DI. Nephrogenic DI is characterized by normal ADH secretion with varying degrees of renal resistance to its antidiuretic effect. Another mechanism is the suppression of ADH secretion by excessive water intake, as seen in primary polydipsia. ADH insufficiency can rarely result from increased metabolic clearance during pregnancy because of the placental production of the aminopeptidase vasopressinase, which rapidly degrades ADH, causing a four- to six-fold increase in ADH metabolism. In most women, the pituitary compensates by producing more ADH. In some women, presumably those with diminished ADH secretory reserves, polyuria develops. This usually occurs during the third trimester and spontaneously resolves after placental delivery.

Central DI can be caused by defects along the ADH neurosecretory pathway, including genetic mutations affecting ADH synthesis and packaging; damage to ADH-producing magnocellular neurons or the supraopticohypophyseal tract; and disorders of neurohypophyseal hormone release. Five percent of central DI cases are familial/genetic; >50 mutations have been identified in the AVP-neurophysin II gene (chromosome 20) and other loci have been described. Furthermore, 0% to 50% of cases are considered "idiopathic" (autoimmune, aberrant posterior pituitary blood supply). Other causes include neoplasms involving the hypothalamus (craniopharyngiomas, germinomas, metastatic disease of the posterior pituitary [breast or lung cancer]) and granulomas (sarcoidosis, tuberculosis, Wegener's granulomatosis, Langerhans cell histiocytosis [histiocytosis X]). In the ICU, common causes are trauma—for example, closed head injury, postcraniotomy, anterior communicating artery (ACA) aneurysmal rupture causing subarachnoid or intracerebral hemorrhage (ACA aneurysms and their treatment can compromise hypothalamic blood supply), brain abscess, subdural hemorrhage (DI persisted for 3 months in 8% of survivors), and ischemic brain injury. Transient or permanent DI occurs in 8% to 9% of endoscopic transsphenoidal surgeries.

Nephrogenic DI may reflect an intrinsic renal defect or may be acquired secondary to metabolic disease or medication. It is characterized by complete or partial deficiency to the renal antidiuretic response to normal or increased ADH concentrations. Adults generally have an acquired form. Normal aging can also result in partial nephrogenic DI. Drugs inducing nephrogenic DI; lithium is the most common offender, with nephrogenic DI reported in 25% to 55% of patients receiving lithium. With long-term use, lithium-induced DI can become irreversible. Hypercalcemia and hypokalemia can partially block renal ADH action. Hereditary forms of nephrogenic DI are due to defective renal ADH V2 receptor (males with X-linked recessive defect in chromosome region Xq28) or aquaporin-2 genes.

Adipsic DI is a condition where impaired thirst complicates deranged water balance. It is closely associated with ACA aneurysm clipping and is characterized by dramatic increases in plasma ADH concentrations during nonosmotic stimuli such as hypotension. This situation reflects intact supraoptic and paraventricular nuclei and posterior pituitary with abnormalities of the anterior pituitary osmoreceptors. Vascular supply to this latter area is from small arterioles supplied by the anterior communicating artery. Disrupting this blood supply causes infarction that impairs ADH secretion response to thirst or hyperosmolality.

Diagnosis of DI is made when urine volume is markedly increased and urine osmolality is very low (<100 mmol/kg), associated with elevated plasma osmolality (>300 mmol/kg) and serum sodium concentrations (>145 mmol/L). However, other causes of polyuria must be excluded—for example, excessive fluid resuscitation, osmotic diuresis, hypertonic saline infusion, and "triple H therapy" (hypervolemia, hemodilution, and hypertension), which are used to treat cerebral vasospasm. When basal plasma osmolality and sodium are within normal ranges, osmotic stimulation with a formal water deprivation test or hypertonic saline infusion (if necessary) to achieve plasma osmolality of >295 to 300 mOsm/kg is indicated. If there is no change in the water loss despite fluid deprivation, the type (central or nephrogenic) of DI should be determined by monitoring the response to

administered ADH or 1-deamino-8-D-arginine vasopressin (DDAVP-desmopressin), a synthetic ADH analog. A significant increase in urine osmolality 1 to 2 hours after subcutaneously or intravenously injecting 1 μ g of DDAVP indicates insufficient endogenous ADH and probable central DI. Little or no increase in urinary concentration indicates renal resistance to ADH and severe nephrogenic DI. Some cases are not as straightforward and require further evaluation with a 2-day therapeutic trial of DDAVP, an MRI of the hypothalamus plus pituitary, and plasma ADH and copeptin measurements.

While diagnosing and identifying the cause of the DI, it is imperative that adequate fluid intake is maintained. The treatment for central DI is either intravenous ADH (vasopressin) or oral, intranasal, or parenteral DDAVP. DDAVP is a synthetic ADH analog with a longer half-life than the native hormone. In nephrogenic DI, therapeutic options are only partially effective: low-sodium diet, thiazide diuretics, prostaglandin E synthetase inhibitors, and nonsteroidal antiinflammatory drugs may partially decrease urine volume. The potassium-sparing diuretic amiloride is used in lithium-induced nephrogenic DI (it induces natriuresis and reduces lithium uptake in the distal tubules and collecting ducts, blunting lithium's inhibition of water reabsorption). Pregnancy-associated DI can be controlled with vasopressinase-resistant DDAVP but not ADH.

Osmotic Diuresis: Osmotic diuresis is characterized by increased urination caused by nonreabsorbed solutes (e.g., glucose and urea) in renal proximal tubules. Increased osmotic pressure within the tubule causes luminal water retention, reducing water reabsorption and increasing urine output. When blood glucose exceeds 160 to 180 mg/dL, the proximal tubule is overwhelmed, causing glycosuria. Osmotic urea diuresis is common in the ICU, associated with enteral nutrition and resolving acute renal failure. The electrolyte-free water loss may cause hypernatremia.

Therapeutic agents (e.g., mannitol) are used to increase urine output and decrease extracellular fluid volume. Mannitol, freely filtered by the glomerulus and not reabsorbed, acts as an osmotic diuretic, increasing urinary losses of electrolyte-free water. Osmotic substances increase blood osmolality, thereby pulling water from the interstitial space and increasing GFR and urine output. Failure to replace fluid losses can lead to volume depletion and hypernatremia. However, if very high doses of hypertonic mannitol are infused, or if it is administered to patients with preexisting renal failure, mannitol is retained in the circulation. The resulting plasma osmolality increase, like that produced by hyperglycemia, causes osmotic movement of water out of cells, leading to extracellular fluid volume expansion and dilutional hyponatremia. This can result in intravascular fluid overload, especially if the excess fluid and osmotic substances cannot be excreted.

Osmotic diuresis generally leads to significant free water losses and can cause or contribute to hypernatremia. However, with glycosuria secondary to uncontrolled diabetes mellitus, diabetic ketoacidosis, and hyperosmolar hyperglycemic state, most patients are mildly hyponatremic. The serum sodium concentration reflects the balance between the dilutional effect of water moving out of cells in response to the hyperglycemia-induced increase in serum osmolality (dilutional hyponatremia—i.e., true hypertonic hypervolemic hyponatremia) and the increased water excretion due to glycosuria-induced osmotic diuresis.

Treating water losses secondary to osmotic diuresis involves reducing the nonreabsorbed solute either by stopping its administration (e.g., mannitol) or treating the underlying pathologic condition (e.g., reduce blood glucose concentrations). Furthermore, excessive dehydration should be prevented by administering sufficient fluids.

Cold Diuresis: Cold or cold-induced diuresis occurs during exposure to a hypothermic environment and during mild to moderate accidental and therapeutic hypothermia. During therapeutic hypothermia, cold diuresis is most apparent during the induction phase. Cold diuresis is characterized by increased sodium and chloride excretion leading to enhanced water loss, decreased blood volume, and increased blood viscosity. The latter augments the increased viscosity secondary to the hypothermia. Vasoconstriction and hypovolemia caused by

hypothermia are most problematic; thus, vasodilation during rewarming must be countered by fluid resuscitation to avoid hypotension.

Possible causes of cold diuresis include the redirection of blood from vasoconstricted extremities to the core, leading to increased core fluid volume. The latter leads to increased renal blood flow and diuresis. ADH appears to be involved in cold diuresis. Some investigators report decreased ADH, while others report that although ADH concentrations are elevated, cold exposure inhibits renal V_2 receptors, decreasing V_2 receptor mRNA expression and inducible renal medullar AQP-2 water channel protein expression.²⁸ ANP does not appear to be involved in cold diuresis.

Heat and Exercise-Induced Disorders: Sweat is hypoosmotic relative to plasma; hence, excessive sweating can lead to significant water loss, reaching >2.5 L/h during strenuous exercise.²⁹ Sweat sodium concentrations range from 15 to 90 mmol/L, with an average of 40 mmol/L. As sweating increases, sodium secretion rates proportionally increase. However, heat acclimatization lowers sodium chloride concentration. Maintaining normal hydration during exercise maintains cardiovascular and thermoregulatory responses. Whenever possible, oral, rather than IV, rehydration should be performed. Although IV fluids rehydrate faster, the benefits are often transient, with the major limitation being the bypassing of the oropharynx. Oropharyngeal stimulation influences thirst sensation, ADH release, cutaneous vasodilation, and mean arterial pressure.³⁰ Therefore, drinking water plus electrolyte solutions to minimize dehydration is necessary during and following significant exercise and heat exposure. To maintain adequate hydration elite athletes ingest ~200 to 800 mL/h. Less acclimatized participants should not drink as much as possible but according to the stimulation of thirst and no more than 400 to 800 mL/h.

In collapsed marathon runners, there is a significant incidence of hypernatremia with hyperosmolality and hyponatremia with hypoosmolality. The latter is often due to hyperhydration, caused by considerable water ingestion. Hyponatremia, hyperthermia, hypertonic hypernatremia, orthostatic hypotension due to decreased peripheral resistance, and dehydration can each contribute to cerebral dysfunction.^{31,32} Moreover, it is crucial to differentiate between hypernatremia and hyponatremia since the immediate management differs. Administering hypotonic fluids to severely hyponatremic patients may cause fatal cerebral edema, evidenced by seizures and/or coma. Therefore, laboratory testing to determine serum sodium concentration is vital to direct therapy.

Heat stress illness (HSI), also called *heat-related illness*, includes benign rash, heat syncope, heat cramps, heat exhaustion (most common HSI), and heat stroke (most severe form). During 2001–2010, ~28,000 HSI hospitalizations occurred in 20 states.³³ HSI occurs during heat exposure with and without exercise. Obesity, heart failure, pre-existing neuropsychiatric disorder, psychotropic drugs intake (e.g., phenothiazines, cocaine), and strenuous outdoor work³⁴ are associated with increased HSI risk. HSI development and severity are significantly related to hydration status and ability to sweat.^{35,36} HSI is exacerbated by hypovolemia and plasma hyperosmolality, which inhibit thermoregulatory responses, such as cutaneous vasodilation and sweating.³⁷ Elevated core temperature does not stimulate ADH secretion except with increased serum osmolality.³⁸ HSI treatment includes rapid cooling, fluid replacement, and physiologic support.

CONCLUSION

Maintaining homeostatic water balance is a vital body function commonly disordered in critically ill patients due to combinations of their acute illness, underlying chronic diseases, treatments, and aging. Modern critical care medicine needs to better understand water metabolism, especially the microcirculatory consequences of edematous and overhydrated states. Such a better understanding should influence treatment—for example, whether to treat with saluretic diuretics that enhance sodium excretion or with aquaretics that increase water excretion.³⁹

KEY POINTS

1. Water, the liquid of life for all organisms, has many functions: carrier of essential substances; body coolant, lubricant, reactant and product in metabolic reactions; and shock absorber.
2. Water homeostasis is controlled by thirst, the ability to find and ingest water, kidney function, sweating, and endogenous systems.
3. Endogenous systems active in water metabolism include ADH, renin-angiotensin-aldosterone system, natriuretic peptides, dopamine, and renal intracrine mechanisms.
4. Environmental conditions—extreme heat and cold—can cause disordered water homeostasis, as can diarrhea, drugs, excessive water ingestion and disorders of endogenous systems (diabetes insipidus, SIADH).
5. In stressed states (e.g., sepsis, burns, and trauma), plasma ADH and aldosterone are increased during the initial phase accompanied by extravascular exudation of protein-rich fluids.
6. Critically ill patients are totally dependent on their care providers for maintaining water homeostasis and for preventing and correcting disordered homeostasis.

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SERUM CALCIUM CONCENTRATION

Calcium is essential to many physiologic phenomena, including the preservation of the integrity of cellular membranes, neuromuscular activity, regulation of endocrine and exocrine secretory activities, blood coagulation, activation of the complement system, and bone metabolism. The normal range for total serum calcium must be established for each laboratory, and it varies according to the method used. Total serum calcium concentration is a combination of protein-bound calcium, ionized calcium, and nonionized calcium.¹

Protein-Bound Calcium

Approximately 40% of total calcium is bound to serum proteins, and 80% to 90% of this calcium is bound to albumin. Variations in serum protein proportionately alter the concentration of the protein-bound and total serum calcium. An increase in serum albumin concentration of 1 g/dL increases protein-bound calcium by 0.8 mg/dL, whereas an increase of 1 g/dL of globulin increases protein-bound calcium by 0.16 mg/dL. However, the validity of this correction in critical illness has been questioned, with multiple authors emphasizing the importance of directly measuring serum ionized calcium concentrations in this patient population.^{2,3} Marked changes in serum sodium concentration also affect the protein binding of calcium. Hyponatremia increases, whereas hypernatremia decreases, protein-bound calcium. Changes in pH also affect protein-bound calcium, and an increase or decrease of 0.1 pH, respectively, increases or decreases protein-bound calcium by 0.12 mg/dL.

Free (Ionized) Calcium

Ionized calcium is the biologically active form of calcium responsible for most physiologic actions of calcium in the body. The serum ionized calcium concentration in normal subjects ranges from 4.0 to 4.9 mg/dL, or 47% of the total serum calcium. Acidosis decreases protein binding, thereby increasing the ionized fraction of calcium. An increase in serum pH of 0.1 unit causes a decrease in ionized calcium of 0.16 mg/dL.

Nonionized Calcium

The nonionized form of calcium is also called *complexed calcium*. Calcium complexes are formed with bicarbonate, phosphate, and acetate and constitute approximately 13% of the total serum calcium. Complexed calcium has been found to be increased twofold in patients with uremia.

Cytosolic Free Calcium

The normal concentration of cytosolic calcium is about 100 nM/L, which is 10,000-fold lower than the concentration of extracellular calcium. This very steep gradient is maintained by an energy-driven calcium pump, known as the *plasma membrane Ca⁺⁺-ATPase*. In certain types of cells, a Na⁺/Ca⁺⁺ exchanger, energized by the Na⁺ gradient, helps drive cytosolic calcium into the extracellular space. Part of the cellular calcium is sequestered in intracellular organelles, including

the endoplasmic reticulum, the sarcoplasmic reticulum in muscle cells, and the mitochondria. These organelles are endowed with their own calcium pumps that help preserve the very low levels of free cytosolic calcium. Calcium-dependent intracellular signaling generally requires a 10-fold increase in free cytosolic calcium. Elevation in cytosolic calcium is mediated by the activation of calcium channels, which allows passive calcium flux down electrochemical gradients.⁴

VITAMIN D METABOLISM

Vitamin D (where D represents D₂ or D₃) is biologically inert and is metabolized in the liver to 25-hydroxyvitamin D [25(OH)D], the major circulating form of vitamin D. 25(OH)D is activated in the kidneys to 1,25-dihydroxyvitamin D [1,25(OH)₂D], which regulates calcium, phosphorus, and bone metabolism.⁵

CALCIUM HOMEOSTASIS

Calcium is regulated by a combination of bone exchange, renal excretion, and intestinal absorption. Decreased ionized calcium increases parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D₂, both of which increase osteoclastic activity and thus stimulate bone resorption. Renal excretion of calcium is regulated by PTH and vitamin D, which increase distal tubular reabsorption of calcium, and by calcitonin, which inhibits calcium reabsorption. Intestinal absorption of calcium depends primarily on 1,25-dihydroxyvitamin D₂, which stimulates calcium absorption from all parts of the small intestine.⁶

Hypocalcemia

Disorders associated with hypocalcemia can be classified into disorders related to vitamin D or PTH.

Disorders Related to Vitamin D Deficiency

Vitamin D Deficiency. Hypocalcemia is a frequently found feature of vitamin D deficiency. The common causes of vitamin D deficiency are listed in [Box 106-1](#). Lack of exposure to sunlight impairs endogenous vitamin D synthesis. Because vitamin D is a fat-soluble vitamin, poor intake of food products containing fatty substances results in nutritional osteomalacia. Gastrectomy may result in dietary deficiency from avoiding the consumption of fatty products and/or malabsorption of vitamin D, as noted with Billroth type II surgery, in which a vitamin D-absorbing bowel segment is bypassed. Deficiency of the bile salts also impairs vitamin D absorption. Small bowel diseases, laxative abuse, and certain anticonvulsants (phenytoin) can interfere with absorption, and urinary loss of vitamin D is associated with Fanconi's syndrome and nephrotic syndrome.⁷ Because the hepatic formation of 25(OH) vitamin D from vitamin D is not tightly controlled and depends primarily on the availability of vitamin D, the serum level of 25(OH) vitamin D₃ is utilized as a measurement of the body stores of vitamin D; low levels of 25(OH) vitamin D indicate vitamin D deficiency.¹

Impaired Metabolism of Vitamin D. Antiepileptic drugs, including carbamazepine, phenobarbital, and phenytoin, may cause hypocalcemia associated with low levels of circulating 25(OH) vitamin D caused by the induction of microsomal enzymes in the liver. Low

BOX 106-1

Common Causes of Vitamin D Deficiency

LACK OF EXPOSURE TO SUNSHINE

NUTRITIONAL

Malabsorption

Following gastrectomy
Tropical and nontropical sprue
Chronic pancreatitis
Biliary cirrhosis
Ingestion of cathartics
Intestinal bypass
Anticonvulsant therapy

Abnormal Metabolism of Vitamin D

Vitamin D–dependent rickets
Ingestion of barbiturates and anticonvulsants
Renal insufficiency
Hepatic dysfunction
Calcium deprivation

Renal Losses of Vitamin D

Nephrotic syndrome
Fanconi's syndrome

circulating levels of 25(OH) vitamin D have also been observed in patients with hepatic failure due to the reduced transformation of vitamin D to 25(OH) vitamin D.⁸

Dietary calcium deprivation increases the clearance and inactivation of 25(OH) vitamin D and causes vitamin D deficiency. This variety of vitamin D deficiency may be caused by secondary hyperparathyroidism, which augments renal synthesis of 1,25(OH)₂ vitamin D and in turn, enhances the degradation of 25(OH) vitamin D to inactive metabolites. Hypothetically, this mechanism may account for vitamin D deficiency in clinical states of calcium malabsorption, including gastrointestinal diseases, anticonvulsant therapy (e.g., phenytoin), and the use of drugs such as colchicine, fluoride, and theophylline. Likewise, increased intake of foods rich in phytate, oxalate, and citrate that chelate calcium in the gastrointestinal tract and render it nonabsorbable may cause vitamin D deficiency.^{1,9}

Vitamin D–dependent rickets type I (VDDR-1), also designated as *pseudovitamin D deficiency*, is inherited as an autosomal recessive disorder in which there is a deficiency in 25(OH) vitamin D-1 α -hydroxylase in the proximal tubules due to defects in the 1 α -hydroxylase gene. It is manifested by early hypocalcemia, hypophosphatemia, severe secondary hyperparathyroidism, and severe rickets. Serum 1,25(OH)₂ vitamin D is undetectable or very low, whereas 25(OH) vitamin D levels are normal. VDDR-1 can be reversed completely by the administration of pharmacologic doses of vitamin D or physiologic doses of 1,25(OH)₂ vitamin D. Linkage analysis in families with VDDR-1 has mapped the disease locus to chromosome 12q13-14.¹⁰

End Organ Resistance to 1,25(OH)₂ Vitamin D. Hypocalcemia refractory to 1,25(OH)₂ vitamin D₃ has been described as type II vitamin D–dependent rickets, also known as hereditary 1,25(OH)₂ vitamin D₃–resistant rickets. This familial disorder is inherited by autosomal recessive transmission and is characterized by hypocalcemia, impaired intestinal absorption of calcium, rickets, and alopecia, which reflects a defect in the physiologic action of 1,25(OH)₂ vitamin D in the skin. In contrast to VDDR-1, in type II, the serum 1,25(OH)₂ vitamin D levels are elevated, and the patients either respond to pharmacologic doses of 1,25(OH)₂ vitamin D₃ or do not respond at all. Mutations of vitamin D receptor genes have been identified in these patients.

Disorders Related to Parathyroid Hormone**Reduced Production of PTH**

Hypoparathyroidism. Hypoparathyroidism is a disorder characterized by hypocalcemia and hyperphosphatemia due to deficient or absent secretion of PTH.

Hypoparathyroidism is a common cause of hypocalcemia. It can present as paresthesias, muscle spasms (i.e., tetany), and seizures. However, mild chronic hypoparathyroidism may cause hypocalcemia so gradually that the only symptoms may be visual impairment from cataracts after years of hypoparathyroidism. Hypoparathyroidism may be either an acquired abnormality designated as secondary hypoparathyroidism or primary hypoparathyroidism, also known as *idiopathic hypoparathyroidism*.

Secondary Hypoparathyroidism. Postoperative hypoparathyroidism may result from the removal of the parathyroid glands or the traumatic interruption of their blood supply. Hypocalcemia following parathyroid adenoma excision results from the functional suppression and hypofunctioning of the remaining normal glands and is usually transient. “Hungry bone” syndrome can develop following parathyroidectomy in patients with markedly elevated preoperative PTH levels. Decreased postoperative levels of PTH cause a “rebound” recalcification of the bones secondary to unbalanced osteoblast and osteoclast activity. This results in profound hypocalcemia, hypophosphatemia, and elevated alkaline phosphatase. Similarly, hypocalcemia has been reported to occur in 15% of patients after thyroidectomy.¹¹

Hypoparathyroidism may be a component of multiple endocrine dysfunctions, including adrenal insufficiency, pernicious anemia, thalassemia, and Wilson's disease. In the last two disorders, the deposition of iron and copper, respectively, in the parathyroid glands are the likely underlying mechanisms.¹²

Hypocalcemia may occur in magnesium depletion, likely secondary to the diminished release of PTH.¹³ Hypomagnesemia has also been reported to induce skeletal resistance to PTH.¹⁴ The magnesium level should always be checked during the workup of profound refractory hypocalcemia. It is speculated that magnesium depletion may impair the activity of calcium pumps and thus alter the distribution of calcium between the extracellular and the intracellular spaces.

Hypocalcemia in association with hypomagnesemia has been reported in 60% of patients with severe acute respiratory distress syndrome.¹⁵ Hypocalcemia may follow the therapeutic use of magnesium sulfate (e.g., in preeclampsia) secondary to magnesium-induced suppression of PTH. Aminoglycosides and cytotoxic agents may exert toxic effects on parathyroid glands, leading to hypocalcemia,^{1,13} and symptomatic hypoparathyroidism has been observed in association with HIV infection.¹

Primary (Idiopathic) Hypoparathyroidism. Primary hypoparathyroidism may occur in association with other endocrine disorders or as an isolated entity. The latter is termed *isolated hypoparathyroidism* and may occur as a sporadic or familial disorder, inherited as either the autosomal dominant or recessive forms.¹⁴

Aplasia or hypoplasia of the parathyroid glands is most commonly caused by the DiGeorge or velocardiofacial syndrome, which is associated with deletions in chromosome 22q11.2. Most cases are sporadic, but familial cases with autosomal dominant inheritance have been reported. The affected patients have abnormalities in the organs derived from the third and fourth branchial arches, including the parathyroid glands, thymus, and the outflow tract of the heart. These patients typically present in the first week after birth with signs of hypocalcemia, such as tetany and seizures. They have characteristic facial features, including an upturned nose and a widened distance between the inner canthi (telecanthus), with a short palpebral fissure. Cardiac defects include truncus arteriosus, tetralogy of Fallot, or interrupted aortic arch, and thymic hypoplasia leads to immune deficiencies. CATCH 22 syndrome is an acronym for cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia caused by chromosome 22q11 deletions.¹⁶

Autoimmune hypoparathyroidism is commonly a part of polyglandular autoimmune syndrome type I, which is a familial syndrome. It occurs during childhood and is inherited as an autosomal recessive trait. It can present as hypoparathyroidism in the absence of the two other disorders. Adrenal insufficiency is a late phenomenon in this syndrome. The acronym APECED stands for *autoimmune polyglandular endocrinopathy with candidiasis and ectodermal dystrophy*,

including vitiligo, alopecia, nail dystrophy, enamel hypoplasia of the teeth, and corneal opacities.¹⁷

Hypoparathyroidism has been reported in association with two mitochondrial cytopathies: Kearns-Sayre syndrome and Kenny-Caffey syndrome.¹⁸

Impaired Action of PTH Due to Peripheral Resistance

Pseudohypoparathyroidism. Pseudohypoparathyroidism is a rare inheritable disorder characterized by mental retardation, moderate obesity, short stature, brachydactyly with short metacarpal and metatarsal bones, exostoses, radius curvus, and an expressionless face.¹⁹ The biochemical abnormalities are hypocalcemia and hyperphosphatemia.

Calcitonin. Calcitonin binds to specific cell membrane receptors on bone-resorbing osteoclasts and depresses their activity. In this regard, it antagonizes the effect of PTH on bone.

Medullary carcinoma of the thyroid is derived from parafollicular cells of the ultimobranchial organ, which secretes calcitonin. It may present as a familial and autosomal dominant or sporadic disorder. Patients with this tumor have high circulating levels of calcitonin, and hypocalcemia has been reported in some patients.²⁰

Hypocalcemia has been described in critically ill patients admitted to intensive care units (ICUs).²¹ The degree of hypocalcemia correlates with the severity of the disease, and it is most commonly detected in patients who are septic. The mechanism of this abnormality is unknown. Circulating levels of calcitonin precursors (CTpr) increase up to several thousand-fold in response to microbial infections, and such increases correlate with the severity of the infection and mortality. The relationship between the elevated CTpr and the emergence of hypocalcemia requires further investigation.²²

Bisphosphonates. Hypocalcemia has been reported in patients with bone metastases of solid tumors who were treated with pamidronate²³ and in a patient treated with alendronate for osteoporosis. In both cases, bisphosphonate induced skeletal resistance, and PTH was proposed as a possible mechanism. Hypomagnesemia may cause hypocalcemia by a similar mechanism.²⁴

Rapid Removal of Calcium from the Circulation

Malignant Neoplasms. Hypocalcemia may develop in patients with malignant neoplasms in association with osteoblastic bone-forming metastases, most commonly cancer of the prostate and breast. These lesions may lead to rapid deposition of minerals in the newly formed matrix, thus causing hypocalcemia.

Hyperphosphatemia. The various causes of hyperphosphatemia that may lead to hypocalcemia are listed in Box 106-2. The oral or intravenous (IV) administration of phosphate lowers serum calcium concentrations in normal animals and hypercalcemic human subjects, which forms the basis for the clinical use of phosphate administration in states of hypercalcemia. The association of hyperphosphatemia and

hypocalcemia has been reported to occur in a variety of circumstances. Hyperphosphatemia has been observed in persons ingesting large quantities of phosphate-containing laxatives or receiving enemas with phosphate. Hyperphosphatemia and hypocalcemia with tetany may develop in infants fed cow's milk, which contains 1220 mg of calcium and 940 mg of phosphorus per liter (human milk contains 340 mg of calcium and 150 mg of phosphorus per liter).^{25,26} The mechanism responsible for lowering serum calcium concentrations by the administration of phosphate is not entirely understood. One possibility is that the decrease in serum calcium concentration is caused by the deposition of calcium phosphate in the bone, soft tissues, or both.

In chronic renal failure, an increase in serum phosphorus concentration is observed when the glomerular filtration rate is 30 mL/min or less, and hyperphosphatemia is a common accompaniment of acute renal failure.

In patients undergoing chemotherapy for neoplastic diseases, particularly of lymphatic origin, large quantities of phosphates may be released into the circulation as a result of cytolysis. Spontaneous tumor lysis may cause hyperphosphatemia and, consequently, hypocalcemia.

Acute Pancreatitis. The hypocalcemia associated with acute pancreatitis is not well understood. The precipitation of calcium soaps in the abdominal cavity, which results from the release of lipolytic enzymes and fat necrosis, has been suggested as the mechanism of hypocalcemia. Recently, endotoxemia has also been implicated.²⁷

Citrate, Bicarbonate, and Poisoning with Ethylene Glycol. Citrate is present in stored blood products (such as plasma and platelets) as an anticoagulant that exerts its action through the binding of ionized calcium. Patients receiving a massive transfusion frequently experience hypocalcemia; however, this is usually transient secondary to rapid hepatic metabolism of citrate.²⁸ Ionized hypocalcemia (with a normal total calcium concentration) can lead to tetany, myocardial dysfunction, or hypotension. Bicarbonate may directly complex calcium or may increase protein binding of calcium from the resulting alkalosis. Low serum ionized calcium may be a complication of ethylene glycol (antifreeze) poisoning because of calcium binding by oxalic acid, which is the metabolite of this poison.

Clinical Consequences of Hypocalcemia

The clinical presentation of hypocalcemia depends on its severity, the rapidity of the fall in serum calcium concentration, the age of the patient, the chronicity of the hypocalcemia, and comorbid conditions.

Most infants with hypocalcemia are asymptomatic. Among those who become symptomatic, the characteristic sign is increased neuromuscular irritability. Generalized or focal clonic seizures may be the first indication of hypocalcemia. Other manifestations may include stridor caused by laryngospasms and wheezing caused by bronchospasms. Vomiting may be caused by pylorospasm.

Neuromuscular manifestations of hypocalcemia in adults are variable (Box 106-3). The characteristic symptom is tetany, which includes perioral numbness and tingling, paresthesias in the extremities, carpopedal spasm, laryngospasm, and focal and generalized seizures. The spasms of the diaphragm and the intercostal muscles may cause respiratory arrest and asphyxia.

The characteristic physical findings in patients with hypocalcemia that are indicative of latent tetany are Trousseau's sign (carpal spasm) and Chvostek's sign (facial muscle contraction). Visual impairment may be caused acutely by papilledema, whereas when chronic hypocalcemia is due to hypoparathyroidism, it usually causes cataracts.

Acute hypocalcemia may be associated with hypotension, which is frequently aggravated by the absence of compensatory reflex tachycardia. The typical electrocardiogram (ECG) change in hypocalcemic patients is prolongation of the QT interval and is associated with a variety of ventricular arrhythmias, most characteristically torsades de pointes. These abnormalities can be reversed with calcium replacement. Calcium therapy significantly shortens the repolarization intervals and decreases the frequency of the premature ventricular contractions.²⁹ Chronic hypocalcemia may cause dilated cardiomyopathy, and partial

BOX 106-2

Hyperphosphatemia as a Cause of Hypocalcemia

ADMINISTRATION OF PHOSPHATE

Oral phosphate
Cow's milk in infants
Laxatives containing phosphate
Potassium phosphate tablets
Phosphate-containing enemas
Intravenous phosphate

RENAL DISEASES

Acute renal failure
Chronic renal failure

NEOPLASMS TREATED WITH CYTOTOXIC AGENTS

Lymphomas
Leukemia
Tumor lysis
Rhabdomyolysis

BOX 106-3**Disorders Associated with Hypercalcemia****PRIMARY HYPERPARATHYROIDISM****Adenoma and Carcinoma**

Hyperplasia

Multiple endocrine adenomatosis

Ectopic secretion of parathyroid hormone by neoplasms (rare)

SECONDARY HYPERPARATHYROIDISM

Malabsorption and vitamin D deficiency

Chronic renal failure

Following kidney transplantation

FAMILIAL HYPOCALCIURIC HYPERCALCEMIA**HYPERCALCEMIA ASSOCIATED WITH MALIGNANCY**

Lytic bone metastases

CIRCULATING TUMOR-SECRETED FACTORS

Parathyroid hormone–related protein

1,25-Dihydroxyvitamin D₃–induced hypercalcemia**LOCALLY ACTING, NONCIRCULATING, TUMOR-SECRETED CYTOKINES**

Interleukin (IL)-1 and IL-6

Tumor necrosis factor beta (TNF-β)

Granulocyte-macrophage colony-stimulating factor

Transforming growth factor alpha (TGF-α)

Prostaglandins

HYPERCALCEMIA IN PATIENTS WITH HYPERABSORPTIVE HYPERCALCIURIA**HYPERVITAMINOSIS D****HYPERVITAMINOSIS A****GRANULOMATOUS DISEASES**

Sarcoidosis

Tuberculosis

Histoplasmosis

Coccidioidomycosis

Leprosy

Foreign body granuloma

HYPERTHYROIDISM**ADRENOCORTICAL INSUFFICIENCY****INFANTILE HYPERCALCEMIA****IMMOBILIZATION****MILK-ALKALI SYNDROME****HYPOPHOSPHATASIA****PARENTERAL NUTRITION****HYPERCALCEMIA ASSOCIATED WITH ACUTE RENAL FAILURE****MEDICATIONS**

Thiazides

Lithium

Theophylline

Calcium ion-exchange resins

calcium can be provided as a drip of 100 to 200 mg of elemental calcium given over several hours until oral calcium takes over. Extravasation of calcium infusions should be avoided because of local irritation and thrombophlebitis.

Chronic treatment of hypocalcemia with oral calcium should follow IV therapy in patients with chronic hypocalcemia due to irreversible causes such as hypoparathyroidism. Oral calcium administration constitutes the best initial therapy in mild cases of hypocalcemia. The commonly used preparations are in tablet form: calcium lactate, 300 mg (60 mg of elemental calcium); chewable calcium gluconate, 1 g (90 mg of elemental calcium); calcium carbonate (Os-Cal; 250 mg of elemental calcium); calcium carbonate, 650 mg (250 mg of elemental calcium); and calcium citrate, 950 mg (200 mg of elemental calcium).

Oral calcium may be used in patients for whom the diagnosis of irreversible hypoparathyroidism has not been firmly established. In patients who fail to respond to oral calcium, vitamin D in large doses is the only available treatment. Both hypoparathyroidism and pseudohypoparathyroidism respond to physiologic doses of 1,25(OH)₂ vitamin D₃ and 1α(OH) vitamin D₃, with restoration of the serum calcium concentrations to normal. Calcitriol is marketed as Rocaltrol and is dispensed in capsules containing 0.25 or 1.0 μg. Chlorothiazides may enhance the calcemic action of vitamin D and its analogs, whereas furosemide may aggravate the hypocalcemia through its hypercalciuric action.

Patients in whom hypocalcemia is associated with hypomagnesemia respond poorly to IV calcium, but the serum calcium concentration is restored to normal levels with correction of the hypomagnesemia.

Symptoms rarely develop in patients with chronic renal failure and hypocalcemia. However, very often, reduction of elevated serum phosphorus with phosphate-binding antacids causes an increase in the serum calcium concentrations.

Hypocalcemia associated with osteomalacia resulting from vitamin D deficiency is rarely symptomatic. It usually responds to physiologic doses of vitamin D and increased oral calcium.

Hypercalcemia

Primary hyperparathyroidism and malignancy account for 80% to 90% of all cases of hypercalcemia.³¹ Primary hyperparathyroidism is the leading cause of hypercalcemia in the outpatient setting, with an incidence of 1% in the normal population.³² Hypercalcemia is most often detected in routinely tested blood specimens. Malignancy is the prevalent cause of hypercalcemia in hospitalized patients. The most common cause of iatrogenic hypercalcemia is milk-alkali syndrome (MAS), which ranks third after malignancy and hyperparathyroidism and accounts for 10% to 15% of the cases of hypercalcemia. The over-the-counter access to the generic brands of calcium carbonate and their widespread use for heartburn and osteoporosis may be an underlying cause for the rise in the incidence of MAS.³³

Hypercalcemia presents a challenge to every clinician. In some instances, the cause of hypercalcemia is self-evident on the basis of circumstantial clinical findings, whereas extensive efforts are required to establish the etiology in other situations. The important causes of hypercalcemia are listed in [Box 106-3](#).

Hyperparathyroidism

Since primary hyperparathyroidism is a surgically curable disease, prompt and accurate diagnosis is important.¹ The disease is more common in females than in males; the incidence increases in women after menopause but is less frequent in older men. Primary hyperparathyroidism is caused by a solitary adenoma in 80% to 85% of patients, multigland hyperplasia in 15% to 20%, and parathyroid carcinoma in less than 1% of patients.³⁴

The morphologic differentiation between adenomas and hyperplasia can be very difficult. The presence of a capsule and a rim of compressed normal gland tissue around the periphery of an adenoma may be helpful in making a definitive diagnosis. The persistence or

recovery of cardiac function has been reported after restoration of normocalcemia.³⁰

Treatment of Hypocalcemia

Symptomatic hypocalcemia generally responds promptly to the IV administration of calcium. The commonly used preparations are 10% calcium gluconate and 10% calcium chloride. Treatment should be instituted immediately, as delay can further aggravate tetany and lead to generalized seizures and even cardiac arrest.

The IV administration of 100 to 200 mg elemental calcium (5 to 10 mEq) should be slow to avoid complications. The administration of

recurrence of hypercalcemia after surgery for a purported adenoma should raise the suspicion of parathyroid hyperplasia. If more than one gland shows histologic features of hyperplasia, then a subtotal or total parathyroidectomy is recommended. Some patients with primary hyperparathyroidism have especially pronounced hypercalciuria despite a very mild degree of hypercalcemia and minimal or no bone disease. In patients with primary hyperparathyroidism, a very strong positive correlation was found between $1,25(\text{OH})_2$ vitamin D_3 in the serum and urinary calcium excretion. Patients with nephrolithiasis and hypercalcemia had circulating levels of $1,25(\text{OH})_2$ vitamin D_3 higher than those present in hyperparathyroid patients without renal stones. The reason for this difference in the $1,25(\text{OH})_2$ vitamin D_3 levels is unknown but stresses the importance of vitamin D metabolism in the clinical presentation of primary hyperparathyroidism.¹

Hyperparathyroidism is associated with multiple endocrine neoplasia (MEN) type I and II, both of which are inherited in an autosomal dominant fashion. MEN I syndrome is characterized by parathyroid hyperplasia, neuroendocrine tumors of the pancreas and duodenum, and pituitary adenomas. MEN II syndrome includes MEN IIA and MEN IIB; MEN IIA syndrome is characterized by pheochromocytoma, parathyroid hyperplasia, and medullary thyroid cancer, while MEN IIB syndrome includes medullary thyroid cancer, pheochromocytoma, mucosal neuromas, and a distinct physical appearance but does not involve hyperparathyroidism. Establishing the diagnosis of hyperparathyroidism associated with MEN syndrome has important surgical implications.^{35,36} The diagnosis of primary hyperparathyroidism requires the findings of elevated serum calcium and intact parathyroid hormone (iPTH) levels, normal renal function, and normal or increased urinary calcium excretion. Patients presenting with bone, renal, gastrointestinal, or neuromuscular symptoms are considered symptomatic and are best treated with surgical excision. Asymptomatic patients with primary hyperparathyroidism are surgical candidates if they meet the criteria established by the National Institutes of Health (NIH Criteria for Parathyroidectomy).^{37,38} These criteria include markedly elevated serum calcium (>12 mg/dL), a history of life-threatening hypercalcemia, creatinine clearance reduced by 30%, markedly elevated 24-h urine calcium (>400 mg/d), nephrolithiasis, age <50 years, osteitis fibrosa cystica, and substantially reduced bone mass (>2 standard deviations below control).

Recent advances in imaging allow preoperative or intraoperative localization of parathyroid adenomas, thus permitting a minimally invasive surgical approach. Options include the $^{99\text{m}}\text{Tc}$ -sestamibi scan with or without single-photon emission computed tomography, computed tomography, ultrasonography, magnetic resonance imaging, and thallium-201/technetium pertechnetate scanning. The most promising preoperative adjunct, however, seems to be intraoperative PTH monitoring.³⁹

Familial hypocalciuric hypercalcemia is an unusual form of parathyroid hyperplasia with autosomal dominant transmission. It is usually asymptomatic and incidentally diagnosed by an elevated serum calcium level and confirmed by a low urinary calcium level. The clinical course is relatively benign, with an absence of nephrolithiasis and an infrequent occurrence of pancreatitis and chondrocalcinosis, and it usually requires no specific therapy.

Malignancy Associated with Hypercalcemia

Hypercalcemia is most commonly associated with tumors of the lung, breast, kidney, and ovary and hematologic malignancies. Two main mechanisms are known to mediate the hypercalcemia of malignancy: local and humoral.⁴⁰ The local mechanism is manifested by the presence of osteolytic lesions in the skeleton. The malignant cells may act to destroy the bone directly; however, even local osteolysis is mediated by activated osteoclasts in most instances. The humoral factor most commonly associated with hypercalcemia of malignancy is parathyroid hormone-related protein (PTHrP).⁴¹ PTHrP induces osteoclastic resorption of bone, increases tubular reabsorption of calcium in the kidneys, and inhibits osteoblast activity through the action of cytokines such as interleukin-6.⁴² These factors explain why serum calcium

rises rapidly in cancer patients in contrast to the gradual rise in hyperparathyroidism.

Multiple Myeloma and Hypercalcemia

Hypercalcemia occurs in approximately one-third of patients with myeloma. Osteolytic bone lesions are the most common skeletal radiographic findings. The bone destruction in myeloma is mediated by osteoclasts that accumulate adjacent to the collections of myeloma cells. This relationship between myeloma cells and osteoclasts explains the rapid destruction of bone in this malignancy.^{43,44}

Vitamin D Intoxication and Hypercalcemia

All patients receiving vitamin D, other than in small doses, may develop hypercalcemia, with the attendant risk of renal failure. The appearance of hypercalcemia in hypoparathyroid patients receiving pharmacologic doses of either ergocalciferol (vitamin D_2) or dihydroxycholesterol 3 is unpredictable, because the margin between normocalcemic and hypercalcemic doses of the vitamin is very narrow. Hypercalcemia associated with vitamin D intoxication may be present from 1 to 6 weeks after discontinuation of treatment, and normocalcemia may persist for an additional 4 months without any treatment. The toxic effect of vitamin D excess is associated with a high circulating level of $25(\text{OH})$ vitamin D_3 , which is continuously produced by the liver from the adipose tissue stores of vitamin D. The serum level of $1,25(\text{OH})_2$ vitamin D_3 is not generally elevated and may even be reduced; however, free non-protein-bound $1,25(\text{OH})_2$ vitamin D_3 levels may be elevated. Hypercalcemia associated with $1,25(\text{OH})_2$ vitamin D_3 administration, however, is much more short lived (3 to 7 days).⁴⁵

Various factors may alter the response to vitamin D. The inhibitory effect of estrogens on bone resorption may be absent after menopause, which allows more calcium to be released from bone for any given dose of vitamin D. The administration of corticosteroids may reduce the effect of vitamin D; in fact, corticosteroids may be used to treat vitamin D intoxication. The most important precaution in preventing the complications of vitamin D intoxication is to measure serum calcium concentrations frequently in these patients. Likewise, the presence of excessive hypercalciuria, even in the absence of hypercalcemia, is a risk factor for nephrocalcinosis and renal failure. Thus, monitoring of urinary calcium excretion in these circumstances is recommended as well.

Vitamin A Intoxication and Hypercalcemia

Hypercalcemia is also associated with excessive intake of vitamin A,⁴⁶ which is readily available in various pharmaceutical preparations. Isotretinoin, a derivative of vitamin A that is effective in the treatment of severe acne, has been reported as a cause of hypercalcemia. The main symptom of vitamin A intoxication is painful swelling in the extremities. Prolonged hypercalcemia in this condition has also been associated with nephrocalcinosis and the impairment of renal function.

Sarcoidosis and Hypercalcemia

Sarcoidosis is a systemic granulomatous inflammatory disease characterized by noncaseating granulomas in multiple organ systems. Hypercalciuria is the most common defect in calcium metabolism; however, hypercalcemia occurs in approximately 5% of patients.⁴⁷

Plasma levels of $1,25(\text{OH})_2$ vitamin D_3 have been found to be increased in patients with sarcoidosis and hypercalcemia, a finding that accounts for the abnormal calcium metabolism in this disease. In most of the patients, glucocorticoids can normalize the serum levels of calcium and $1,25(\text{OH})_2$ vitamin D_3 . Low levels of serum immunoreactive PTH have been found in patients with sarcoidosis, regardless of the presence or absence of hypercalcemia.⁴⁷

Hyperthyroidism, Hypothyroidism, and Hypercalcemia

Hyperthyroidism is associated with accelerated bone turnover, which is caused by the direct stimulation of bone cells by the high thyroid

hormone concentrations.⁴⁸ Biochemical markers of bone formation and resorption (osteocalcin, alkaline phosphatase, bone-specific alkaline phosphatase, and urinary collagen pyridinoline) are elevated in hyperthyroid patients, indicating increased bone turnover in favor of osteoclastic bone resorption.⁴⁹ The resultant hypercalcemia may be reversed by antithyroid therapy.⁵⁰

Serum calcium and phosphate levels are normal and alkaline phosphatase is low in the vast majority of patients with hypothyroidism; however, some patients may manifest hypercalcemia. The calcium balance in patients with hypothyroidism tends to be positive as a result of increased intestinal absorption and reduced urinary excretion. Both changes predispose to the development of hypercalcemia. Bone turnover in hypothyroid patients is reduced.

Adrenal Insufficiency and Hypercalcemia

Hypercalcemia is a common abnormality in adrenal insufficiency, although the mechanism is not well understood. One study has indicated that the increase in serum calcium concentration is due to an increase in the protein-bound fraction of serum calcium that results from the accompanying volume depletion. Volume depletion may also cause an increase in the renal tubular reabsorption of calcium, and vitamin D's enhancement of calcium absorption from the intestine may be greater in the absence of glucocorticoid hormone.⁵¹

Idiopathic Infantile Hypercalcemia

Idiopathic infantile hypercalcemia (IIH) is a rare cause of hypercalcemia in the first year of life and is a diagnosis of exclusion. Clinical features include vomiting, irritability, constipation, increased thirst, and failure to thrive.⁵² While the pathophysiology of IIH remains unclear, some authors attribute the hypercalcemia to intestinal vitamin D sensitivity that leads to increased calcium absorption and contributes to persistent hypercalciuria.⁵³ Treatment options for IIH include corticosteroids, low-calcium diet, calcitonin, and cellulose phosphate. Patients usually experience spontaneous resolution of hypercalcemia.

Immobilization and Hypercalcemia

Immobilization may be associated with excessive loss of bone minerals, hypercalcemia, and rapidly developing osteoporosis. The lack of postural mechanical stimuli to the skeleton disturbs the balance between bone formation and resorption, thus leading to the loss of bone mass. Usually, the amount of calcium released from bone is excreted in the urine and does not increase the serum calcium concentrations. Due to a reduced ability to excrete calcium in the urine, patients with pre-existing renal impairment are prone to develop immobilization hypercalcemia.⁵⁴

Milk-Alkali Syndrome

MAS may occur in patients who ingest large amounts of milk and alkali as a therapy to relieve the symptoms of peptic ulcers. This syndrome is characterized by hypercalcemia, hyperphosphatemia, alkalosis, metastatic calcifications, and progressive renal failure. The ingestion of large amounts of calcium carbonate (at least 4 to 5 g daily) and absorbable alkali is a prerequisite for establishing the diagnosis.³³ For hypercalcemia to develop, calcium intake must be excessive, but the inability to excrete this excessive calcium may also be important. Preexisting renal insufficiency has been implicated in the pathogenesis of MAS, as have medications that affect renal calcium excretion, such as thiazide diuretics.

Thiazide Diuretics and Hypercalcemia

Chronic administration of thiazide diuretics may lead to hypercalcemia in patients treated with large doses of vitamin D (hypoparathyroid patients and patients with osteoporosis) and in patients with hyperparathyroidism. The mechanism of action may involve (1) reduced urinary excretion of calcium due to a direct tubular effect or extracellular fluid depletion with a secondary increase in tubular reabsorption of sodium and calcium or both; and (2) increased bone responsiveness to the resorptive actions of vitamin D and PTH.

Lithium and Theophylline Toxicity

Patients treated chronically with lithium may develop hypercalcemia with elevated PTH levels. The incidence of primary hyperparathyroidism in patients with bipolar affective disorders treated with lithium is 47-fold higher than in the general population. To date, 50 cases of parathyroid adenomas and hyperplasia associated with chronic lithium therapy have been reported.^{55,56} Theophylline toxicity may be associated with hypercalcemia, probably due to the stimulation of the beta-adrenergic receptors in bone.

Clinical Manifestations of Hypercalcemia

The symptoms of hypercalcemia depend on the rate of onset, magnitude, duration, underlying disorder, and comorbid conditions. Acute hypercalcemia may induce acute renal failure due to extracellular volume contraction and direct renal vasoconstriction. This abnormality is reversible, whereas chronic hypercalcemia may cause nephrolithiasis and nephrocalcinosis with tubulointerstitial scarring and chronic renal failure. Hypercalcemia may cause constipation, nausea and vomiting, and peptic ulcer disease. Polyuria is caused both by its natriuretic effect and impaired urinary concentration with features of nephrogenic diabetes insipidus.

Hypercalcemia leads to membrane hyperpolarization with a shortened QT interval, but cardiac arrhythmias are rare.

Neuromuscular effects of hypercalcemia include impaired concentration and memory, muscle weakness and fatigue, confusion, lethargy, stupor, and coma (Table 106-1).

Bone pain can occur in patients with hyperparathyroidism or malignancy. Osteoporosis of the cortical bone is associated with hyperparathyroidism. Familial hypocalciuric hypercalcemia is rarely associated with bone disease, but chondrocalcinosis and pseudogout have been reported to occur at high frequency.

Hypercalcemic crisis is a life-threatening emergency that warrants aggressive treatment. It may be a complication of primary hyperparathyroidism, malignancy, and other hypercalcemic disorders. It is characterized by very high serum calcium levels exceeding 15 mg/dL. The treatment is aimed at restoring the extracellular volume to normal and lowering the serum calcium levels. Acute hemodialysis with calcium-free dialysate may become a necessity.

Treatment of Hypercalcemia

Lowering of serum calcium concentration can be produced by: (1) inhibiting calcium release from the bone, increasing its deposition in the bone and other tissues, or both; (2) increasing the removal of calcium from the extracellular fluid or inhibiting its absorption in the bowel; and (3) decreasing the ionized fraction by complex formation with chelating substances.

Hypercalcemia augments urinary losses of sodium and water, resulting in the contraction of extracellular volume and reduced glomerular filtration rate. The latter leads to diminished urinary excretion of calcium and further aggravation of hypercalcemia. Therefore, the first therapeutic goal is to restore the extracellular volume to normal by IV administration of normal saline, which usually requires 3 to 4 liters of saline. This therapeutic action lowers the serum calcium concentration, partly by the dilutional effect and partly by the increased urinary excretion of calcium. There is a risk of extracellular volume overload during rapid IV administration of saline, which is particularly hazardous in elderly patients. Therefore, monitoring of the central venous pressure in this situation may be very helpful. Likewise, the addition of loop diuretics as an adjunct therapy may minimize the risk of fluid overload and increase the urinary excretion of calcium. The effect of loop diuretics as calciuretic agents requires prompt replacement of the urinary losses of sodium and water. The use of loop diuretics may be particularly beneficial in patients who develop hypercalcemia as a result of excessive secretion and high serum levels of PTH, PTHrP, or both. Hormone-induced, excessive tubular reabsorption of calcium plays a major role in the development and maintenance of hypercalcemia in these circumstances.

Bisphosphonates. Bisphosphonates (formerly diphosphonates) represent a group of drugs with a high therapeutic potential for the treatment of hypercalcemia in general and that are associated with malignancy in particular. Bisphosphonates have a great affinity for bone and bind tightly to calcified bone matrix, impairing both the mineralization and resorption of bone. In addition, they interfere with the function of osteoclasts and appear to have several direct effects on osteoclast function, including the prevention of osteoclast attachment to the bone matrix and the prevention of osteoclast differentiation and recruitment. Bisphosphonates are very potent inhibitors of bone resorption.

Ethane hydroxybisphosphonate (etidronate [Didronel]), is available for clinical use, but its potency as an antihypercalcemic agent is limited, at least when given orally. Reduction of the serum calcium concentration has been more successfully achieved with the second generation of bisphosphonates, including dichloromethylene bisphosphonate (clodronate) and amino-hydroxypropylidene bisphosphonate (pamidronate; ADP), which cause a reduction in bone resorption with a dose that has a negligible effect on bone mineralization. Pamidronate and etidronate are approved for the treatment of hypercalcemia of malignancy in the United States. Pamidronate is most effective when given via the IV route, with doses of 60 to 90 mg generally recommended. When compared, the effect of 30 mg of pamidronate is equal to that of 600 mg of clodronate and 1500 mg of etidronate in controlling hypercalcemia. In preliminary studies, the third generation of bisphosphonates, including alendronate, risedronate, and tiludronate, was found to be 500 times more efficient in inhibiting bone resorption than clodronate. Zoledronic acid is one of a new generation of nitrogen-containing bisphosphonates that has been found to be superior to pamidronate in clinical studies. This agent has been approved for clinical use.

Glucocorticoids. Glucocorticoids are effective at lowering serum calcium in states of vitamin D intoxication; possible mechanisms are the suppression of bone resorption and the reduction of intestinal absorption. Glucocorticoids are more effective in hypercalcemia associated with lymphoma, leukemia, and multiple myeloma than with other neoplasms. This effect might be related to a tumor lytic effect, interference with the production of osteoclast-activating cytokines, or both. The fall in serum calcium concentration occurs 1 to 2 days after starting the therapy.

Calcitonin. Calcitonin lowers serum calcium concentrations by inhibiting bone resorption and increasing urinary calcium excretion. The administration of calcitonin is associated with negligible toxicity; however, its therapeutic action has a limited duration because of the osteoclast escape phenomenon, which is apparent several days after starting therapy. The addition of glucocorticoids may be helpful to maintain efficacy.

Mithramycin (Plicamycin). Mithramycin is a cytotoxic substance derived from an actinomycete of the genus *Streptomyces* and is used mainly in the treatment of testicular tumors. Mithramycin lowers serum calcium concentrations by suppressing bone resorption and is available commercially as Mithracin. Its effect starts 24 to 48 hours after injection and lasts several days. Side effects include the suppression of bone marrow activity and hepatocellular and renal toxicity, which usually occurs with repeated doses.

Phosphate. Oral and IV salts of phosphorus lower the serum concentration and reduce the urinary excretion of calcium. This effect has been variously attributed to: (1) the deposition of mineral in the bone, (2) increased deposition of calcium in soft tissues, and (3) the suppression of bone resorption. The major untoward side effects of this therapy are extraskeletal calcifications, including nephrocalcinosis with resulting renal failure. Thus, the use of phosphates to treat hypercalcemia should be discouraged in patients with high serum phosphate and renal insufficiency. Phosphates may be given via the IV route at a dose of 20 to 30 mg of elemental phosphorus per kilogram of body weight over 12 to 16 hours. Serum calcium concentration should be determined at frequent intervals. The commercially available preparation for IV use is InPhos; 40 mL of this solution contains 1000 mg of phosphorus, 65 mEq of sodium, and 8 mEq of potassium.

Other Therapies. Gallium nitrate has been approved by the Food and Drug Administration for the treatment of hypercalcemia. It inhibits bone resorption by reducing the solubility of hydroxyapatite crystals. Nephrotoxicity is a major side effect of gallium nitrate. The use of a somatostatin congener (lanreotide) has been reported to successfully inhibit hypercalcemia in a patient with a PTHrP-secreting pancreatic neoplasm. The calcium-lowering effect is associated with the suppression of the serum levels of PTHrP.

The hypercalcemia associated with thyrotoxicosis and theophylline toxicity has been successfully treated with IV propranolol.

Intestinal absorption of calcium may be reduced by dietary restrictions and the binding of calcium in the bowel with cellulose phosphate and sodium phytate. Calcium also may be removed directly from the extracellular fluid with hemodialysis or peritoneal dialysis by employing calcium-free dialysate solution.

The reduction of serum-ionized calcium may be accomplished with IV Na-ethylene diamine tetraacetic acid (EDTA), which is a chelating agent. The complexed calcium is then excreted in the urine. The main disadvantage of this therapy is the nephrotoxicity of EDTA.

DISORDERS OF MAGNESIUM METABOLISM

Magnesium is the second most abundant intracellular cation. The intracellular concentration of magnesium ranges between 10 and 20 mEq/L; however, most of it is bound to organic compounds, including adenosine triphosphate (ATP). Of the fraction found in the extracellular space, one-third is bound to serum albumin. Therefore, the plasma levels of magnesium may be a poor indicator of the total body stores in the presence of hypoalbuminemia. The exchange between the extracellular and intracellular compartments appears to be slow, and changes in intake and intestinal absorption are tightly balanced by parallel changes in urinary excretion.^{57,58}

In the presence of normal kidney function, the serum levels of magnesium are maintained at nearly constant values ranging from 1.4 to 1.7 mEq/L (1.7–2.1 mg/dL). Hypermagnesemia can be encountered primarily with impaired kidney function and excessive oral or parenteral load. Hypomagnesemia results from decreased dietary intake, intestinal malabsorption, or renal losses.⁵⁷

Magnesium plays an important role in the function of many key enzymes including ATP. Intracellular magnesium is key to protein synthesis, oxidative phosphorylation, nucleic acid stability, the storing and utilization of energy, and enzymatic reactions. Extracellular magnesium is essential for nerve conduction, neuromuscular transmission, cardiac conduction and contractility, and vascular tone.

Although the total serum magnesium concentration is commonly utilized to assess magnesium, it is not ideal.⁵⁹ Changes in serum protein concentrations may affect the total serum concentration but are not reflective of total body magnesium. A magnesium tolerance test can be used to determine magnesium status but requires calculating the amount of retained parenteral magnesium. Measurement of ionized magnesium is not yet readily available.

Hypomagnesemia and Magnesium Depletion

Hypomagnesemia is a common problem in hospitalized patients, particularly in the ICU. The kidney is primarily responsible for magnesium homeostasis through regulation by calcium/magnesium receptors on renal tubular cells that sense serum magnesium levels.⁶⁰ Hypomagnesemia results from a variety of etiologies, ranging from poor intake, increased renal excretion, gastrointestinal (GI) losses, malabsorption, and a variety of endocrine dysfunctions. The causes of hypomagnesemia can be divided into two major categories: (1) extrarenal magnesium losses, including deficient intake, and (2) renal losses.

Extrarenal Losses of Magnesium

Dietary deprivation, prolonged malnutrition, tube feeding, and parenteral nutrition deficient in magnesium may induce cumulative

magnesium depletion and hypomagnesemia. GI losses may be caused by steatorrhea, severe diarrhea, or acute pancreatitis. Hypomagnesemia may also follow surgery for morbid obesity with short bowel syndrome and diarrhea.⁵⁷

Endocrine causes for hypomagnesemia include hyperthyroidism, hypercalcemia associated with malignancy, and hyperaldosteronism.⁶¹ Hungry bone syndrome after parathyroidectomy may lead to both hypocalcemia and hypomagnesemia owing to increased deposition of both divalent ions in the newly deposited bone mineral.

Chronic alcoholism is one of the leading causes of magnesium depletion. Poor nutrition, diarrhea, chronic pancreatitis, and renal tubular defects may contribute to hypomagnesemia.⁶² Severe burns may lead to sequestration of magnesium in necrotic tissue, including necrotic fat, leading to magnesium depletion. Acute dialysis for severe refractory hypercalcemia without the addition of magnesium to the dialysate may cause hypomagnesemia.

Renal Losses of Magnesium

Osmotic diuresis induced by salt loads, diabetic ketoacidosis, and mannitol all increase urinary excretion of many electrolytes, including magnesium. During recovery from ketoacidosis, especially after phosphate replacement, a precipitous fall in serum magnesium may occur.

Hypercalcemia as seen with primary hyperparathyroidism, hyperthyroidism, and IV administration of calcium causes renal losses of magnesium. Similarly, loop diuretics cause renal magnesium and calcium wasting, whereas thiazides enhance urinary excretion of magnesium but cause tubular retention of calcium. Primary hyperaldosteronism and the syndrome of inappropriate antidiuretic hormone are associated with modest increases in urinary magnesium excretion.

Renal magnesium wasting has been observed in patients treated with aminoglycosides, amphotericin B, and cisplatin.⁶³⁻⁶⁵ These agents may lead to potassium wasting and renal tubular acidosis. Cyclosporine and tacrolimus cause magnesium wasting with potassium retention. Loop diuretics can also lead to magnesium wasting. The diuretic phase of acute renal failure also may lead to magnesium loss.

Inherited Disorders of Renal Magnesium Losses

Isolated Dominant Hypomagnesemia. These patients present with generalized seizures in childhood. Hypocalciuria, but not hypocalcemia, is present.

Isolated Recessive Hypomagnesemia. Affected individuals present with symptoms of hypomagnesemia during infancy. Hypomagnesemia due to increased urinary magnesium excretion is the only biochemical abnormality. Linkage analysis has thus far excluded all established gene loci.⁶³

Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis (FHHNC). FHHNC is an autosomal recessive disorder characterized by renal magnesium and calcium wasting, bilateral nephrocalcinosis, and nephrolithiasis with progressive renal failure. FHHNC patients present during early childhood with recurrent urinary tract infections, polyuria and polydipsia, failure to thrive, abdominal pain, vomiting, tetanic episodes, and generalized seizures. PTH levels are increased before renal failure.

Autosomal Dominant Hypocalcemia. Activating mutations of the calcium-sensing receptor lead to hypocalcemia, hypocalciuria, and in about 50% of patients, hypomagnesemia.

Classic Bartter Syndrome. Classic Bartter syndrome is caused by mutations in the *CLCNKB* gene encoding the basolaterally located renal chloride channel CIC-KB, which mediates chloride efflux from the tubular epithelial cells to the interstitium. Hypomagnesemia is detected in up to 50% of patients with mutations in *CLCNKB* in chromosome 1p36.⁶³

Gitelman Syndrome. Gitelman syndrome is an autosomal recessive disorder. Symptoms include muscle weakness and tetanic episodes that are related to profound hypomagnesemia. Patients always present with hypocalciuria; the presence of both hypomagnesemia and hypocalciuria is diagnostic. Loss-of-function mutations in the gene coding for the NaCl cotransporter of the distal convoluted tubule is the underlying abnormality.

TABLE 106-1

Clinical Manifestations of Abnormalities in Magnesium and Calcium

| INCREASED SERUM LEVELS | | |
|------------------------|--|---|
| SYSTEM | MAGNESIUM | CALCIUM |
| Gastrointestinal | Nausea/vomiting | Anorexia, nausea/vomiting, abdominal pain, constipation |
| Neuromuscular | Weakness, lethargy, ↓ reflexes | Depression, confusion, coma, muscle weakness, back and extremity pain |
| Cardiovascular | Hypotension, cardiac arrest | Hypotension, arrhythmias |
| Renal | — | Polydipsia, polyuria |
| DECREASED SERUM LEVELS | | |
| SYSTEM | MAGNESIUM | CALCIUM |
| Gastrointestinal | — | — |
| Neuromuscular | Hyperactive reflexes, muscle tremors, tetany, delirium, seizures | Hyperactive reflexes, paresthesias, weakness, paralysis, tetany, seizures, carpal spasm |
| Cardiovascular | Arrhythmia | Heart failure |

Clinical Consequences of Magnesium Depletion

The clinical manifestations of hypomagnesemia depend on its severity, duration, and coexistent electrolyte abnormalities. Hypomagnesemia and the depletion of intracellular magnesium stores, especially in the cardiac muscle, have been considered to underlie cardiovascular and other functional abnormalities, including cardiac arrhythmias such as atrial fibrillation and torsades de pointes, impairment of cardiac contractility, and vasoconstriction. This may be especially important in patients undergoing coronary artery bypass graft surgery.⁶⁶ Magnesium depletion is also characterized by neuromuscular and central nervous system hyperactivity, and the symptoms are similar to those of calcium deficiency, including hyperactive reflexes, muscle tremors, and tetany with a positive Chvostek's sign (see Table 106-1). Severe deficiencies in magnesium can lead to delirium and seizures. The neurologic effects of magnesium balance were recently demonstrated in a prospective observational study that demonstrated an association between high dietary magnesium intake and reduced stroke rate.⁶⁷

Hypomagnesemia is important not only for its direct effects on the nervous system but also because it can produce hypocalcemia and lead to persistent hypokalemia. When hypokalemia or hypocalcemia coexists with hypomagnesemia, magnesium should be aggressively replaced to assist in restoring the potassium or calcium homeostasis. Prolonged insufficiency of magnesium results in anorexia, nausea, vomiting, and weakness within weeks and in paresthesias and muscle weakness, cerebral seizures, and cardiac manifestations within months.

ECG changes in magnesium depletion include widening of the QRS complex and peaking of T waves, followed by prolongation of the PR interval and diminution of T waves. Ventricular arrhythmias are more common during myocardial ischemia after cardiopulmonary bypass. Magnesium prevents the increase in action potential duration and prolongation in membrane repolarization, which normally occurs in ischemic myocardium.⁶⁶

Treatment of Hypomagnesemia

The amount and route of magnesium replacement depend on the degree of hypomagnesemia and severity of the symptoms. In patients with asymptomatic hypomagnesemia, treatment of the underlying disorder (e.g., diarrhea) and dietary adjustments may solve the problem.

Correction can be oral if the hypomagnesemia is asymptomatic and mild. Oral magnesium can lead to diarrhea, which may limit its utility. Magnesium oxide tablets have high magnesium content compared with other oral preparations such as magnesium chloride, magnesium sulfate, and magnesium acetate. Oral replacement of magnesium can also be made with antacids that contain both magnesium and aluminum in patients who develop diarrhea from magnesium oxide. If hypomagnesemia is associated with the use of diuretics that need to be continued, the addition of potassium-sparing diuretics such as amiloride may be helpful. Amiloride may also be considered in other states of magnesium wasting such as Bartter or Gitelman syndrome.

The use of IV magnesium repletion depends on the severity and symptoms associated with hypomagnesemia. For patients with severe deficits (<1.0 mEq/L) or those who are symptomatic, administer 1 to 2 g of magnesium sulfate IV over 15 minutes. Caution should be exercised when giving large amounts of magnesium, as magnesium toxicity may develop. Administration of simultaneous calcium gluconate counteracts the adverse side effects of rapidly rising magnesium levels and corrects hypocalcemia, which is frequently associated with hypomagnesemia.

In states of emergency such as torsades de pointes, 2 g of magnesium sulfate over 2 minutes is recommended to suppress early depolarization. Magnesium is also a first-line drug for use in eclampsia.⁶⁸ Magnesium has a potentially deleterious effect on arteriovenous conduction; therefore, it is relatively contraindicated in greater than first-degree arteriovenous block and sinus bradycardia.

Hypermagnesemia

Normal kidneys can dispose of large filtered loads of magnesium by attenuating tubular reabsorption to a minimum after the renal tubular T_m is exceeded. Thus, intact kidneys are the major regulating organ for maintaining magnesium balance. The most common cause of hypermagnesemia is the concurrence of excessive magnesium load in the presence of impaired renal function. Often, a large magnesium load is the consequence of therapeutic employment of magnesium salts as laxatives or enemas. Hypermagnesemia may be more common in the elderly, who often consume magnesium salts as antacids and laxatives and display aging-related reduction in renal function.

Endogenous magnesium loads may be released in rhabdomyolysis from necrotic muscles and in tumor lysis from malignant cells

destroyed by chemotherapy. Acute IV magnesium loads, such as those given in preeclampsia, may cause transient hypermagnesemia occasionally accompanied by hypocalcemia as a result of the acute suppression of PTH by high serum magnesium. Children born to mothers with preeclampsia may have hypermagnesemia as well.

Patients with chronic renal failure may present with mild elevation of serum magnesium; however, the ingestion of magnesium salts should be avoided because they may induce life-threatening hypermagnesemia.

Adrenal insufficiency, primary hyperparathyroidism, MAS, and familial hypocalciuric hypercalcemia may be associated with hypermagnesemia. Lithium and theophylline have also been reported to cause hypermagnesemia.

Clinical Manifestations

Mild hypermagnesemia with serum magnesium levels less than 3 mEq/L (3.6 mg/dL, 1.5 mmol/L) is usually asymptomatic. Above these values, the severity of the symptoms parallels the magnitude of the elevation in serum magnesium. The major manifestations of hypermagnesemia are neuromuscular, central nervous system, and cardiovascular abnormalities (Table 106-1).

Neuromuscular manifestations relate to the curare-like action of hypermagnesemia, hindering the neuromuscular impulse transmission. Such neuromuscular abnormalities are first manifested as reduced deep tendon reflexes progressing to areflexia, muscle paralysis, and apnea. Central nervous system abnormalities consist of lethargy and coma.

The cardiovascular effects of hypermagnesemia may be related to its activity as an ion channel blocker. These effects lead to bradycardia and hypotension and may progress to cardiac arrest. ECG abnormalities are similar to those seen with hyperkalemia and consist of an increased PR interval, widened QRS, and peaked T waves. With a rise in serum magnesium above 10 mEq/L, complete heart block and cardiac arrest are the terminal events.

Treatment of Hypermagnesemia

Treatment for hypermagnesemia consists of measures to withhold exogenous sources of magnesium, correct volume deficit, and correct acidosis if present. To manage acute symptoms, calcium chloride (5–10 mL) should be administered to antagonize the cardiovascular effects. If elevated levels or symptoms persist, dialysis is indicated.

KEY POINTS

Hypocalcemia

1. Serum levels of 25(OH) vitamin D serve as an estimate of the body stores of vitamin D. Low serum concentrations of 25(OH) vitamin D indicate a state of vitamin D deficiency.
2. Hypoparathyroidism is a common cause of hypocalcemia. Magnesium depletion inhibits parathyroid hormone (PTH) secretion and peripheral responses to PTH and to vitamin D; it also blunts the calcemic effect of intravenous calcium. Thiazides enhance the calcemic effect of vitamin D, whereas furosemide aggravates the hypocalcemia.
3. Neuromuscular manifestations of hypocalcemia include confusion or coma, focal and generalized seizures, and respiratory arrest. Cardiovascular complications of acute hypocalcemia include hypotension, bradycardia, and ventricular arrhythmias such as torsades de pointes.
4. Hypoparathyroidism, and particularly, the variant autosomal dominant hypocalcemia, should be treated cautiously. Raising

serum calcium levels may cause hypercalciuria, with increased risk of nephrocalcinosis and renal failure.

Hypercalcemia

1. Malignancy is the prevalent cause of hypercalcemia, accounting for 70% to 80% of all cases, and is most commonly seen in hospitalized patients. Primary hyperparathyroidism is common in the outpatient setting, accounting for 10% to 20% of all cases of hypercalcemia. Milk-alkali syndrome ranks third.
2. Familial hypocalciuric hypercalcemia is a form of parathyroid hyperplasia with autosomal dominant transmission. It is caused by an inactivating mutation of a calcium-sensing receptor. The clinical course is benign, without nephrolithiasis, but hypermagnesemia, pancreatitis, and chondrocalcinosis may occur.
3. Hypercalcemic crisis is a life-threatening emergency. It may be a complication of primary hyperparathyroidism, malignancy, and

Continued

KEY POINTS—cont'd

other hypercalcemic disorders. It warrants aggressive treatment to lower the serum calcium concentration.

4. The first goal in treating hypercalcemia is to restore the extracellular volume to normal by intravenous administration of normal saline.

Hypomagnesemia

1. Hypomagnesemia is common in hospitalized patients (>10%) and even more so in the intensive care unit setting (>50%). Concerns regarding hypomagnesemia are focused on its potential role in cardiac arrhythmias (e.g., torsades de pointes) and sudden death.
2. Hypomagnesemia leads to renal losses of potassium, and vice versa, hypokalemia augments urinary losses of magnesium. In the former, hypokalemia may be refractory to potassium replacement unless magnesium repletion is accomplished first.

Hypermagnesemia

1. The most common cause of hypermagnesemia is excessive magnesium loads in the presence of impaired renal function. Very often, a large magnesium load comes from the therapeutic use of magnesium salts as laxatives or enemas.
2. Neuromuscular manifestations of hypermagnesemia relate to its curare-like effect, leading to the loss of reflexes, muscle weakness and paralysis, and apnea. Central nervous system abnormalities are lethargy, drowsiness, dilated pupils, and coma.
3. The cardiovascular effects of hypermagnesemia consist of bradycardia and hypotension. The electrocardiogram shows an increased PR interval and QRS complex. Complete heart block and cardiac arrest are the terminal events.

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This is a comprehensive review of magnesium balance with an in-depth classification of hypomagnesemia and magnesium deficiency as well as hypermagnesemia.

■ References for this chapter can be found at expertconsult.com.

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The goals of fluid administration are to optimize tissue oxygenation by augmenting intravascular volume, improving left ventricular preload, and increasing cardiac output.¹ This chapter reviews the timing and considerations for choice of therapy in volume repletion, as well as the effects of fluid volume overload in the postresuscitation period.

TIMING OF INITIAL VOLUME THERAPY

Studies from the early 2000s suggested that earlier recognition and treatment of septic shock correlated with improved outcomes. In a report by Rivers et al., the Early Goal-Directed Therapy Collaborative Group randomized subjects to receive either intensive treatment for septic shock within the initial 6 hours of therapy versus standard therapy provided in the emergency department.² Standard and early goal-directed therapy (EGDT) groups received antibiotics, vasoactive medications, and intravenous (IV) fluid for volume resuscitation. Goals for fluid administration included infusion of crystalloid in 500-mL boluses every 30 minutes in order to achieve a central venous pressure of 8–12 mm Hg as a marker of effective repletion of intravascular volume and response to fluids. Whereas the total volume of fluid administered by 72 hours was equivalent, the EGDT group received substantially more IV fluid in the first 0–6 hours of treatment. Compared with the standard therapy group, significant improvements related to in-hospital mortality were observed in the group assigned to earlier administration of volume-based resuscitation in conjunction with other therapies, including the optimization of central venous oxygen saturation with red cell transfusions and the use of inotropes, if necessary. In-hospital mortality was 30.5% in the EGDT group, compared with 46.5% in the standard therapy group ($P = 0.009$). Replication of results in other studies prompted guidelines for the treatment of sepsis to include early volume repletion as part of protocol-based, quantitative resuscitation to reverse tissue hypoperfusion.^{3,4} In the Surviving Sepsis Campaign, initial resuscitation recommendations for the first 6 hours included treatment aimed at maintaining a central venous pressure of 8–12 mmHg, a mean arterial pressure more than or equal to 65 mm Hg, urine output more than or equal to 0.5 mL/kg/h, and mixed venous oxygen saturation greater than 65%.⁵

Meeting hemodynamic stabilization endpoints in such a manner with goal-directed therapy and other supportive measures remains desirable in most cases, especially in patients who prove to be responsive to fluid. However, more recent multicenter studies re-examining this topic have not replicated survival benefits, and the advantages of EGDT have been questioned. The Australasian Resuscitation in Sepsis Evaluation (ARISE) study examined EGDT resuscitation in patients with septic shock.⁶ Sixteen hundred patients were randomized to EGDT or usual care. On average, patients in the EGDT group received larger volumes of IV fluid in the first 6 hours than the usual care group. Those in the EGDT group were also more likely to receive red blood cell transfusions. At 90 days, however, no significant differences were observed in patient survival. In-hospital mortality, the duration of organ support, and the length of hospital stay were also similar. The Protocol-based Care for Early Septic Shock (ProCESS) investigative group showed comparable results, with no benefits found with EGDT.⁷ ProCESS was a multicenter trial that randomized 1341 patients with septic shock to receive protocol-based EGDT, protocol-based standard

therapy, or usual care for 6 hours of resuscitation. The investigators did not require placement of central venous catheters, administration of inotropes, or blood transfusions in the protocol-based standard therapy group, as compared with the use of these therapies in the EGDT group. Overall, the total volume of fluid administered during the 6-hour study period was reported as being significantly different between the groups. Again, no differences in survival were observed at 90 days. There was also no significant impact on 1-year mortality, the duration of time spent on mechanical ventilation, or the duration of time on renal replacement therapy.

TYPE OF VOLUME THERAPY

When deciding on IV fluid therapy, the choices can be broadly classified into three major categories. Crystalloid fluids have long been considered the mainstay of volume replacement in the hospital setting and include normal saline (NS), lactated Ringer's (LR) solution, Hartmann's solution, and other balanced salt solutions such as Plasma-Lyte. A second broad category includes colloid preparations such as albumin, hydroxyethyl starch (HES), dextran, and gelatin. Finally, blood products, including packed red blood cells, can be used for volume repletion in the treatment of hypoperfusion due to inadequate circulating volumes. Table 107-1 compares the osmolality and composition of human plasma and common isotonic crystalloid fluid preparations.

Crystalloids Versus Colloids

For years, the choice between crystalloids and colloids as therapeutic fluids in the intensive care unit (ICU) has been a topic of debate and investigation. In an analysis of multiple population studies, Goldwasser and Feldman observed that mortality was inversely associated with serum albumin levels.⁸ For each 2.5-g/L decrement in the serum albumin concentration, a correlative 24% to 56% increase in the risk of death was detected. This relationship held true in healthy populations as well as in those who suffered from acute and chronic illnesses. Several mechanisms for the protective effects of the albumin molecule have been explored. Among these, infused albumin reportedly has free radical scavenging antioxidant properties that may have clinical importance.⁹ Moreover, the proposed advantages for prescribing colloid over crystalloid fluid in resuscitation strategies for critically ill patients include concepts based on hemodynamic Starling's principles and the role of plasma oncotic pressure. Theoretically, large colloid molecules that persist in the circulation enhance water reabsorption from the interstitial space and maintain the volume within the vasculature for longer periods.¹⁰ Ideally, this characteristic would reduce the large fluid volumes that are often required for resuscitation and improve clinical outcomes.¹¹

Despite the potential benefits for albumin and colloids in lieu of crystalloid solutions in volume repletion strategies, prospective and randomized controlled studies undertaken to prove these advantages have yielded variable results. For example, investigations have demonstrated benefit with albumin administration and support its clinical safety. In one such study, a group of 100 patients with hypoalbuminemia in the ICU were randomized to receive (versus not receive) albumin as part of their treatment regimen.¹² The groups were well matched and had similar baseline serum albumin concentrations and

TABLE 107-1 Osmolality and Composition of Plasma Versus Common Isotonic Crystalloid Fluid Preparations

| | PLASMA | 0.9% NORMAL SALINE (NS)* | LACTATED RINGER'S (LR)* | PLASMA-LYTE A (PL)* | STERILE WATER WITH 150 MEQ/L SODIUM BICARBONATE* |
|-----------------------|---------|--------------------------|-------------------------|---------------------|--|
| Osmolality (mOsmol/L) | 280-310 | 308 (calc) | 273 (calc) | 294 (calc) | 300 (calc) |
| Sodium (mEq/L) | 135-145 | 154 | 130 | 140 | 150 |
| Potassium (mEq/L) | 4.0-5.0 | — | 4.0 | 5.0 | — |
| Chloride (mEq/L) | 95-110 | 154 | 109 | 98 | — |
| Calcium (mEq/L) | 2.2-2.6 | — | 2.7 | — | — |
| Magnesium (mEq/L) | 1.0-2.0 | — | — | 3.0 | — |
| Lactate (mEq/L) | 0.8-1.8 | — | 28 | — | — |
| Acetate (mEq/L) | — | — | — | 27 | — |
| Gluconate (mEq/L) | — | — | — | 23 | — |
| Bicarbonate (mEq/L) | 24-31 | — | — | — | 150 |

*Baxter Healthcare Corp. Sodium Chloride Injection, USP. Package Insert.

*Baxter Healthcare Corp. Lactated Ringer's Injection, USP. Package Insert.

*Baxter Healthcare Corp. Plasma-Lyte A Injection pH 7.4, USP. Package Insert.

*Hospira, Inc. Sodium Bicarbonate Injection, USP. Package Insert.

Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. Significant improvements in Sequential Organ Failure Assessment (SOFA) scores were observed in the albumin-treated group. Interestingly, significant decreases in fluid gains were also seen in the albumin-treated group. These results led the investigators to suggest that albumin administration may improve organ function in critically ill patients with hypoalbuminemia. The Saline versus Albumin Fluid Evaluation (SAFE) study was a large trial that included nearly 7000 ICU patients with trauma, acute respiratory distress syndrome (ARDS), and severe sepsis.¹³ The participants were randomized to receive either 4% albumin or NS for intravascular fluid resuscitation. In a subgroup analysis of patients with severe sepsis, those in the albumin-treated group had a significantly lower heart rate and a significantly higher central venous pressure on days 1-3.¹⁴ No between-group differences were detected in the total SOFA score, and similar numbers of patients required renal replacement therapy in the saline- and albumin-treated groups. Multivariate logistic regression analysis revealed that the adjusted odds ratio for death in the albumin-treated versus saline-treated group was 0.71 (85% confidence interval [CI]: 0.52-0.97; $P = 0.03$), suggesting that albumin treatment may decrease the risk of death in severe sepsis. Furthermore, data from a meta-analysis suggested that albumin administration is safe. In 55 trials that evaluated many different types of patients including those with trauma, burns, hypoalbuminemia, and ascites, albumin administration did not adversely affect mortality.¹⁵

In contrast to the studies suggesting benefit with albumin therapy in sepsis, other large prospective randomized trials have failed to support a clear benefit of infusing albumin over crystalloid solutions in patients in the ICU setting. In the larger and more diverse group of original SAFE study participants discussed above, investigators found no between-group differences in death or new episodes of single- or multiorgan system failure between those treated with albumin versus saline.¹³ There was also no significant difference in the number of days spent in the ICU, length of hospital stay, or days of renal replacement therapy in the subgroup analyses. Similarly, the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial tested colloids compared with crystalloids for fluid resuscitation in critically ill patients with shock from sepsis, trauma, or hypovolemia without sepsis.¹⁶ In addition to 4% and 20% albumin, the colloid arm of CRISTAL included gelatins, dextrans, and HES. At 28 days after study enrollment, even though colloid resuscitation was associated with fewer days of mechanical ventilation and more days without vasopressor therapy, no significant differences in mortality were observed between the patients who received colloids and those who received

crystalloids. Patients with severe sepsis have also been randomized to receive crystalloid plus albumin therapy compared with crystalloids alone. In the more than 1800 randomized patients in the Albumin Italian Outcome Sepsis (ALBIOS) study, significantly higher mean arterial pressures and lower net fluid gains were observed in the albumin plus crystalloid therapy group.¹⁷ However, the investigators also noted that the total daily amount of fluids administered did not differ between the groups and, more importantly, there were no significant differences in patient survival at 28 or 90 days between the groups. The Cochrane analysis of pooled data on this topic also found no evidence that colloids reduced the risk of death compared with crystalloids in the treatment of critically ill patients.¹⁸ Overall, there remains a paucity of data to suggest that clear benefits exist for administering albumin or other colloid solutions instead of crystalloids in critically ill patients requiring volume repletion. The lack of resounding benefit is compounded by the high cost of albumin, which also makes it less attractive for routine use.¹⁸

There is opposing evidence that suggests that colloid solutions such as albumin may be associated with harmful effects. Though they tended to have higher critical illness severity scores, patients in the Sepsis Occurrence in Acutely ill Patients (SOAP) study who received albumin at any time during their ICU stay had a higher risk of death.¹⁹ A systematic review of 37 randomized trials comparing crystalloid to colloid administration also hinted at safety concerns. The investigators found that colloid resuscitation was associated with a 4% increase in the absolute risk of mortality (95% CI, 1.00-1.08) and concluded that the difference in the effect of the colloids was not due to the types of inciting injuries.²⁰

The harm associated with colloid infusion may be more pronounced with respect to specific organ systems or types of colloids. In a post-hoc analysis of the SAFE study, albumin administration in patients with traumatic brain injury was associated with higher mortality compared with those who received crystalloids.²¹

Hydroxyethyl Starch

Convincing evidence for harm was reported for critically ill patients treated with the synthetically derived HES. Of 7000 randomized patients in the Crystalloid versus Hydroxyethyl Starch Trial (CHEST), there was no significant mortality difference in those resuscitated with NS versus HES.²² There was, however, a significant difference in the adverse outcomes. Renal replacement therapy was required in 235 of 3352 patients (7.0%) in the HES group versus 196 of 3375 (5.8%) in the NS group (relative risk, 1.21; 95% CI, 1.00-1.45; $P = 0.04$). In the

HES- and saline-treated patient groups, renal injury occurred in 34.6% and 38.0% ($P = 0.005$) and renal failure occurred in 10.4% and 9.2% ($P = 0.12$), respectively. Overall, HES was associated with significantly more adverse events (5.3% vs. 2.8%, $P < 0.001$). Similarly, among patients with sepsis who were randomized to receive IV fluid resuscitation with HES versus Ringer's acetate, the risk of death at 90 days was higher in those who received HES.²³ In that study, patients with sepsis who were treated with HES were also more likely to require renal replacement therapy. These findings were confirmed in meta-analyses from more than 35 trials in which HES was associated with a significantly increased risk of mortality and acute kidney injury (AKI).²⁴ Mechanistically, the total mass of the HES molecule has been proposed as being directly toxic to renal proximal tubular cells, leading to the pathologic sequence of events that culminates in AKI.²⁵ This is contrary to other reports suggesting that it is the origin of the HES molecule (potato or corn), the carrier solution, or the effects of systemic inflammation that may be damaging to kidney cells.

Albumin Use in Select Clinical Settings

Just as there are clinical situations in which the infusion of albumin and colloid solutions may be harmful, there are also specific circumstances where these fluids could have important and beneficial roles in the treatment of critically ill patients. In a randomized, non-blinded clinical trial that examined 126 patients with cirrhosis and spontaneous bacterial peritonitis, participants were randomized to treatment with either IV antibiotics alone or IV antibiotics with albumin.²⁶ The dose of albumin administered was 1.5 g/kg at diagnosis, with another 1 g/kg infused on day 3. In the patients who received albumin as well as antibiotics, statistically significant reductions in renal impairment and death were observed. Additionally, a recent meta-analysis in 688 burn shock patients reported that treatments that included IV albumin were associated with statistically significant reductions in mortality, as well as in the occurrence of compartment syndrome.¹¹ The authors attempted to exclude what they felt were potentially biased studies from the meta-analysis. Although larger, prospective randomized trials are needed to guide management in burn shock resuscitation, these results suggest that albumin has the potential to improve outcomes.

In the majority of cases that require IV fluid volume resuscitation in the ICU, there does not seem to be a robust signal favoring infusion of albumin or other colloid therapies over crystalloid fluids as first-line treatment for hypovolemia and septic shock. Crystalloids remain the treatment of choice in most settings.

Chloride Restrictive and Balanced Crystalloid Strategies

Increasing evidence indicates that isotonic crystalloid fluid preparations are not uniform or equivalent with respect to their side-effect and physiologic profiles. Despite isotonicity, NS is hyperchloremic compared to plasma (Table 107-1). In animal studies, the effects of high chloride levels have been implicated in severe renal vasoconstriction, the suppression of plasma renin activity, and reduced glomerular filtration rate.²⁷⁻²⁹ In healthy human volunteers, magnetic resonance imaging studies have demonstrated that infusions of NS can cause significant reductions in renal blood flow velocity, as well as reductions in the perfusion of renal cortical tissue.³⁰

Organ hypoperfusion is common in critically ill patients, but lactic acid production alone is not sufficient to explain all the cases of metabolic acidosis in the ICU.³¹⁻³³ In addition to the aforementioned renal hemodynamic changes, IV fluids with superphysiologic concentrations of chloride, such as NS, have been associated with the development of hyperchloremic metabolic acidosis. McFarlane and Lee observed this phenomenon while studying surgical patients who were randomly assigned to receive either 0.9% NS or Plasma-Lyte 148 during major abdominal surgery.³⁴ Patients receiving NS had significantly higher serum chloride concentrations, lower

serum bicarbonate concentrations, and higher base deficit measurements compared with those who received Plasma-Lyte 148. Administration of NS has reproducibly been associated with decreases in serum bicarbonate levels or acidemic-range arterial pH values.^{30,35-37} Extracellular dilution of buffer caused by the infusion of large volumes of fluid that lack bicarbonate may explain some of these changes.³⁸ Another postulate employs the strong ion difference (SID) theory of acid-base evaluation to describe these effects. In the SID theory, acidosis can occur if the apparent difference between strong cations and anions in solution is reduced.³⁹ As such, hyperchloremia due to excessively larger gains in chloride (anion) concentration may contribute to the metabolic acidosis that has been observed with NS administration.⁴⁰⁻⁴³

In large-cohort observational studies, the deleterious physiologic effects of hyperchloremia and NS administration are reflected in clinical outcomes. In 22,851 surgical patients with normal preoperative kidney function and normal serum chloride concentrations, postoperative hyperchloremia was associated with higher 30-day mortality, longer hospital stays, and more postoperative kidney dysfunction.⁴⁴ A similar study in more than 30,000 adult patients undergoing major abdominal surgery found that those who received NS had more postoperative complications, including infection, renal failure requiring dialysis, and blood transfusions.⁴⁵ Among patients in the ICU with sepsis, a retrospective analysis of more than 50,000 patients showed that balanced fluid administration (e.g., LR) was associated with a significantly lower in-hospital mortality (19.6% vs. 22.8%; relative risk, 0.86; 95% CI, 0.78-0.94).⁴⁶ Similarly, among patients with systemic inflammatory response syndrome, in-hospital mortality was lower when the total chloride load was reduced.⁴⁷ Yunos et al. detected adverse events associated with chloride-liberal IV fluid administration in critically ill ICU patients.⁴⁸ These investigators conducted a prospective, open-label pilot study that examined patients in an academic ICU. Patients were treated with standard IV fluids during a 6-month control period, after which NS and other chloride-rich fluids were restricted to specialty-attending approval. The primary outcomes included a rise in serum creatinine concentration from baseline and incident AKI as defined by RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) classification. During the intervention period, saline administration decreased significantly. When the study periods were compared, those who received chloride-restrictive therapy had a lower mean rise in serum creatinine concentration while in the ICU and the incidence of AKI was significantly diminished. After adjustment for covariates, an increased risk of requiring renal replacement therapy was observed in the chloride-liberal cohort.

It has been more difficult to quantify the adverse effects of administering chloride-liberal crystalloids in prospective randomized clinical trials. Although these studies included predominantly perioperative and trauma patients, the results were less striking. When comparing resuscitation with 0.9% NS versus Plasma-Lyte A in 65 trauma patients, administration of Plasma-Lyte resulted in a lower frequency of hyperchloremia and was associated with greater correction of acid-base abnormalities.⁴⁹ However, investigators noted that there were no significant differences in cumulative urine output, measures of resource utilization, or mortality between those resuscitated with saline versus Plasma-Lyte at 24 hours. Similarly, a report in 60 patients undergoing abdominal aortic aneurysm repair revealed that intraoperative randomization to LR or NS (double-blinded) resulted in a higher frequency of acidosis requiring bicarbonate therapy in those receiving NS, but did not significantly impact the duration of mechanical ventilation, length of ICU stay, length of hospital stay, or postoperative complications.⁵⁰ In patients undergoing kidney transplantation, the use of NS versus balanced crystalloids has been associated with a higher incidence of metabolic acidosis; however, fluid type did not negatively impact kidney allograft function as determined by serum creatinine concentration on postoperative day 3.^{35,51}

Although we await large clinical trials directly comparing various crystalloid solutions in patients with sepsis and other common ICU conditions, based on the aforementioned evidence, there may be a

role for chloride-restrictive alternatives to NS in patients who have developed (or are at risk for developing) metabolic acidosis and/or renal insufficiency. Concerns with administering physiologically balanced solutions more closely matched to serum include the perceived risk of hyperkalemia due to their higher potassium concentrations. Even in clinical situations potentially associated with higher risk for hyperkalemia, evidence supports that these balanced solutions are generally safe with appropriate monitoring. For example, in a prospective randomized trial of patients with rhabdomyolysis, treatment with LR was not associated with significant differences in serum potassium concentration compared with treatment with NS.⁵² In patients with diabetic ketoacidosis, in which serum potassium levels can rise due to the combination of hyperosmolality, insulin deficiency, and AKI, patients who were resuscitated with balanced Plasma-Lyte instead of NS had faster resolution of acidosis and lower 6- and 12-hour serum potassium concentrations.⁵³ After kidney transplantation, patients who received NS had higher frequencies of hyperkalemia relative to those who received LR.³⁵

Blood Transfusions

In critically ill patients with severe blood loss and hemorrhagic shock, blood transfusions are appropriately considered a foundation of treatment. In patients suffering from sepsis and other acute illnesses, red blood cell transfusions have been used to enhance oxygen delivery to poorly perfused tissue as a supplement to other fluid resuscitation and vasopressor/inotropic support. Unfortunately, data sufficient to guide management and support the benefit of red blood cell transfusion in critically ill patients with sepsis have yet to emerge.

Observational studies have detected possible mortality benefits with red blood cell transfusions in critically ill patients with sepsis.^{54,55} Among the European ICUs that participated in the SOAP study, multivariate analysis of more than 3,000 patients revealed that blood transfusions were not associated with significantly higher mortality rates. In matched-pair propensity analysis, a higher 30-day survival rate was observed in the group that had a transfusion at any time while in the ICU ($P = 0.004$).⁵⁴ In contrast, other multicenter and randomized trials have not shown similar benefit. In 838 critically ill patients in the ICU that were randomized to receive either restrictive or liberal blood transfusion strategies when hemoglobin concentrations were less than 9.0 g/dL, the mortality rate during hospitalization was significantly lower when patients were randomized to the transfusion restrictive-strategy group (22.2% vs. 28.1%, $P = 0.05$).⁵⁶ In an examination of 45 observational cohort studies that combined data from 272,596 ICU, trauma, and surgical patients, red blood cell transfusions were associated with increased morbidity and mortality.⁵⁷ The pooled odds ratio for death generated from the results of 12 studies was 1.7 (95% CI, 1.4-1.9). Transfusions were also associated with infectious complications, risk for developing multiorgan dysfunction syndrome, and ARDS.

The Surviving Sepsis Guidelines include recommendations to provide blood transfusions in order to maintain hematocrits above 30% during the first 6 hours of resuscitation if there is evidence of tissue hypoperfusion after adequate repletion of the circulating volume. Guidelines for transfusion after the resolution of tissue hypoperfusion aim to keep the hemoglobin concentration between the targets of 7.0 g/dL and 9.0 g/dL in most patients.⁵ To examine these thresholds, Holst et al. randomized approximately 1000 patients with septic shock and hemoglobin concentrations ≤ 9 g/dL to receive red blood cell transfusions to hemoglobin thresholds of 7 g/dL or 9 g/dL.⁵⁸ Those who were randomized to the higher threshold received a median of 4 units of blood during the study period, whereas those in the lower threshold group received a median of 1 unit of blood. At 90 days, there was no significant difference in mortality between the groups. These results held true after adjusting for baseline risk factors. In addition, there was no significant difference in the number of ischemic events, severe reactions, or use of life support between the two groups. As such, the optimal hemoglobin target in patients with sepsis in the ICU remains uncertain.

EFFECTS OF VOLUME OVERLOAD

Volume therapy in critically ill patients aims to avoid and reverse the consequences of hypoperfusion and end organ damage. Due to the large volumes of IV fluid that are often required, deleterious effects from volume overload can develop during the management of shock. These effects may be manifested systemically, for example, by hypertension and increased myocardial demand, pulmonary congestion with respiratory failure, and/or peripheral edema.⁵⁹ Recent evidence supports that fluid resuscitation resulting in clinical volume overload is not beneficial to critically ill patients and negatively affects clinical outcomes. An early signal came from a retrospective study of patients who had sepsis.⁶⁰ Achieving a net negative fluid balance greater than or equal to 500 mL within the first three hospital days correlated with improved survival independent of age, critical illness, and kidney function. The SOAP study evaluated more than 3000 ICU patients with sepsis; a positive net fluid balance was among the strongest predictors of death.⁶¹ Multivariate regression analysis implicated positive fluid balance as an independent predictor of outcome despite disease severity. Similarly, the Vasopressin and Septic Shock Trial (VASST) investigators determined that more positive fluid balance was significantly associated with an increase in mortality.⁶² In these patients with sepsis, the cumulative mean fluid balance was 11 L fluid positive by post-enrollment day 4. In patients who received conservative fluid management after the initial resuscitation, equating to net “even” or negative fluid balance on at least two consecutive days during the first week after the onset of septic shock, lower in-hospital mortality was observed.⁶³ Volume overload is associated not only with increasing mortality but also with greater use of related medical interventions, including thoracentesis and the prescription of diuretic agents.⁵⁹

Higher cumulative fluid balance has been associated with acute lung injury (ALI), as well as ARDS.⁶⁴ Both disorders portend poorer ICU outcomes. In contrast, more conservative fluid management strategies are associated with shorter durations of mechanical ventilation and improved outcomes in patients with ALI.⁶⁵ In cancer patients admitted to the ICU, mean cumulative fluid balances exceeding 1.1 L in 24 hours were more frequently observed in the nonsurvivors.⁶⁶ Among patients admitted to the neurosurgical ICU for subarachnoid hemorrhage, positive net fluid balances after 3 days predicted the occurrence of vasospasm by transcranial Doppler and was associated with a longer length of hospital stay.⁶⁷

Volume overload is common in critically ill patients who develop AKI, particularly with oliguria. In patients who require renal replacement therapy, fluid overload at the time of dialysis initiation has been associated with a higher 90-day mortality.⁶⁸ These differences in mortality persist after adjusting for disease severity, the timing of initiation of renal replacement therapy, dialytic modality, and sepsis. Additionally, patients enrolled in the Program to Improve Care in Acute Renal Disease (PICARD) study who had evidence of volume overload when the serum creatinine concentration was at its peak had significantly lower chances of recovering kidney function; their odds ratio for death was 2.07 (95% CI, 1.27-3.37) when volume overload was present at dialysis initiation.⁶⁹ Complicating this issue is the fact that the assessment of volume overload and cumulative fluid balance is often subjective; results may be inconsistent due to errors in recording intakes and outputs and inaccurately measuring patient weights. A positive fluid balance might not correlate with clinical evidence of volume overload.⁵⁹ Furthermore, objective measurements of volume status, such as central venous pressure readings, may not always correlate with fluid balance. Additional clinical trials are necessary to further guide clinical decision making in volume administration after the initial resuscitation.

CONCLUSION

Replenishing and maintaining an adequate intravascular volume in critically ill patients remains somewhat of an art, without a universally applicable “recipe” to guide fluid replacement. Individualization of care is required, often balancing the administration of vasopressors with proper fluid repletion. Nonetheless, recent randomized trials

support several guiding principles that appear to optimize patient outcomes. In sepsis, early goal-directed fluid administration using IV crystalloids before colloids or blood products remains a mainstay of therapy in patients who lack active blood loss or symptomatic anemia. In the settings of cirrhosis with peritonitis and possibly severe burns, albumin infusion along with crystalloids may improve outcomes. Infusion of HES appears to be associated with higher complication rates, particularly AKI. Recently, prescription of chloride-containing crystalloids has begun to lose favor based on the desire to avoid the adverse effects of hyperchloremia and metabolic acidosis. Finally, excessive transfusion of packed red blood cells for sepsis-induced hypoperfusion in lieu of crystalloids appears to provide little benefit.

The threshold for transfusion is being investigated, but hemoglobin levels above 7 g/dL do not seem to improve outcomes. It remains imperative to avoid volume overload, electrolyte abnormalities, and acid-base imbalance when replenishing intravascular volume in critically ill ICU patients.

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KEY POINTS

1. Prior to considering the administration of colloids or blood products in critically ill patients with an inadequate vascular volume, intravenous crystalloids remain the mainstay of volume repletion therapy (except in the settings of active bleeding or symptomatic anemia).
2. In patients with cirrhosis and accompanying peritonitis, albumin infusion along with intravenous crystalloids may improve outcomes.
3. Administration of hydroxyethyl starch appears to be associated with higher complication rates, particularly acute kidney injury.
4. Chloride-containing crystalloid infusions, including normal saline, have begun to lose favor based on their risk of inducing hyperchloremia and metabolic acidosis.
5. Excessive transfusion of packed red blood cells in patients with sepsis and hypoperfusion appears to provide little added benefit to the infusion of crystalloids alone.

■ References for this chapter can be found at expertconsult.com.

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The fundamental principles that govern fluid and electrolyte physiology in pediatric practice are, in many instances, similar to those in adults, particularly in older children. However, some important differences in factors affecting fluid management, mainly in infants and young children, have to be taken into account when prescribing IV fluids in this age group. In addition, many of the principles used to estimate normal fluid losses and requirements for replacement in hospitalized patients (maintenance fluids) are based on limited studies published over 50 years ago, at a time when the complexity of illness was far less than that seen today. The formulae were developed based on principles established for normal physiology and did not take into account that the hormonal influences that govern fluid and electrolyte balance may be seriously perturbed in critical illness. The challenge is now to rethink some of these principles in the light of new knowledge of how acute illness may influence them.

BODY WATER DISTRIBUTION IN CHILDREN

Body water content in children changes significantly with age.^{1,2} Total body water (TBW) is high in the fetus and preterm infant. During early fetal life, TBW represents 90% of total body weight, with 65% located in the extracellular fluid (ECF) compartment. By term, the ECF and the intracellular fluid (ICF) volume has fallen to 45% and 30% of TBW, respectively. The preterm infant commonly undergoes a relative expansion of both TBW and ECF volume and a diuresis in the first few days of postnatal life. Fractional excretion of sodium correlates inversely with age in the preterm infant, who is susceptible to both sodium loss as well as sodium and volume overload.³ In addition, the glomerular filtration rate is lower than in the term infant, and water losses caused by the large surface area-to-body weight ratio leads to considerable evaporative losses.⁴⁻⁷ Further discussion of fluid and electrolyte physiology in the preterm infant is beyond the scope of this chapter (Table 108-1).

Significant changes occur in TBW over the first year of life, decreasing from 75% of body weight at birth to 65% at 6 months and 60% at 1 year of life. Some of this loss is accounted for by an increase in body fat. By puberty TBW is approximately 60% of body weight in males, with a slightly lower percentage in females. The extracellular fluid volume decreases over the first year of life to 30% of TBW and decreases with age thereafter, reaching adult values early in childhood. The relatively high ECF volume in infancy is largely caused by the greater interstitial-lymph space. In contrast, the ICF volume remains relatively constant during childhood.

FLUID HOMEOSTASIS IN CHILDREN

To achieve normal fluid homeostasis, fluid intake must balance losses. The latter consist of urine output plus insensible losses (evaporative from the skin surface and respiratory tract), with the addition of fluid loss in the stool, which should be minimal in the absence of diarrhea. Insensible losses are mainly in the form of electrolyte-free water (EFW) from the respiratory tract (15 mL/100 kcal/day). This loss is eliminated during positive pressure ventilation. Sweat mainly contains water with a small amount of sodium, except in situations where sweat glands contain excessive amounts of sodium as in patients with cystic fibrosis.

Evaporative losses also increase with elevations in body temperature, and during thermal stress, water losses may increase to as much as 25 mL/100 kcal/day.

Obligate water excretion in the urine is dependent upon solute load and the ability to concentrate and dilute the urine. The average osmolar excretion in newborn infants receiving formula feeds is 16 to 20 mOsm/kg/day.² Infants are somewhat disadvantaged compared to older children and adults in that they cannot maximally dilute (infant, 200 mOsm/L; adult, 80 mOsm/L) and concentrate the urine (infant, 800 mOsm/L; adult, 1200 mOsm/L). In addition, the infant's high metabolic rate and the solute load from the enteral feeding formula means that they require more water excretion per unit solute. The high solute load and the limited urine-concentrating ability make them prone to significant ECF contraction (dehydration) when there are excessive amounts of water loss. Typically, this occurs in gastroenteritis where reduced oral intake is combined with excessive water and electrolyte loss in the stool (Table 108-2).

The urine is the major source of electrolyte loss in the body. The commonly used values for sodium (Na) and potassium (K) requirements in parenteral fluids in children are 2-3 mmol/kg/day and 1 to 2 mmol/kg/day, respectively.⁸ These values assume that these are the amounts of cations needed for normal homeostasis. However, in critically ill children, the urinary Na⁺ and K⁺ concentrations can be much higher.

PARENTERAL FLUIDS ADMINISTERED AS MAINTENANCE THERAPY

In the normal healthy individual water intake is regulated by thirst stimulated via osmoreceptors in the hypothalamus. Infants and small children are unable to regulate their intake because they do not have access to water for the same reasons that apply in older children or adults in coma or with reduced levels of consciousness. When oral intake is replaced by parenteral fluids in children, the amount of fluid (i.e., water) given is related to body weight and energy expenditure. In 1957 Holliday⁸ published a formula that linked body weight to energy expenditure, which formed the basis for the prescription of maintenance fluids in hospitalized children. An allowance of 100 mL/100 kcal/day was made for insensible water loss, with 66.7 mL/100 kcal/day to replace urine output. Factoring in water of oxidation of 16.7 mL/100 kcal/day leaves a total of 100 mL/100 kcal/day for replacement of normal losses (Table 108-3).

The estimates for Na⁺ (3 mmol/100 kcal/day) and K⁺ (2 mmol/100 kcal/day) in maintenance fluids were calculated using the sodium and potassium concentrations of cow's milk and breast milk.⁸ This paper became the standard reference for parenteral fluid administration in pediatrics. Although the simple mathematical calculations for obtaining these estimates were convenient, the assumptions made for the daily requirements for sodium, potassium, and EFW mandated the use of hypotonic intravenous solutions and became the universal practice in pediatric medicine over the next 50 years. However, nonphysiologic stimuli for antidiuretic hormone (ADH) secretion (pain, anxiety, narcotics, positive pressure ventilation), which inhibit the excretion of EFW, are common in critically ill patients. Therefore, it is not surprising that mild degrees of hyponatremia are a common finding in pediatric patients even before they receive parenteral fluid

TABLE 108-1 Water Content of Body Compartments in Children

| AGE | TBW (% BODY WEIGHT) | EXTRACELLULAR FLUID (% BODY WEIGHT) | INTRACELLULAR FLUID (% BODY WEIGHT) |
|---------------------|------------------------|--|--|
| Premature | 80 | 45 | 35 |
| Full-term newborn | 75 | 40 | 35 |
| 12 months to 1 year | 65 | 30 | 35 |
| 1 to 12 years | 60 | 20 | 40 |
| Adolescents | 60 | 20 | 40-45 |
| Males | 55 | 18 | 40 |
| Females | | | |

TABLE 108-2 Water Losses in Normal Children (mL/100 kcal/24 hr)

| SOURCE | NEWBORN TO 6 MONTHS | 6 MONTHS TO 5 YEARS | 5-10 YEARS | ADOLESCENTS |
|------------|---------------------|---------------------|------------|-------------|
| Insensible | 40 | 30 | 20 | 10 |
| Urine | 60 | 60 | 50 | 40 |
| Fecal | 20 | 10 | — | — |
| Total | 120 | 100 | 70 | 50 |

TABLE 108-3 Requirements for Maintenance Parenteral Fluids Based on the Formula of Holliday⁸

| BODY WEIGHT | 0-10 kg | 1-20 kg | >20 kg |
|-------------------|---------------|---|--|
| Water requirement | 100 mL/kg/day | 1000 mL + 50 mL/kg/day for each kg >10 kg | 1500 mL + 20 mL/kg for each kg above 20 kg |

TABLE 108-4 Water and Principal Electrolyte Content of Commonly Used Intravenous Solutions

| FLUID TYPE | Na ⁺ (mmol/l) | Cl ⁻ (mmol/l) | OSMOLALITY | OTHER ANIONS (mmol/l) | pH | ELECTROLYTE-FREE WATER/L |
|-------------------|-----------------------------|-----------------------------|------------|--------------------------|-----|--------------------------|
| 0.9% NaCl | 154 | 154 | 308 | | 5.5 | 0 |
| 0.45% NaCl | 77 | 77 | 154 | | 5.5 | 500 |
| 0.9% NaCl 5% dex | 154 | 154 | 560 | | 4 | 0 |
| 5% dex 0.45% NaCl | 77 | 77 | 406 | | 4 | 500 |
| 5% dex 0.2% NaCl | 34 | 34 | 321 | | 4 | 780 |
| 4% dex 0.18% NaCl | 31 | 31 | 284 | | 4 | 800 |
| 5% dex | 0 | 0 | 252 | | 4 | 1000 |
| Ringer's lactate | 130 | 109 | 272 | Lactate 28 | 6.5 | 114 |
| Plasma-Lyte 148 | 140 | 98 | 294 | acetate 27, gluconate 23 | 6 | 0 |
| 3% saline | 513 | 513 | 1027 | | 5.5 | 0 |

therapy. In a study by Gerigk⁹ of 103 children admitted to the hospital with acute medical illnesses, the median plasma Na⁺ value was 136 mmol/L, with plasma ADH levels higher than would be expected for that degree of hyponatremia. In 31 control patients, the median serum Na⁺ level was 139 mmol/L, with lower ADH levels than those of the ill children. Similar observations were made in children admitted through a hospital emergency department who subsequently developed hospital-acquired hyponatremia. They received twice as much EFW compared with a control group of nonhyponatremic patients.¹⁰ The nonphysiologic secretion of ADH has been reported in association with many acute medical illnesses, including meningitis, bronchiolitis, encephalitis, traumatic brain injury, and gastroenteritis.¹¹⁻²² In addition, the hyponatremia that develops has been shown to be associated with an adverse outcome in children with acute bronchiolitis admitted to the pediatric intensive care unit (PICU).²³ This observation led to an increased number of publications recommending the use of isotonic or near-isotonic fluids for standard maintenance in children to avoid the potentially hazardous administration of EFW in situations where ADH secretion is not inhibited.^{10,24-27} The accumulated evidence strongly suggests that hypotonic fluids should be reserved for patients with a demonstrated need for EFW (serum Na⁺ >145 mmol/L) rather than being the default solution for pediatric patients (Table 108-4).

PARENTERAL FLUID ADMINISTERED IN THE PERIOPERATIVE PERIOD

Standard practice in perioperative fluid management is to replace intravascular volume losses with blood or colloid solutions and to use electrolyte solutions to provide for ongoing fluid requirements, replacement of evaporative losses from exposed serosal surfaces in open body cavities in thoracic and abdominal surgery, and losses from third space fluid sequestration. Extra IV fluid is also frequently administered to treat hypotension due to the vasodilating effects of anesthetic agents. The preferred electrolyte solution used in pediatric anesthesiology practice for intraoperative fluid administration is Ringer's lactate or isotonic saline because of concerns about the development of postoperative fluid retention and hyponatremia associated with elevated ADH levels.²⁸⁻³⁰ The potential for this problem is increased when hypotonic dextrose/saline solutions are used.^{29,31-33} This inability to excrete a sodium-free water load is amply illustrated in scoliosis surgery, where patients seem to be particularly at risk for the development of hyponatremia postoperatively.³⁴ Prospective studies have shown that the degree of hyponatremia is less when isotonic or near-isotonic solutions are used.^{35,36} Burrows³⁶ reported a nonrandomized trial comparing Ringer's lactate with 0.2% NaCl in a group of children following scoliosis surgery. He found that the postoperative plasma Na⁺ level fell in

both groups but that the decrease was marked in those patients receiving the hypotonic fluid. A more recent randomized trial that compared Ringer's lactate with 5% dextrose and 0.45% NaCl with 5% dextrose as a postoperative maintenance fluid in children after spinal or neurosurgical procedures observed an 18% incidence of hyponatremia ($\text{Na}^+ < 135 \text{ mmol/L}$) in the 0.45 NaCl group versus zero in the Ringer's lactate group.³⁷

The EFW retention due to nonphysiologic stimulation of ADH secretion it does not fully explain the reduction in plasma Na^+ commonly seen with Ringer's lactate. Further insights to explain this observation come from a study by Steele,³⁸ in which plasma and urine Na^+ were measured in adult patients undergoing elective surgery, all of whom received Ringer's lactate as their perioperative fluid. They found that the urine Na^+ concentration was consistently above 150 mmol/L and as high as 350 mmol/L in some instances. This was associated with a significant positive water balance and a fall in the plasma Na^+ , a process they termed *postoperative desalination*. In a similar study of children undergoing elective surgery, all of whom received Ringer's lactate, we found similar levels of urinary Na^+ loss (unpublished observations). This desalination process is consistent with the kidney's attempts to deal with a volume overload after the vasodilating effects of anesthetic agents are no longer present but ADH is still being actively secreted. In this situation, it would be unwise to prescribe hypotonic fluids in the postoperative period and impose an extra burden of more EFW to be excreted by the kidney.

Further evidence has now emerged that supports the use of isotonic rather than hypotonic fluid in the perioperative period. A prospective observational study in patients admitted to the PICU postoperatively documented an increased risk of the development of hyponatremia associated with the use of hypotonic saline due to water retention and increased sodium excretion.³⁹ Several recent prospective randomized trials have compared the use of isotonic with hypotonic saline in a postsurgical population. These studies have shown that the incidence of hyponatremia was significantly decreased by the use of isotonic saline, without the development of hypernatremia.⁴⁰⁻⁴² There is now clear evidence that the use of hypotonic saline in the perioperative period places patients at risk of developing acute hyponatremia.

THE MANAGEMENT OF ACUTE WATER AND ELECTROLYTE DEFICITS IN CHILDREN

The three most common conditions for which IV fluids are used to replace volume loss in critically ill children are DKA, acute gastroenteritis, and septic shock.

Water and Electrolyte Deficits in Diabetic Ketoacidosis (DKA)

Diabetic ketoacidosis is characterized by losses of water and electrolytes caused by hyperglycemia-induced osmotic diuresis. The high osmolality of the ECF results in the shift of water from the ICF compartment across the cell membrane. A study of adults with type I diabetes for whom insulin therapy was withheld showed fluid deficits of 5 to 10 liters together with up to 20% loss of total body sodium and potassium.⁴³ At the time of presentation, patients are ECF contracted; clinical estimates of the deficit are usually in the range of 7% to 10%, although shock with hemodynamic compromise is a rare event in DKA in children. The hyperglycemia in DKA results in a hyperosmolar state, but the serum Na^+ concentration is an unreliable measure of the degree of ECF contraction due to the dilutional effects of the fluid shift from the ICF to the ECF compartment. The *effective* osmolality (PeffOsm), calculated as $(2 [\text{Na}^+ + \text{K}^+] + [\text{glucose}])$, all in mmol/L, at the time of presentation is frequently in the range of 300 to 350 mOsm/L. An elevated hematocrit may be a useful marker of severe ECF contraction. Urea is not used in the calculation of PeffOsm because it moves freely across the cell membrane. An estimate of true ECF deficit can be made

by correcting the measured serum Na^+ for the increase in ECF water using the formula developed by Katz:⁴⁴

$$\text{Na}^+ + \frac{([\text{Glucose (mmol/L)}] - 5.6)}{5.6} \times 1.6$$

The ECF contraction is associated with a reduction in GFR that results in reduced glucose and ketone clearance from the blood and worsening DKA. Studies in humans have shown that IV fluid administration alone results in substantial decreases in blood glucose even before insulin has been given because of the increase in GFR.⁴⁵ The serum K^+ is also frequently elevated at the time of presentation⁴⁶ but falls rapidly as GFR increases and insulin reprimed the Na/K/ATPase cell membrane pump.⁴⁷

Cerebral edema is the most important potentially life-threatening event seen in children with DKA. The reported occurrence rate in the pediatric literature varies between 0.2% and 1%.⁴⁸⁻⁵¹ However, this number is likely to be an underestimate, as it is based on retrospective reviews that rely on the clinical diagnosis of increased intracranial pressure. The incidence is also reported to be higher in new-onset diabetes and in younger children.^{48,51,52} Series of brain imaging studies in children with DKA have shown decreased ventricular size (increased ICP) either early (<12 hr) in the treatment course⁵³ or even before therapy has commenced.⁵⁴ The ultimate consequence of this is brainstem herniation. The total adverse outcome rate (death or permanent neurologic injury) in cerebral edema associated with DKA (CE-DKA) is as high as 40% to 50% in some series, with few intact survivors where brainstem herniation has occurred.^{48,55} For these reasons, children with severe DKA ($\text{pH} < 7.2$) should be admitted to the ICU for close monitoring of CNS status during the first 24 hours of fluid deficit correction and acid-base disturbance. Symptoms such as diminished level of consciousness, headache, and vomiting are signs of impending cerebral edema.

Many hypotheses have been proposed to explain brain swelling in association with DKA, including overzealous rehydration with hypotonic IV fluids, the rapid reduction of blood glucose with insulin, activation of the Na/H transporter system, change in oncotic pressure, increased permeability of the blood-brain barrier, and changes in cerebral blood flow. Most of these hypotheses are based on individual case reports or small case series. Although the precise cause is not fully understood, there is general agreement that the pathogenesis of CE-DKA involves an osmolar shift that results in fluid accumulation in the ICF compartment and cell swelling. Changes in serum osmolality as a risk factor have been identified in several series. A rapid reduction in the PeffOsm caused by either a fall in blood glucose or serum Na^+ or both is associated with the rapid administration of IV fluid and possibly by the use of bolus dose insulin.⁵⁶ The consequence is that water follows the osmotic gradient back into the ICF compartment. Other risk factors that were identified for the development of cerebral edema in a large retrospective series, which included age-matched controls, were a low PaCO_2 and a high urea at the time of presentation.⁵¹ These parameters are probably reflective of the severity of the acidosis and ECF contraction.

In the absence of a single unifying hypothesis as to the cause of cerebral edema in DKA, it is not possible to mandate a definitive treatment approach that will predictably prevent CE-DKA. It remains likely that the pathogenesis of CE-DKA is multifactorial in nature and includes both patient- and treatment-related factors. The objective of treatment should be the gradual reduction in serum osmolality, which can be achieved by conservative fluid resuscitation and the avoidance of hypotonic fluids in the initial resuscitation period. Current consensus guidelines⁵⁷ do not recommend the use of an IV fluid bolus but that initial replacement of 10 mL/kg of isotonic saline be given over 1 to 2 hours followed by an insulin infusion at 0.05 to 0.1 U/kg/hr. Potassium is added as the calculated deficit recovers over 48 hours. A guiding principle is that failure of the serum Na^+ to rise during IV fluid replacement indicates too rapid a rate of fluid infusion and the risk of CE-DKA. It remains to be seen whether this approach will lower the risk of cerebral edema associated with the onset and management of

DKA in children. A retrospective study from our center demonstrates that the use of isotonic saline with the associated rise in serum sodium as serum glucose decreases protects against the development of cerebral edema.⁵⁶

Children presenting with DKA require close monitoring for changes in the level of consciousness and other signs of increased ICP, such as headache and vomiting. This level of care is best provided in an ICU setting. In the event that cerebral edema is suspected, the serum osmolality should immediately be raised by the administration of mannitol (1 gm/kg IV)⁵⁸ or 2 to 3 mL/kg of 3% saline⁵⁹ and a decrease in the IV fluid and insulin infusion. These measures should be taken without waiting for a CT scan, which may fail to demonstrate cerebral edema.

Fluid and Electrolyte Deficits in Gastroenteritis

Acute gastroenteritis is the most common cause of disturbed fluid and electrolyte homeostasis seen in childhood. Infants with diarrhea are particularly vulnerable to significant losses of fluid, sodium, chloride, and bicarbonate from the small intestine and present with what is frequently classified as either hypotonic, isotonic, or hypertonic dehydration based on the serum Na^+ level. This terminology is technically incorrect, as only in the hypertonic form is there loss of fluid from the ICF compartment; these patients are truly dehydrated. Patients with diarrheal illnesses associated with fluid loss with normal or reduced serum Na^+ have loss of TBW and ECF, with normal or increased ICF volume.⁶⁰ Infants with severe hypernatremic dehydration are at greatest risk of an adverse neurological event, but seizures from severe hyponatremia have been reported in infants presenting with acute gastroenteritis caused by the administration of oral salt-free fluids as a replacement.^{11,61,62} The degree of ECF deficit is usually assessed on clinical grounds using the time-honored clinical signs of capillary refill time, dry mucous membranes, and skin turgor.⁶³ However, these signs are open to subjective interpretation, and there may be a tendency to overestimate the degree of ECF contraction in less severely ill children. In a study by Mackenzie,⁶⁴ the fluid deficit in children with gastroenteritis and mild to moderate dehydration was overestimated, resulting in the overuse of IV fluids. Skin turgor, increased capillary refill time, high urea, low pH, and increased base deficit all correlated with the degree of ECF contraction but not the presence of thirst or oliguria. Other studies have shown that a reduced serum bicarbonate concentration is the most common electrolyte abnormality associated with significant ECF contraction in gastroenteritis.^{65,66}

Patients with gastroenteritis whose serum is isotonic and hypotonic should be managed with isotonic or near-isotonic saline (Ringer's lactate), while those who are significantly hypertonic may receive solutions that contain some EFW. An observational study found that ADH levels are frequently elevated in these patients.⁶⁷ A randomized controlled trial of IV fluid rehydration in children with gastroenteritis showed that the use of isotonic saline protected against the development of hyponatremia without the development of hypernatremia when compared with hypotonic solutions.²² Infants with severe hypernatremia should have their free water deficit corrected slowly because of the danger of rapid fluid shift to the ICF compartment. There is an increasing trend to rapidly rehydrate patients with gastroenteritis with IV solutions in the emergency department before discharging them.^{68,69} A simpler and more effective technique is to use oral rehydration therapy (ORT), which has a proven efficacy in clinical trials of patients with acute gastroenteritis. These solutions contain Na^+ concentrations between 45 and 90 mmol/L.⁶⁹⁻⁷²

Fluid Deficit Replacement in Sepsis and Septic Shock

The importance of early IV fluid resuscitation in sepsis and septic shock in children was established in the landmark study by Carcillo in 1991⁷³ and forms the basis of published guidelines for the administration of fluid boluses of 20 mL/kg of isotonic saline or an equivalent colloid solution to patients in shock.⁷⁴ Although this remains a key

recommendation for the early treatment of sepsis in the most recently published Surviving Sepsis guidelines,⁷⁵ this approach may not be applicable to all patients. A large randomized trial in resource-limited countries in Africa, which included children with malaria, showed increased mortality in patients who received IV bolus fluid therapy compared to those who did not receive IV fluid resuscitation.⁷⁶ However, unless further evidence emerges to confirm this finding, IV bolus fluids remain one of the cornerstone treatments for children with sepsis. What remains unresolved is which fluid is preferred in such situations. Guideline recommendations suggest that either 0.9 NaCl or Ringer's lactate can be used, but increasing evidence suggests that a balanced salt solution may have some advantages because of the reduced chloride load and higher pH.

BALANCED SALT SOLUTIONS IN PEDIATRICS

In 1934, the pediatrician and biochemist Alexis Hartmann developed a solution to treat gastroenteritis and dehydration in children using Ringer's solution and buffered with lactate. Ringer's lactate or Hartmann's solution, with its lower sodium concentration and higher pH, is widely used in pediatric anesthesia practice but less so as a maintenance fluid in other hospitalized children. The increasing awareness of the dangers associated with the use of hypotonic saline together with concerns about the high chloride concentration in 0.9 NaCl has made this near-isotonic solution an attractive option. An alternative balanced saline solution, PlasmaLyte 148, is now available in some parts of the world. This solution has the same sodium concentration as isotonic saline, with lower chloride and a higher pH. It is now being used in Australasia and the UK as a maintenance fluid in anesthesia and for nonsurgical and PICU patients⁷⁷⁻⁷⁹ but is not yet licensed by the FDA for use in children (Table 108-5).

DISORDERS OF SODIUM HOMEOSTASIS

Sodium is the principal cation of the ECF compartment. Movement of Na^+ into the ICF compartment is reversed by activation of the Na/K/ATPase pump. Sodium is absorbed in the proximal tubule under the influence of aldosterone. The serum Na^+ reflects the osmolality and the ECF water volume, which is tightly regulated by ADH secretion.

Hyponatremia

Hyponatremia (serum $\text{Na}^+ < 136$ mmol/L) is the most common electrolyte disorder seen in the hospitalized population and implies an expansion of the ICF compartment. It is caused by either water gain (e.g., use of hypotonic fluids) or salt loss (e.g., gastroenteritis) (Table 108-6).

Acute hyponatremia, defined as a fall in plasma Na^+ to less than 130 mmol/L within 48 hr, leads to rapid movement of water from the ECF to the ICF compartment and can cause cerebral edema, with

TABLE 108-5

Electrolyte Composition of Body Fluids (mmol/L)

| | Na^+ | K^+ | Cl^- | HCO_3^- |
|---------------|---------------|--------------|---------------|------------------|
| Sweat | 50 | 5 | 55 | |
| Saliva | 30 | 20 | 35 | 15 |
| Gastric juice | 60 | 10 | 90 | |
| Bile | 145 | 5 | 110 | 40 |
| Duodenum | 140 | 5 | 80 | 50 |
| Ileum | 130 | 10 | 110 | 30 |
| Colon | 60 | 30 | 40 | 20 |

TABLE 108-6 Principal Causes of Hyponatremia**WATER GAIN**

Excessive water ingestion
Hypotonic fluid administration
SIADH
Congestive heart failure
Chronic renal failure

SALT LOSS

Gastroenteritis
Cerebral salt wasting

catastrophic outcomes reported in children.^{31,80,81} The clinical findings include elevated intracranial pressure (nausea, vomiting, headache), and the condition is frequently undiagnosed until the onset of seizures. This event is usually followed by apnea, indicating that brainstem coning has occurred. Acute symptomatic hyponatremia (seizures, etc.) rarely occurs at serum Na^+ levels greater than 130 mmol/L, but when it does, it constitutes a medical emergency. The primary objective is to raise serum Na^+ above this level to prevent brainstem herniation, which can be most effectively achieved by the administration of hypertonic (3%) saline.⁸² Once this threshold has been reached, the serum Na^+ can be allowed to correct by fluid restriction with or without the use of furosemide. Intravenous mannitol has also been used successfully in the emergency treatment of acute symptomatic hyponatremia.⁸³

Acute hyponatremia is an iatrogenic abnormality seen in pediatrics, most commonly due to excess administration of EFW in hypotonic saline solutions used as maintenance in this population. The use of isotonic saline provides a physiologic rationale to reduce the risk of this potentially life-threatening complication but has not been used because of concerns about the administration of excess sodium. Compelling evidence has now emerged from randomized trials both in postsurgical and nonsurgical populations demonstrating that isotonic saline reduces the incidence of acute hyponatremia compared with hypotonic saline without the development of hypernatremia.^{41,42,77,84} Continuing to use hypotonic saline in a pediatric population puts patients at risk for the development of acute hyponatremia.⁸⁵

Chronic hyponatremia is a common finding in patients with heart failure and renal failure and is associated with increased total body water and salt retention. It is not associated with cerebral edema, and correction of chronic hyponatremia by rapid infusion of isotonic or hypertonic saline should not be attempted because such treatment is associated with brain damage secondary to central pontine demyelination.⁸⁶⁻⁸⁸

Hypernatremia

Hypernatremia is defined as a serum Na^+ greater than 145 mmol/L and is caused by either water deficit or salt gain. The former is seen in infants with severe gastroenteritis, with a loss of water in excess of sodium, sometimes compounded by increased solute intake from incorrect mixing of infant formula. The absence of ADH secretion causing diabetes insipidus is seen in patients with pituitary tumors, traumatic brain injury, and CNS infections.⁸⁹⁻⁹² Water loss in critically ill children may also be associated with the use of loop diuretics or mannitol. Hypernatremia secondary to salt gain is seen with the excessive use of hypertonic saline solutions or with the administration of IV bicarbonate.

A rise in serum Na^+ is associated with the movement of water from the ICF to the ECF compartment and the development of a hyperosmolar state. Brain cells adapt with an increase in electrolytes and ideogenic osmoles (inositol, taurine), which tends to mitigate the fluid shift with partial restoration of intracellular osmolality and brain cell volume.⁹³⁻⁹⁵ Levels of Na^+ greater than 165 mmol/L are frequently associated with abnormal CNS findings, and there is an increased risk of

TABLE 108-7 Causes of Hypernatremia**WATER LOSS**

Gastroenteritis
Central diabetes insipidus
Nephrogenic diabetes insipidus
Use of loop diuretics
Use of osmotic diuretics
Use of radiology contrast medium
Excessive insensible cutaneous loss (burns, sweating)
Diabetic ketoacidosis or hyperosmolar nonketotic diabetes

SALT GAIN

Use of high Na^+ -content solutions (hypertonic saline, intravenous bicarbonate)
Hypertonic enteral feeding formulas
Cathartic agents

subdural hemorrhage and infarction in infants with hypernatremic dehydration.⁹⁶⁻⁹⁹ There is also the added danger of brain edema developing during the attempt to correct these hyperosmolar states rapidly with the use of solutions that are hypoosmolar compared to the ICF compartment.¹⁰⁰⁻¹⁰⁵ Published recommendations suggest that the rate of correction of serum Na^+ should be less than 0.5 mmol/L/hr using the following formula for correction, which estimates the effect of 1 liter of any infusate on serum Na^+ .

$$\text{Change in serum Na}^+ = \frac{\text{infusate Na}^+ - \text{serum Na}}{\text{TBW} + 1}$$

In severe hypernatremia (serum $\text{Na}^+ > 170$ mmol/L), it is recommended that the maximum not be corrected to below 150 mmol/L in the first 48 to 72 hrs.¹⁰⁶

The epidemiology of hypernatremia in children has changed recently from gastroenteritis with dehydration as the principal cause to one of a hospital-acquired problem in association with either excess salt administration or a free water deficit. In a study by Moritz of children with a serum Na^+ greater than 150 mmol/L, the problem was hospital acquired in 60% of cases, and the mortality was 11%.¹⁰⁷ In a similar series of adult patients, the ICU mortality rate for patients with plasma Na^+ levels greater than 150 mmol/L was 30%¹⁰⁸ (Table 108-7).

CHLORIDE

Chloride is the principal anion of the ECF compartment. It is filtered at the glomerulus, and 80% is reabsorbed in conjunction with sodium in the proximal tubule. It is also reabsorbed in the ascending limb of the loop of Henle, a process that is blocked by furosemide. Chloride is exchanged for bicarbonate in the distal tubule. In ECF volume depletion, excess Cl^- , along with Na^+ , is reabsorbed in the proximal tubule, resulting in lower distal delivery and less HCO_3^- secretion. With chloride depletion, less Na^+ is reabsorbed in the proximal tubule. Increased distal delivery results in increased exchange with K^+ and H^+ . This contraction alkalosis is invariably associated with hypochloremia, most commonly caused by the overuse of loop diuretics. Hypochloremia is also caused by gastric suctioning and respiratory acidosis. In addition, many of the conditions that cause hyponatremia also result in hypochloremia.

Hyperchloremia is seen in association with respiratory alkalosis, hypernatremic dehydration, and the administration of large volumes of isotonic saline. The use of large amounts of isotonic saline during fluid resuscitation can result in hyperchloremic metabolic acidosis.¹⁰⁹ If the serum Cl^- is not measured, an increased base deficit could be wrongly interpreted as indicating inadequate volume resuscitation in shock.¹¹⁰

Plasma chloride measurements are an integral part of the calculation of the anion gap, which is important for the diagnosis of metabolic acidosis.¹¹¹ This value is the difference between the measured cations (Na^+) and anions ($\text{Cl}^- + \text{HCO}_3^-$), which is normally in the range of 12 to 16. The anion gap increases when unmeasured anions such as lactate

and accumulated β -hydroxybutyrate in DKA are present. A normal or reduced anion gap acidosis is seen in association with hyperchloremia from saline administration or other situations in which serum Cl^- is elevated.^{109,112,113}

POTASSIUM

Potassium is the major cation of the ICF compartment, with an intracellular concentration of 150 mmol/L. Measurement of serum K^+ reflects the ECF concentration, which is only 2% of the total body K^+ . The gradient between the ICF and ECF compartments is maintained by activation of the $\text{Na}^+/\text{K}^+/\text{ATPase}$ pump in the cell membrane. The movement of K^+ from the ECF to ICF compartment is enhanced by insulin, hypothermia, alkalosis, catecholamines, and β -agonist therapy.

Potassium filtered at the glomerulus is reabsorbed in the proximal tubule and the thick ascending limb of the loop of Henle. It is secreted in the distal nephron under the influence of aldosterone, plasma K^+ concentration, and urine flow rate.

Hypokalemia

Hypokalemia in children is commonly seen with gastroenteritis and diarrhea, where ECF contraction leads to stimulation of aldosterone secretion. There is also total body potassium depletion in DKA, although the initial measured level is high due to acidosis.⁴⁶ Adolescents with anorexia nervosa can present with profound degrees of hypokalemia, which is a known cause of sudden death in this syndrome.¹¹⁴ In the critical care setting, hypokalemia is most commonly associated with diuretic use, nasogastric suction, hypomagnesemia, and metabolic alkalosis. In acute metabolic alkalosis, each 0.1-unit rise in pH results in a decrease of 0.2 to 0.4 mmol/L in serum K^+ .¹¹⁵ In chronic metabolic alkalosis, K^+ is exchanged for H^+ in the distal nephron. Increased K^+ output in the urine is also associated with renal tubular defects (Bartter's syndrome, renal tubular acidosis) and the use of drugs such as amphotericin, ticarcillin, carbenicillin, and steroids.¹¹⁶

Potassium supplementation therapy in the critical care setting is usually in the form of KCl, as there is frequently an associated Cl^- deficiency. Acetate and phosphate can be used as alternative anions in the hyperchloremic state (e.g., DKA).

The clinical manifestations of hypokalemia include muscle weakness (which may prolong the effect of neuromuscular blockers), intestinal ileus, and cardiac arrhythmias. The latter are rarely a problem except in children with congenital heart disease, particularly in the post-cardiopulmonary-bypass setting. The potential for digoxin toxicity is enhanced with hypokalemia. In situations where hypokalemia needs to be treated in the setting of fluid restriction, high-concentration K^+ infusions (up to 0.5 mmol/mL) can be infused through central lines, with frequent measurements of serum K^+ levels. Hypokalemia may remain resistant to treatment when significant hypomagnesemia is present.

Hyperkalemia

Hyperkalemia is caused by either failure of potassium excretion (renal failure) or in the movement of K^+ from the ICF to the ECF compartment. Common causes of the latter include cellular breakdown or injury in tumor lysis syndrome, rhabdomyolysis, burns, and trauma. The use of the depolarizing neuromuscular blocker succinylcholine in this setting or in patients with muscle dystrophy or spinal cord injury

can lead to an abrupt rise in serum K^+ and cardiac arrest. Severe hyperkalemia is also seen in malignant hyperthermia, caused by a combination of hemolysis and acidosis. Both captopril and propranolol can cause hyperkalemia by decreasing aldosterone synthesis. Propranolol also blocks β -adrenergic-mediated movement of K^+ across the cell membrane. Acute metabolic acidosis also results in a rapid movement of K^+ from the ICF to ECF compartment, and severe hyperkalemia is frequently seen during cardiac arrest and CPR without necessarily implying causality.

Acute hyperkalemia represents a medical emergency, and serum levels in excess of 6 mmol/L can result in cardiac arrest and sudden death, particularly in the post-cardiopulmonary-bypass setting. Frequently, the only clinical manifestation is the finding of tall-peaked T waves and widening of the QRS complex on the EKG tracing, but the absence of these findings does not exclude the diagnosis. Patients with borderline high levels of serum K^+ can develop life-threatening hyperkalemia with the development of acidosis. As it is the extracellular K^+ level that is harmful, emergency measures should be directed at increasing the transmembrane flux from ECF to the ICF compartment. Such measures include the use of bicarbonate to correct acidemia, β -agonist therapy, and glucose/insulin administration.^{115,117} The use of IV calcium chloride will help protect the heart against the development of cardiac rhythm disturbances. These are temporizing measures while steps are taken to increase K^+ removal from the body, either by using sodium/potassium exchange resins (rectally or via NG tube) or acute dialysis.

CALCIUM

The ECF concentration is maintained under the control of vitamin D, parathyroid hormone, and calcitriol. The majority is in the bone, and in the absence of parathyroid hormone, there is reduced calcium reabsorption from bone and increased urinary secretion because of the decreased renal production of calcitriol. Forty percent of the calcium is protein bound, and the most common cause of a low total calcium in critically ill children is hypoalbuminemia. In this situation, the ionized level is normal. Conversely, the ionized level is reduced when there is increased protein binding.

Hypocalcemia is seen in neonates with birth asphyxia, preterm infants, term newborns in the first week of life, and infants of diabetic mothers. This finding is invariable in newborn infants with DiGeorge syndrome, where it is seen in association with conotruncal congenital heart defects, typically truncus arteriosus and an interrupted aortic arch. The majority of these infants have microdeletions of the long arm of chromosome 22 (22q minus syndrome) and immunodeficiency. For this reason, all transfused blood products should be irradiated. Hypocalcemia is a common finding in critically ill older children, with a reported incidence of 49% in one study.¹¹⁸ Causes include cardiopulmonary bypass, the use of citrated blood and blood products, albumin transfusions, burns, sepsis, the use of loop diuretics, and aminoglycosides. Hyperphosphatemia, seen in tumor lysis syndrome and renal failure, can also result in hypocalcemia.

Hypercalcemia in critically ill children is usually the result of excessive calcium administration frequently in association with diuretic administration. The end result may be the development of nephrocalcinosis. Other less common causes include neonatal severe primary hyperthyroidism caused by mutations of the CaSR gene and Williams syndrome, where it is associated with supravalvular aortic stenosis and peripheral pulmonary artery stenosis.

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Acute kidney injury (AKI) is recognized as one of the most serious complications in critically ill patients. AKI is strongly associated with higher short- and long-term mortality, increased resource utilization, and a higher risk for the development of chronic kidney disease (CKD). AKI is characterized by an abrupt decrease in the glomerular filtration rate (GFR) that results in the accumulation of nitrogenous waste products and an inability to maintain fluid and electrolyte homeostasis.¹ AKI can result from decreased renal perfusion not severe enough to cause cellular injury, such as an ischemic, toxic, or obstructive injury of the renal tubule, tubulointerstitial process with inflammation and edema, or a primary reduction in the filtering capacity of the glomerulus.

If renal tubular and glomerular function is intact, but solute clearance is limited by factors compromising renal perfusion, the injury is termed *prerenal azotemia*. If renal dysfunction is related to an obstruction of the urinary outflow tract, it is termed *postrenal azotemia*. AKI due to a primary intrarenal cause is called *intrinsic renal injury* or *renal azotemia*. Prerenal azotemic and intrinsic renal injury due to sepsis, ischemia, and nephrotoxins are responsible for most episodes of AKI.^{2,3}

Renal blood flow is approximately 1200 mL/min and constitutes 20% of cardiac output. Given this apparently generous perfusion, it may seem surprising that the kidneys are so susceptible to hemodynamic insults. The majority of perfusion (80%-90%), however, is to the renal cortex, where glomerular filtration occurs. The medulla is designed to concentrate and dilute urine. During urine concentration, the high osmotic gradient required for the reabsorption of water is associated with a low rate of blood flow. In fact, oxygen tension in the outer medulla in the region of the metabolically active thick ascending limb of Henle is only around 10 mm Hg.⁴ This combination of low blood flow and diminished oxygen tension in a metabolically active environment makes the kidneys very susceptible to ischemic injury.

■ PRERENAL CAUSES OF AKI

Prerenal azotemia is a consequence of the reduction in renal perfusion without cellular injury. As such, this is a reversible process if the underlying cause is corrected. It may be secondary to decreased blood volume (e.g., vomiting, dehydration, and hemorrhage), or it may be due to a reduction in the effective arterial blood volume (e.g., congestive heart failure and cirrhosis). Further, the administration of medications that interfere with the normal autoregulatory ability of the kidney can contribute to prerenal azotemia. In settings of diminished renal perfusion, the administration of nonsteroidal antiinflammatory drugs (NSAIDs) or renin-angiotensin-aldosterone system (RAAS) inhibitors can precipitate overt prerenal azotemia.³

During prerenal azotemia, the RAAS becomes activated secondary to a decrease in renal blood flow accompanied by increased activity of the adrenergic nervous system. Increased levels of angiotensin II and adrenergic activation increase proximal reabsorption of sodium, whereas aldosterone increases sodium reabsorption in the distal tubule. Together, these actions decrease the urine sodium concentration to less than 20 mmol/L and fractional excretion of sodium (FE_{Na}) to less than 1%.⁵

Prerenal azotemia accounts for approximately 70% of community-acquired cases of AKI⁶ and 40% of hospital-acquired cases.⁷ Therefore,

prerenal causes should be excluded in all cases of AKI. Therapy of prerenal AKI involves reversing the underlying cause, such as volume replacement or discontinuation of offending agents.

■ POSTRENAL CAUSES OF AKI

Postrenal AKI occurs when there is a bilateral (or unilateral in the case of a single kidney) obstruction of urine flow. In this setting, intratubular pressure increases and, in turn, decreases the net glomerular filtration pressure. Obstruction of urine flow is a relatively uncommon cause of AKI and is more frequent in the community than in the intensive care unit (ICU). Several case series have placed the incidence of postrenal AKI at 3% to 25% of all cases of AKI.^{8,9,10} Postrenal AKI can be divided into renal and extrarenal causes. Extrarenal causes include prostatic disease, pelvic malignancy, and retroperitoneal disorders. Intrarenal causes include crystal deposition, as occurs in ethylene glycol ingestion or uric acid nephropathy in tumor lysis syndrome. Cast formation and tubular obstruction also occur in light-chain diseases, such as multiple myeloma.

Possible postrenal causes of AKI should be evaluated with renal ultrasonography and the measurement of postvoid residual urine in the bladder (>50 mL is abnormal). It is important to rule out these causes rapidly because the potential for renal recovery is inversely related to the duration of obstruction.¹¹

■ INTRARENAL CAUSES OF AKI

Intrarenal causes of AKI can be classified according to the anatomic location of the injury: glomerulus, vasculature, interstitium, or tubule. Suspicion of glomerulonephritis or vasculitis should be raised in a patient with renal failure who has an active urine sediment with red cells and red cell casts. In contrast, acute interstitial nephritis classically presents with pyuria and white cell casts in the urine; on occasion, hematuria is also present. Most cases of AKI from interstitial nephritis are drug related, commonly due to antibiotics or NSAIDs. Recovery usually occurs with the removal of the offending agent and may be hastened by a short course of steroids, such as 60 to 80 mg of prednisone for 10 days. The most common cause of intrinsic renal failure is acute tubular necrosis (ATN).³ Specific causes of ATN can be broadly classified as hemodynamically mediated, such as in prolonged prerenal azotemia, hypotension, and sepsis, or toxic, secondary to antibiotics, chemotherapeutic agents, and contrast media. Concerns have been raised regarding the accuracy of the term *acute tubular necrosis* given that it is a histologic diagnosis that is rarely confirmed by biopsy.¹²

The most common cause of AKI in critically ill patients is sepsis. The pathophysiology of sepsis-induced AKI remains incompletely understood. Until recently, sepsis-induced AKI was considered primarily a disease of the renal macrocirculation¹³ resulting from global renal ischemia, cellular damage, and ATN. However, an increasing body of evidence suggests that AKI in the setting of sepsis can occur in the absence of hypoperfusion.^{14,15} A consistent finding in septic patients, independent of the severity of AKI, is the presence of microcirculatory dysfunction, inflammation, and adaptive bioenergetic response to injury. The role of these mechanisms in the genesis of sepsis-induced AKI and the potential therapeutic implications have been discussed.¹⁶

TABLE 109-1 Laboratory and Microscopic Findings in Prerenal Azotemia and Acute Tubular Necrosis

| LABORATORY TEST | PRERENAL AZOTEMIA | ACUTE TUBULAR NECROSIS |
|---|---------------------------------|--|
| Urine osmolality (mOsm/kg H ₂ O) | >500 | <400 |
| Urine sodium (mEq/L) | <20 | >40 |
| Urine plasma/creatinine ratio | >40 | <20 |
| Fractional excretion of sodium (%) | <1 | >2 |
| Urinary sediment | Normal, occasional hyaline cast | Renal tubular epithelial cells, granular and muddy brown casts |

Data from Esson ML, Schrier RW. Diagnosis and treatment of acute tubular necrosis. *Ann Intern Med* 2002;137:744-52.

Differentiation of ATN from prerenal azotemia can be aided by evaluating urinary indices (Table 109-1).¹⁷ In established ATN, the tubular function is impaired, and tubular sodium reabsorption is hindered. This results in a urine sodium value greater than 40 mmol/L and FE_{Na} greater than 2%. Urine concentrating ability is also abnormal, resulting in isosthenuria with a urine osmolality less than 350 mOsm/kg H₂O.¹⁸ However, a low FE_{Na} may be seen in entities causing ATN (e.g., rhabdomyolysis and myoglobinuria),¹⁹ as well as in contrast-mediated AKI²⁰ and sepsis.²¹ In patients with prerenal azotemia who are treated with diuretics that may affect FE_{Na}, fractional excretion of urea (FE_{Urea}) or a urine-to-plasma ratio of creatinine may be more discriminatory. An FE_{Urea} less than 35% or a urine-to-plasma ratio of creatinine higher than 15 is indicative of prerenal azotemia.²² However, in patients with AKI who received diuretics, the distinction between transient and persistent AKI cannot be made accurately using FE_{Urea} because it lacks specificity.²³ An increasingly common form of AKI in the hospital is secondary to the use of contrast media. Nash and colleagues found contrast nephropathy to be the third most common form of AKI in the hospital.⁷ The pathogenesis of AKI in this setting involves both the hemodynamic and toxic effects of contrast. Contrast media cause renal vasoconstriction and medullary ischemia, as well as direct tubular toxicity.²⁴ Patients with preexisting renal disease and diabetes are at high risk, as are patients who are volume depleted.

■ **EPIDEMIOLOGY AND OUTCOMES**

Several definitions of AKI have recently been proposed. When the risk, injury, failure, loss, and end-stage renal failure (RIFLE) criteria are employed, AKI is a common complication occurring in up to a third of ICU patients and is usually a manifestation of multiorgan failure syndrome.²⁵⁻²⁷ A retrospective cohort study of 31,970 hospitalizations at an academic medical center sought to define AKI stages according to Kidney Disease: Improving Global Outcomes (KDIGO) and other criteria, and AKI incidence was 18.3%. AKI according to all definitions was associated with a significantly higher risk of death and resource utilization.²⁸ The most common cause of intrinsic renal failure is ATN.³ In a large prospective analysis by Liano and coworkers, sepsis was the most common cause (35%); postsurgical (25%) and toxic (31%) causes were also common.¹⁰ Many, if not most, patients have a multifactorial cause of AKI (Fig. 109-1). Recent data also indicate that even transient perturbations in kidney function in hospitalized patients increase the risk of death.²⁹ In a study by Thakar et al.,³⁰ the risk of death increased with the increasing severity of AKI: Acute Kidney Injury Network (AKIN) stage 1, odds ratio (OR) 2.2; stage 2, OR 6.1; and stage 3, OR 8.6 (see AKIN staging below). Furthermore, evidence suggests that a substantial percentage of patients who suffer from AKI do not return

TABLE 109-2 Risk Factors for Developing Acute Kidney Injury

| |
|------------------------|
| Age > 65 years |
| Infection on admission |
| Cardiovascular failure |
| Cirrhosis |
| Respiratory failure |
| Chronic heart failure |
| Lymphoma or leukemia |

Adapted from de Mendonca A, et al. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. *Intensive Care Med* 2000;26:915-21.

TABLE 109-3 Risk Factors for Mortality in Acute Kidney Injury

| |
|--|
| Higher severity index score |
| Age > 65 years |
| Male gender |
| Oliguric acute renal failure |
| Sepsis |
| Nonrenal organ failure (cardiovascular, hepatic, or respiratory failure) |
| Thrombocytopenia |
| Mechanical ventilation |
| Prior compromised health status |

to normal renal function.³¹ AKI is now increasingly recognized as having a bidirectional relationship with CKD in hospitalized patients. Although preexisting CKD increases the susceptibility toward the development of AKI, AKI has also been found to accelerate the development of CKD.³² Moreover, AKI superimposed on CKD leads to end-stage renal disease (ESRD) at a higher frequency than AKI alone. Despite improving supportive interventions in the ICU, the mortality rate for AKI, particularly ATN requiring dialysis, has not changed in the past three decades, remaining at 40% to 80% depending on the study.³³ The risk of developing AKI in the ICU was evaluated by de Mendonca and associates, who found that seven characteristics, if present on admission, were associated with an increased risk of developing AKI (Table 109-2).³⁴ Several other studies addressed the risk factors for mortality in the setting of AKI.^{7,10,35} As indicated in Table 109-3, the risk of death in those with AKI is increased by the presence of nonrenal organ failure, more severe renal dysfunction, as indicated by oliguria, sepsis, advanced age, and male gender. Liano and colleagues found that as the number of organ failures increased, mortality increased.¹⁰ With two organ failures, mortality was 53%, increasing to 80% with three organ failures and 100% with five organ failures. Data clearly show that patients, especially those in the ICU, are dying of AKI and not with AKI alone. The detrimental effects of AKI are not limited to the well-known classical symptoms, such as fluid overload and electrolyte abnormalities. AKI can also cause problems that are not readily appreciated at the bedside and can extend well beyond the ICU stay. Experimental and small observational studies provide evidence that AKI negatively affects innate immunity and is associated with higher rates of infection.³⁷

■ **DEFINITION**

AKI is the abrupt decrease in GFR with resultant retention of urea and other nitrogenous waste products along with dysregulation of body fluids and electrolytes. The term *acute kidney injury* was proposed by the Acute Kidney Injury Network (AKIN) as an alternative to acute renal failure (ARF) to encompass the entire range of failure based on data showing that a small change in serum creatinine influences

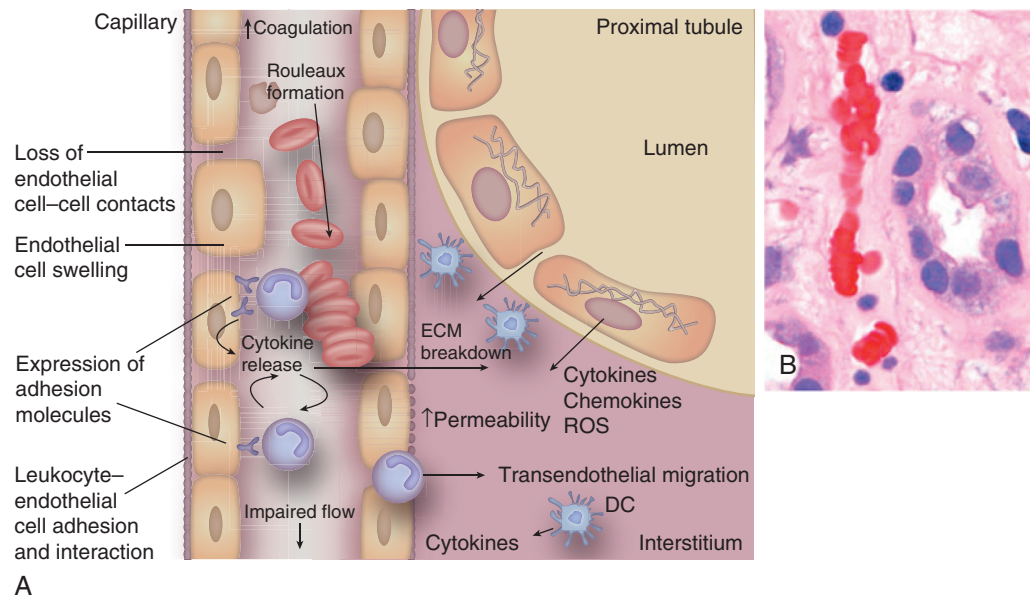


FIGURE 109-1 ■ Pathophysiology of ischemic acute kidney injury: events in endothelial cell activation, injury, and reduced microvascular flow. (A) Ischemia causes upregulation and expression of genes encoding various cell surface proteins, such as E-selectin, P-selectin, vascular cell adhesion protein 1, and intercellular adhesion molecule 1, as well as the downregulation of thrombomodulin. Activated leukocytes bind to endothelial cells through these adhesion molecules. Endothelial injury increases the production of endothelin-1 and decreases endothelium-derived nitric oxide synthase, which induces vasoconstriction and platelet aggregation, promoting a hypercoagulable environment. The combination of leukocyte adhesion and activation, platelet aggregation, and endothelial injury serves as the basis for vascular congestion of the cortical and medullary microvasculature. Permeability defects between endothelial cells occur as a result of alterations in tight junctions and adherens junctions. The proximity and crosstalk between the epithelial proximal tubular cells and microvascular endothelial cells, as well as the release of cytokines and chemokines, further increase inflammation. Dendritic cells also have a role in this inflammatory cascade and amplify the inflammatory signals between endothelial cells and epithelial cells. **(B)** Hematoxylin and eosin stain of a human kidney biopsy from a patient with AKI following an ischemic injury. AKI, acute kidney injury; DC, dendritic cell; ECM, extracellular matrix; ROS, reactive oxygen species. (From Sharfuddin AA, Molitoris BA. Pathophysiology of ischemic acute kidney injury. *Nat Rev Nephrol* 2011;7(4):189-200.)

outcome. The Acute Dialysis Quality Initiative (ADQI) group proposed a consensus categorized definition, the RIFLE criteria,³⁸ which was validated and shown to correlate with hospital mortality and patient outcomes in several populations in large international databases. Subsequently, AKIN proposed a revision of the RIFLE criteria^{39,40,41} to better account for small changes in serum creatinine not captured by RIFLE. The revision indicates that AKI can be diagnosed with a period of oliguria of at least 6 hours or a serum creatinine increase of ≥ 0.3 mg/dL from baseline. However, diagnostic increments of serum creatinine should occur during a period of no more than 48 hours, compared to 7 days for the RIFLE criteria. AKIN criteria caution that adequate volume resuscitation should be ascertained and urinary tract obstruction ruled out prior to using urine output to identify AKI. Moreover, it should be noted that a change in urine flow is less helpful as a diagnostic criterion because of the high incidence of nonoliguric AKI.⁴² The KDIGO Clinical Practice Guidelines for AKI included a revision to the definition of AKI while retaining the AKIN staging criteria.⁴³ In the KDIGO definition, the time frame for an absolute increase in serum creatinine of ≥ 0.3 mg/dL is retained from the AKIN definition (48 hours), while the time frame for a $\geq 50\%$ increase in serum creatinine reverted to the 7 days originally included in the RIFLE criteria. All criteria mentioned above have the greatest utility in epidemiologic studies and in designing clinical studies in AKI. It is likely that they will eventually be revised or changed with the developing body of sensitive and specific biomarkers of renal tubular injury (Table 109-4).

DIAGNOSIS

AKI diagnosis in the ICU typically occurs in the context of another acute illness and can often be linked with a specific precipitating event, such as the development of sepsis, hemodynamic compromise, cardiac surgery, radiocontrast exposure, or nephrotoxic medications. The aforementioned diagnostic criteria can be used to establish the diagnosis utilizing serum determinations of creatinine and urea. However, patients who receive aggressive volume resuscitation will have the rise in serum creatinine blunted due to a dilution in a larger volume of distribution.⁴⁴ Oliguria is not sensitive to renal dysfunction but may improve the diagnostic yield of AKI when added to creatinine.⁴⁵ An attempt should be made to establish whether the patient has AKI, CKD, or an episode of acute superimposed on chronic disease. In some situations, the presentation is less clear, the possibility of obstruction as a cause of AKI or acute-on-chronic kidney disease should be considered, and renal sonography may be of use. Often, patients present with AKI in the absence of obstruction or a clear prerenal cause. Urine microscopy using a quantitative evaluation of the urine sediment for renal tubular epithelial cells, renal tubular epithelial cell casts, and granular casts has recently been shown to differentiate prerenal AKI from ATN and also provide prognostic information.^{46,47} Urinary microscopy occasionally suggests glomerular pathologic changes, with hematuria, proteinuria, fragmented red cells, red cell casts, white cell casts, granular casts, or a combination of these factors.¹² Urine biochemical analysis is of limited use in determining the etiology of AKI,

TABLE 109-4 Criteria for Acute Kidney Injury

| | SERUM CREATININE CRITERIA | | | URINE OUTPUT CRITERIA |
|--------------------|--|---|--|--|
| | RIFLE | AKIN | KDIGO | |
| Definition | Increase in serum creatinine of >50% developing over <7 days | Increase in serum creatinine of 0.3 mg/dL or >50% developing over <48 hours | Increase in serum creatinine of 0.3 mg/dL developing over 48 hours >50% developing over 7 days | Urine output of <0.5 mL/kg/h for >6 hours |
| STAGING | | | | |
| RIFLE-Risk | Increase in serum creatinine of >50% | Increase in serum creatinine of 0.3 mg/dL or >50% | Increase in serum creatinine of 0.3 mg/dL or >50% | Urine output of <0.5 mL/kg/h for >6 hours |
| AKIN/KDIGO stage 1 | | | | |
| RIFLE-Injury | Increase in serum creatinine of >100% | Increase in serum creatinine of >100% | Increase in serum creatinine of >100% | Urine output of <0.5 mL/kg/h for >12 hours |
| AKIN/KDIGO stage 2 | | | | |
| RIFLE-Failure | Increase in serum creatinine of >200% | Increase in serum creatinine of >200% | Increase in serum creatinine of >200% | Urine output of <0.3 mL/kg/h for >12 hours |
| AKIN/KDIGO stage 3 | | | | |
| RIFLE-Loss | Need for renal replacement therapy for >4 weeks | | | |
| RIFLE-End-stage | Need for renal replacement therapy for >3 months | | | |

AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease: Improving Global Outcomes.

Data from Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure-definition, outcome measures, animal models, fluid therapy, and information technology needs the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004;8:B204. Copyright © 2004 BioMed Central Ltd.

Data from Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11:R31. Copyright © 2007 BioMed Central Ltd.

Data from Kidney Disease: Improving Global Outcomes (KDIGO). Acute Kidney Injury Work Group. KDIGO clinical practice guidelines for acute kidney injury. *Kidney Int Suppl* 2012;2:1.

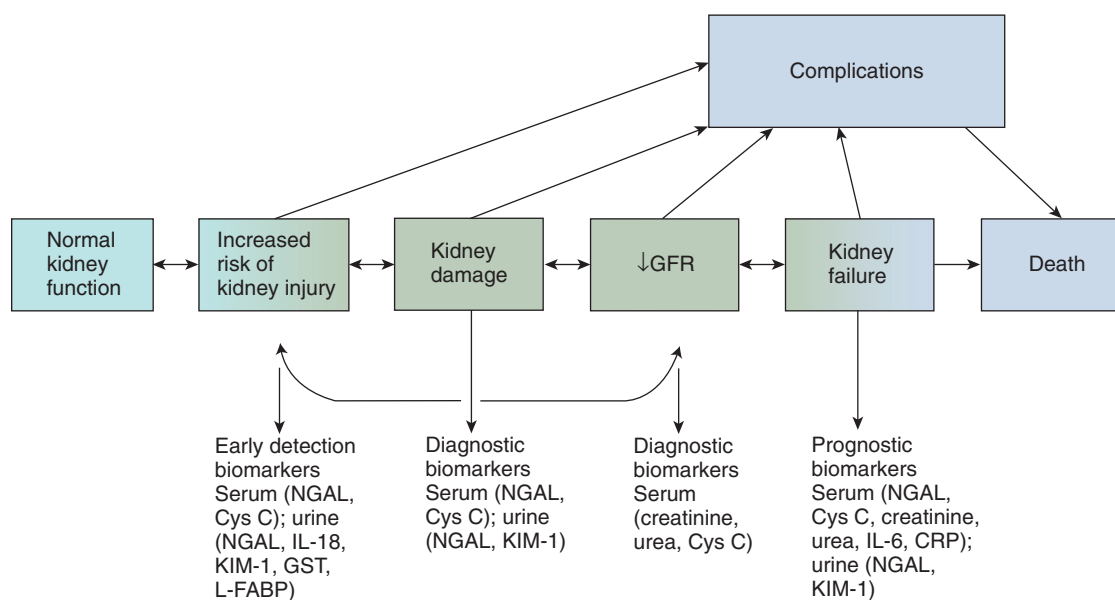


FIGURE 109-2 ■ Evolution of acute kidney injury and novel biomarkers. Injury begins before the excretory function is lost (i.e., decreased GFR) and in some cases can be detected by the measurements of biomarkers. Such biomarkers can also be used for diagnostic and prognostic assessment. CRP, C reactive protein; Cys C, cystatin C; GFR, glomerular filtration rate; GST, glutathione-S-transferase; IL-18, interleukin-18; IL-6, interleukin-6; KIM-1, kidney injury molecule 1; L-FABP, liver fatty-acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin. (From Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet* 2012;380(9843):756-66.)

especially in sepsis. Measurement of the fractional excretion of sodium or urea has not been consistently shown to have a clear correlation with histopathologic findings in systematic reviews.^{48,49}

■ NOVEL BIOMARKERS

Several novel biomarkers are currently being developed (Fig. 109-2). In patients with AKI, the concentrations of some of these biomarkers seem to change earlier than the serum creatinine concentrations and thereby may allow early intervention. In addition, biomarkers appear capable of differentiating etiologies of renal injury.¹² For example,

cystatin C concentrations seem to reflect changes in GFR,^{50,51} whereas concentrations of neutrophil gelatinase-associated lipocalin are related to tubular stress or injury.^{52,53} Moreover, these biomarkers seem to change with treatment or recovery, suggesting that they can be used to monitor interventions.⁵⁴ Several other biomarkers are also under investigation, such as urinary interleukin (IL)-18, urinary liver-type fatty acid-binding protein,⁵⁶ and kidney injury molecule 1 (KIM-1).⁵⁷

Further studies are required to establish any of these or other potential biomarkers as practical diagnostic tools in the early clinical diagnosis of AKI. Such tools may facilitate timely and aggressive therapeutic interventions.

TREATMENT

In light of its dismal outcome, it is imperative that therapies to prevent or ameliorate AKI be developed. The fundamental principle of prevention of AKI is to treat the cause. If prerenal factors contribute, they should be identified and intravascular volume maintained or rapidly restored.

With the increasing use of contrast agents in diagnostic and therapeutic procedures, prevention of contrast-mediated nephropathy has been studied extensively. Intravenous fluids have long been used to prevent contrast nephropathy, but in patients with chronic renal insufficiency, the incidence is still high. Data suggest that low- or iso-osmolal rather than high-osmolal contrast agents are associated with a decreased risk of contrast-induced nephropathy. Since alkalization may protect against free radical injury, the possibility that sodium bicarbonate may be superior to isotonic saline has been examined in a number of randomized trials and meta-analyses. The majority of these studies suggest that both are equivalent or that sodium bicarbonate was better. However, a recent randomized trial comparing a prolonged infusion of isotonic saline (1 mL/kg/h for at least 12 hours prior to and after the contrast-associated procedure) with briefer infusions of isotonic bicarbonate (3 mL/kg for 1 hour prior to the procedure and 1 mL/kg/h for 6 hours after the procedure or 3 mL/kg over 20 minutes prior to the procedure plus oral sodium bicarbonate 500 mg per 10 kg) observed a lower rate of contrast nephropathy with isotonic saline.⁵⁸ N-Acetylcysteine (NAC) has been studied in contrast-induced nephropathy (CIN) prevention for its antioxidant and vasodilatory effects, with mixed results. In the largest study of ST-segment elevation myocardial infarction (STEMI) patients undergoing PCI examining NAC 1200 mg twice daily for 48 hours, NAC was shown to reduce oxidative stress but not the risk for CIN when compared with the placebo.⁵⁹ Two subsequent randomized clinical trials failed to show a difference in the incidence of CIN with NAC treatment.⁶⁰

There is growing interest in the use of statins for the prevention of CIN. Findings from the largest meta-analysis, including five single-center randomized controlled trials (RCTs) and three multicenter RCTs, support the use of short-term statin therapy for prevention of CIN.⁶¹

Currently, our recommendation for preventing contrast nephropathy in high-risk patients (Table 109-5) is to seek an alternative procedure not requiring contrast whenever possible. If that is not feasible, high osmolal contrast should not be used. Adequate hydration with isotonic sodium chloride or bicarbonate should be performed. Despite conflicting evidence, the oral administration of 1200 mg acetylcysteine twice daily the day before and day of the procedure should be considered (given its tolerability and relatively low cost).

Dopamine has long been used to treat AKI. The renal effects of dopamine include an increase in GFR, as well as sodium and water excretion. Clinically, the first response is an increase in diuresis.⁶⁴ These responses occur in patients with normal renal function, but it is unknown whether they are also seen in patients with AKI. In patients with early renal dysfunction (serum creatinine >1.8 mg/dL or urine output <0.5 mL/kg/h), dopamine did not alter peak serum creatinine or the need for renal replacement therapy (RRT).⁶⁵ This was confirmed in a meta-analysis to determine whether the progression of AKI, need for RRT, or mortality was affected by dopamine.⁶⁶

Aside from the lack of efficacy in AKI, dopamine has deleterious side effects. It hastened the onset of gut ischemia in an experimental model⁶⁷ and clinically worsened contrast nephropathy.⁶⁸ In cardiac surgery

patients, dopamine was independently associated with an increased risk of postoperative atrial fibrillation.⁶⁹ Higher doses may increase mortality,⁷⁰ perhaps by worsening myocardial ischemia.⁷¹ Therefore, low-dose dopamine currently has no role in the treatment or prevention of AKI.

Diuretics are also frequently used in patients with AKI, especially in an attempt to convert oliguric into nonoliguric AKI, given the improved prognosis of the latter.⁷²⁻⁷⁴ Loop diuretics, most commonly furosemide, inhibit Na⁺/K⁺-ATPase in the thick ascending loop of Henle and therefore decrease the active reabsorption of sodium. Theoretically, this has some potential benefits, such as decreasing energy expenditure and increasing the flow rate to flush out tubular casts. Ho et al. recently conducted a comprehensive systematic review of the use of furosemide in AKI.⁷⁵ They have shown that furosemide is not associated with any significant clinical benefits in the prevention or treatment of ARF in adults. High doses may be associated with an increased risk of ototoxicity. Although the use of loop diuretics in early or established AKI facilitates management of fluid overload, hyperkalemia, and hypercalcemia, any active role in the prevention or amelioration of the AKI course remains unproven. Any putative role in the prevention or amelioration of the AKI course remains unproven. Therefore, if diuretics are employed, care must be taken to avoid delaying the initiation of dialysis if clinically necessary.

Atrial natriuretic peptide (ANP) is a hormone secreted by the cardiac atria that increases GFR and glomerular filtration pressure by dilating the afferent arteriole and constricting the efferent arteriole.⁷⁶ It also decreases tubular reabsorption of sodium and chloride,⁷⁷ redistributes medullary blood flow,⁷⁸ disrupts tubuloglomerular feedback,⁷⁹ and reverses endothelin-induced vasoconstriction.⁸⁰ Sezi et al. studied the postoperative changes in serum creatinine and the need for dialysis 1 year following surgery among 285 patients with CKD not yet on dialysis who were undergoing on-pump coronary artery bypass grafting. Patients who received ANP had a significantly smaller postoperative increase in serum creatinine, compared to the controls. In the early postoperative period and 1 year later, fewer patients in the ANP group required dialysis.

Fenoldopam, a dopamine receptor-1 agonist, has been studied for the prevention of AKI following cardiac surgery and in other patients, including those with sepsis. A randomized controlled trial on patients admitted to intensive care units with early AKI following cardiac surgery found that fenoldopam infusion, compared with placebo, did not reduce the need for renal replacement therapy or the risk of 30-day mortality but was associated with an increased rate of hypotension.⁸¹

HEMODYNAMIC MANAGEMENT

Intravascular volume is critical in maintaining hemodynamic stability, tissue oxygenation, and organ function.⁸² In a study by Rivers and associates, it was shown that early goal-directed therapy (EGDT) based on optimizing the mixed control venous oxygen saturation in the first 6 hours resulted in decreased mortality in septic patients.⁸³ However, studies have shown increased mortality in patients with positive fluid balance and acute respiratory distress syndrome (ARDS).⁸⁸⁻⁹⁰

With ARDS and prolonged ventilatory support, a very high mortality occurs, particularly in the presence of renal and multiorgan failure. Bouchard and colleagues have reported results of a prospective multicenter observational study of 618 patients that aimed to determine whether fluid overload (>10% increase in body weight) in critically ill patients with AKI is associated with increased mortality. After an adjustment for severity of illness, the study found that fluid overload was independently associated with mortality in AKI patients who did and did not receive dialysis therapy.⁹² A randomized study demonstrated that pulmonary function in critically ill patients was worse in those treated with a liberal fluid management strategy (to achieve a mean central venous pressure [CVP] of ~12 mm Hg) than in those who were treated with a conservative strategy (to achieve a mean CVP ~ 8 mm Hg).⁹³ Moreover, fewer patients in the conservative strategy group required dialysis than in the liberal strategy group. Several pediatric studies, comprising more than 400 children, have demonstrated an association between worsening fluid overload (higher than 10% to

TABLE 109-5 Risk Factors for Contrast Nephropathy

| |
|---|
| Preexisting renal impairment |
| Diabetes mellitus |
| Decrease in effective arterial volume (e.g., congestive heart failure, volume depletion, cirrhosis) |
| High dose of contrast media |
| Concurrent use of nephrotoxic agents (e.g., nonsteroidal antiinflammatory drugs) |

20%) and mortality.⁹⁴⁻⁹⁶ Among patients who developed AKI within 2 days in the NIH ARDS Network FACTT trial, the positive fluid balance was associated with lower 60-day survival in a post hoc analysis.⁹⁷ The RENAL study also demonstrated that a negative fluid balance in patients requiring RRT was associated with increased survival and shorter ICU and hospital stay.⁹⁸ Thus, there are reasons to believe that fluid overload is not just a marker but rather a pathologic factor for high mortality of critically ill patients with AKI. Prospective randomized clinical trials will be needed to confirm this possibility. Until such studies are available, however, we recommend the avoidance of fluid overload in patients with AKI on the basis of knowledge of body weight changes and cumulative fluid balance.⁹⁹

Fluid management in critical illness is aimed at improving organ perfusion. When volume replacement is indicated, both crystalloids (e.g., isotonic saline and Ringer's lactate) and colloid-containing solutions (e.g., albumin solution and colloidal substances) have been used to replace the extracellular fluid deficit. Crystalloids are the most common form of volume replacement, but their effect on plasma volume is limited. Each liter of fluid administered increases plasma volume 200 mL, but the intravascular half-life is only 20 to 30 minutes.⁸²

Colloidal substances, such as albumin, dextran, and hydroxyethyl starches (HESs), because they are macromolecules, are better retained within the intravascular space and have a greater effect on plasma volume. Albumin has been used for decades, but it is expensive and may cause an increase in mortality, according to the Cochrane Injuries Group.¹⁰⁰ Nevertheless, a randomized controlled trial was conducted to compare human albumin with crystalloid in ICU patients (Saline versus Albumin Fluid Evaluation [SAFE] study). This study found that albumin is safe, albeit no more effective than saline for fluid resuscitation. The SAFE study also demonstrated no difference in renal outcomes based on the duration of RRT.¹⁰¹ Dextran cannot be recommended for plasma volume expansion because of serious side effects, such as coagulation abnormalities and increased development of AKI.

HESs are polymers of amylopectin that vary in molecular weight and the number of substitutions of hydroxyethyl groups. As molecular weight and the number of substitutions increase, side effects also increase. Two recent randomized controlled trials using newer HES with lower molecular weights and less substitution showed a neutral or negative effect on mortality, as well as an increased need for RRT.^{102,103} The CHEST trial compared fluid resuscitation with 6% HES 130/0.4 versus 0.9% saline. This randomized controlled trial showed no significant mortality difference at 90 days between the two groups but did demonstrate an increased need for RRT in the HES group, as well as greater numbers of treatment-related adverse events. A meta-analysis indicated similar tendencies of increased RRT with the absence of survival benefit.¹⁰⁴ Therefore, synthetic colloids should be avoided in patients with AKI or at risk of developing AKI, including most patients in the ICU and operative settings.

Although crystalloids remain the first choice for fluid therapy in critically ill patients, there may be differences in renal outcomes among them. A recent study demonstrated decreased renal artery flow and cortical perfusion in subjects who received 0.9% saline compared to a balanced solution (Plasma-Lyte 148).¹⁰⁵ An Australian prospective study found lower increases in creatinine, lower incidence of RIFLE "injury," and a diminished need for RRT in ICU patients treated with a chloride-restrictive approach as opposed to a chloride-liberal strategy.¹⁰⁶ These results will need to be confirmed with other studies. In sepsis and septic shock, hypotension may occur despite normal or increased cardiac output.¹⁰⁷

Sepsis-associated hypotension is often unresponsive to fluid and requires the administration of vasopressor agents. Since such agents cause vasoconstriction, there has been concern about their use in AKI. A large randomized trial comparing dopamine to norepinephrine as initial vasopressors in patients with septic shock showed no significant differences between groups with regard to renal function or mortality through norepinephrine, was associated with less tachycardia in the initial hours following treatment, and was superior concerning survival in cardiogenic shock patients.¹⁰⁸

Vasopressin is a hormone secreted by the posterior pituitary gland and increases systemic vascular resistance by activating V_{1a} receptors on vascular smooth muscle. During septic shock, there is a biphasic response with early high levels of endogenous vasopressin followed by a subsequent decrease.¹⁰⁹ The renal effects of vasopressin are complex and involve the interplay between V_1 and V_2 receptors that regulate the antidiuretic function of vasopressin.¹⁰⁹ In clinical trials, vasopressin increases blood pressure and enhances diuresis in hypotensive oliguric patients with sepsis but has not yet been proven to enhance survival nor been shown to prevent or ameliorate AKI.¹¹⁰

It has been proposed that tight glycemic control can reduce the incidence and severity of AKI in critical patients. However, recent studies have highlighted significant concerns regarding the effectiveness and safety of using intensive insulin therapy with tight glycemic control to prevent or ameliorate morbidity and mortality of AKI or other forms of organ injury. The international Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study enrolled over 6000 patients and set out to determine the risk/benefit of tight glycemic control in critically ill patients.¹¹¹ It showed that in contrast to conventional insulin therapy, intensive glucose control increased mortality among these patients. A blood glucose target of ≤ 180 mg/dL resulted in a lower mortality than a target of 81 to 108 mg/dL. Therefore, it may be prudent to use conventional insulin therapy in ICU patients at risk of AKI to target plasma glucose of less than 150 mg/dL to avoid hypoglycemia.

NUTRITIONAL SUPPORT

Nutritional support in patients with AKI does not differ significantly from that of critically ill patients. AKI affects water, electrolyte, and acid-base balance, but it also induces changes in protein, carbohydrate, and lipid metabolism.¹¹² Patients with AKI should be supplemented with 20 to 30 kcal/kg body weight per day. Even in hypermetabolic states such as sepsis, energy expenditure is rarely greater than 130% of the calculated basic energy expenditure. In a randomized trial in AKI patients, comparing 30 and 40 kcal/kg/d energy provision, the higher energy prescription did not induce a more positive nitrogen balance but was associated with a higher incidence of hyperglycemia and hypertriglyceridemia and a more positive fluid balance.¹¹³ Therefore, supplementation should not exceed 30 kcal/kg/d. In the past, protein restriction was employed in AKI patients to control uremia, but this is likely to be detrimental to the patient and results in a profoundly negative nitrogen balance.¹¹⁴ With the advent of continuous modalities of RRT, it is possible to adequately supplement protein and control uremia. Therefore, some authors recommend aggressive protein replacement at 2.5 g/kg/d, as opposed to the standard 1 to 1.5 g/kg/d.¹¹⁴ However, no compelling data are currently available concerning the efficacy and safety of such high protein intakes. Also, it is important to realize that hypercatabolism cannot be simply overcome by increasing protein or amino acid intake. We suggest administering 0.8 to 1.2 g/kg/d of protein in patients with AKI without the need for dialysis, and 1 to 1.5 g/kg/d in patients with AKI on RRT.

INDICATIONS FOR NEPHROLOGY CONSULTATION

Currently, there are wide variations in the timing of nephrology consultation in patients with AKI. Some physicians prefer to consult at the first elevation in serum creatinine, whereas others wait until RRT is needed. In a study evaluating the effect of nephrology consultation on patient outcome, Mehta and associates found that a delay in nephrology consultation (>48 hours after ICU admission with AKI) led to higher mortality.¹¹⁵ In this study, patients with delayed consultation had a lower serum creatinine concentration and higher urine output but a greater extent of organ failure and higher total body water content. In the multivariate analysis, delayed consultation was no longer significant, but a trend remained toward this being a factor in the outcome. A study by Ponce et al. explored the associations between

nephrology consultation, ICU stay, and in-ICU mortality in 148 ICU patients with AKI at a Brazilian teaching hospital. Multivariable logistic regression showed that delayed consultation was associated with increased ICU mortality.¹¹⁶ Why would early consultation affect mortality? This association could result from a delayed recognition of renal failure. Higher total body water content likely leads to tissue edema and organ dysfunction (i.e., pulmonary edema). Therefore, in ICU patients, early recognition of AKI and its appropriate management may lead to better outcomes.

RENAL REPLACEMENT THERAPY

Indications

As mentioned previously, up to a third of patients in the ICU develop AKI. Of those, 30% to 70% require RRT.^{25,26,27} Many practitioners delay initiating RRT as long as possible because of concerns that dialysis may delay the recovery of renal function.^{117,118} The optimal timing of initiation of dialysis is not defined. There is little disagreement in commencing dialysis in the presence of life-threatening conditions, such as diuretic-resistant volume overload, severe hyperkalemia, acidosis, azotemia, or overt symptoms and signs of uremia (e.g., encephalopathy and pericarditis). Medical treatment approaches for hyperkalemia result in intracellular shifts of potassium. When intermittent hemodialysis is used to correct hyperkalemia after such measures have been utilized, dialytic potassium removal will be reduced, and higher serum levels of postdialysis potassium can occur.¹¹⁹ Metabolic acidosis is common in severe AKI but can be corrected with bicarbonate and rarely requires urgent dialysis if not accompanied by volume overload or uremia.¹²⁰ Some poisons, drug overdoses, and toxic compounds can contribute to acid-base disturbances and AKI. In such cases, dialysis can be supportive and facilitate the removal of these substances and their metabolites. In acute salicylate poisoning, RRT is indicated when the serum concentration is above 100 mg/dL and the patient exhibits altered mental status, pulmonary or cerebral edema, renal impairment, fluid overload that prevents the administration of sodium bicarbonate, or clinical deterioration despite aggressive and appropriate supportive care.¹²¹ Ethylene glycol and methanol poisoning are important causes of anion-gap metabolic acidosis. Dialysis treatment has been shown to reduce the development of subsequent AKI and organ dysfunction.¹²² Metformin-associated lactic acidosis may be an indication for dialysis, especially in critically ill patients at risk of death. In particular, such patients demonstrate a low pH (<6.9), as well as high serum lactate and metformin concentrations.¹²³

The level of azotemia at which RRT should begin is unknown. Several early retrospective studies that used blood urea or blood urea nitrogen (BUN) suggest that early initiation of RRT results in survival improvements.¹²⁴ More recent studies have continued to focus on BUN as a marker for starting dialysis. Serum concentrations of BUN and creatinine are recognized to be inherently subject to a multitude of factors other than kidney function, such as catabolic rate, volume status, age, race, and muscle mass. Single-center observational studies that were restricted to AKI after trauma¹²⁵ and coronary artery bypass surgery^{126,127} suggested a benefit to dialysis initiation at lower BUN concentrations. A prospective multicenter observational study analyzed dialysis initiation, as inferred by BUN concentration in 243 geographically and ethnically diverse patients.¹²⁸ Survival rates were slightly lower for patients who started dialysis at higher BUN concentrations, despite a lower burden of organ system failure. In a prospective multicenter observational trial study conducted at 54 ICUs in 23 countries, the timing of RRT was stratified into “early” or “late” by median urea at the time RRT was initiated and also categorized temporally from ICU admission into early (<2 days), delayed (2–5 days), or late (>5 days).¹²⁹ Timing by serum urea showed no significant difference in mortality. However, when the timing was analyzed in relation to ICU admission, late RRT (this may also be late AKI) was associated with greater overall mortality and covariate-adjusted mortality. Late RRT was also associated with a longer duration of RRT

TABLE 109-6

Potential Indications for Renal Replacement Therapy in the ICU

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|---|
| Nonobstructive oliguria (urine output <200 mL/12 h) or anuria |
| Severe acidemia |
| Azotemia (blood urea nitrogen >80 mg/dL) |
| Hyperkalemia (K^+ >6.5 mmol/L)* |
| Uremia (encephalopathy, pericarditis, neuropathy, myopathy) |
| Severe dysnatremia (Na^+ >160 or <115 mmol/L) |
| Clinically significant organ edema (especially lung) |
| Drug overdose with dialyzable toxin |
| Coagulopathy requiring large amounts of blood products in a patient at risk for acute respiratory distress syndrome |
| NOTE: Any one of these indications is sufficient to consider initiating renal replacement therapy. Two of these indications make renal replacement therapy desirable. |

*Intermittent hemodialysis removes K^+ more efficiently than continuous modalities.

and stay in the hospital, and greater dialysis dependence. Vaara et al. recently published a study addressing the question of timing by defining a set of classic indications for RRT in AKI, including hyperkalemia, acidosis, and volume overload.¹³⁰ Using data from the FINNAKI study, a prospective, multicenter ICU cohort study in which 33.7% of 2901 patients developed AKI, the authors identified four groups of individuals: (1) those who received RRT within 12 hours of developing conventional indications; (2) those who received RRT >12 hours after developing conventional indications; (3) those who received RRT before conventional indications; and (4) a propensity-matched group of individuals who never received RRT. Regarding the 90-day mortality rate, preemptive RRT appeared to be the most effective treatment strategy (the mortality rate was 26.9% compared with 48.5% among those who received RRT for conventional indications). There are ongoing trials of dialysis timing in AKI. Until the results of these are available, it would be prudent not to base a dialysis initiation decision on single BUN and creatinine thresholds but rather on the broader clinical context and trends of laboratory tests. Finally, it is important to consider the volume status when deciding the time for initiating RRT because volume overload, as previously discussed, appears to be an important factor associated with mortality in AKI. Table 109-6 depicts accepted indications for initiating RRT in the ICU.

Adequate Dialysis Dosing

In chronic hemodialysis patients, adequacy of dialysis is primarily determined by the level of small-solute (urea) clearance. This is determined by the Kt/V formula, where K is the dialysis membrane clearance of urea, t is the time on dialysis, and V is the volume of distribution of urea, which is equal to the total body water content. In chronic hemodialysis, a Kt/V of 1.2–1.4 per session is considered adequate.¹³¹ As seen from the formula, one can increase the time on dialysis or increase the dialyzer clearance to enhance urea clearance. Dialyzer clearance depends on blood flow and dialysate flow rates, as well as the inherent properties of the membrane.

In the United States, intermittent hemodialysis and continuous RRT are the most commonly used modalities of RRT, with sustained low-efficiency dialysis and other “hybrid” treatments used in fewer than 10% of patients. Intermittent hemodialysis is most commonly provided on a thrice-weekly or every-other-day schedule.¹³² Concerning intermittent modalities, there is currently no standard Kt/V for adequate dialysis in AKI, but it has been suggested that a higher target Kt/V confers better patient outcomes. Schiffil and colleagues studied 160 patients with AKI who were divided into two groups: (1) a group that received daily hemodialysis; and (2) a group that received alternate-day hemodialysis. It was found that daily hemodialysis resulted in less

TABLE 109-7 Practical Comparison of Acute Renal Replacement Therapy Modalities

| | INTERMITTENT HEMODIALYSIS | SUSTAINED LOW-EFFICIENCY DIALYSIS | CONTINUOUS RENAL REPLACEMENT THERAPY |
|---------------------------|------------------------------|--------------------------------------|---|
| Session duration (h) | 3-5 | 8-12 | 24 |
| Blood flow, mL/min | 300-400 | 200-300 | 100-200 |
| Dialysate flow, mL/min | 500-800 | 200-350 | 25-40 |
| Anticoagulant requirement | Heparin or none | Heparin or none | Heparin or regional citrate |

Data from Fieghen H, Wald R, Jaber BL. Renal replacement therapy for acute kidney injury. *Nephron Clin Pract* 2009;112:222-9.

hypotension, sepsis, gastrointestinal bleeding, and respiratory failure, as well as a significant decrease in mortality.¹³³ This study has been criticized because the Kt/V delivered to the alternate-day group was only 0.94, which is significantly less than the prescribed dose of 1.2. Therefore, the results could be explained by the fact that the alternate-day group received inadequate dialysis. In contrast, the VA/NIH Acute Renal Failure Trial Network Study (ATN study) did not find a benefit for a more intensive dosing strategy for RRT.¹³⁴ This study compared intermittent hemodialysis (hemodynamically stable patients) or sustained low-efficiency dialysis (hemodynamically unstable patients) performed three (less intensive) versus six (more intensive) times a week in 563 critically ill patients with AKI and the failure of at least one nonrenal organ or sepsis. The prescribed Kt/V per session was 1.2 to 1.4, and the actual delivered mean dose was 1.3 in the less intensive arm. The 60-day mortality rate and percentage of patients recovering renal function were similar in both groups. The Hannover Dialysis Outcomes study was a prospective randomized, parallel group study that used intensified extended dialysis (dosed to maintain plasma urea levels < 90 mg/dL) versus standard dialysis (dosed to maintain plasma urea levels between 120 and 150 mg/dL) on 14- and 28-day mortality and renal function.¹³⁵ The mortality and frequency of renal function recovery were similar between the two groups. Based on these two well-designed and performed clinical trials, it appears that increasing urea target clearances do not improve mortality or rates of renal recovery. Therefore, at least the smaller dose used in these trials should be pursued, with monitoring of the delivered dose of therapy to ascertain a minimum delivery of Kt/V of 1.2 per treatment when using extended or intermittent RRT in AKI patients. The significant difference between the prescribed and delivered dialysis dose was studied by Evanson and coworkers, who found that the prescribed dose was a Kt/V of 1.25, whereas the dose delivered was only 1.04.¹³⁶ These authors found that the most significant factor predicting the actual delivered dose was the patient's predialysis weight. It follows that a higher weight in critically ill patients represents higher total body water and, therefore, a larger volume of urea distribution. This would be expected to decrease the Kt/V if it were not accounted for in the prescription of dialysis.

CRRT has been advocated in patients with AKI because of its ability to remove solute more efficiently¹³⁷ and provide hemodynamic stability, but the optimal dosing in CRRT is not known. CRRT depends on convection, not diffusion, for solute clearance, meaning that there is no dialysate involved and the solute is removed with water during ultrafiltration. In the aforementioned VA/ATN study, 201 patients received predilutional continuous venovenous hemodiafiltration (CVVHDF) in the less intensive arm (mean delivered effluent of 22 mL/kg/min) and 179 in the intensive therapy group (mean delivered effluent of 36 mL/kg/min).¹³⁴ A higher dose of CRRT did not influence mortality or renal recovery. The Randomized Evaluation of Normal versus Augmented Level of RRT (RENAL) study was conducted at 35 centers throughout Australia and New Zealand.¹³⁹ It compared the effects of postdilutional CVVHDF doses of 25 and 40 mL/kg/h on the 24-day and 90-day mortality rates of 1508 critically ill AKI patients. Treatment with a higher intensity regimen did not reduce the mortality at 90 days. In conclusion, the results of these two recent

well-designed and executed large clinical trials (ATN and RENAL) did not show any benefit of higher CRRT doses for critically ill AKI patients beyond a threshold necessary to optimize clinical outcome. Therefore, when using CRRT for treating such patients, a minimum dose to be targeted may be the minimal efficient one used in these trials: 20 to 25 mL/kg/h.

Dialysis Modality

When RRT is indicated in the ICU for severe AKI, physicians must choose between intermittent techniques (e.g., traditional intermittent hemodialysis [IHD; used in ESRD]), slow low-efficiency dialysis (SLED), or continuous therapies (e.g., CVVH and peritoneal dialysis [PD]) (Table 109-7). SLED is performed by utilizing dialysis machines to deliver a slow dialysate flow for periods ranging from 8 to 12 hours per day. Advantages of this technique include high hemodynamic tolerance, excellent solute-removal capability, and the capacity to be instituted using regular hemodialysis machines without acquiring new equipment. Availability and expertise with the technique, as well as the hemodynamic status of the patient, are typical determining factors for modality choice for AKI.

RRT is required in severe AKI to remove uremic toxins and maintain fluid, electrolyte, and acid-base balance. CRRT and IHD are effective therapies that may be utilized and exchanged according to the hemodynamic status or coagulation problems of the patient. The effect of these modalities on patient outcomes has been evaluated. Lins et al. performed a multicenter, randomized controlled trial to study the effect of intermittent versus continuous dialysis modalities for the treatment of 316 AKI patients who were admitted to the ICU.¹⁴⁰ They demonstrated that ICU stay, hospitalization, mortality, and renal recovery rates were not different between the groups. Moreover, two systematic reviews that collectively analyzed 45 studies found that outcomes were similar in critically ill AKI patients (stratified according to severity of illness) with CRRT and IHD for hemodynamically stable patients for the relative risk of death, ICU mortality, in-hospital mortality, length of hospitalization, and requirement for chronic dialysis or renal recovery in survivors.^{141,142}

Control of both uremia and volume is the major goal of RRT in AKI. A few studies have suggested that CRRT has advantages over intermittent therapies, including hemodynamic stability, improved survival, greater likelihood of renal recovery,^{141,143,144} and better fluid balance.¹⁴⁵ IHD is complicated by hypotension in 20% to 30% of patients.¹⁴⁶ In hemodynamically unstable patients, this can significantly limit therapy and delay the recovery of renal function. Therefore, some clinicians favor initiating CRRT for hemodynamically unstable patients with AKI, but this has not been supported by a prospective randomized trial¹⁴⁷ or systematic reviews.^{141,142} Moreover, Bagshaw et al. performed a systematic review and meta-analysis of nine randomized trials and concluded that it is impossible to make definitive recommendations about the initial RRT modality because of numerous issues related to study design, conduct, and quality of these trials.¹⁴⁸ The main disadvantage of CRRT is the need for prolonged anticoagulation. SLED is gaining popularity as an intermittent modality in ICUs. Two RCTs that

compared SLED with CVVH or CVVHD^{149,150} found similar outcomes concerning hemodynamic stability and uremic clearance. Furthermore, a decreased anticoagulation requirement was reported for SLED.¹⁵⁰ Based on such evidence, all of these modalities should be viewed as complementary. CRRT or SLED may be utilized for severe AKI with hemodynamic instability and transitioned to IHD once stability is attained. Peritoneal dialysis is an alternative modality for AKI in which vascular access may be difficult, in conditions where anticoagulation may be problematic, in under-resourced regions, or following large disasters with mass casualties.¹⁵¹ A prospective randomized study of daily IHD versus PD in 120 AKI patients showed no difference in survival or recovery of renal function.¹⁵² These results contrast with a previous study that showed decreased survival associated with PD in comparison to CVVH¹⁵³ and suggest that PD remains an acceptable option to CRRT when dosed appropriately.

In certain situations, CRRT is preferable to IHD, including in patients with or at risk for increased intracranial pressure. Studies have shown that CRRT prevents the increase in intracranial pressure associated with intermittent RRT and may be preferred in patients with acute brain injury or fulminant hepatic failure.^{154,155} The use of CRRT in patients with severe sepsis or septic shock has also received much attention. Sepsis is associated with hemodynamic instability, making CRRT an attractive option. It has been shown that CRRT has beneficial effects on the hemodynamics in animal models of sepsis.¹⁵⁶ This is thought to be secondary to the removal of inflammatory cytokines by both convective and adsorptive measures. Hemofiltration membranes allow the ultrafiltration of mid-molecular-weight molecules, such as cytokines. Furthermore, the continuous blood-membrane contact allows the membrane to adsorb an increased number of mediators. There is some evidence that hemofiltration may provide some benefit in sepsis and AKI.^{157,158}

Despite the potential hemodynamic advantage over IHD, CRRT has some disadvantages as well. With CRRT, there is a need for continuous anticoagulation to prevent clotting of the filter. This can be done with low-dose systemic heparin; however, there remains the risk of bleeding or heparin-induced thrombocytopenia. Regional citrate anticoagulation (RCA) is used in some centers. A number of recent clinical studies have shown advantages of RCA compared with heparin regarding prolonged circuit life, reduced incidence of hemorrhagic complications, and lower transfusion needs.¹⁵⁹ On the basis of these data, the KDIGO Clinical Practice Guidelines for AKI recommend the use of RCA as the preferred anticoagulation modality for CRRT in patients without contraindications for citrate, even in the absence of an increased bleeding risk or deranged coagulation.¹⁶⁰

Dialysis Buffer

In determining the adequacy of dialysis, factors other than solute clearance must be considered. One goal of RRT is to maintain a normal acid-base balance in patients with AKI to prevent the complications of acidemia concerning cardiovascular performance, hepatic metabolism, and hormonal response. To maintain a normal pH, the dialysate must contain a buffer. Bicarbonate-based solutions are currently the buffer of choice and are available in separate solutions that are mixed just before use. When regional citrate anticoagulation is utilized, the buffer may need to be decreased or deleted from the dialysate. In this setting, the citrate infusion provides an alkali load and may result in the development of metabolic alkalosis.

Medication Dosing

During AKI, drugs normally eliminated by the kidney exhibit a markedly decreased clearance. As the physiochemical characteristics of the drugs affect the removal by dialysis and hemofiltration, the amount of the drug removed during these procedures may be sufficient to require supplemental dosing. For patients on hemodialysis, a supplemental dose of the drug is most commonly administered at the completion of

the dialysis session.¹⁶² Drug clearance with CVVH is through convective transport and approximates the unbound drug concentration in plasma multiplied by the ultrafiltration rate.¹⁶³ Drugs with molecular weights of less than 500 D are readily removed by either conventional hemodialysis or CVVH, but those with higher weights of 1000 to 5000 D are eliminated more efficiently by CVVH because of the use of high-flux membranes that allow the passage of larger molecules.

The volume of distribution greatly impacts the clearance of a drug, in that drugs with large volumes of distribution are likely to be bound to a greater extent in the tissues. In this setting, only a small amount has access to the vasculature at any time. For such drugs, clearance with CVVH is greater than with intermittent therapies because of the continuous nature of the clearance.¹⁶⁴ The extent of protein binding of a drug is important because the protein-drug complex has a molecular weight greater than 50,000 D. At this size, neither intermittent nor continuous therapies will efficiently remove the drug. However, the extent of protein binding is dependent on pH, uremia, concentration of free fatty acids, heparin therapy, and relative concentrations of drug and protein.¹⁶⁵ In critically ill patients, serum albumin is often decreased, thereby making more drug available for clearance during RRT. Because of the potential medication toxicities, as well as the need to maintain therapeutic levels of multiple medications, it is important to consider and adjust dosing during AKI and with RRT. Dosages of medications must be adjusted for the type of RRT, as well as for the specific characteristics of the drug.

CONCLUSION

Despite extensive clinical experience and improvements in supportive care, the mortality rate of critically ill patients with AKI remains high. Table 109-8 summarizes current recommendations for the care of patients with AKI. These recommendations are based on evidence from clinical trials as well as clinical judgment.

TABLE 109-8

Recommendations for the Evaluation and Treatment of Acute Kidney Injury

- Evaluate patient for AKI when serum creatinine increases by >0.3 mg/dL.
- Exclude prerenal causes (e.g., volume depletion, CHF, cirrhosis, NSAIDs, ACE inhibitors).
- Exclude postrenal causes with renal ultrasonography and postvoid residual.
- Review urine sediment (muddy brown casts, ATN; RBC casts, glomerulonephritis or vasculitis; pyuria, acute interstitial nephritis; bland sediment, prerenal or postrenal azotemia).
- Evaluate urine electrolytes in the absence of diuretics.
- After exclusion of pre- and postrenal azotemia and examination of the urine sediment and electrolytes, notify a nephrologist when serum creatinine is >2 mg/dL.
- Note the projected need for dialysis: oliguric ATN (urine volume <400 mL/24 h), 60%-70% of patients; nonoliguric ATN (urine volume >400 mL/24 h), 30%-40% of patients.
- Avoid excessive fluid resuscitation leading to pseudo-ARDS, ventilator support, and multiorgan complications.
- Avoid hypotension as generally there is no need to treat hypertension aggressively in the absence of a hypertensive crisis.
- Maintain fluid balance and treat hyperkalemia; do not use "renal-dose" dopamine.
- Review active medications for necessary dose adjustments.
- When indicated, use enteral rather than parenteral alimentation.
- Discuss timing for initiation and mode of renal replacement with a nephrologist (intermittent versus continuous and use of circuit anticoagulation).

ACE, angiotensin-converting enzyme; ARDS, acute respiratory distress syndrome; AKI, acute renal failure; ATN, acute tubular necrosis; CHF, congestive heart failure; NSAIDs, nonsteroidal antiinflammatory drugs; RBC, red blood cell.

KEY POINTS**Prerenal Causes**

1. Prerenal azotemia accounts for about 70% of community-acquired acute kidney injury (AKI) and 40% of hospital-acquired AKI.
2. Since there is no cellular injury in prerenal azotemia, it is reversible with the correction of causative factors such as volume depletion, use of nonsteroidal antiinflammatory drugs, or congestive heart failure.
3. Prerenal azotemia is characterized by bland urine sediment and a fractional excretion of sodium (FE_{Na}) less than 1%.

Postrenal Causes

1. Postrenal azotemia occurs when there is a bilateral obstruction to urine flow.
2. It is an uncommon cause of AKI in the ICU.
3. The evaluation includes renal ultrasonography and postvoid residual, which should be less than 50 mL.

Intrarenal Causes

1. These causes are defined according to the anatomic location of injury: glomerulus, tubule, interstitium, or vasculature.
2. The most common cause of intrinsic renal failure is acute tubular necrosis (ATN). Specific causes of ATN can be classified as hemodynamically mediated, such as in prolonged prerenal azotemia, hypotension, and sepsis toxic AKI; secondary to antibiotics, chemotherapeutic agents, and contrast media; or postsurgical AKI.
3. Differentiation from prerenal azotemia is suggested by the examination of urine sediment, which may demonstrate muddy brown casts, as well as an FE_{Na} greater than 1%. Novel biomarkers are promising in the early identification of kidney injury and may allow timely interventions able to improve outcome.

Epidemiology and Outcomes

1. AKI is a common complication of critical illness, occurring in up to a third of ICU patients.
2. In the majority of patients, it is multifactorial in nature with components of hypotension, sepsis, and drugs.
3. AKI mortality is as high as 50% of patients and part of the multiorgan failure.
4. The risk of developing AKI increases with age and in the presence of baseline chronic kidney disease (CKD), oliguria, and sepsis.
5. AKI can negatively affect the immune system and may eventually result in the development of CKD.

Definition of AKI

1. Blood urea nitrogen (BUN) and creatinine are the most common parameters measured, but they are not sensitive indicators of renal dysfunction in an acute setting. Ongoing research is evaluating early diagnostic roles of injury biomarkers.
2. The Acute Dialysis Quality Initiative (ADQI) has proposed a categorized definition of ARF called the RIFLE criteria, which were subsequently revised by the Acute Kidney Injury Network (AKIN) to better account for the small changes in serum creatinine not captured by RIFLE, and shorten the necessary time to establish the diagnosis.

3. AKIN has defined AKI as an increase in serum creatinine (Scr) from baseline to 48 hours: stage 1, an increase in Scr of 0.3 mg/dL or 150% to 200%; stage 2, an increase in Scr of 200% to 300%; stage 3, an increase in Scr of greater than 300% or greater than 4 mg/dL, or acute renal replacement therapy (RRT) commencement (irrespective of the preceding Scr increase or urine output). The latest Kidney Disease: Improving Global Outcomes criteria retained the AKIN but reverted the time frame for a $\geq 50\%$ increase in Scr to the 7 days originally included in the RIFLE criteria.

Treatment

1. To prevent contrast-induced AKI in patients at risk, hydration with isotonic saline or sodium bicarbonate is beneficial, with the possible addition of *N*-acetylcysteine before and after the procedure.
2. There is no role for dopamine in the treatment of AKI.
3. Diuretics have not been shown to prevent or ameliorate AKI. They can be used in the initial management of AKI to facilitate fluid balance and treat hyperkalemia or hypercalcemia, but their use should not delay commencing RRT when deemed clinically necessary.

Hemodynamic Management

1. Early goal-directed management may reverse adverse hemodynamics before tissue injury occurs and result in a better outcome.
2. Available evidence supports crystalloid use for resuscitating volume-depleted patients when the condition is not due to a hemorrhage.
3. When vasopressors are indicated, the effect on systemic hemodynamics outweighs the direct renal vasoconstriction.

Nutritional Support

1. Patients with AKI have increased protein catabolism due to insulin resistance.
2. Enteral nutrition is recommended.
3. Caloric supplementation should be 20 to 30 kcal/kg/d.
4. Protein restriction has no role in the management of AKI.

Indications for Nephrology Consultation

1. Early nephrology consultation may lead to improved outcome due to earlier recognition and interventions for AKI.

Renal Replacement Therapy

1. Dialysis initiation should not be based on a numeric BUN and creatinine threshold but rather on the broader clinical context (e.g., volume status and pericarditis), trends of laboratory tests, and metabolic indicators (e.g., refractory hyperkalemia and acidosis).
2. When using extended or intermittent dialysis in AKI, monitoring the delivered dose of therapy is recommended to ascertain the minimum delivered Kt/V of 1.2 per treatment.
3. With continuous venovenous hemofiltration, ultrafiltration rates of at least 20 mL/kg/h should be attained.

KEY POINTS—cont'd

Modality

1. Patients with delayed recovery from ATN often have fresh areas of necrosis on a renal biopsy. Dialysis-associated hypotension may exacerbate this condition.
2. Current evidence does not support the superiority of CRRT over intermittent therapies in the treatment of AKI.
3. RRT modalities should be viewed as complementary. CRRT or hybrid therapies may be utilized for severe AKI with hemodynamic instability and transitioned to IHD once stability is attained.
4. Drawbacks to the use of CRRT include an increase in nursing care, higher expense, and the need for continuous anticoagulation.
5. Regional citrate anticoagulation is the preferred anticoagulation modality for CRRT in patients without contraindications for citrate.

Dialysis Buffer

1. The bicarbonate-based buffer is currently the standard.
2. The buffer may need to be modified when regional citrate anticoagulation is utilized to avoid metabolic alkalosis.

Medication Dosing

1. In critical illnesses, both the volume of distribution and the extent of protein binding of the drugs change.
2. Owing to potential toxic effects, it is important to consider the degree of renal function when determining medication dosage.

ANNOTATED REFERENCES

Bagshaw SM, Uchino S, Bellomo R, et al. Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury. *J Crit Care* 2009;24:129-40.

This prospective multicenter observational study showed that the timing of RRT might exert an important influence on patient survival. Late RRT (days from admission) was associated with a longer duration of RRT, longer hospital stay, and higher dialysis dependence.

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These two prospective, randomized clinical trials have shown that intensive RRT in critically ill patients with AKI did not decrease mortality, improve the recovery of kidney function, or reduce the rate of nonrenal organ failure compared to less intensive therapy.

■ References for this chapter can be found at expertconsult.com.

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A patent urinary tract is necessary for optimal kidney function. Under normal circumstances, urine passes unimpeded from the renal pelvises to the tip of the urethra. Obstruction can occur anywhere along this pathway and may lead to both acute and progressive kidney parenchymal damage.

Several definitions may be encountered when considering urinary tract obstruction:

- *Obstructive uropathy* refers to any disorder that interferes with drainage of the urine. It may be acute or chronic and either partial or complete; the resulting symptom complex typically depends on both the acuity and severity.
- *Obstructive nephropathy* refers to cases in which obstructive uropathy causes a decline in renal function.
- *Hydronephrosis* refers to dilatation of the urinary collecting system, with renal parenchymal changes. Typically, however, the term is used to describe any dilatation of the urinary tract, regardless of renal parenchymal involvement. Hydronephrosis is usually, but not exclusively, seen in obstructive disorders. Nonobstructive pathogenesis of hydronephrosis includes vesicoureteral reflux or excessive flow through the collection system, such as with habitual water drinking or diabetes insipidus.

■ EPIDEMIOLOGY

Urinary tract obstruction is a common disorder. On autopsy, 3.1% of adults have hydronephrosis.¹ Data from the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample (based on ICD-9 codes) indicate that 1.75% of all hospital discharges are complicated by either hydronephrosis or obstruction.² When hydronephrosis is excluded, urinary tract obstruction occurs in approximately 1% of hospital discharges.² Urinary tract obstruction accounts for approximately 10% of community-acquired acute kidney injury³⁻⁵ and is a factor in 2.6% of acute kidney injury cases in the intensive care setting.⁶

■ ETIOLOGY

Many disorders may lead to urinary tract obstruction. A useful classification is to first separate pathology arising from within the urinary tract itself (intrinsic obstruction) from those diseases that arise outside the urinary tract causing external compression of the system (extrinsic obstruction). This discussion will also consider upper (from the renal pelvis to the ureterovesicular junction [UVJ]) and lower (from the bladder to the urethra) urinary tract obstruction separately.

Intrinsic Obstruction

Intrinsic urinary tract obstruction may be due to pathology within the lumen (*intraluminal*) or within the walls of the collecting system (*intramural*).

Intraluminal Causes

Obstruction at the level of the renal tubules may be due to crystal-induced disease, uric acid nephropathy (as in tumor lysis syndrome), or cast nephropathy due to multiple myeloma. Crystal-induced nephropathy has been classically described with sulfadiazine, acyclovir, indinavir, triamterene, and methotrexate.⁷ Newer literature also implicates orlistat⁸ and ciprofloxacin.⁹

Nephrolithiasis is a common cause of upper urinary tract obstruction at the level of the ureter, with the size of the stone determining the likelihood of obstruction. Stones ≤ 2 mm, 3 mm, 4 to 6 mm, and >6 mm will pass spontaneously 97%, 86%, 50%, and 1% of the time, respectively.¹⁰ Typically the obstruction occurs at one of the three narrowest portions of the ureter: the ureteropelvic junction (UPJ), the UVJ, or at the point where the ureter crosses over the pelvic brim. Neoplasms, blood clots, and sloughed renal papillae are rarer causes of intraluminal obstruction at the level of the ureter.

The causes of intraluminal obstruction at the level of the bladder are similar to those affecting the ureter, with urolithiasis, blood clots, and neoplasms being the most common. Worldwide, infection with *Schistosoma haematobium* with resulting fibrosis is a common cause of bladder obstruction¹¹; although it is rare in industrialized nations, it should be suspected in patients from endemic areas such as Africa and the Middle East.

Intramural Causes

Congenital malformations of the genitourinary tract can cause intramural obstruction of the upper urinary tract. UPJ obstruction (UPJO) warrants specific mention, as it is the most common congenital genitourinary disorder likely to present in adulthood. Kinks, valves, or an adynamic segment of ureter results in failure of peristalsis at the UPJ.¹² The widespread use of maternal prenatal ultrasound (US) has led to increased antenatal diagnosis of UPJO. The diagnosis may be made by US, intravenous urography (IVU), or in equivocal cases, isotope renography (see later imaging section).

Another intramural cause of upper urinary tract obstruction is ureteral stricture due to genitourinary tuberculosis (GU TB). Although rare in the developed world, GU TB complicates up to 40% of patients with extrapulmonary tuberculosis.¹³ Hematogenous spread of mycobacteria can seed the renal cortex and ureters, causing inflammation with resultant fibrosis, obstruction, and secondary infections.¹³ Seeding of the retroperitoneum and bladder can also lead to complications in patients with GU TB.

More common are disorders affecting the neuromuscular control of the lower urinary tract such as cerebrovascular accidents,¹⁴ spinal cord injury,¹⁵ multiple sclerosis,¹⁶ and diabetic neuropathy,¹⁷ which may lead to bladder outlet obstruction. Multiple medications, including anticholinergics, opioid analgesics, nonsteroidal antiinflammatory agents, α -adrenoreceptor antagonists, benzodiazepines, and calcium channel blockers, have also been associated with urinary retention.¹⁸ Stricture of the urethra may also lead to obstruction.

Extrinsic Compression

Pregnancy is typically associated with right-sided dilation of the renal pelvis, calyx, and ureter. Hormonal mechanisms and mechanical compression from an enlarging uterus and ovarian vein plexus have been implicated in these changes.¹⁹ Clinically meaningful obstruction from the gravid uterus is extremely rare.

Malignancies can cause obstruction by several different mechanisms. Local ureteric compression may be seen in metastatic cancers of the cervix, bladder, and prostate, as well as with expanding retroperitoneal soft-tissue masses. Alternatively, the ureters may be compressed or encased by metastatic retroperitoneal lymphadenopathy.²⁰

Retroperitoneal fibrosis may lead to the obstruction of one or both ureters via inflammation. It is an uncommon disorder, with a reported incidence rate of 1.3 cases per million population and a male:female ratio of 3.3:1.²¹ Although the majority of these cases are idiopathic (>75%),²² numerous conditions are suspected to cause retroperitoneal fibrosis, including malignancies, medications, infection, trauma, radiation, and IgG4-related systemic disease.^{23,24} Treatment of idiopathic retroperitoneal fibrosis is initially with steroids, but recurrences are common. Case reports have described the use of cyclophosphamide, azathioprine, colchicine, mycophenolate, or tamoxifen for treatment relapses or steroid-resistant disease, although conclusive data are absent.²²

Abdominal aortic aneurysms (AAA) may also cause obstruction due to compression of the ureter or via inflammation. A recent series evaluated 999 cases of inflammatory AAA and found preoperative hydronephrosis in 7.4% of these cases.²⁵ The clinician must always bear in mind that hydroureter and/or hydronephrosis may be absent in obstruction due to retroperitoneal processes. Thus, one must maintain a high degree of suspicion and use alternative imaging modalities when considering these disorders.

One congenital extrinsic cause of obstruction at the UPJ includes abnormal rotation of the kidney during development, leading to ureteral compression and entrapment of the ureter by blood vessels, although significant controversy exists regarding this disease.^{12,26}

Extrinsic compression of the lower urinary tract is more common in males, and the cause is usually either benign prostatic hypertrophy or prostate cancer. The etiology of urinary tract obstruction is summarized in [Box 110-1](#).

CLINICAL PRESENTATION

The clinical presentation of urinary tract obstruction depends on the location, duration, and severity of obstruction and may therefore be quite variable.

Pain

Acute ureteral obstruction often presents with severe flank pain, otherwise known as *renal colic*. This is usually due to urolithiasis but may be due to other causes of ureteral obstruction (see earlier). Obstruction causes increased intraluminal pressure and spasm of the ureteral muscles, which are responsible for the colicky pain.²⁷ Partial ureteral obstruction may present with a chronic dull pain. Bladder outlet obstruction may lead to distention and subsequent abdominal discomfort.

Changes in Urine Output

One pitfall in the diagnosis of obstruction is the expectation that patients will be anuric. While this is true of patients with the obstruction of all functioning renal mass—complete bilateral ureteral obstruction, complete obstruction of a solitary functioning kidney, or complete obstruction distal to the bladder neck—this is not the case in patients with less severe disease. The degree of urine output does not reliably predict the presence or absence of obstruction; patients may present with normal urine output or even polyuria due to the effects of obstruction on renal salt and water handling (reviewed later).

Lower Urinary Tract Symptoms

Obstruction of the lower urinary tract often presents with some or all of a constellation of symptoms known collectively as *lower urinary tract symptoms*, or *LUTS*. LUTS include voiding symptoms (difficulty urinating, incomplete emptying), postmicturition symptoms (postvoid dribbling), and storage symptoms (urgency, frequency, hesitancy, incontinence).²⁸ Alternatively, patients with lower urinary tract obstruction may be asymptomatic.

BOX 110-1 Causes of Urinary Tract Obstruction

INTRINSIC CAUSES

Intraluminal

Renal Tubules

Crystal-induced disease
Uric acid nephropathy
Cast nephropathy (in multiple myeloma)

Upper Urinary Tract

Nephrolithiasis
Neoplasms
Blood clots
Sloughed renal papillae

Lower Urinary Tract

Urolithiasis
Blood clots
Neoplasms
Schistosomiasis

Intramural

Upper Urinary Tract

Congenital ureteropelvic junction obstruction
Genitourinary tuberculosis

Lower Urinary Tract

Disorders affecting neuromuscular control
Cerebrovascular accident
Spinal cord injury
Multiple sclerosis
Diabetic neuropathy
Medications
Anticholinergic agents
Opiates
Nonsteroidal antiinflammatory agents
 α -Adrenoreceptor antagonists
Benzodiazepines
Calcium channel blockers
Urethral structure

EXTRINSIC CAUSES

Upper Urinary Tract

Pregnancy
Malignancy
Retroperitoneal fibrosis
Abdominal aortic aneurysms

Lower Urinary Tract

Benign prostatic hypertrophy
Prostate cancer

Renal Dysfunction

If asymptomatic, the initial clue to the underlying obstruction may be elevated serum creatinine on blood drawn for an unrelated reason. The fact that urinary tract obstruction may be asymptomatic mandates its inclusion in the differential diagnosis of unexplained kidney failure. If blood work is not obtained during the course of the obstruction, the kidney function may deteriorate such that the first presentation is with uremic symptoms and the need for dialysis.

Infection

The urinary retention associated with lower urinary tract obstruction provides an excellent culture medium for bacteria. Patients may present with cystitis, pyelonephritis, or sepsis. An obstructing renal stone may also be a nidus for infection. Recurrent infection should raise suspicion for possible anatomic abnormalities, especially in men. In one study, 25 out of 83 men (30%) with a febrile urinary tract infection had anatomic lesions in the lower urinary tract, supporting imaging of the lower tract in men with this presentation.²⁹ More recent data refute this finding in men younger than 45 years old.³⁰

Laboratory Values

There are no laboratory values specific to obstruction. Blood tests may show no abnormalities or may show values consistent with kidney failure, such as elevated blood urea nitrogen, creatinine, potassium, and phosphorus levels, and decreased calcium, bicarbonate, and hemoglobin values. The blood tests may also be indicative of renal tubular acidosis (RTA; see later). The urinalysis may be bland or may include red blood cells (in the setting of a stone or malignancy) or white blood cells (in the setting of infection). Significant albuminuria is uncommon, although low-grade proteinuria can be observed, especially in the setting of infection. An experienced observer may also be able to discern crystals in freshly voided urine. The fractional excretion of sodium (FE_{Na}) may be less than 1% in acute obstruction, but it is generally greater than 1% when the obstruction is chronic, owing to renal tubular dysfunction.

IMAGING IN URINARY TRACT OBSTRUCTION

Various imaging modalities may be used to diagnose obstruction: plain abdominal radiography, US, computed tomography (CT), IVU, retrograde pyelography, and nuclear scanning. It is important to understand the indications and limitations of each modality.

Plain Abdominal Radiography

Abdominal radiography (kidney, ureter, and bladder [KUB]) is often the first imaging modality performed in patients with acute flank pain. Although most stones are composed of calcium and should in theory be visible, only 59% of stones are detected on plain film.³¹ Compared with CT scanning, the sensitivity and specificity of abdominal films were 45% to 59% and 77%, respectively.³¹ Further, plain films may not always be able to differentiate phleboliths from calculi. This limits the utility of plain abdominal films to the diagnosis of recurrent disease in those with known radiopaque stones.

Ultrasound

US is inexpensive, does not expose the patient to radiation, and is typically readily available. Its accuracy in detecting hydronephrosis makes US a good screening tool for obstruction in patients with unexplained kidney failure or patients with suspected lower urinary tract obstruction (Fig. 110-1). When CT is used as a reference, US has a traditionally reported sensitivity of 24% and a specificity of 90% for

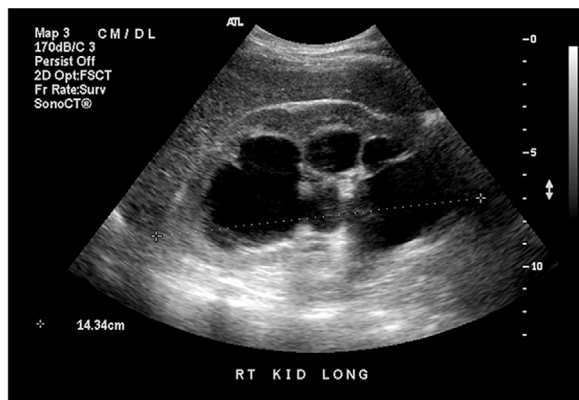


FIGURE 110-1 ■ Typical appearance of a hydronephrotic kidney showing renal pelvis and calyceal dilatation. Note the increase in the kidney length (14.34 cm) compared with normal (~10-11 cm).

the detection of kidney stones and is likely to miss those less than 3 mm in size.³² Another disadvantage of US compared with CT is that bowel gas may obscure visualization of the ureters.³³ Other conditions such as peripelvic cysts and renal artery aneurysms may mimic hydronephrosis on US.³³ These conditions are easily distinguished via CT scanning.

However, in a recent large multicenter randomized controlled trial of adults presenting to the emergency department with suspected nephrolithiasis, US was found to be noninferior with regard to the rates of repeat hospitalizations for missed high-risk diagnoses and adverse events as compared with CT.³⁴ Additionally, US may be the initial imaging modality of choice when radiation is contraindicated, such as in pregnant women and children.

Computed Tomography

The major utility of CT scanning as it relates to urinary tract obstruction is in the evaluation of acute flank pain and suspected nephrolithiasis (Fig. 110-2). In this setting, CT offers a sensitivity of 96% and a specificity of 98% for the detection of stones.³⁵ The retroperitoneum is also well visualized, making CT ideal to detect retroperitoneal fibrosis or obstruction due to retroperitoneal lymphadenopathy. In addition to defining the anatomy of the collecting system, CT has the added benefit of visualizing other organ systems, thereby providing information regarding other conditions in the differential diagnosis of acute flank pain.

One concern raised with CT scanning is the high radiation dose administered. Each CT scan is equivalent to approximately 10 KUBs.³⁶ The reported dose of radiation, quantified in millisieverts (mSv), was significantly higher in patients initially undergoing CT (14.1 mSv) versus US (4.7 to 6.5 mSv) when presenting to the emergency department with acute flank pain and suspected nephrolithiasis.³⁴ Furthermore, this initial radiation exposure was cumulative and persisted at 6 months with CT (17.2 mSv) versus US (9.3-10.1 mSv) regardless of subsequent imaging.³⁴ Lower dose radiation CT protocols have previously been investigated. One study found that lower dose radiation CT scans (equivalent to that of plain film) have a sensitivity of 97% and a specificity of 96% for the diagnosis of acute renal colic when compared with the standard dose. The lower dose CT was inferior at detecting stones less than 3 mm in size,³⁷ which may impair its ability to diagnose non-collecting system pathology. Because of these limitations, it is unclear whether or not spiral CT will remain the initial imaging procedure of choice for the evaluation of suspected nephrolithiasis.

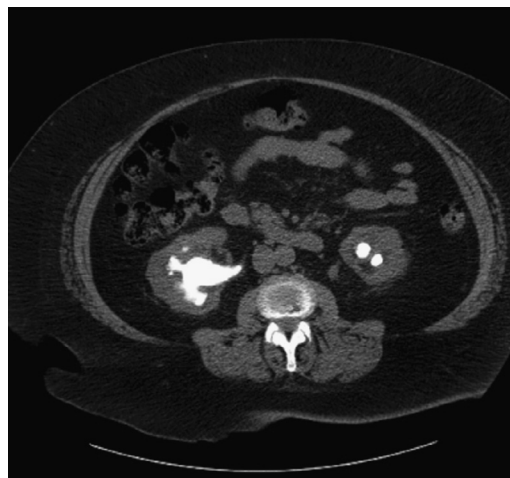


FIGURE 110-2 ■ Bilateral nephrolithiasis on an unenhanced computed tomography scan. Note the staghorn appearance on the left.

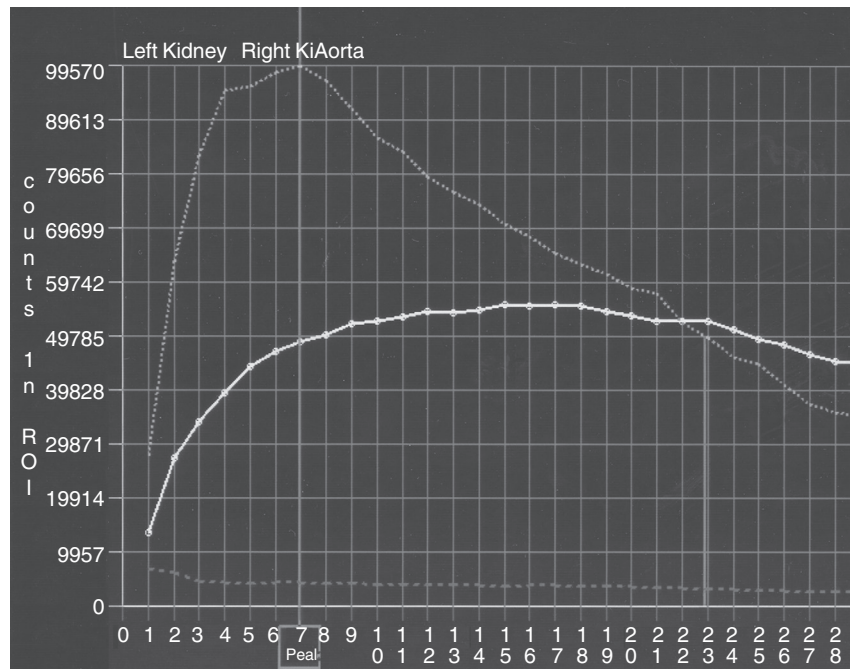


FIGURE 110-3 ■ Renogram showing left-sided obstruction. Note that both kidneys take up the tracer. On the right side, this is followed by an excretion of the tracer, whereas on the left, the tracer remains at peak value.

Isotope Renography

In conventional renography, radiographic tracers are injected into the patient's bloodstream and renal uptake and excretion are measured with a scintillation counter (Fig. 110-3). This test provides functional information by demonstrating decreased excretion in an obstructed kidney. The sensitivity of the test may be enhanced by administering a loop diuretic prior to the scan. The increased urine flow may unmask an occult obstruction. Isotope renography may be used if obstruction is suspected clinically but hydronephrosis is absent or to diagnose a nonobstructive cause of hydronephrosis. In this case, excretion will be normal despite the presence of hydronephrosis. However, as it is a functional scan, radiotracer uptake can be diminished and excretion prolonged with severely compromised GFR. This may lead to both false-negative and false-positive results, limiting its use in such situations.³⁸ Renography also does not provide anatomic information.

Intravenous Urography

IVU, in which the collecting system is imaged after the administration of intravenous (IV) contrast, used to be the study of choice for patients with acute flank pain. The need to administer nephrotoxic IV contrast and the delay in obtaining information render IVU less attractive than a CT scan.³⁵

Retrograde Pyelography

CT scanning and US have largely superseded retrograde pyelography for the diagnosis of obstruction. Retrograde pyelography may be indicated when obstruction is highly suspected on clinical grounds, the US is negative for hydronephrosis, and the patient is unable to receive IV contrast.¹

■ PATHOPHYSIOLOGY OF OBSTRUCTION

Urinary tract obstruction may cause intrinsic kidney dysfunction. The most important effects are changes in renal blood flow, increased

tubular hydrostatic pressure (as a result of increased ureteral pressure), and the development of fibrosis in long-standing obstruction. Specific tubular derangements in sodium, water, potassium, acid, and divalent cation handling occur as well.

Changes in Renal Blood Flow, Tubular Hydrostatic Pressure, and Glomerular Filtration Rate

Over the past 3 decades, various animal models have provided a basis for understanding the renal hemodynamic changes with urinary obstruction. The initial renal response to obstruction follows a triphasic pattern.³⁹ During the first 2 hours of obstruction, there is an initial increase in both renal blood flow and ureteral pressure. This is followed by a brief (2-3 hour) period in which renal blood flow declines due to increased afferent arteriolar resistance, yet ureteral pressures continue to rise. Ultimately, the decrease in renal blood flow leads to a decrease in ureteral pressure, with the pressure returning to normal levels by 10 to 12 hours after obstruction.

The glomerular filtration rate (GFR), which is determined by Starling's forces between the glomerular capillary and renal tubules, is initially diminished by transmitted tubular hydrostatic pressure but is maintained by the augmented renal blood flow. Unresolved obstruction leads to persistent afferent arteriolar constriction and a sustained decrease in both renal blood flow and GFR.

Structural Changes, Maladaptive Cell Signaling, and Renal Fibrosis

Early in ureteral obstruction, dilatation of the ureter and renal pelvis causes mechanical compression of the medulla and cortex, with tubular injury progressing in a retrograde manner.⁴⁰ Injured tubular epithelial cells lose polarity and likely de-differentiate, secreting chemokines that recruit circulating myeloid cells. A complex feed-forward loop of inflammatory cell signaling and oxidative stress ensues in the renal microenvironment.^{41,42} If obstruction is not reversed, cellular apoptosis, senescence, capillary rarefaction, and the formation of atubular

glomeruli are observed.⁴² These changes ultimately result in the deposition of fibrillar collagen, with the contraction and loss of renal parenchymal volume typical of an end-stage kidney.

As with other progressive renal diseases, angiotensin-2 (AT-2) plays a central role in the perpetuation of renal parenchymal damage in chronic obstructive nephropathy. Independent of its vasoconstrictive properties, AT-2 has many other biologic functions, including the upregulation of several profibrotic mediators such as transforming growth factor beta-1, tumor necrosis factor alpha, and nuclear factor kappa B.⁴³

Given the importance of the renin-angiotensin system in promoting renal injury after obstruction, antagonizing AT-2 would appear to be a viable strategy to attenuate injury. Although human data are lacking, animal data show benefits, provided the intervention is conducted after renal development is complete.⁴² Other therapies to halt or reverse fibrosis in urinary obstruction have shown proof of principle in animal models but have not yet translated to clinical use in humans.

Tubular Function

Tubular responses to unilateral or bilateral obstruction differ, with bilateral obstruction (or unilateral obstruction in a patient with a solitary kidney) being much more severe and having more important clinical implications. The following discussion will be limited to bilateral obstruction. Urinary tract obstruction impairs all aspects of renal tubular function including the ability to transport sodium, potassium, and hydrogen and to regulate urine concentration.

Sodium Reabsorption

Upon release of a bilateral obstruction, sodium excretion increases five to nine times that of normal.⁴⁴ Because the GFR is also decreased due to the obstruction, the FE_{Na} may be 20 times higher than normal.⁴⁴ Clinically, this failure of sodium reabsorption may manifest as hypovolemia.

Sodium reabsorption in the kidney is accomplished by various apical membrane transporters, which are coupled to the basolateral sodium-potassium ATPase. Many of these transporters, including the sodium/proton exchanger, sodium-phosphate cotransporter, sodium-potassium-2/chloride cotransporter, and thiazide-sensitive cotransporter, are downregulated during and after the release of the obstruction.⁴⁵ Recent studies suggest that the amiloride-sensitive epithelial sodium channel may be downregulated as well.⁴⁶ In addition to the downregulation of transporters, upregulation of atrial natriuretic peptide, a potent stimulus for sodium excretion, has been demonstrated during and after the release of bilateral obstruction.⁴⁷

Renal Water Handling

Several mechanisms render the kidneys unable to either concentrate or dilute urine after the release of an obstruction. In the case of urinary concentration, the sodium-potassium-2/chloride cotransporter is required to establish the medullary concentration gradient needed for osmotic water movement out of the collecting tubule. Dilution requires the removal of solute in both the loop of Henle and distal convoluted tubule via the sodium-potassium-2/chloride cotransporter and the thiazide-sensitive cotransporter, respectively. Osmotic diuresis due to retained solutes may also lead to an inability to conserve water.

In addition to the effects of abnormal sodium reabsorption on water metabolism in the postobstructed kidney, animal data have demonstrated a direct role of antidiuretic hormone in the concentrating defect as well. Many studies have shown a downregulation of aquaporins in the obstructed kidney,⁴⁸⁻⁵⁰ which may persist for weeks, accompanied by a long-term defect in urinary concentration.⁴⁸ Clinically, this inability to conserve water may manifest as nephrogenic diabetes insipidus and hypernatremia.

Acid-Base and Potassium Balance

Acid-base balance is accomplished by reclamation of filtered bicarbonate and excretion of acid, either as titratable acidity (buffering of hydrogen ions by phosphates, sulfates, and other buffers) or by ammonium excretion. Clinically, obstructed or postobstructed patients often manifest hyperkalemic, hyperchloremic metabolic acidosis. Although this may be solely due to the decreased GFR, some patients have persistent metabolic abnormalities long after the release of obstruction and stabilization of GFR.⁵¹ Human data have revealed several pathophysiologic mechanisms. The majority of patients studied have a distal RTA in which systemic acidosis did not lower the urinary pH below 5.5.⁵¹ Abnormalities in sodium transport in the distal nephron (see earlier) may render this tubular segment unable to generate the lumen negative transepithelial difference needed for proton excretion—a so-called voltage-dependent defect.⁵² This voltage defect can also lead to potassium retention and hyperkalemia.

Other patients are able to acidify their urine to a pH of below 5.5. These patients have low plasma levels of aldosterone with subsequent hyperkalemia, which is typical of a type 4 RTA.⁵¹ The underlying mechanism in this case is decreased ammoniogenesis, most likely due to the hyperkalemia, although the hypoaldosteronism may also contribute.⁵² Patients with a type 4 RTA retain the ability to excrete acid (via titratable acidity) and usually have a mild, self-limited acidosis, whereas those with a distal RTA cannot excrete acid, and the resultant acidosis may be severe.

Recent animal studies have also demonstrated downregulation of key renal acid-base transporters in urinary tract obstruction, including the cortical and medullary sodium hydrogen exchanger and several basolateral sodium-bicarbonate transporters.⁵³

Postobstructive Diuresis

The release of a bilateral obstruction (or unilateral obstruction of a solitary kidney) may lead to a profound diuresis. Several of the mechanisms have already been described. Defects in sodium and water handling predispose to large urinary losses of both. The osmotic load of retained solutes also contributes. Much of the diuresis is appropriate, however, in that previously retained salt and water must be excreted. Typically, postobstructive diuresis is mild and transient and requires no treatment. Often the degree and duration of this diuresis is worsened by overzealous fluid administration in the face of a large, but potentially appropriate, urine output.

The clinical manifestations of post-obstructive diuresis that require treatment include volume depletion and hypernatremia (which may be managed by the administration of iso-osmotic and hypo-osmotic fluid, respectively). Careful attention to potassium, magnesium, phosphorus, and calcium levels is warranted as well.

Other Tubular Functions

After the release of bilateral obstruction, phosphorus excretion rises proportionally to sodium excretion.⁴⁴ This may be mediated by a decrease in the number of proximal sodium/phosphate cotransporters.⁴⁵ Magnesium excretion also rises, likely from decreased absorption in the thick ascending loop of Henle due to a decrease in the transepithelial voltage difference created by the decreased sodium-potassium-2/chloride cotransporter activity.⁴⁴ Calcium handling after obstruction is unclear and differs depending upon the species studied.⁴⁴

TREATMENT

Management of obstructive uropathy depends on the location, severity, symptomatology, and etiology of the obstruction, as well as the presence of concomitant factors such as infection or a decline in kidney function. The clinical scenario guides timing and whether initial management should be conservative or aimed at reestablishing the patency of the urinary tract. Chronic asymptomatic partial obstruction does

not need emergent release, whereas acute, complete obstruction accompanied by infection, pain, or evidence of kidney dysfunction does.

Lower tract obstruction may be relieved simply by placing a urethral catheter, whereas upper urinary tract obstructions may be managed either with percutaneously inserted nephrostomy tubes or via retrograde (i.e., via cystoscope) ureteral stenting. In both cases, subsequent input from a urologist for specific therapy and follow-up is indicated.

Factors that may cause or exacerbate obstruction, such as constipation or the use of medications associated with urinary retention, should be addressed. Other supportive measures such as antibiotics and IV hydration should be instituted if clinically warranted. The metabolic abnormalities of kidney failure, particularly hyperkalemia, should be addressed. If needed, dialysis should not be withheld while awaiting decompressive therapy.

Should the obstruction be chronic and the kidney deemed non-functional, it may be appropriate to proceed with nephrectomy if there is persistent pain or unresolved infection. This decision requires an estimate of the likelihood of recovery of kidney function.

RECOVERY OF KIDNEY FUNCTION

Whether or not an obstructed kidney will regain function is of paramount importance to the clinician and may dictate whether aggressive interventions are indicated or if the affected kidney should be removed. Unfortunately, data addressing this question, particularly human data, are scant. Currently, there are no methods available that reliability predict kidney recovery after relief of an obstruction,⁴⁴ although one recent study found that a GFR of less than 10 mL/min in the obstructed kidney and abnormal renal perfusion (determined via isotope renography) predicted poor recovery in patients with unilateral ureteral occlusion.⁵⁵

Animal studies demonstrate that the likelihood of renal recovery diminishes with longer duration of obstruction.⁴⁴ Even with the recovery of GFR, there may be ongoing injury and progressive long-term kidney damage after the release of the obstruction, likely due to interstitial fibrosis associated with prolonged urinary tract obstruction.⁵⁵ In

humans, the cutoff point at which renal function is unlikely to return has not been determined, and partial recovery has been seen even after months of obstruction,⁵⁶ suggesting that all obstructions should be relieved and followed by serial determinations of kidney function. If desired, a kidney biopsy may be performed to assess the degree of interstitial fibrosis and provide prognostic information.

KEY POINTS

1. Urinary tract obstruction may be due to pathology anywhere from the renal tubules to the tip of the urethra and should be considered in all cases of unexplained kidney injury.
2. Upper urinary tract obstruction may present as renal colic with or without hematuria. Lower tract obstruction may present with frequency, urgency, nocturia, hesitancy, and incomplete emptying. Urinary tract obstruction may also be completely asymptomatic.
3. The presence of urine output does not exclude urinary tract obstruction.
4. Due to its sensitivity, CT is the most commonly used initial imaging modality for suspected nephrolithiasis; however, this practice has been challenged by recent data comparing US with CT.
5. Renal tubular dysfunction may manifest as sodium wasting, abnormal water handling, and acidosis with or without hyperkalemia.
6. Release of obstruction may result in postobstructive diuresis. The diuresis is usually an appropriate response to the retention of nitrogenous waste products.
7. Recovery of renal function is dependent on the duration of obstruction, with reports of recovery in patients who were dependent on dialysis for months.

ANNOTATED REFERENCES

Chevalier R, Thornhill B, Forbes M, Kiley S. Mechanisms of renal injury and progression of renal disease in congenital obstructive nephropathy. *Pediatr Nephrol* 2010;25:687-97.

This article reviews the cellular and molecular mechanisms responsible for the progressive kidney injury associated with obstruction. Pertinent cytokines and growth factors, as well as mediators of renal injury, are discussed. The authors discuss current and future strategies for preventing this injury.

Li C, Wang W, Kwon TH, et al. Altered expression of major renal Na transporters in rats with bilateral ureteral obstruction and release of obstruction. *Am J Physiol Renal Physiol* 2003;285:F889-901.

This article provides the molecular basis for the salt wasting observed after relief of bilateral obstruction. Levels of expression of renal sodium transporters were examined in rats after 24 hours of bilateral ureteral obstruction and at days 3 and 14 after relief of the obstruction. This article demonstrates the downregulation of essentially all transporters during obstruction and the rates at which transporter function begins to normalize.

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This is an excellent overall review to the approach of renal colic. Newer data regarding pathophysiology, diagnosis, and treatment are reviewed. The article provides a rational approach to imaging in this disorder, focusing on the newer imaging modalities.

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Smith-Bindman R, Aubin C, Bailitz J, et al. Ultrasonography versus computed tomography for suspected nephrolithiasis. *N Engl J Med* 2014;371(12):1100-10.

This trial randomized patients presenting to the emergency department (ED) with suspected nephrolithiasis to initial ultrasound (US) performed by ED personnel or a US technician versus spiral computed tomography (CT). As compared with CT, both US arms were noninferior with respect to missed major diagnoses at 30 days, adverse events, and the rates of return ED visits and hospitalizations. Cumulative radiation exposure at 6 months was also lower in both US arms.

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This study provides an excellent overview of the changes in renal tubular function during obstruction. The authors provide data implicating upregulation of the renal renin-angiotensin-aldosterone system. The mechanisms of fibrosis are discussed, and the authors present current and future strategies to prevent the development and progression of kidney disease due to obstructive uropathy.

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Iodinated contrast agents, which are administered intravascularly for medical imaging, are widely used pharmaceutical agents, with greater than 80 million doses administered annually.¹ While vital for diagnostic and therapeutic purposes, they can result in the impairment of kidney function, resulting in a condition called *contrast-induced acute kidney injury* (CI-AKI) or previously *contrast-induced nephropathy*. In most cases, kidney dysfunction due to contrast exposure is mild and transient and is only detected by sensitive tests. Clinically significant kidney injury is much less common, especially among individuals with previously normal kidney function.

CI-AKI has been traditionally defined as an absolute increase of 0.5 mg/dL (44 μ mol/L) or a relative increase of 25% in serum creatinine, within 72 hours, in the absence of another explanatory etiology.² However, the slightly different and more recent AKI Network definitions (absolute increase in serum creatinine of 0.3 mg/dL [26.4 μ mol/L] or a relative increase of 50% within 48 hours) have gained popularity in recent years.^{2,3} These definitions, however, are mainly used for research purposes and are likely to evolve further with the advent of biomarkers such as neutrophil gelatinase-associated lipocalin. For clinical purposes, severe AKI requiring renal replacement therapy (RRT, i.e., dialysis) is much more important. However, even milder forms of AKI, as defined above, are significant, since they not only result in longer hospital stays but also because they are associated with increased long-term morbidity and mortality.^{4,5}

Awareness of the factors predisposing to contrast-associated nephrotoxicity has increased over time to the point that clinicians may now overestimate the risk associated with some specific medical conditions. However, the increasing use of radiographic contrast media, possibly combined with increasing age and comorbidities of the treated population, has contributed to the continuing importance of CI-AKI. In reality, given the mild and transient nature of the AKI in most cases, it is the association with subsequent clinical adverse events that drives the current interest in preventing CI-AKI.

EPIDEMIOLOGY

CI-AKI is the most common iatrogenic cause of AKI and overall the third most common cause of AKI in the hospital setting.^{6,7} The actual incidence of AKI after contrast-enhanced imaging varies from as low as 1% to as high as 30% and depends on the nature of the contrast administered and the underlying risk factors in the patient population.⁸⁻¹³ In addition, these estimates are clouded by the fact that AKI after contrast administration can often be caused by other etiologies (e.g., acute tubular necrosis from cardiogenic shock in a patient with acute coronary syndrome undergoing coronary angiography or severe sepsis in a patient undergoing a contrast-enhanced computed tomography [CT] scan, or atheroembolic renal disease^{14,15}), leading some researchers to use the term *contrast-associated AKI*.¹⁶

The risk of contrast nephropathy varies with the route of administration. Typically, after elective coronary angiography, about 10% to 15% of patients develop AKI (as defined by the rise in creatinine), although the incidence of severe AKI requiring dialysis is much lower, at less than 1%. The incidence of AKI after intravenous administration of contrast (as with contrast-enhanced CT scans) is believed to be much lower. A prospective study reported this incidence at 2.5%

overall, with the risk sequentially increasing as the underlying baseline kidney function decreases.¹⁷ However, other studies have questioned whether the true incidence of contrast nephropathy after intravenous contrast is this high, given that there are underlying fluctuations in serum creatinine levels.¹⁸ Recent studies that incorporated propensity-matched controls who did not receive contrast have made a reasonable case that there is little additional increase in AKI after intravenous contrast administration when adjusted for the underlying baseline risk of AKI.^{19,20} Given that there is possible selection bias in such observational studies (i.e., patients at high risk of AKI may not receive contrast and may be overrepresented in the controls), the debate whether intravenous contrast causes CI-AKI continues.

The most important underlying risk factor for development of CI-AKI is compromised baseline kidney function. The incidence is less than 2% in the unselected general population but has been reported to be as high as 20% to 30% with the addition of decreased kidney function and other risk factors.²¹ The incidence of CI-AKI increases in a graded manner as the severity of the underlying kidney function worsens. Among patients undergoing percutaneous coronary intervention, the risk of AKI has been reported²¹ to be just under 20%, with a baseline glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m², compared with less than 1% in unselected populations.²² For outpatient CT scans, the risk has been reported to increase from 2.4% (GFR 45-59 mL/min/1.73 m²) to 11.1% (GFR 30-44 mL/min/1.73 m²) in one study²³ and to be at 0% (GFR 45-59 mL/min/1.73 m²), 2.9% (GFR 30-44 mL/min/1.73 m²), and 12.1% (GFR <30 mL/min/1.73 m²) in another study,¹⁷ with protocolized prophylactic measures playing a role, among other factors, for the lower risk in the latter case.

Other risk factors for CI-AKI described in the literature include diabetes, older age, cirrhosis, proteinuria, and other comorbid conditions, including congestive heart failure, hypotension, volume depletion, and concomitant administration of other nephrotoxic agents (e.g., nonsteroidal antiinflammatory drugs). It is unclear if some of these risk factors constitute an additional risk after adjusting for the underlying GFR. In addition, some of these risk factors, such as hypotension and congestive heart failure, are risk factors for AKI irrespective of contrast administration. A risk score that incorporates many of these factors for the development of AKI after percutaneous coronary interventions has also been described²⁴ and is available in online calculators and apps.

Metformin is often considered to be a risk factor for CI-AKI (since the package insert advises withholding it for at least 48 hours before contrast imaging), but this is untrue. In patients who develop AKI, there is a higher incidence of metformin-associated lactic acidosis, which is associated with a high fatality rate. However, metformin-associated lactic acidosis only occurs in a fraction of those patients who are not only taking metformin but also either have unstable kidney function at baseline or do develop severe CI-AKI and in whom the recognition of kidney failure does not result in discontinuation of the metformin.^{25,26}

Among patients who are already dialysis dependent, either on peritoneal dialysis (in which they often do have significant residual kidney function) or on hemodialysis, contrast imaging does not cause a decline in the residual kidney function.^{27,28} There is no role for early or intensive dialysis to remove contrast material in these patients.

■ PATHOPHYSIOLOGY

Decreased renal blood flow, tubular cell damage, and tubular obstruction are the most commonly described pathways to AKI occurring after contrast administration.²⁹ Coronary angiography and left ventriculography have been shown to cause a decrease in renal blood flow measured directly using renal artery catheterization.³⁰ In addition, animal data suggest differential vasoconstriction of afferent more than efferent arterioles, causing a direct effect on decreasing GFR.³¹ The vasoconstriction also occurs in the renal medulla, via decreased blood flow in the vasa recta.³² Tissue hypoxia then results in free radical release, leading to oxidant damage to the tubular cells from reactive oxygen species.³² Tubular filtration of relatively higher osmolar contrast media also results in osmotic diuresis, increasing medullary oxygen consumption and exacerbating the medullary hypoxia. Last, reabsorption of water leaves a high concentration of viscous contrast material in the tubules, which can result in intratubular physical obstruction.²⁹

■ CLINICAL FEATURES AND DIAGNOSIS

Patients with CI-AKI are generally asymptomatic but have an acute rise in serum creatinine concentration 24 to 72 hours after the administration of the contrast agent.³³ Kidney failure is usually nonoliguric in mild cases, but it may be oliguric, especially if there is significant preexisting renal impairment.³⁴ Clinically significant deterioration is unlikely if the serum creatinine concentration does not increase by more than 0.5 mg/dL within 24 hours.³³ To make an unequivocal diagnosis of CI-AKI, other potential causes of AKI must be ruled out. Prerenal factors, atheroembolic disease, and other nephrotoxic insults should be excluded.^{14,15} The relatively rapid onset and typical course may help differentiate CI-AKI from other causes of AKI. Urinalysis may be unremarkable or may show granular casts, tubular cells, or small amounts of proteinuria. Fractional excretion of sodium may be low and is unhelpful in differentiating CI-AKI from prerenal, volume-responsive causes of AKI.³⁴

■ PROGNOSIS

Usually, the natural course of CI-AKI is peak creatinine (i.e., the lowest point of kidney function) occurring between 24 and 72 hours and then relatively rapid improvement over the next few days to baseline serum creatinine levels by 7 to 14 days.³³ Overall, less than 1% of patients with CI-AKI will develop kidney failure that requires dialysis, and a smaller proportion of these (estimated at 10%-50%) will remain dialysis dependent. The minority that remains dialysis dependent consists of a mixture of cases of true CI-AKI along with atheroembolic disease and other causes of AKI that often occur in these patients.^{14,15} Nevertheless, despite the fact that most patients with CI-AKI recover, a large body of literature has emerged showing that an episode of AKI is associated with poor long-term outcomes, with a faster decline in kidney function and higher rates of subsequent RRT requirement, as well as higher rates of hospitalization for heart failure and all-cause mortality.^{4,35}

Although the association of CI-AKI with adverse clinical outcomes has been clearly and consistently shown, it is not yet known whether CI-AKI is on the causal pathway to these outcomes or if it is merely a marker of patients who are at high risk of these events.³⁶⁻³⁸ If the latter is true, CI-AKI may indeed be a less important health issue. Future trials using a variety of interventions with different mechanisms of action showing parallel diminution in CI-AKI and adverse events are required to establish more robust evidence for causality.

■ PREVENTION

The most effective method of preventing CI-AKI is to not give iodinated contrast unless absolutely essential, especially in patients at high risk, such as those with advanced kidney disease. Unfortunately, the risks with contrast-enhanced magnetic resonance imaging in this

patient population (i.e., the risk of nephrogenic systemic fibrosis from gadolinium),³⁹ also limit the imaging options, though these risks are much lower with the currently used cyclic gadolinium compounds.⁴⁰ Given the elective nature of the nephrotoxic insult that allows for attempting prophylaxis, many different interventions have been tested for CI-AKI prevention. Many of the studies are contradictory, and the numbers of systematic reviews and meta-analyses are also quite high, so the reader needs to look at the entire body of literature in order to interpret the data.⁴¹

Fluid Administration

Periprocedural volume administration has been the mainstay of preventive efforts and presumably works by reducing the concentration of the contrast medium in the tubules, improving medullary blood flow (via suppression of vasopressin), and increasing the urinary flow itself.²⁹ Isotonic saline has been shown to be superior to half-normal (0.45%) saline.²² There has been significant research in the possible superiority of a bicarbonate-based strategy compared with normal saline, under the hypothesis that the resultant alkaline urine in the tubules will decrease free radical formation and the subsequent oxidant tubular damage. However, the initial promise from the first trial has been belied by the results of subsequent larger trials and meta-analyses.⁴²⁻⁴⁵ A large ongoing prospective trial, which plans to enroll almost 9000 patients, may resolve this question.⁴⁶ Another approach with very promising results relied on using left ventricular end-diastolic pressure (LVEDP) to guide fluid administration in patients undergoing cardiac catheterization, with a relative risk of 0.41 (95% confidence interval: 0.22-0.79; $P = 0.005$) for CI-AKI compared with the standard saline protocol.⁴⁷ This trial also showed a reduction in clinically meaningful outcomes (reduction in persistent renal impairment and all-cause mortality at 6 months), although the number of events was small. Another point to be noted is that the intervention group received significantly larger amounts of fluid (mean 1727 mL compared with 812 mL in the control group), thus questioning the role of LVEDP-guided therapy vis-à-vis more fluid alone. Further, LVEDP measurement is not practical in many settings, such as intravenous contrast administration with CT scans, especially in outpatient settings. Small trials have tested oral hydration strategies compared with intravenous strategies, and although they may be as effective, the small numbers of events in these trials preclude any definitive recommendations at this stage.⁴⁸

Choice and Volume of Contrast Agent

Since the direct kidney damage occurs due to the contrast agent, significant research has been performed with respect to the physicochemical properties, specifically, the ionicity, osmolality, and viscosity, of the contrast agents and modifications to decrease CI-AKI (see [Table 111-1](#) for the classification of the different types). High-osmolality contrast agents, such as diatrizoate, have been shown to be worse with respect to low-osmolality agents and are thus no longer used in routine clinical practice.⁴⁹ When low-osmolality contrast agents were compared with iso-osmolar contrast agents (mainly iodixanol), the first trial showed a significantly lower risk of CI-AKI with iodixanol compared with iohexol¹⁵⁰; however, subsequent larger trials have had different results.^{13,51} Systematic reviews and meta-analyses have suggested the possibility of a small nonsignificant benefit with iodixanol but with significant heterogeneity. This heterogeneity has been resolved either by grouping trials based on the route of contrast (e.g., there is a lower risk of CI-AKI in intraarterial contrast imaging with iodixanol use⁵²) or by specific contrast agents (e.g., iodixanol resulted in less CI-AKI compared with iohexol but not with other low-osmolar agents⁵³). The volume of contrast agent administration also matters, suggesting a lower risk of CI-AKI with lower doses of contrast agent. A ratio of the volume (of contrast dose in mL) to creatinine clearance (variously from >2.6 to >4) has also been reported to be associated with a higher risk

TABLE 111-1 Classification of Iodinated Contrast Media

| IONICITY | RELATIVE OSMOLALITY | OSMOLALITY (MOSM/KG H ₂ O) | EXAMPLES |
|-------------------|---------------------|---------------------------------------|---|
| Ionic monomers | High osmolality | 1500-1900 | Diatrizoate, iothalamate, metrizoate, iodamide, ioxithalamate |
| Ionic dimers | Low osmolality | 600 | Ioxaglate |
| Nonionic monomers | Low osmolality | 500-700 | Iopamidol, iohexol, iomeprol, iopentol, iopromide, ioversol, ioxitol, metrizamide |
| Nonionic dimers | Iso-osmolal | 290-320 | Iodixanol, iotrolan |

of CI-AKI, suggesting that the higher the creatinine clearance, the lower the necessary volume of contrast agent.^{54,55}

Prophylactic RRT

Hemodialysis and hemofiltration, which are performed soon after contrast administration, have been studied for CI-AKI prevention with mixed results.⁵⁶ The rationale for doing this is to help remove the offending iodinated contrast material, especially in patients with reduced kidney function who may not be able to clear it quickly. However, biologically, the iodinated contrast material injected into, say, the coronary circulation or the left ventricle for ventriculography reaches and causes damage to the nephrons within a few cardiac cycles, so the efficacy of removing the contrast agent after the length of time it takes to set up RRT is not very plausible. Indeed, the results of the largest trial studying this were emphatically negative.^{57,58} Other trials have reported a decrease in the proportion of patients with a decrease in creatinine clearance on the fourth day post contrast administration⁵⁹ or even in in-hospital mortality.⁶⁰ These trials are very challenging to interpret given that the hemofiltration or hemodialysis itself would change creatinine clearance directly, and it is not possible to tease the effect of RRT on creatinine clearance from the effect of the CI-AKI attenuation. In addition, these procedures have inherent risks, such as those associated with central line placement and hemodynamic issues with the RRT procedure itself.⁵⁶

Pharmacologic Strategies

N-Acetylcysteine

N-acetylcysteine (NAC) replenishes endogenous glutathione, acts as a biological antioxidant, and may also possess antiinflammatory effects. It has been reported to reduce the risk of CI-AKI in a small trial⁶¹; however, subsequent trials have provided conflicting results. Heterogeneity with respect to the dose and route of administration, and the possible effect of NAC on creatinine levels rather than kidney function, make it difficult to determine the true efficacy of NAC.^{62,63} The largest trial on this topic, which included 2308 patients and measured not just CI-AKI on the basis of the change in creatinine but also clinical events such as the need for RRT and mortality, did not show any benefit of NAC.⁶⁴ Arguments regarding the benign nature of NAC should take into account that the intravenous route can cause anaphylactoid reactions.⁶⁵ In addition, although NAC is not expensive, oftentimes, it has been used in place of—rather than in addition to—truly effective prophylactic strategies such as volume expansion.⁶⁶ Thus, at present, NAC has no role in CI-AKI prevention strategies.

Diuretics

Diuretics, by their inherent effect, can increase urine flow and have been investigated for CI-AKI prevention since they may have a diluting effect on the iodinated contrast agent being filtered in the tubules. By themselves, the use of furosemide and mannitol has actually been shown to be detrimental⁶⁷ and increases the incidence of CI-AKI, which is not entirely unsurprising given the protective effect of volume expansion. More recently, however, the use of furosemide in addition

to intravenous fluids (in the “RenalGuard” system), dosed to achieve a urine output of >300 mL/h, at which point contrast administration is permitted, with subsequent titration of intravenous fluids (and furosemide as required) to match urine output, has been shown to be more effective than hydration alone.^{68,69} Of note, both the RenalGuard system and the LVEDP-guided hydration strategies result in a higher volume administered to the intervention group than to the controls, and the nature of both designs allows this to be performed in a safe manner.

Statins

Statins have been found to be protective as compared with placebo, as well as when high-dose statins (e.g., atorvastatin 80 mg) are compared with low-dose statins in the prevention of CI-AKI.^{70,71} However, these trials have been conducted in patients undergoing coronary angiography and/or interventions and not patients receiving intravenous contrast and typically enrolled limited numbers of patients with chronic kidney disease; therefore, these results cannot be easily translated into such populations. Last, under most current guidelines, the typical patient profile undergoing coronary angiography should be on a statin in the long term and not just for CI-AKI prevention.⁷²

Others

Small trials with ascorbic acid, calcium channel blockers, dopamine, fenoldopam, atrial natriuretic peptides, prostaglandin E1, and nonselective endothelin antagonists have all either failed to show any benefit in CI-AKI prevention or have shown benefit in small trials that need replication.⁷³⁻⁷⁷

MANAGEMENT

In most instances, CI-AKI never becomes clinically evident, and kidney function returns to baseline within 2 weeks. In more severe cases, management is no different from that for AKI of any other cause. Careful control of fluid and electrolyte balance, avoidance of further nephrotoxic insults, attention to nutrition, and surveillance for complications are generally all that is required, although dialysis may be necessary in the occasional patient. Indications for dialysis are no different from those in other patients with AKI, taking into account clinical and biochemical factors such as hyperkalemia and volume overload. Prophylactic hemodialysis soon after the administration of a contrast agent in patients with high serum creatinine concentrations has had inconsistent effects as previously noted. Moreover, dialysis should not be performed for routine removal of contrast medium after imaging in previously dialysis-dependent patients.

CONCLUSION

CI-AKI remains a concern, especially with interventions involving intraarterial contrast. CI-AKI is not common in the absence of risk factors, and these are generally detectable with a history and physical examination and the determination of the serum creatinine concentration. Since CI-AKI can be associated with other adverse clinical outcomes, preventive measures are advisable, especially with advanced

preexisting kidney disease when there is a risk that the patient may require dialysis. Although CI-AKI is associated with later adverse events, causality has not been proven, and the efficacy of preventive measures directed at CI-AKI in preventing these associated events has not been established. At this time, the optimal approach to prevent CI-AKI, which is summarized in the Key Points, includes minimizing the contrast dose, using either iodixanol or a low-osmolar contrast agent other than iohexol, and the use of isotonic sodium bicarbonate or saline. Ongoing trials will elucidate the validity of these approaches

and may especially refute or confirm the newer hydration strategies. Finally, supportive care is indicated if severe CI-AKI does occur.

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KEY POINTS

Recommendations to Reduce the Risk of Contrast-Induced Acute Kidney Injury

1. Assess the risk of CI-AKI in patients requiring a contrast imaging test.
 - a. Use the Mehran risk score if the patient is undergoing percutaneous coronary intervention.
 - b. For patients undergoing intravenous contrast administration, consider an estimated glomerular filtration rate <30 mL/min/1.73 m² as the principal risk factor.
 - c. Additional risk factors include:
 - i. Older age
 - ii. Diabetes mellitus
 - iii. Unstable kidney function
2. Assess the risk/benefit of the proposed contrast imaging, and consider alternative imaging in high-risk patients.
3. Modify correctable risk factors, and hold medications that may act as nephrotoxins.
4. Use the lowest possible dose of contrast media; consider using iodixanol or a low-osmolar contrast agent (other than iohexol)
5. In high-risk patients, correct dehydration, hold diuretics, and consider intravenous fluids if there are no contraindications. Either normal (0.9%) saline or isotonic sodium bicarbonate, started at an initial rate of 3 mL/kg/h at least 1 hour before and continued at 1 mL/kg/h for 6 hours later, are commonly recommended.
6. In high-risk patients, monitor creatinine within 24 to 72 hours post contrast administration.

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A well-written and lucid overview of the different pathophysiology pathways that lead to contrast-induced acute kidney injury.

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■ References for this chapter can be found at expertconsult.com.

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Over half of all critically ill patients develop some degree of acute kidney injury (AKI), and nearly 5% require renal replacement therapy (RRT). For those with severe AKI requiring RRT, mortality can be as high as 70%, and up to 30% of surviving patients remain dialysis dependent.¹⁻⁶ AKI may be a consequence of prerenal causes, intrinsic kidney disease, or urinary tract obstruction. In critically ill patients, the majority of AKI is related to ischemic or toxic tubular injury that is treated supportively and is often reversible. AKI related to acute glomerulonephritis (GN) and acute interstitial nephritis (AIN) occurs in a smaller percentage of patients, but the incidence may be as high as 20% of all AKI.⁷ In addition to supportive care, initiation of appropriate management is paramount for optimal patient and renal survival. This chapter focuses on the clinical presentation and management of GN.

■ GLOMERULONEPHRITIS

Patients with GN most commonly present with features of the nephritic syndrome characterized by hematuria, proteinuria, AKI, edema, and hypertension.⁸ Hematuria may be microscopic or macroscopic, and the urine sediment demonstrates dysmorphic erythrocytes and erythrocyte casts. The urinary protein excretion typically exceeds 1 gram per day. Measuring the urine protein-to-creatinine and/or the urine albumin-to-creatinine ratio can rapidly assess the degree of proteinuria. The simultaneous measurement of these parameters enables one to calculate the urinary albumin-to-total protein ratio (UAPR; $\text{UAPR} = \text{urine albumin-to-creatinine ratio} \div \text{urine protein-to-creatinine ratio}$). A value less than 0.4 for the UAPR is most consistent with tubular or light chain proteinuria, whereas values greater than 0.6 suggest glomerular proteinuria.⁹ In some instances, patients may have nephrotic-range proteinuria (>3 g/d) with associated clinical manifestations including edema, hypoalbuminemia, and hyperlipidemia. Leukocyturia with or without white blood cell casts may be observed with GN of inflammatory origin but is more characteristic of interstitial nephritis.

In a biopsy series of patients with unexplained AKI, the most common diagnoses included various forms of GN (anti-neutrophil cytoplasmic antibody [ANCA]-associated GN, immunoglobulin [Ig] A nephropathy, postinfectious GN, lupus nephritis, anti-glomerular-basement-membrane [anti-GBM] disease) and AIN.^{7,10-12} Indeed, the third most common cause of end-stage renal disease (ESRD) in the United States and Europe is GN.⁸ Distinguishing the type of GN using kidney biopsy is critical for diagnosis and assessing the degree of acute versus chronic disease, which helps guide treatment and prognosis.

The most aggressive form of GN is described clinically as *rapidly progressive glomerulonephritis* (RPGN). Rather than a single disease entity, RPGN is the most severe form of many of the glomerular diseases that are divided into renal-limited etiologies and systemic diseases that involve the kidneys (Table 112-1). RPGN is defined as rapidly declining renal function, progressive oliguria, hematuria, proteinuria, and hypertension.⁸ Although many critically ill patients may have hematuria associated with infection or trauma, hematuria and AKI should always prompt consideration of acute GN. The kidney ultrasound in most cases of RPGN shows normal to slightly enlarged kidneys with increased echogenicity. Kidney biopsy reveals a high degree of glomerular injury with extensive crescent formation

(Fig. 112-1). Importantly, the transition from an acute cellular crescent to chronic, irreversible injury may occur rapidly over days. RPGN is a nephrologic emergency that requires prompt diagnosis with early intervention and therapy to interrupt a natural progression to chronic kidney disease. In adults, the most common cause of RPGN is ANCA-associated small-vessel vasculitis and GN, followed by immune-complex diseases such as lupus nephritis or mixed cryoglobulinemia, and anti-GBM disease (called Goodpasture disease when there is pulmonary involvement).^{8,13} Immunofluorescence microscopy shows pauci-immune staining in ANCA-associated GN, linear IgG staining of the GBM in anti-GBM disease, and immune complex deposition in lupus nephritis, IgA nephropathy, and infection-related GN.

Pulmonary renal syndrome characterized by RPGN and pulmonary capillaritis that may manifest as diffuse alveolar hemorrhage (DAH) is a medical emergency requiring early aggressive treatment.¹⁴⁻¹⁶ It is associated with high mortality rates and rapid progression to ESRD if left untreated. Admission to the intensive care unit (ICU) and mortality are related to both the disease itself and infection. Patients often present with dyspnea, fever, cough, and hemoptysis, with chest radiography documenting diffuse alveolar infiltrates. Alveolar hemorrhage may be difficult to distinguish from pneumonia, especially in patients without hemoptysis. Roughly 30% of patients with DAH do not have hemoptysis. The presence of AKI and hematuria in patients with pulmonary symptoms should raise suspicion of a pulmonary renal syndrome. Although the term *Goodpasture's syndrome* was first used in 1958 to describe patients presenting with pulmonary hemorrhage and GN,¹⁷ the most common cause of pulmonary renal syndrome is ANCA-associated small-vessel vasculitis.⁸ Anti-GBM disease now refers to the triad of DAH, RPGN, and the presence of anti-GBM antibodies. Goodpasture disease is the second most common cause of pulmonary renal syndrome. Much less common causes of pulmonary renal syndromes are SLE (systemic lupus erythematosus), thrombotic microangiopathies, and other systemic vasculitides.

A thorough history and physical examination may provide evidence for a systemic vasculitis (e.g., scleritis, purpuric rash, and oral or sinus lesions). Bronchoscopy is critical to confirm DAH and to evaluate for infection. The gold standard for diagnosis is kidney or lung biopsy, but critically ill patients are often high risk for these procedures. Kidney biopsy is favored over lung biopsy because it is relatively less invasive. Because ANCA-associated small-vessel vasculitis and anti-GBM disease are treated similarly in the acute setting of RPGN and DAH, treatment with plasma exchange, corticosteroids, and cyclophosphamide may be initiated rapidly, before knowing the results of serologic testing.

■ ANCA-ASSOCIATED SMALL-VESSEL VASCULITIS

ANCA-associated disease may present as a systemic small-vessel vasculitis, pulmonary renal syndrome, or renal limited disease. The spectrum of disease includes microscopic polyangiitis, granulomatosis with polyangiitis (GPA, formerly called Wegener granulomatosis), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly called Churg-Strauss syndrome^{18,19}). Histopathology shows focal and segmental crescentic GN, fibrinoid necrosis, and a paucity of immune staining within the glomeruli by immunofluorescence microscopy.

TABLE 112-1

Diseases Associated with Rapidly Progressive Glomerulonephritis and Pertinent Laboratory Studies**RENAL LIMITED**

| | |
|--|--|
| IgA nephropathy | |
| Infection-related glomerulonephritis | Low complement, streptococcal serologies, bacterial cultures |
| ANCA-associated glomerulonephritis (pauci-immune glomerulonephritis) | ANCA titers |
| Anti-GBM disease (Goodpasture's syndrome) | Anti-GBM antibodies |

SYSTEMIC DISORDERS

| | |
|---|---|
| Lupus nephritis | Low complement, ANA, dsDNA antibodies |
| ANCA-associated small-vessel vasculitis | ANCA titers |
| Anti-GBM disease | Anti-GBM antibodies |
| Henoch-Schönlein purpura | None |
| Cryoglobulinemic vasculitis | Low complement, cryoglobulins, hepatitis C serologies, positive rheumatoid factor |

ANCA, antineutrophil cytoplasmic antibodies; ANA, antinuclear antibodies; dsDNA, double-stranded DNA; GBM, glomerular basement membrane; IgA, immunoglobulin A.

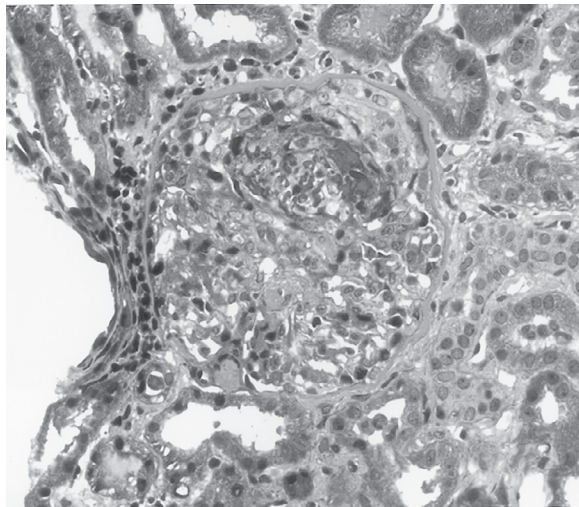


FIGURE 112-1 ■ Rapidly progressive glomerulonephritis. Cellular crescent is present in glomerulus (4- to 8-o'clock position), with fibrinoid necrosis of the glomerular capillary tuft (x200, trichrome).

Either anti-myeloperoxidase (MPO) or anti-proteinase 3 (PR3) antibodies are detectable in most patients. However, about 10% of patients with characteristic clinical manifestations of these diseases and pauci-immune GN do not have detectable antibodies.

Mortality of untreated disease is roughly 90% at 2 years following disease onset.²⁰ However, systematic studies of different treatment regimens have led to significant progress in this field and have improved patient outcomes.²¹ Approximately 80% to 85% of patients attain clinical remission with effective immunosuppressive strategies. Treatment consists of pulse intravenous (IV) methylprednisolone followed by oral corticosteroids and IV cyclophosphamide, rituximab, or both.^{15,22-27} Even patients who are dialysis dependent on presentation often recover renal function with appropriate treatment. Poor prognostic indicators for patient and renal survival are the presence of DAH, severity of renal injury at diagnosis, degree of glomerular injury, extent of

tubulointerstitial lesions on biopsy, and older age.²⁸⁻³² Patients with DAH have a high mortality rate, and plasma exchange improves patient survival. Coagulation factors should be replaced in patients with active hemorrhage.^{20,33-36} For severe pulmonary disease, a few patients have been successfully treated with ECMO (extracorporeal membrane oxygenation).^{37,38} Patients with severe renal disease (i.e., serum creatinine >5.7 mg/dL) have an increased likelihood of renal recovery when treated with plasma exchange. The ongoing “plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS) study” will clarify whether plasma exchange is of value in patients with a glomerular filtration rate less than 50 mL/min.^{29,31,35,39-41}

With appropriate treatment, roughly 80% to 90% of patients achieve remission.^{20,28,33,42,43} Treatment resistance is more common in women, blacks, and patients with severe renal disease. Relapse is more common in patients with anti-PR3 antibodies and involvement of the pulmonary and upper respiratory systems. The ANCA-associated small-vessel vasculitides (AAV) follow a remitting and relapsing course, with the exception of drug-induced AAV (e.g., levamisole-adulterated cocaine, hydralazine),⁴⁴ making long-term monitoring a key component of patient and kidney survival.

ANTI-GLOMERULAR-BASEMENT-MEMBRANE GLOMERULONEPHRITIS

Anti-GBM disease (Goodpasture disease when accompanied by pulmonary capillaritis) is characterized by DAH and RPGN with evidence of anti-GBM antibodies on serologic testing that target the noncollagenous domain of the $\alpha 3$ chain of type IV collagen. It is the most aggressive form of RPGN,¹³ and roughly 30% to 40% of patients have renal limited disease without pulmonary involvement. Anti-GBM disease is more common in white patients, with a bimodal age distribution that peaks during the third and seventh decades.^{15,45-47} Kidney biopsy shows fibrinoid necrosis and glomerular crescent formation, with linear deposition of IgG along the GBM.

Untreated anti-GBM disease is highly fatal. Death is usually caused by pulmonary hemorrhage or renal failure. Treatment with therapeutic plasma exchange, cytotoxic agents, and corticosteroids was introduced in the 1970s, resulting in improved patient and renal survival.⁴⁸ In patients with pulmonary and renal involvement, prompt initiation of plasma exchange is crucial for rapid clearance of anti-GBM antibodies⁴⁹ and should be continued daily until antibodies are undetectable.⁴⁷ Long-term outcomes are related to the degree of pulmonary compromise and renal dysfunction at presentation. With appropriate treatment, survival rates may exceed 90% for acute disease, but patients requiring RRT on initial presentation have lower survival rates.^{46,47,50} Fewer than 10% of patients with renal-limited anti-GBM disease requiring RRT at presentation recover renal function at 1 year despite treatment with plasma exchange, corticosteroids, and cyclophosphamide.^{46,50}

In contrast, one study demonstrated that patients with serum creatinine (SCr) below 5.7 mg/dL on presentation had 100% 1-year patient survival and 95% renal survival.⁵⁰ In addition to dialysis dependence and elevated creatinine, predictors of poor renal outcome include oligoanuria, high anti-GBM antibody titers, and a high percentage of glomeruli with crescent formation and extensive tubulointerstitial disease on renal biopsy.^{45,49,51,52} Although patient and renal survival is generally worse with anti-GBM disease than with ANCA-associated disease, late recurrence of anti-GBM disease is less common than recurrence of ANCA-associated disease.^{13,47}

Both ANCA-associated vasculitis and anti-GBM disease are rare, and interestingly, a subset of these patients has both types of antibodies on serologic testing. Roughly 15% to 30% of patients with ANCA-associated disease also have anti-GBM antibodies, while only 5% to 10% of patients with anti-GBM antibodies also have detectable ANCA titers.^{13,46,47,53-55} Although outcome data are limited in this small group of patients, the outcomes of these patients may be better than those with only anti-GBM antibodies.

LUPUS NEPHRITIS

Lupus nephritis occurs in 50% to 60% of patients with SLE during the first 10 years of disease and is present in 35% of patients at the time of initial diagnosis.⁵⁶ Less than 5% of patients have RPGN or pulmonary renal syndrome. However, 10% to 20% of patients with lupus nephritis ultimately progress to ESRD. In addition to history and physical examination, patient evaluation should include analysis of the urinary sediment because lupus nephritis may present as nephritic or nephrotic syndrome despite normal serum chemistries. Additional testing should also include quantification of proteinuria (by 24-hour urine when possible), measurement of serum complement levels, and assays for antinuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA) antibodies. Kidney biopsy is critical for diagnosis, prognosis, and guiding treatment.

Kidney biopsy is used to divide lupus nephritis into six categories according to the International Society of Nephrology (ISN) classification: class I, minimal mesangial lupus GN; class II, mesangial proliferative lupus GN; class III, focal proliferative lupus GN; class IV, diffuse proliferative lupus GN; class V, membranous lupus GN; and class VI, advanced sclerosing lupus GN.⁵⁷⁻⁵⁹ Proliferative lesions in class III/IV lupus nephritis have poor renal survival in the absence of aggressive treatment. These classes often present with hematuria, proteinuria, hypertension, and AKI. Sclerosing lupus nephritis is a chronic, irreversible lesion that carries a poor prognosis.

Treatment of the more severe forms of lupus nephritis includes pulse methylprednisolone followed by oral corticosteroids and IV cyclophosphamide.⁶⁰⁻⁶³ Similar to treatment of pauci-immune GN, pulse IV cyclophosphamide is preferred over oral cyclophosphamide. Over 80% of patients respond to treatment.^{60,64} Importantly, about 5% to 10% of patients who require RRT initially recover enough renal function to become dialysis independent following treatment.⁶⁵ Plasma exchange did not show additional benefit in a clinical trial using standard glucocorticoid plus cyclophosphamide for proliferative LN induction.⁶⁶ However, plasma exchange may have a role in select patients with LN and a microangiopathy caused by anti-phospholipid antibodies or ADAMTS13 antibodies.⁶⁷ Studies comparing mycophenolate mofetil (MMF) to cyclophosphamide show equivalence but not superiority of one agent over the other; however, relapse appears to be more common in patients treated with MMF.⁶⁸⁻⁷¹ Induction should be followed by maintenance therapy. MMF in combination with low-dose prednisone is the preferred regimen. Additional IV cyclophosphamide or oral azathioprine may be considered depending on response and side effects.^{60,72-74} Other potential therapies include abatacept and belimumab, but their incorporation into the treatment of lupus nephritis requires further study and validation.

Poor prognostic indicators at the onset of disease include male sex, black race, severe hypertension, antiphospholipid syndrome (APS), and delayed initiation of immunosuppressive therapy. Following induction treatment, poor prognostic indicators are failure to achieve remission at 6 months and uncontrolled hypertension.^{60,75} Roughly one-third to one-half of patients will have disease relapse. In some patients, falling complement levels and rising anti-dsDNA titers precede recurrence of disease. However, some patients with severe lupus nephritis have negative titers.^{60,76} Patients with only partial remission often recur sooner than those with complete remission and are more likely to progress to ESRD.⁷⁷ All patients with a history of lupus nephritis should be carefully monitored for recurrence of disease, and repeat kidney biopsy is often required to guide treatment decisions.

INFECTION-RELATED GLOMERULONEPHRITIS

Bacterial, viral, fungal, protozoal and helminth infections all can result in infection-associated glomerulonephritis. Poststreptococcal glomerulonephritis (PSGN) presents with nephritic syndrome 1 to 6 weeks after bacterial infection. It commonly occurs in children following a skin or pharyngeal infection with a nephritogenic strain of group A

β -hemolytic *Streptococcus*.^{78,79} Although PSGN remains the most common cause of acute nephritic syndrome in the pediatric population in developing countries, the incidence of this disease has declined dramatically in the industrialized world. Recently, cases of infection-related GN (IRGN) due to *Staphylococcus* and gram-negative bacteria have become more prevalent, especially in the setting of bacterial endocarditis and ventriculovascular shunt infections. In contrast to cases associated with group A β -hemolytic streptococci, renal insufficiency associated with *Staphylococcus* and other infections occurs during active infection.

Children with PSGN usually have nephritis characterized by hematuria, proteinuria, hypertension, edema, and mild renal impairment. Severe hypertension with encephalopathy and seizures is uncommon and may require admission to the ICU.^{80,81} Laboratory findings demonstrate depressed complement levels (CH50 and C3) consistent with activation of the alternate complement cascade; levels return to normal by 8 to 10 weeks.¹⁸ Serologic studies may be used to confirm recent streptococcal infection, particularly with recent pharyngitis.^{82,83} Renal biopsy demonstrates endocapillary proliferation and granular deposition of immune complexes by immunofluorescence microscopy.^{78,82,84,85}

The acute nephritic syndrome usually resolves in 7 to 14 days, and the prognosis of children with PSGN is excellent. However, about 10% to 20% of children have persistent urinary abnormalities including proteinuria and hematuria.^{6,8,83,86-88} Treatment is generally supportive, with antihypertensives and diuretics as needed in the acute phase. Active infections should be treated, and prophylactic antibiotics are often indicated in endemic areas and for household contacts in regions with high prevalence of disease.

In contrast to children, outcomes for IRGN in adults in the industrialized world are much worse, particularly for patients with underlying chronic disease or risk factors including diabetes, cancer, alcoholism, liver disease, or IV drug use.^{18,78,79,89-92} Elderly patients often have concurrent AKI, congestive heart failure, and nephrotic-range proteinuria. Treatment consists of supportive care including diuretics, antihypertensives, renal replacement therapy as indicated, and eradication of infection. Although evidence from randomized controlled trials is lacking, pulse IV methylprednisolone can be considered in patients with extensive glomerular crescents and RPGN based on management of other glomerulonephritides.¹⁸ One-quarter to one-half of patients have persistent renal dysfunction, and as many as 15% may progress to ESRD.^{89-91,93} Long-term prognosis is worse in patients with persistent proteinuria >1 g/dL after 6 months, and these patients should receive treatment with angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers.¹⁸ Other important causes of infection-related GN include cryoglobulinemic GN due to hepatitis C virus (HCV), hepatitis B virus (HBV), or human immunodeficiency virus (HIV) infection. Signs and symptoms of systemic disease may include palpable purpura, arthralgias or arthritis, and peripheral neuropathy.⁹⁴ Laboratory findings may include hypocomplementemia (especially undetectable C4), elevated rheumatoid factor (RF), circulating cryoglobulins, and positive viral serologies. Kidney biopsy demonstrates intraluminal thrombi on light microscopy with immunoglobulin and C3 deposition on immunohistology. Management of cases of rapidly progressive kidney disease may include plasma exchange, rituximab or cyclophosphamide, and antiviral therapy.⁹⁴⁻⁹⁶

IGA NEPHROPATHY

IgA nephropathy (IgAN) is an extremely common form of GN worldwide. It usually manifests in the second or third decade of life in North America and affects men twice as frequently as women.^{97,98} The majority of patients present with macroscopic hematuria coinciding with an upper respiratory tract or gastrointestinal infection. Patients may develop hypertension and varying degrees of proteinuria. Crescentic IgAN is associated with nephrotic-range proteinuria, severe hypertension, and rapidly declining renal function in less than 10% of cases.^{99,100} Severe AKI at initial presentation may also be caused by coincident

acute tubular necrosis due to macroscopic hematuria or crescentic disease. No specific serologic study to date can establish the diagnosis; renal biopsy is required. The severity of inflammation (e.g., crescents and capillary immune deposits, in addition to usual mesangial deposits), tubulointerstitial fibrosis, and glomerular sclerosis by light microscopy is variable but predictive of clinical outcomes. Immunofluorescence microscopy demonstrates mesangial IgA deposits.

The long-term prognosis of patients with IgA nephropathy is highly variable, but many patients develop progressive renal failure. Progression to ESRD is approximately 15% to 25% at 10 years and 25% to 30% at 20 years following diagnosis.¹⁰¹

Hypertension should be aggressively treated with angiotensin blockade and other agents if necessary.^{18,102} Patients with significant proteinuria (often defined as >0.5 to 1 g/dL) and declining renal function may benefit from corticosteroids or immunosuppressive agents. Corticosteroids appear to reduce the risk of progression to ESRD and decrease proteinuria in selected patients.¹⁰³⁻¹⁰⁷ Immunosuppressive medications such as cyclophosphamide or azathioprine should be reserved in rare cases of RPGN and crescentic GN.^{18,99,101} Predictors of disease progression include the degree of renal dysfunction at diagnosis, significant proteinuria, hypertension, and evidence of chronic disease by renal biopsy.^{97,98,108,109}

■ IGA VASCULITIS

IgA vasculitis (IgAV, formerly called Henoch-Schönlein purpura [HSP]) is indistinguishable from IgAN on kidney biopsy. However, IgAV is a systemic disease characterized by a palpable purpuric rash, arthritis or arthralgias, and gastrointestinal involvement. It occurs much more commonly in children than in adults. The classic presentation is sudden onset of rash, progressing from nonblanching erythematous macules to urticarial papules to purpura, with a symmetric distribution on the extensor surfaces of the distal extremities and buttocks.^{110,111} Children present more frequently with gastrointestinal manifestations and fever, whereas adults often have more severe renal involvement as well as joint symptoms.^{112,113} Renal involvement occurs in roughly one-third of children and two-thirds of adults.¹¹⁴ The most common manifestation is microscopic hematuria with or without RBC casts and nonnephrotic proteinuria.¹¹⁵

Renal involvement in IgAV is usually more severe at presentation than IgAN, but most children recover completely.^{112,116,117} Estimates of recovery and chronic kidney disease vary widely, but the prognosis for renal recovery is worse in adults. Poor prognostic indicators include renal dysfunction and significant proteinuria at presentation, hypertension, and extensive glomerular inflammation on histology.^{113,114,117,118} Treatment is primarily supportive, and trials to date do not support any specific treatment regimen.¹¹⁹ Conservative therapy is generally sufficient in most cases of IgA vasculitis. Patients with more severe skin, joint and/or gastrointestinal manifestations may benefit from a short course of oral corticosteroids. However, there is no clear evidence that prednisone prevents serious long-term renal disease.^{120,121} Intravenous corticosteroids may be required when there is severe abdominal pain and nausea that precludes oral therapy. Corticosteroid therapy is also indicated when there is severe crescentic disease accompanied by worsening kidney function.^{120,121} Kidney Disease Improving Global Outcomes (KDIGO) recommendations suggest that persistent IgAV be treated as isolated IgAN.¹⁸ There are limited reports on the use of plasmapheresis for the management of severe disease.^{122,123} Two adults with severe systemic manifestations refractory to corticosteroids and immunosuppressive agents were treated with plasmapheresis with subsequent improvement.¹²⁴

■ THROMBOTIC MICROANGIOPATHIES

Thrombotic microangiopathy (TMA) is characterized by widespread thrombosis of arterioles and capillaries, with intraluminal platelet aggregation and vessel wall thickening.¹²⁵⁻¹²⁷ The underlying pathophysiologic cause of TMA is endothelial damage caused by a variety

of insults. Primary TMA syndromes include thrombotic thrombocytopenic purpura (TTP), hereditary hemolytic uremic syndrome (HUS; Upshaw-Sculman syndrome), and primary atypical HUS. Secondary TMA syndromes include typical or diarrheal HUS (Shiga-toxin mediated), drug-induced syndromes, autoimmune disease (SLE, systemic sclerosis), pregnancy-related TMA (preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, and a low platelet count [HELLP] syndrome), pancreatitis-related TTP/HUS, cancer and stem cell transplant-induced TTP/HUS, malignant hypertension, and infection-related TTP.

Clinical manifestations and laboratory findings of TTP and HUS overlap considerably. Therefore, patients presenting with microangiopathic hemolytic anemia and thrombocytopenia should be initially classified as having undifferentiated TMA or TTP-HUS. The classic pentad of findings in TTP includes microangiopathic hemolytic anemia, thrombocytopenia, neurologic symptoms and signs, impaired renal function, and fevers.^{125,127,128} However, all five manifestations are seen in less than one-third of patients. Neurologic symptoms may predominate, manifesting as confusion, headache, seizures, and coma. Renal manifestations are usually more prominent in HUS, and the typical presentation in children includes microangiopathic hemolytic anemia, thrombocytopenia, and AKI. Laboratory hallmarks include microangiopathic hemolytic anemia with schistocytes on peripheral smear, elevated lactate dehydrogenase levels, and thrombocytopenia, with platelet counts that are usually less than 60,000/ μ L.

Remarkable progress has been made in elucidating the molecular basis of TTP and HUS. TTP occurs in hereditary (Upshaw-Shulman syndrome) and acquired forms related to deficiency or the presence of antibodies that disrupt the function of the zinc metalloprotease ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13).¹²⁷⁻¹²⁹ This protein is involved in the cleavage of von Willebrand factor (vWF), and deficiency of ADAMTS13 leads to the accumulation of large multimers of vWF that bind platelets, leading to microvascular thrombosis. Historically, untreated TTP had a mortality rate of over 90%. However, mortality has fallen to 10% to 20% with the advent of treatment using plasma exchange.^{130,131} Other therapies include glucocorticoids, rituximab, and splenectomy in the case of refractory or relapsing disease.^{132,133} Hereditary forms require treatment with fresh frozen plasma or cryosupernatant that contains ADAMTS13. Since hereditary TTP is rare, acquired TTP is the presumed diagnosis in new cases.

Hemolytic uremic syndrome is the most common cause of AKI in children and presents with hemolytic anemia, thrombocytopenia, and AKI.^{125,134-136} The typical, or diarrheal, form of HUS (d-HUS) occurs most commonly following diarrheal infection with Shiga-toxin-producing *Escherichia coli* (*E. coli* O157:H7), which accounts for 90% of cases. The peak incidence occurs in children younger than 5 years of age. The illness begins with abdominal cramps and nonbloody diarrhea, followed by hemorrhagic diarrhea in 70% of patients. As the diarrheal illness is improving, patients develop severe renal failure, anemia, and thrombocytopenia. These children are often critically ill, and roughly one-half to two-thirds of patients require RRT. Hypovolemia is common, and rapid volume repletion is a critical component of early therapy. About 70% of patients will require RBC transfusions, and 25% will have neurologic involvement. Over the past few decades, mortality rates have fallen from roughly 40% to 50% to 3% to 5%, primarily due to aggressive supportive care with red blood cell transfusions and RRT as needed. Numerous therapies for HUS have been investigated without clear benefit, and treatment remains largely supportive. Antibiotic treatment of the diarrheal illness associated with *E. coli* O157:H7 is associated with increased risk of developing HUS. Spontaneous resolution occurs 1 to 3 weeks following disease onset, and the majority of patients demonstrate renal recovery. Unfortunately, some children develop ESRD, and up to 40% have long-term sequelae including chronic kidney disease, persistent proteinuria, and hypertension. Non-diarrheal-associated HUS occurs in a minority of patients and may be associated with other infections such as *Streptococcus pneumoniae*.

A small percentage of patients with HUS have sporadic or familial forms, known as atypical HUS. These patients have defects in the alternative complement pathway, and mutations have been described in complement factor H, complement factor I, and membrane cofactor protein.¹²⁷⁻¹²⁹ Mortality rates are highest in patients with complement factor H mutations, and most survivors progress to ESRD. Therapies with fresh frozen plasma, plasma exchange, and eculizumab, a monoclonal antibody targeting the terminal complement cascade, are under investigation for treatment of this devastating disease.¹³⁷ Eculizumab should be considered for patients with a presumptive diagnosis of atypical HUS based on the absence of features of secondary TMAs and failure to respond to 5 days of intensified plasma exchange.

An extensive variety of drugs have been associated with TMA. The pathophysiologic mechanisms underlying drug-induced TMA are not well understood, but immune-mediated effects or direct endothelial toxicity are likely important.¹³⁸ Immune-mediated TMA may occur when drugs induce the formation of antibodies that ultimately react with endothelial cells, platelets, and/or neutrophils and cause platelet microthrombi in addition to microvascular injury. The antibodies form when the drug or its active metabolites are present in the circulation or tissues. Once the drug is entirely cleared, no new antibody formation occurs.¹³⁹ Drugs associated with this phenomenon include quinine, gemcitabine, mitomycin C, quetiapine, and oxaliplatin.^{140,141}

Scleroderma renal crisis presents as acute kidney injury with abrupt onset of moderate to severe hypertension and may be accompanied by encephalopathy with seizures or flash pulmonary edema.¹⁴² A subset of patients may not be hypertensive but have blood pressures higher than baseline values, which purports a worse prognosis.¹⁴³ Roughly 10% of patients develop scleroderma renal crisis, usually occurring within 4 years of disease onset. The risk is greatest with diffuse cutaneous disease, and antecedent treatment with high-dose corticosteroids increases the risk of scleroderma renal crisis.^{144,145} Patients demonstrate microangiopathic hemolytic anemia, thrombocytopenia, proteinuria,

microscopic hematuria, and marked increases in plasma renin. In the past, untreated disease had a dismal prognosis, with less than 10% survival. The use of angiotensin-converting enzyme (ACE) inhibitors has revolutionized treatment; acute mortality rates are now below 25% with appropriate treatment.^{142,146,147} About one-half to two-thirds of patients will require RRT, but half of these patients recover enough renal function to become dialysis independent. Poor outcomes are associated with Cr above 3 mg/dL at the initiation of ACE-inhibitor therapy, dialysis dependence, poor blood pressure control, male sex, older age, and congestive heart failure. Patients with scleroderma renal crisis who do not require RRT have 90% survival rates at 5 years. In contrast, patients who become dialysis dependent have only 40% survival at 5 years. Early recognition and treatment are critical for both patient and renal outcomes. ACE inhibitors should be initiated rapidly and continued even if patients develop progressive renal failure or require RRT.

■ ANTIPHOSPHOLIPID SYNDROME

A small percentage of patients with antiphospholipid syndrome (APS) present with “catastrophic” APS, characterized by AKI and widespread small, and in some cases large, vessel venous and arterial thrombosis affecting multiple organs.¹⁴⁸ The disease progresses over days to weeks and commonly affects the kidneys, lungs, central nervous system, heart, and skin. The kidney is the most common organ affected, with renal involvement in over 70% of patients. Renal disease manifests as malignant hypertension and AKI, with 25% of patients requiring RRT. Mortality is estimated at 50%, and management includes treatment of the underlying cause (e.g., infection, SLE), high-dose corticosteroids (methylprednisolone, 500 g IV for 3 consecutive days, followed by prednisone, 1 mg/kg/day), systemic anticoagulation, plasma exchange to remove anticardiolipin antibodies, and intravenous immunoglobulin.¹⁴⁹

KEY POINTS

1. Many underlying causes for acute kidney injury (AKI) due to glomerulonephritis are reversible. Because the transition of active glomerular lesions to irreversible scar occurs rapidly, prompt diagnosis and early intervention are crucial.
2. Pulmonary renal syndromes constitute a medical emergency. Studies demonstrate that early aggressive treatment improves patient and renal survival.
3. Detailed histories and physical exams are important for distinguishing renal-limited disease from systemic diseases.
4. Initial evaluation should include basic chemistries, evaluation of the urine sediment, complete blood counts with review of the peripheral blood smear, assessment for proteinuria, and kidney ultrasound.
5. Serum complement levels are important tools for distinguishing causes of glomerulonephritis (GN): (a) normal serum complement

levels in most cases of IgA nephropathy, IgA vasculitis, ANCA-associated GN, and anti-GBM disease; and (b) depressed serum complement in immune complex GN including infection-related GN and lupus nephritis.

6. Depending on the clinical scenario, additional evaluations may include anti-neutrophil cytoplasmic antibodies (ANCA), anti-GBM antibodies, anti-nuclear antibodies (ANA), anti–double-stranded DNA (dsDNA) antibodies, serologies for streptococcal infection, viral serologies, and bacterial cultures.
7. The gold standard for diagnosis of glomerulonephritis remains kidney biopsy. However, critically ill patients are often at increased risk for complications, and it may be necessary to proceed with empiric treatment in the absence of biopsy in certain situations.

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This study evaluates the long-term outcomes of patients with scleroderma renal crisis, with emphasis on renal outcomes.

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Acute interstitial nephritis (AIN) is an important cause of AKI characterized by inflammation of the renal interstitium and tubules. It is more properly called *acute tubulointerstitial nephritis* (Fig. 113-1). This disorder results from a hypersensitivity reaction most commonly induced by medications or infections. AIN may also result from autoimmune disorders including SLE, sarcoidosis, and Sjögren syndrome.^{1,2} AIN is seen in about 2% to 6% of kidney biopsy series, but the incidence may be as high as 25% in patients with unexplained AKI.^{1,3-5} Medications account for over two-thirds of cases. Many critically ill patients are treated with medications commonly associated with AIN, such as antibiotics, proton pump inhibitors, and diuretics (Table 113-1).^{6,7} It is important to recognize AIN early in order to identify inciting drugs that should be discontinued to minimize ongoing renal injury. Early improvement of kidney impairment and patchy infiltrates on biopsy indicate a more favorable prognosis.^{2,8} Poor prognostic indicators include advanced age, prolonged renal

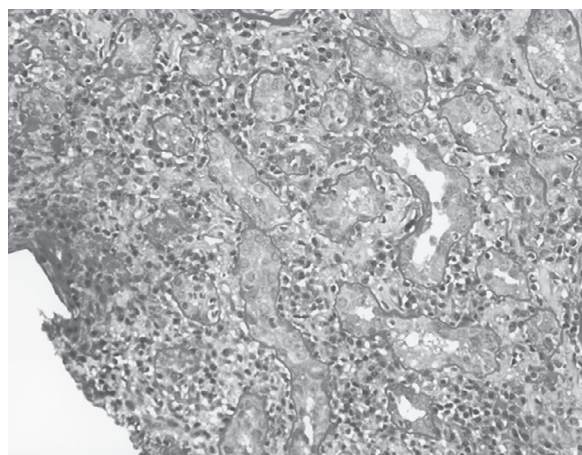


FIGURE 113-1 ■ Acute interstitial nephritis. Diffuse, predominantly mononuclear cell infiltrate is present within an expanded and mildly edematous interstitium, and periodic acid–Schiff (PAS)-positive tubular basement membranes have wrinkling. Foci of tubulitis are also present (×200, PAS).

TABLE 113-1

Common Medications Associated with Acute Interstitial Nephritis

| |
|--|
| Antibiotics—penicillins, cephalosporins, sulfonamides, ciprofloxacin, rifampin |
| Anticonvulsants—phenytoin, carbamazepine, phenobarbital, valproate |
| Diuretics—thiazides, loop diuretics, triamterene |
| Herbal medications |
| NSAIDs |
| Proton-pump inhibitors |

impairment, and degree of chronic tubulointerstitial changes on kidney biopsy. Approximately 30% to 40% of patients will have some degree of long-term renal impairment.^{2,6,7}

Drug-induced AIN usually presents a few weeks following initiation of the medication but can occur after one dose in some cases. With removal of the offending agent, the duration of AKI can vary from a few weeks to months.^{1,2,7} The prototypical example of AIN is that of methicillin-associated AIN. The majority of patients with methicillin-induced AIN developed fevers, eosinophilia, pyuria, and hematuria a few weeks following exposure. About half of patients developed AKI for a duration of several weeks, followed by full recovery in 90%.⁶ Unfortunately, the classic triad of fever, rash, and eosinophilia occurs in only 10% to 15% of patients.^{1-3,6} Patients may present with mild renal impairment or severe AKI requiring RRT. The urine sediment may be bland or demonstrate sterile pyuria, leukocyte casts, and hematuria. In most cases, patients have subnephrotic-range proteinuria (<3 g/day), with a predominance of low molecular weight proteinuria, but two-thirds of patients with NSAID-induced AIN present with nephrotic syndrome.^{2,6} The diagnosis of AIN can be difficult, as systemic manifestations may mimic infection. Patients with pyelonephritis often have leukocyturia, hematuria, and mild proteinuria. Urine culture is essential to document infection, and sterile pyuria should prompt consideration of AIN as a diagnosis. AIN may be difficult to distinguish from acute tubular injury, particularly in patients with bland urinary sediments. Eosinophiluria, based on Wright or Hansel stain, is suggestive of acute AIN but is neither sensitive nor specific for this disorder.^{6,9,10} Eosinophiluria is also found in a variety of other disorders including pyelonephritis, cystitis, prostatitis, acute tubular necrosis, and crescentic and proliferative glomerulonephritis. As such, the significance of eosinophiluria must be carefully interpreted in the context of the entirety of the clinical picture. The absence of eosinophiluria does not exclude the diagnosis of AIN, making biopsy an important diagnostic tool to differentiate these entities and guide therapy.

The initial management of a patient with AIN is largely supportive, with dialysis as indicated. Removal of the suspected offending agent is the cornerstone of therapy. Identification of all candidate etiologic agents, elimination of potentially causative medications, and control of potential infectious causes are fundamental to the control of AIN.^{2,6} When replacing medications, it is important to choose medications that are not likely to cross-react with the original agent. The use of corticosteroid therapy remains controversial, and no large randomized trials have thoroughly examined the effectiveness of corticosteroid therapy in AIN.^{6,11} One small study in which the majority of patients developed AIN from antibiotics or NSAIDs demonstrated improved renal recovery with early steroid use.¹² Another study demonstrated that the majority of patients improved with medication withdrawal, but those patients who do not respond after a few weeks may subsequently benefit from corticosteroid administration.¹³ In another retrospective study in which over 90% of patients had drug-induced AIN and 60% received corticosteroids, there was no difference in renal outcome.⁴ MMF has been used successfully in 8 patients who were unable to taper off maintenance corticosteroids for AIN due to relapsing course.¹⁴

KEY POINTS

1. The diagnosis of acute tubulointerstitial nephritis (AIN) should be considered in patients with acute kidney injury and sterile pyuria or systemic manifestations of hypersensitivity, especially when temporally associated with infection or medication initiation.
2. Medications, particularly antibiotics, are responsible for over two-thirds of cases of AIN.
3. A definitive diagnosis of AIN can only be made with kidney biopsy.
4. Treatment of drug-induced AIN begins with discontinuation of the causative agent. Subsequent use of a causative agent may result in prolonged renal failure.

ANNOTATED REFERENCES

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This study analyzes risk factors important in the development of chronic renal insufficiency following acute tubulointerstitial nephritis.

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Antimicrobial stewardship is an important concept that is pertinent to virtually every clinician. Its goals are to combat the emergence of resistance, improve clinical outcomes, and decrease healthcare costs (Fig. 114-1).¹⁻⁷ In this chapter, we will focus on the advances in and obstacles to antimicrobial stewardship as outlined in Table 114-1 by breaking this discussion into two major areas: optimization of antimicrobial therapy and avoidance of unnecessary antibiotic administration.

OPTIMIZATION OF ANTIMICROBIAL THERAPY

Appropriate Antimicrobial Selection

Appropriate antibiotic therapy is the cornerstone of management in septic shock as well as in any serious infection requiring intensive care unit (ICU) care and has a great influence on hospital mortality. Appropriate antibiotic therapy is defined as an initial antimicrobial regimen that demonstrates *in vitro* activity against the isolated organism(s) responsible for the infection, while inappropriate antibiotic therapy is defined as an initial regimen demonstrating a lack of *in vitro* activity against the causative pathogen(s).⁸ The administration of inappropriate initial antibiotic therapy can lead to treatment failures and adverse outcomes.⁹⁻¹⁵ Similar associations between the administration of inappropriate initial antimicrobial therapy and greater mortality have been shown for bloodstream infections by *Candida*.¹⁶⁻¹⁸ Moreover, the importance of treating all pathogens associated with serious infection is further emphasized by a recent retrospective analysis of patients with severe sepsis and septic shock.¹⁹ For the entire cohort, the number needed to treat with appropriate antimicrobial therapy to prevent one patient death was 4.0 (95% confidence interval [CI], 3.7-4.3).

The importance of selecting appropriate initial antimicrobial therapy has been emphasized in the most recent Surviving Sepsis Guidelines.²⁰ The guidelines recommend that initial empiric anti-infective therapy include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that the antibiotics penetrate, in adequate concentrations, into the tissues presumed to be the source of sepsis (grade 1B).²⁰ This guideline urges clinicians to utilize the patient's history, including drug intolerances, recent receipt of antibiotics, underlying disease, the clinical syndrome, and susceptibility patterns of pathogens in the community and hospital and that have been previously documented to colonize or infect the patient when making decisions regarding initial antimicrobial regimen selection.

Timing of Antibiotic Administration

In addition to selecting an appropriate antimicrobial regimen, the timing of antibiotic delivery is an essential element in determining the outcome of critically ill patients with infection. Several studies have found strong relationships between delays in effective antimicrobial initiation and in-hospital mortality for serious infections including ventilator-associated pneumonia (VAP) and septic shock.^{21,22} A recent meta-analysis of randomized and observational studies evaluating the

impact of goal-directed bundles on the outcomes of patients with septic shock found that timely antibiotic administration was statistically more common among patients receiving protocolized management of septic shock.²³ One of the studies in this meta-analysis was a prospective observational study that evaluated adult patients with severe sepsis from 77 ICUs in Spain.²⁴ Using a propensity-adjusted multivariate analysis, the authors identified early broad-spectrum antibiotic treatment to be associated with lower mortality. Members of the Surviving Sepsis Campaign subsequently performed a retrospective analysis of a large dataset collected prospectively from 165 ICUs in Europe, the United States, and South America.²⁵ In-hospital mortality was 29.7% for the cohort as a whole, and there was a statistically significant increase in the probability of death associated with the number of hours of delay for the first antibiotic administration.

Timely administration of effective antibiotics seems to be an important element in determining the outcome of critically ill patients. As discussed below, prediction tools for the presence of antibiotic resistance and rapid diagnostics may allow for a more rapid administration of appropriate therapy. However, emergency departments and ICUs should also ensure that they have processes in place to obtain and deliver antibiotic therapy expeditiously once the order for such therapy is received from the treating physicians.

Adequate Dosing of Antimicrobials and Pharmacokinetic/Pharmacodynamic Considerations

In addition to delivering timely appropriate antibiotic regimens, adequate drug concentrations at the site of infection are needed to optimize clinical outcomes. β -lactam and carbapenem antibiotics are time-dependent antimicrobials whose activities are primarily related to the duration the free drug concentration exceeds the pathogen minimum inhibitory concentration ($T_{\text{FREE}}/\text{MIC}$).²⁶⁻²⁸ Many factors influence the pharmacokinetics of antimicrobials in critically ill patients. Hypoalbuminemia, large-volume crystalloid administration, large pleural effusions or abdominal ascites, catecholamines, augmented renal clearance (ARC), and renal replacement therapies can all significantly alter infection site concentrations of administered antibiotics.²⁹

In VAP treatment, particularly for gram-negative bacteria (GNB), dose and duration of treatment might need to be augmented despite having selected an appropriate initial regimen. For instance, meta-analyses of tigecycline showed an increased mortality in nosocomial pneumonia, particularly VAP driven by GNB infections.³⁰⁻³² A randomized trial of patients with hospital-acquired pneumonia (HAP) found that tigecycline with or without ceftazidime had inferior cure rates to imipenem-cilastatin with or without vancomycin across all pathogens.³³ The hypothesis that the tigecycline dose (75 mg every 12 hours) was too low to achieve high enough concentrations above the MICs of pathogens prompted a higher dose study (100 mg every 12 hours) compared to imipenem-cilastatin.³⁴ Similarly, ceftobiprole, a cephalosporin with activity against MRSA and an extended GNB spectrum equivalent to ceftazidime or cefepime, was compared to linezolid and ceftazidime in patients with HAP/VAP.³⁵ Even though it achieved similar cure rates in patients with HAP, ceftobiprole was inferior to linezolid and ceftazidime in patients with VAP, in large part thought to be due to the underdosing of ceftobiprole in critically ill patients. This concern has led to a doubling of the dose of ceftolozone/tazobactam in the ongoing clinical registration trials of HAP/VAP.³⁶

*CONFLICTS OF INTEREST: Dr. Kollef's effort was supported by the Barnes-Jewish Hospital Foundation.

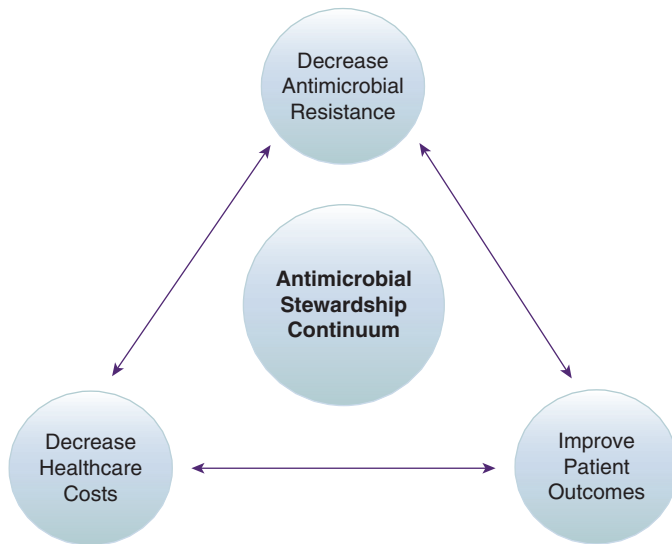


FIGURE 114-1 ■ The goals of antimicrobial stewardship programs.

TABLE 114-1

Antimicrobial Stewardship Program for the ICU Setting

1. Optimization of antimicrobial therapy
 - a. Appropriate antimicrobial selection
 - b. Timing of antibiotic administration
 - c. Adequate dosing of antimicrobials and PK/PD considerations
 - d. Duration of antibiotic treatment
 - e. Augmented renal clearance
 - f. Therapeutic drug monitoring
2. Avoidance of unnecessary antibiotic administration
 - a. Deescalation of empiric antibiotic regimen
 - b. Use of antibiotic resistance prediction tools
 - c. Biomarker guidance of antimicrobial therapy
 - d. Formalized antimicrobial stewardship programs
 - e. Rapid microbiological diagnostics

ICU, intensive care unit; PK/PD, pharmacokinetic/pharmacodynamic.

Critically ill patients display different pharmacokinetics; therefore, newer drug administration strategies for β -lactams and carbapenems have been investigated to include the use of prolonged infusions in order to optimize antibiotic delivery to infection sites. Even though observational studies showed better clinical cure with prolonged or continuous infusion, two meta-analyses have failed to confirm these findings.^{37,38} A subsequent meta-analysis that included 13 RCTs and 13 cohort studies, 12 of them focusing on nosocomial pneumonia, partially contradicted the previous meta-analysis findings.³⁹ Similar findings were observed in another recent meta-analysis demonstrating that administration of piperacillin-tazobactam or carbapenems by prolonged infusion, rather than by bolus administration, is associated with a lower mortality.⁴⁰ The results from the largest multicenter trial performed to date of prolonged antibiotic infusion in critically ill patients failed to demonstrate any mortality benefit.⁴¹

One of the best examples of the need for proper antibiotic dosing and drug exposure at the site of infection was recently demonstrated in a multicenter trial.⁴² These investigators aimed to determine whether β -lactam antibiotic dosing in critically ill patients achieves concentrations associated with maximal activity and whether antibiotic concentrations affect patient outcome. Of the 248 patients treated for infection, 16% did not achieve $T_{\text{FREE}}/\text{MIC}$ ratio greater than 1 at 50% of the dosing interval, and these patients were 32% less likely to have a positive clinical outcome. Positive clinical outcome was associated with a

$T_{\text{FREE}}/\text{MIC}$ ratio greater than 1 at both 50% and 100% of the dosing intervals. These data suggest that many critically ill patients experience adverse outcomes as a result of inadequate antibiotic exposure.

Duration of Antibiotic Therapy

For most critically ill patients, empiric antibiotic courses of 7 to 8 days of treatment should suffice, unless specific infections are identified, such as bacteremia, fungemia, endocarditis, osteomyelitis, or meningitis, which would require longer treatment durations. The data supporting the use of shorter courses of antibiotic therapy are probably strongest for VAP, depending on clinical severity, rapidity of clinical improvement, and most important, the underlying microbiology.⁴³⁻⁴⁶ The exceptions to shorter courses of antibiotic therapy in VAP are the difficulty to treat pathogens such as *Pseudomonas aeruginosa* and other nonfermenters that experience higher recurrence rates with shorter treatment regimens.⁴³ At least one randomized trial has found a greater mortality among patients with *P. aeruginosa* VAP receiving only 7 days of treatment.⁴⁷ Longer durations of treatment for nonfermenting GNB may be most important in situations where antibiotic exposure in the lung is limited by host factors such as increased volume of drug distribution and ARC.

The inflammatory biomarker procalcitonin has been shown to aid in limiting the duration of antibiotic exposure for patients with VAP as well as other types of infections.⁴⁸⁻⁵⁰ However, other clinical trials have failed to replicate these findings. A study performed in nine ICUs in Denmark enrolled 1200 critically ill patients to receive either the “standard-of-care-only,” receiving treatment according to the current international guidelines and blinded to procalcitonin levels, or the “procalcitonin arm,” in which current guidelines were supplemented with a drug-escalation algorithm and intensified diagnostics based on daily procalcitonin measurements.⁵¹ Although there was no mortality difference, length of stay in the ICU was increased by 1 day in the procalcitonin arm. A recent multicenter trial from Australia that enrolled 400 patients with suspected bacterial infection/sepsis also failed to demonstrate reductions in the overall median number of antibiotic treatment days with the use of procalcitonin.⁵²

In summary, clinicians should be aware that 7 to 8 days of therapy should suffice for empiric antibiotic therapy in most ICU patients. However, even shorter courses of empiric therapy should be used when the presence of infection is excluded, and longer treatment regimens may be required when dealing with specific host- and pathogen-related factors such as ARC, increased volume of distribution, and presence of infection with *P. aeruginosa* or other nonfermenters. It is probably most important to critically review all antibiotics on a daily basis to ensure that they are indeed necessary and, if so, that they are delivered in adequate concentrations.⁵³

Augmented Renal Clearance

ARC is defined as an 8-hour creatinine clearance more than or equal to 130 mL/min/1.73 m². At least one recent study has suggested that over 65% of ICU patients have ARC on at least one occasion during the first 7 days of their critical illness.⁵⁴ ARC has been linked with subtherapeutic β -lactam⁵⁵ and glycopeptide concentrations⁵⁶ as well as increased therapeutic failures in patients receiving antimicrobial therapy, resulting in adverse patient outcomes.^{42,57,58} One group of investigators has developed a scoring system to identify patients at high risk for ARC based on the following factors: age of 50 years or younger (6 points), trauma (3 points), and SOFA score of 4 or less (1 point).⁵⁹ A subsequent study found that the ARC score was 100% sensitive and 71.4% specific for detecting ARC.⁶⁰ Monte Carlo pharmacokinetic simulations demonstrated increased time at therapeutic antibiotic levels with the use of extended infusion dosing in the setting of ARC at drug cost savings of up to 66.7% over multiple intermittent dosing regimens. In addition to ARC, the use of renal replacement therapies can result in underexposure of antibiotics at the site of infection, requiring careful dosing adjustments.⁶¹

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) for β -lactams and carbapenems can be accomplished by several methodologies, allowing serum concentrations of antibiotics to be assessed in order to optimize delivery and minimize the occurrence of toxicity.^{62,63} However, the use of TDM for antibiotics other than vancomycin, aminoglycosides, and voriconazole has not become a routine or standard practice in most ICUs. Recent studies have demonstrated the ability of TDM to identify the need for antibiotic dosing adjustments in the setting of continuous renal replacement therapy due to excess serum antibiotic concentrations⁶⁴ as well as during treatment of MDR *P. aeruginosa* with fluctuating renal function.⁶⁵ Unfortunately, at the present time large variations exist in the types of β -lactams tested, the patients selected for TDM, drug assay methodologies, pharmacokinetic/pharmacodynamic targets, and dose adjustment strategies employed among critically ill patients.⁶⁶

AVOIDANCE OF UNNECESSARY ANTIBIOTIC ADMINISTRATION

Deescalation of Empiric Antibiotic Regimen

Antimicrobial deescalation is a clinical approach to empiric antibiotic therapy of serious infections that attempts to balance the need for appropriate initial therapy with the need to limit unnecessary antimicrobial exposure in order to curtail the emergence of resistance.⁵⁷ A deescalation approach usually requires initial combination antimicrobial treatment targeting nonfermenting GNB and methicillin-resistant *Staphylococcus aureus*.⁶⁸ However, depending on the clinical presentation, patient risk factors, and local epidemiology, other pathogens such as *Candida* species and *Clostridium difficile*, especially when diarrhea is present, may also need to be covered. Once the microbiological results are available and the patient's clinical response is observed, the antibiotic regimen can be narrowed based on the susceptibilities of the identified pathogens. Our local experience, as well as that of other groups, bears this out in demonstrating that the administration of appropriate initial antibiotic therapy with subsequent antimicrobial deescalation is associated with improved survival and shorter hospital stays.^{14,69-71} Moreover, local antibiotic deescalation guidelines have been able to successfully limit the use of broad-spectrum antibiotics targeting GNB in patients with skin and skin structure infections, representing an example of antimicrobial stewardship.^{72,73}

Computer decision support systems have also been employed to facilitate antimicrobial deescalation practices in the ICU setting. Thursky et al. employed a real-time microbiology browser and computerized decision support system for pathogen isolate-directed antibiotic prescription and found significant reductions in the proportion of patients prescribed carbapenems, third-generation cephalosporins, and vancomycin.⁷⁴ Similarly, our hospital has developed an automated decision-support system with real-time access to patients' prior antibiotic exposures and microbiological results.⁷⁵ Our experience with this system has shown that the use of inappropriate therapy can be reduced by almost 50% and that access to these data assist in the performance of timely deescalation.⁷⁵

Use of Antibiotic Resistance Prediction Tools

Knowledge of patient risk factors for the presence of infection with antibiotic-resistant pathogens should be a routine part of antibiotic decision making. For example, antibiotic-resistant pathogens are more commonly found in patients with community-acquired pneumonia (CAP) who have healthcare-associated risk factors (recent hospitalization, admission from a nursing home, or recent antibiotic treatment).^{76,77} However, a recent meta-analysis found that the current definition employed for healthcare-associated pneumonia (HCAP) did not accurately identify infections attributed to antibiotic-resistant

pathogens, providing further support for the use of more specific criteria to make this clinically important determination.⁷⁸

Shindo et al. demonstrated that independent risk factors for antibiotic-resistant bacteria occur in both patients diagnosed with CAP and HCAP including prior hospitalization, immunosuppression, previous antibiotic use, gastric acid-suppressive therapy, tube feeding, and nonambulatory status.⁷⁹ Another Japanese study prospectively applied a therapeutic algorithm based on the presence of risk factors for MDR pathogens in a multicenter cohort study of patients with CAP and HCAP.⁸⁰ These investigators found that MDR pathogens were more common in patients with HCAP than in those with CAP. However, it is not clear that clinicians can effectively apply such prediction tools prospectively in order to target broad-spectrum antibiotics to patients at greatest risk for antibiotic-resistant infections. This has served as the impetus for the development of rapid microbiological diagnostic tests to facilitate such decision making at the patient's bedside.

Clinical decision support systems represent one way of automating informatics data to include risk factors for antibiotic-resistant bacteria.^{74,75} Potential benefits derived from the use of such computerized systems include improvements in the efficiency and costs of existing stewardship programs, improvements in clinicians' knowledge regarding the treatment of infectious diseases, and improvements in pathogen prediction.⁸¹⁻⁸⁵ Thiel and colleagues demonstrated that the implementation of a standardized order set for patients with sepsis—that is currently automated and includes orders for antimicrobial therapy—resulted in more appropriate initial antimicrobial therapy and improved clinical outcomes in patients with severe sepsis and bacteremia.⁸⁶ Micek et al. designed an automated alert that provided feedback on prior antibiotic exposure and microbiological culture results in formulating current treatment approaches.⁷⁵ Based on clinical information available in the alert, 34 of 64 of the alerted patients who received inappropriate therapy (53.1%) could have received an alternative β -lactam antibiotic with in vitro susceptibility to the identified pathogen. These data suggest that an opportunity exists to employ hospital informatics systems to improve the identification of patients infected with antibiotic-resistant bacteria in order to prescribe more appropriate initial therapy.

Biomarker Guidance of Antibiotic Therapy

Procalcitonin has demonstrated utility, especially in the ambulatory setting, in guiding decisions regarding antimicrobial therapy.⁴⁸⁻⁵⁰ However, not all experiences with procalcitonin-guided decision making have shown reductions in duration of antibiotic exposure.^{51,52} A recent comprehensive literature review of procalcitonin-guided antibiotic management in critically ill patients found that the diagnostic value of serum procalcitonin concentrations to discriminate among systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock was unestablished.⁸⁷ On the other hand, at least two meta-analyses suggest that procalcitonin guidance is used to shorten the duration of antimicrobial therapy in the ICU setting.^{88,89} The routine use of procalcitonin as an aid in antibiotic decision making should depend on whether a particular ICU has an already established culture of successful antimicrobial deescalation and stewardship.⁵³

The serum markers (1,3)- β -D-glucan and galactomannan have been used in identifying pathogens associated with invasive fungal infections to assist clinicians in guiding antifungal therapy. Based on their high negative predictive value in the appropriate clinical setting, the most suitable use of these markers seems to be in excluding the presence of invasive fungal infections.^{90,91} However, one study suggests that the use of (1,3)- β -D-glucan is the most rapid method for the identification of intraabdominal candidiasis in order to provide timely therapy in such patients.⁹² In addition, an investigation that measured galactomannan levels in BAL fluid obtained from ICU patients lends support to its use in pathogen identification and early treatment of pulmonary infection.⁹³ Nonetheless, a more recent study only showed modest agreement between galactomannan in BAL fluid and validated

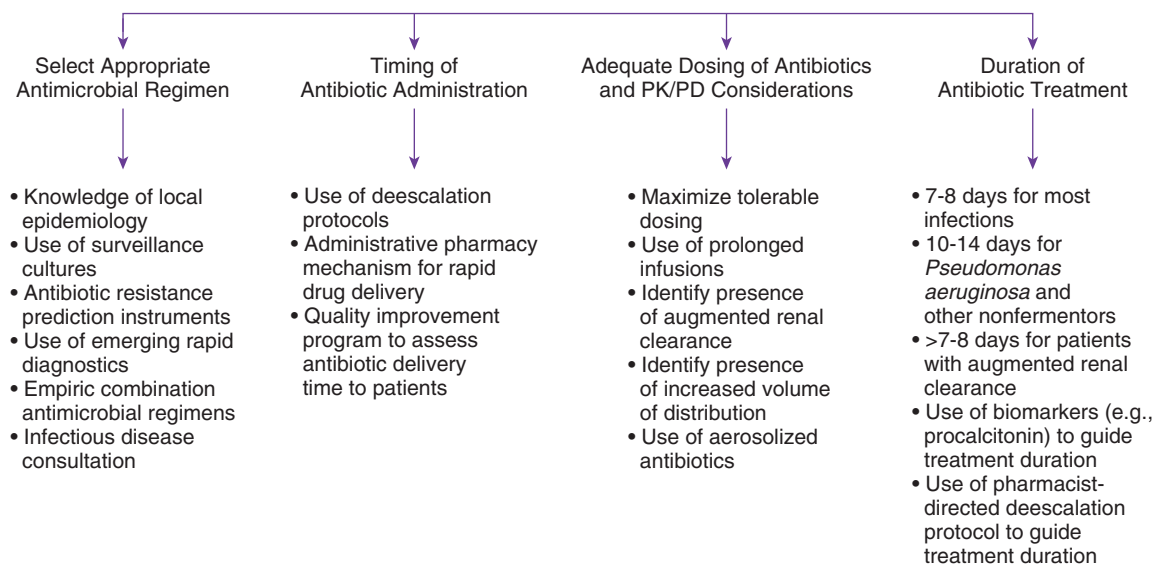


FIGURE 114-2 ■ Optimization of appropriate antimicrobial therapy as part of an antimicrobial stewardship program.

clinical diagnostic criteria for invasive fungal disease.⁹⁴ These markers of infection certainly have the potential to enhance stewardship—primarily through deescalation once a fungal infection has been excluded—and future clinical experience with these markers will determine if this potential can be fully realized.

Formalized Antimicrobial Stewardship Programs

Formally implemented antimicrobial stewardship programs (ASPs) have been associated not only with reduced infection rates but also with significant cost saving associated with reductions in the defined daily doses of antimicrobials targeted by the ASP.^{73,95,96} ASPs have been shown to increase the appropriateness of therapy for serious infections such as CAP as well as to increase the number of infectious disease consultations, which might also dramatically improve patient outcomes including mortality, hospital lengths of stay, and rates of readmission by providing a more precise antibiotic prescription.^{73,97-100} These attributes of ASPs account for why they are now recognized as mandatory components of hospital quality improvement efforts.

A recently updated meta-analysis of ASPs has solidified the benefits of these quality improvement initiatives.¹⁰¹ This meta-analysis found that ASPs could significantly result in less antimicrobial usage and reductions in *C. difficile* infections and colonization or infection with aminoglycoside- or cephalosporin-resistant GNB, methicillin-resistant *S. aureus*, and vancomycin-resistant *Enterococcus faecalis*.¹⁰¹ Additionally, more effective antibiotic prescribing practices for pneumonia due to the presence of an ASP were associated with a significant reduction in mortality, whereas practices aimed at decreasing excessive antibiotic prescribing were not associated with any significant increase in mortality.

Rapid Microbiological Diagnostics

Conventional microbiological procedures typically require several days for isolation, identification, and antimicrobial susceptibility testing of isolated bacteria from clinical samples including blood, respiratory tract, urine, and sterile site specimens. Recently, several molecular diagnostic platforms have been introduced and evaluated including the LightCycler SeptiFast Test (Roche, Basel, Switzerland), peptide nucleic acid fluorescence in situ hybridization (AdvanDx, Woburn,

MA), matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS) (VITEK® MS, bioMérieux, Inc., Durham, NC), and DNA-based microarray platforms (Prove-it sepsis assay [Mobidiag, Keilaranta, Finland] and the Verigene Gram-Positive Blood Culture assay [Nanosphere, Northbrook, IL]).¹⁰² Additionally, automated microscopy methods such as the ID/AST system (Accelerate Diagnostics, Tucson, AZ) are in development, utilizing both genomic and phenotypic technologies to provide pathogen identification and antimicrobial susceptibilities in a rapid manner.¹⁰³

Huang et al. performed a quasi-experimental study to analyze the impact of MALDI-TOF MS in conjunction with an ASP in patients with bloodstream infections.¹⁰⁴ Use of MALDI-TOF MS significantly decreased time to organism identification and improved time to effective antibiotic therapy as well as optimal-directed antibiotic therapy. Mortality, length of ICU stay, and recurrent bacteremia were significantly lower during the intervention period. Similarly, the PCR-based GeneXpert MRSA/SA diagnostic platform (Cepheid, Sunnyvale, CA) was studied at the Veterans Affairs Medical Center in Houston, demonstrating that for methicillin-susceptible *S. aureus* bacteremia, the mean time to initiation of appropriate therapy decreased from 49.8 hours to 5.2 hours and the duration of unnecessary methicillin-resistant *S. aureus* drug therapy was reduced by 61 hours per patient.¹⁰⁵ It is expected that the clinical impact of rapid diagnostics will increase due to the enhanced ability of these methods to direct early appropriate treatment and avoidance of unnecessary antibiotic therapy.

CONCLUSION

Although antimicrobial therapy is frequently prescribed, clinicians should realize that these important therapeutic agents should be used wisely. Judicious use of antibiotics serves to combat the emergence of resistance, improve clinical outcomes, and decrease costs. Clinicians should realize the advances that have been made with regard to antimicrobial stewardship and utilize these tools, as well as future advances, to promote improved antimicrobial use. We are currently at a crossroads where antimicrobial stewardship offers us an opportunity to move forward in terms of enhancing the treatment of antibiotic-resistant infections for years to come (Fig. 114-2). ICU clinicians must be leaders in ensuring that their institutions have robust and effective ASPs.¹⁰⁶

KEY POINTS

1. All intensive care units should participate in active antimicrobial stewardship programs (ASPs) directed at optimizing the use of antimicrobials in critically ill patients.
2. The ASPs should focus on both optimizing the delivery of antimicrobial agents to infected patients and avoiding the unnecessary use of these agents.
3. Optimal antibiotic administration can be achieved by ensuring appropriate selection of drugs, timely administration of antibiotics, adequate dosing of these agents, avoidance of prolonged durations of therapy, and adjustments in delivery of drugs based on the physiology of critically ill patients (e.g., potential use of higher drug doses and/or prolonged infusions in the setting of augmented renal clearance and increased volume of distribution).
4. Minimizing the unnecessary use of antibiotics can be achieved with the use of deescalation strategies, use of antibiotic resistance prediction tools or biomarkers, and in the future, rapid diagnostics for pathogen detection and antimicrobial susceptibility.

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Preventing pneumonia in the critically ill is a daunting task, and even controlling the incidence is difficult. Despite this challenge, many in the patient safety movement have suggested that nosocomial pneumonia should be a “never” event.^{1,2} While complete prevention of nosocomial pneumonia is unlikely,³ substantial progress has been made in reducing the incidence.⁴

Pneumonia is the most common nosocomial infection in the ICU.⁵ A large, 1-day point prevalence study of pneumonia demonstrated that nearly 10% of ICU patients were being treated for pneumonia.⁵ Post-operative patients, especially those undergoing cardiothoracic, neurosurgical, and trauma-related surgery, appear to have the highest rates.⁶ Coronary care unit patients appear to have the lowest rates; medical, respiratory, and other surgical patients demonstrate intermediate rates.

The influence of endotracheal intubation is so dominant that nosocomial pneumonia in the ICU has been almost synonymous with ventilator-associated pneumonia (VAP). Endotracheal intubation increases the rate of nosocomial pneumonia between 3- and 21-fold.⁷ Research on hospital-acquired pneumonia (HAP) has been dominated by VAP, and very little is known about pneumonia in nonintubated ICU patients. In addition, the role of both HAP and healthcare-associated pneumonia (HCAP)—pneumonia occurring in other healthcare settings, such as chronic ventilator facilities, inpatient rehabilitation units, and high acuity nursing homes—has been increasingly recognized. These ICU pneumonia cases are the cause of respiratory failure rather than a consequence of intubation as in VAP but with a frequency of multidrug-resistant (MDR) pathogens equivalent to that of VAP.⁸

Lack of diagnostic accuracy severely compromises efforts to prevent nosocomial pneumonia. Etiologic diagnosis is difficult in patients who are not intubated. Radiographic interpretation is also problematic. NNIS proposed an alternative definition of infectious ventilator-associated complications (IVAC) that does not require a chest radiograph to meet the definition.⁹ Multiple subsequent studies have demonstrated that the IVAC definition is neither sensitive nor specific and question the ability of VAP prevention strategies to alter the frequency of IVAC.¹⁰ Others ignore the need for abnormal chest radiographs and instead combine VAP with a newly defined ventilator-associated tracheobronchitis (VAT).¹¹⁻¹² Whether VAT is an early stage of VAP that progresses to VAP is still debatable.

A distinction should be made between prevention of all nosocomial pneumonia and prevention of life-threatening nosocomial pneumonia. The crude mortality rate for VAP ranges from 24% to 76%, with an estimated attributable mortality of 20% to 30%.^{7,13} The highest crude and attributable mortality rates are associated with typical late-onset MDR microorganisms such as *Pseudomonas aeruginosa*, *Acinetobacter* species, and methicillin-resistant *Staphylococcus aureus* (MRSA). Unfortunately, the most effective and well-documented strategies to prevent pneumonia work predominantly or exclusively in early-onset VAP and therefore have not resulted in a significant improvement in mortality. Conversely, one of the most consistent adverse effects of VAP (including early onset) is a prolonged duration of mechanical ventilation. Because duration of ICU stay is the principal determinant of cost of care, prevention measures may be cost-effective even if they do not result in improved mortality.

■ PATHOGENESIS

The key to prevention and control strategies is a clear understanding of the underlying pathogenesis of nosocomial pneumonia. The essence of nosocomial pneumonia pathogenesis involves three basic steps:

1. Colonization of the oropharynx with pathogenic microorganisms
2. Aspiration of oropharyngeal contents into the lower respiratory tract
3. Overwhelming of the host defense processes in the lower respiratory tract.

Effective prevention and control measures can be analyzed by their effect on one or more of these steps.

Despite the simplicity of this paradigm, assumption that the pathogenesis of all types of nosocomial pneumonia is the same would be naive and incorrect. An example is the role of gastric colonization preceding oropharyngeal colonization, the basis for attention to enteral feedings and stress ulcer prophylaxis in VAP prevention. Although possibly important for pneumonia due to Enterobacteriaceae, gastric and enteric colonization has no role in the pathogenesis of *S. aureus* or *P. aeruginosa* pneumonia, the two most common causes of VAP. Conversely, daily chlorhexidine baths did not prevent VAP in a trauma population but did significantly decrease VAP from MRSA.¹⁴ Therefore, prevention strategies should be individualized to the patients, pathogens, and processes prevalent in a specific ICU.

Colonization with Pathogenic Microorganisms

The major antecedent event to most nosocomial pneumonias is colonization of the oropharynx with pathogenic bacteria. The oropharynx is not sterile, but the character of the normal flora is remarkably constant. A variety of factors alter the normal flora, allowing replacement by more pathogenic microorganisms. The importance of the normal flora is illustrated by the adverse effects of iseganan, an antimicrobial peptide active against almost all bacteria. Iseganan treatment not only failed to decrease VAP rates but was associated with a trend toward increased mortality.¹⁵

Time of exposure to these selective forces is critical. Early-onset pneumonia, even early-onset VAP, tends to be caused by less pathogenic microorganisms such as streptococci, *Hemophilus influenzae*, and methicillin-sensitive *S. aureus*. Most selective forces are introduced in the hospital environment itself rather than specifically in the ICU. Therefore, patients who develop pneumonia during the first few days of ICU admission or mechanical ventilation are at risk for MDR pathogens if preceded by a 3- to 5-day hospital stay. Many of the same factors also operate in skilled-care nursing home facilities and have led to the designation of HCAP.

Previously, colonization of the oropharynx by gram-negative enteric bacilli, generally from the Enterobacteriaceae family, was emphasized. As part of the normal bowel flora, oropharyngeal colonization occurs by one of two main routes. The first is reflux of bacteria into the stomach from the duodenum, with subsequent gastroesophageal reflux into the esophagus and oropharynx. Colonization and proliferation in the stomach are critical intermediate steps in this pathway. Therefore, many prevention strategies logically target the stomach. The

other route is self-inoculation by the fecal-oral route, through contamination of equipment or the hands of health care providers or the patient.

The colonization pattern differs among many HAP/VAP pathogens. *S. aureus*, *P. aeruginosa*, and *Acinetobacter* species are common causes of VAP in many institutions. None of these microorganisms has a colonization pattern typical of Enterobacteriaceae. *S. aureus* normally colonizes the skin and the nasopharynx. Colonization of the oropharynx from the nose, especially with the use of nasogastric tubes in critically ill patients, can occur quite easily. Similarly, *Acinetobacter* is found on moist body surfaces and in the gingival crevices of patients with poor oral hygiene. *P. aeruginosa* is usually not part of normal bowel flora but is ubiquitous in the environment. One of the unique aspects of *Pseudomonas* VAP is the appearance of tracheal colonization before oropharyngeal colonization. Because colonization of the stomach is not an important intermediary step for these pathogens, the pneumonia they cause is unlikely to be affected by prevention measures directed at the stomach. Conversely, both MRSA and *Acinetobacter* colonization can be decreased with chlorhexidine whole-body bathing.¹⁴

Avoidance of Antibiotics

The single most important factor that leads to colonization of the oropharynx with pathogenic microorganisms is the use of systemic antibiotics, especially broad spectrum.¹⁶ Antibiotic killing of the usual oropharyngeal flora gives pathogens a selection advantage; at the same time, some pathogens are also eliminated. For this reason, antibiotics function more as amplifying agents rather than as true causes of colonization. The pathogenic microorganisms must still reside in the area normally, such as nasopharyngeal carriage of *S. aureus*, or be transferred from other sites, including the environment, to colonize. Thus, pneumonia can still occur despite avoidance of antibiotics. However, the causative microorganisms are more likely to be less virulent pathogens or even normal flora, such as α -hemolytic streptococci, and less likely to lead to life-threatening pneumonia.

Diagnostic strategies for fever in the ICU that result in the use of fewer antibiotics have been associated with lower mortality.¹⁷ Shorter courses and fewer antibiotics for documented infections in critically ill patients have also been associated with a decreased risk of superinfection.¹⁸⁻²⁰ Although avoiding antibiotics may have only a small effect on the risk of developing the first episode of pneumonia, limiting their use has a major effect on secondary pneumonia and infection-related death in the ICU.

Topical Antibacterial Agents. In contrast to systemic antibiotics, the use of topical antibiotics for the prevention of colonization may be beneficial. In general, strategies rely on controlling pathogenic microorganisms at specific sites, despite the effect on normal flora. Topical agents generally do not have the toxicity of systemic agents, and although the use of topical antibiotics can lead to MDR isolates, the risk may not be as great as with systemic antibiotics.

Selective Digestive Tract Decontamination (SDD). SDD is by far the most extensively studied and most aggressive topical antibiotic strategy to prevent colonization. Although the specific agents used in different studies vary, the major focus is on controlling oropharyngeal colonization by almost sterilizing the entire gastrointestinal tract, including the large bowel. SDD is discussed more extensively in Chapter 119. In summary, despite more than 40 randomized, controlled trials, the benefit of SDD remains unclear.

Topical Oropharyngeal Agents. Controlling colonization of the oropharynx alone has also generated interest, since little disruption of the normal bowel flora is expected by treating only the primary area of concern. Oropharyngeal decontamination alone appears to be equivalent to SDD for prevention of VAP.²¹ Chlorhexidine oral rinse has been the most extensively studied.²² Unfortunately, different concentrations of chlorhexidine have been used, and different populations have been compared. The strongest support for efficacy is for the 2% concentration. Chlorhexidine may not prevent infection with MDR pathogens such as *Pseudomonas* and *Acinetobacter*. Oral decontamination with

other agents, such as povidine/iodine and antimicrobial peptides,¹⁵ has not demonstrated benefit.

Recently interest in universal decolonization of patients with daily chlorhexidine for 5 days and nasopharyngeal mupirocin demonstrated lower bacteremia rates with MRSA and all pathogens.²³ No significant impact on MRSA pneumonia was demonstrated.

Aerosolized Antibiotics. The earliest studied form of topical colonization prevention was aerosolized antibiotics. In the early era of mechanical ventilation, daily aerosolized polymyxin B resulted in a dramatic decrease in the rate of gram-negative VAP.²⁴ Not surprisingly, routine use was soon complicated by the emergence of antibiotic-resistant microorganisms. This feature, combined with a lack of mortality benefit, led to abandonment of this strategy. In a recent study, aerosolized ceftazidime did not decrease VAP rates in trauma patients but also did not increase MDR pathogen colonization.²⁵ A recent variation of this practice is to use aerosolized antibiotics for purulent tracheobronchitis, thought to be a precursor to VAP.²⁶

Avoidance of Increased Gastric pH

The normally acidic environment of the gastric lumen is extremely effective in preventing colonization with either swallowed oropharyngeal flora or refluxed enteric flora. Several prevention strategies focus on this aspect of prevention.

Stress-Ulcer Prophylaxis. Because gastrointestinal bleeding from stress ulceration was at one time a substantial problem in ventilated patients and a major cause of death, prophylaxis against stress ulceration was considered critical for ventilated patients. However, the incidence of stress mucosal ulceration has decreased markedly as a result of better hemodynamic resuscitation, improved ventilatory strategies, and earlier use of enteral nutrition.

The debate regarding the optimal gastrointestinal bleeding prophylaxis has therefore evolved over the past few decades. Initially, antacids were found to be inferior to histamine type 2 blockers (H_2 blockers). In addition to increasing gastric pH, antacids increase gastric volume, which is probably an independent risk factor for VAP. Subsequently, sucralfate was hypothesized to be superior to H_2 blockers because it does not affect gastric pH and might have intrinsic antibacterial properties. No clear-cut benefit of sucralfate over H_2 blockers in reducing VAP has been found, while a slight but consistent increase in gastrointestinal bleeding has been documented.²⁷ Proton pump inhibitors (PPIs) appear equivalent to H_2 blockers.

A more important issue is whether stress-ulcer prophylaxis is needed at all in most mechanically ventilated patients. The few placebo-controlled trials suggest that H_2 blockers and sucralfate may lead to an increased risk of VAP compared with controls. Several multivariate analyses found PPIs associated with increased pneumonia rates, including HAP/VAP,^{28,29} HCAP, and even community-acquired pneumonia.³⁰ A subgroup of patients at increased risk for gastrointestinal hemorrhage can be identified, and patients without these high-risk factors may not need prophylaxis.

Enteral Nutrition Strategies. Malnutrition is clearly associated with an increased risk of pneumonia and increased mortality in the critically ill. In addition to classic effects on cell-mediated immunity, an effect specific to pneumonia is increased binding of gram-negative bacilli, including *Pseudomonas*, to epithelial cells.³¹

Enteral administration of nutrition is the preferred route for treating and preventing malnutrition in the critically ill, although parenteral nutrition in high-risk patients is preferable to no nutrition.³² Meta-analysis has suggested that patients can even be fed soon after gastrointestinal surgery.³³ However, continuous enteral nutrition infusions may increase both gastric pH and gastric volume, increasing VAP risk.^{34,35} A randomized trial found that the risk of VAP was increased with early aggressive feedings compared with low-level enteral nutrition (approximately 20% of goal feeding rate).³⁶ The lower rate was chosen to avoid atrophy of the microvilli of the enteric mucosa, a potential source of nosocomial infection. The increased risk of VAP was attributed to an increased risk of aspiration, which is also seen in surgical series.³³ However, meta-analysis of early versus delayed enteral

nutrition suggests a mortality benefit and probable decreased risk of VAP with early feedings.³⁷ A balance between potential risks would be early initiation of enteral feeding but avoidance of aggressive infusions that might cause high gastric residuals and gastric distention. Neither bolus feedings³⁸ nor acidification of enteral feedings³⁹ improved VAP rates but were associated with increased adverse events.

Modified Endotracheal Tubes

Bacteria can adhere to the polyvinyl chloride surface of endotracheal tubes through secretion of a glycocalyx. Protected from systemic antibiotics and host defense processes, microorganisms in this glycocalyx can become a source of reinoculation of the lower respiratory tract. This mechanism may explain the high rates of recurrent VAP, particularly for *Pseudomonas*. A silver-impregnated endotracheal tube demonstrated a lower incidence of VAP and a delay in onset in those who do develop VAP,⁴⁰ although cost remains a barrier to routine use.

Cross-Infection

The role of cross-contamination in the ICU should never be underestimated. Cross-contamination can cause colonization with specific pathogenic bacteria in a patient who has no other risk factors for that microorganism. In particular, *P. aeruginosa* and MRSA appear to have the greatest potential to cause cross-contamination and subsequent infection.

By far the most important factor in cross-infection is hand washing among caregivers. Multiple studies document poor infection control practices of medical personnel, including physicians and bedside nurses. The risk of inadequate hand washing increases with the intensity of care needed for an individual patient and with the number of patients per nurse.⁴¹ Use of an alcohol-based, self-drying hand wash appears to be effective and to increase compliance with hand washing.⁴² Routine decolonizing also appears to decrease rates of cross-infection.²³

Avoiding cross-contamination via medical equipment is also important. Contaminated equipment remains a major cause of epidemic outbreaks of nosocomial pneumonia. Any clustering of VAP, especially when caused by an unusual agent, should raise this possibility. Respiratory therapy equipment is particularly suspect, and adherence to standards for the sterilization of ventilators, bronchoscopes, and other reusable equipment should be rigorous.

Probably the best prevention strategy is a continuous, multifaceted, multidisciplinary program of infection control.⁴³ An important component of this program is monitoring VAP rates and providing feedback to individual units on their infection rates. Although such a program is costly to develop, the substantial cost-benefit of avoiding pneumonia usually justifies the expense.

Aspiration

The role of aspiration in nosocomial pneumonia is probably the least controversial. Evidence from a variety of sources documents the importance of aspiration, although the definition varies.

Large-Volume Aspiration

Large-volume aspiration is clearly a risk factor in nonintubated ICU patients. Predisposing factors for this type of aspiration are gastrointestinal, such as protracted vomiting from bowel obstruction or gastrointestinal bleeding, and neurologic, including seizures, induction of anesthesia, and alcohol intoxication. Appropriate use of endotracheal intubation is actually a protective factor for this type of aspiration. If large-volume aspiration has occurred, selective use of bronchoscopy to extract solid material that might occlude a bronchus and cause post-obstructive pneumonia may be of benefit. Empirical antibiotics, especially prolonged courses, do not clearly prevent pneumonia but do select for more virulent microorganisms.

Small-Volume Aspiration

Aspiration of a smaller volume of secretions is also associated with pneumonia in both intubated and nonintubated patients. Neurologic

disease with an inability to protect the upper airway is consistently documented as a risk factor for pneumonia. In this situation, aspiration occurs before or in conjunction with endotracheal intubation. A large inoculum of oropharyngeal flora reaches the lower respiratory tract, and clinical pneumonia usually occurs within 48 to 72 hours. High levels of amylase in BAL fluid is a marker of this risk.⁴⁴

Prevention of pneumonia from small-volume aspiration is probably best achieved by prophylactic antibiotics. Prospective observational studies suggest that antibiotics early in the course of mechanical ventilation are associated with a lower incidence of pneumonia.³⁴ However, the best evidence is a prospective, randomized trial of short-course cephalosporin prophylaxis (two doses) in patients intubated for non-traumatic coma.⁴⁵ The incidence of VAP was only 23% in the prophylaxis group, compared with 66% in the control group. These findings are corroborated by a before/after quality improvement study⁴⁶ and by the many SDD studies reporting a decreased incidence of pneumonia when a short course of systemic antibiotics was included with the topical antibiotics. Prophylactic antibiotics are effective only in the initial intubation of patients not previously hospitalized for a significant period and is dependent on the aspirated bolus containing mainly normal oral flora rather than MDR pathogens.

This prevention strategy seems to contradict the importance of avoiding unnecessary antibiotics discussed earlier. Two aspects outweigh the potential downside of increased risk of oropharyngeal colonization with more pathogenic bacteria. First, antibiotics are continued for only 24 hours. Second, the 40% lower risk of pneumonia in patients given prophylaxis avoids a subsequent longer course of antibiotics, often with a wider spectrum.

Microaspiration

Microaspiration is by far the most important form of aspiration in intubated patients. Oropharyngeal secretions pool above the cuff of the endotracheal tube in most intubated patients. Extremely small volumes of secretions can pass below the cuff during small movements of the endotracheal tube associated with head repositioning, coughing, and other activities. Up to 45% of patients have abundant aspiration in the first 48 hours post intubation.⁴⁷ Because oropharyngeal secretions contain 10^6 to 10^{10} bacteria/mL, even secretions of 0.1 mL can present a significant infectious challenge to the host defenses of the lower respiratory tract.

Shorter Duration of Endotracheal Intubation. The risk of VAP is not linear; the greatest risk occurs early, with subsequent tapering in frequency with each week. In addition, early-onset VAP (within 5-7 days of intubation) has the lowest attributable mortality. Therefore, the sooner the patient is extubated, the lower the cumulative risk of pneumonia and the lower the risk of lethal nosocomial pneumonia.

The best strategy is avoiding intubation completely. Management of many patients with noninvasive ventilation (NIV) is now standard practice in most ICUs. However, patients who fail NIV appear to have an increased duration of subsequent endotracheal intubation and thus an increased risk of VAP. Careful selection of candidates for NIV and early abandonment in unsuccessful cases are critical to decreasing the pneumonia risk.

Even when patients are intubated, variations in duration of mechanical ventilation for the same type and severity of critical illness suggest that efforts to shorten the duration are a viable approach to prevent VAP. Several protocolized strategies demonstrate significant benefits, including daily interruption of sedation and assessment of ability to wean.⁴⁸

The downside of an aggressive extubation strategy is the association between reintubation and a three-fold increase in risk of VAP.⁴⁹ Reintubation reexposes the patient to the risk of small-volume aspiration. In addition, colonization of the oropharyngeal secretions by more pathogenic bacteria is more likely because of the prior episode of intubation and short-course antibiotics will not have the same beneficial effect. Therefore, although avoiding or shortening the duration of mechanical ventilation is clearly a laudable goal, an increase in the risk of VAP may occur with an overly aggressive approach.

Avoidance of Ventilator Tubing Manipulation. Condensation of exhaled gas in the expiratory limb of the tubing or from humidifiers in the inspiratory limb can become heavily colonized with bacteria. Instillation of this liquid bolus into the patient's airway during manipulation of the tubing or movement of the patient can present a significant bacterial challenge to lower respiratory tract defense. The most consistent evidence that ventilator tube manipulation increases the risk of VAP is that increasing the interval between ventilator tubing changes decreases the incidence of VAP. Most institutions no longer change ventilator tubing unless gross contamination is present.

Meta-analysis of eight randomized controlled trials of heat and moisture exchangers (HMEs) rather than heater-humidifiers suggested a 30% reduction in VAP rates, especially if the patient was ventilated for more than 7 days.⁵⁰ Increased rates of endotracheal tube occlusion secondary to inspissated secretions with the use of HMEs and other considerations, especially cost, determine the frequency of their use.

Transporting ventilated patients outside the ICU, usually for diagnostic procedures, is also associated with an increased risk of VAP. In a prospective study, 24% of patients requiring transport outside of the ICU developed VAP, compared with only 4% of patients who did not.⁵¹ More than half of ventilated patients required transport at least once. Need for ambu bagging, changing ventilators, moving the patient out of bed, and other aspects of the process all increase the possibility of inadvertent introduction of ventilator tubing condensate into the patient. In addition, unintentional extubation is greater when transferring ventilated patients.

Maintenance of Artificial Airway Cuff Pressure. Adequate pressure (generally ≥ 25 cm H₂O) to maintain a seal around the cuff of artificial airways is critical to prevent microaspiration. Maintaining continuous control of tracheal cuff pressure resulted in a decrease in VAP incidence from 22 to 9.7 confirmed cases/1000 ventilator days.⁴⁷ Maintenance of cuff pressures may also decrease proximal airway secretions, the hallmark for the diagnosis of VAT.²⁶ The addition of low levels of positive end expiratory pressure (PEEP) has been associated with decreased aspiration and risk of VAP, possibly due to the greater attention to tracheal cuff pressures required in patients on PEEP. Inattention to tracheal cuff pressure obviates the benefit of other interventions, such as continuous aspiration of subglottic secretions (CASS).⁵²

Modified Endotracheal Tubes. A variety of modifications of the endotracheal tube itself have been designed to decrease microaspiration. Most attempt to minimize longitudinal folds in standard tracheal tube cuffs by changing the type of material or the shape of the cuff. No significant difference in VAP rates has been found in tapered versus cylindrical or polyurethane versus polyvinyl chloride cuffs.⁵³

An endotracheal tube that allows continuous aspiration of subglottic secretions (CASS) pooled above the endotracheal tube cuff has been extensively studied. The extra channel with a lumen on the dorsal surface, just above the level of the inflatable cuff, allows aspiration of secretions pooled above the cuff. One clinical practice guideline found the greatest level of evidence for VAP prevention was CASS.⁵⁴ Studies of CASS have variably demonstrated lower VAP rates but mainly in early-onset VAP: no decrease in VAP due to MDR microorganisms and no mortality differences have been demonstrated. The benefit of CASS is obviated if the patient receives antibiotics early in the course of mechanical ventilation, and pneumonia can also occur if the system malfunctions, usually caused by plugging of the lumen or low cuff pressures, allowing secretions to drain into the distal trachea rather than collecting above the cuff. These factors and the high cost have limited the use of this modality.

Early Tracheostomy. Tracheostomy has potential benefits for VAP prevention: the glottis is not held open by the endotracheal tube and the vocal cords can be opposed, decreasing the risk of aspiration significantly. The security of a tracheostomy may allow greater mobilization and a greater amount of time spent in the upright position, also decreasing aspiration. Routine tracheostomy may be one explanation for the leveling off of VAP incidence after several weeks of mechanical ventilation. The benefit of early tracheostomy remains unsettled.⁵⁵

Technique may also matter, with tracheostomy performed by the percutaneous dilatational technique more beneficial.⁵⁶

Semirecumbent Positioning. The degree of gastroesophageal reflux is significantly greater in supine patients than in semirecumbent patients.⁵⁷ Not only is reflux greater, but bowel flora were found to colonize the oropharynx and bronchial tree in 68% of patients ventilated in the supine position, compared with only 32% in the semirecumbent position. A prospective, randomized trial clearly demonstrated that both clinically suspected and microbiologically confirmed cases of VAP were more common in patients ventilated in the supine position (8% of clinically suspected VAPs vs. 34% for semirecumbent).³⁵ Supine body position (odds ratio 6.8) and enteral nutrition (odds ratio 5.7) were both independent risk factors for VAP, with the highest frequency in patients receiving enteral nutrition in the supine position (50%).

Avoiding the supine position as much as possible is a simple and effective preventive measure that should be practiced in all ICUs.⁵⁴ However, compliance with elevation of the head of the bed to 45° is difficult, and smaller degrees of elevation are not associated with decreased VAP rates.⁵⁸ In patients unable to be placed in the semirecumbent position, continuous lateral rotation with specialized beds may be beneficial.⁵⁹

Avoidance of Gastric Overdistention. Even in a semirecumbent position, many patients still have gastroesophageal reflux and microaspiration when given enteral feedings. The major issue of overdistention of the stomach can be addressed several ways. The first is use of nasogastric tubes rather than nasogastric tubes. Although attractive theoretically, meta-analysis of eleven randomized, controlled trials did not show a VAP prevention benefit of postpyloric feeding compared with gastric feeding.⁶⁰ The major limitation is the difficulty placing postpyloric tubes.

A second strategy is the use of gastric prokinetic agents such as metoclopramide. An additional benefit of these agents is increased tone of the lower esophageal sphincter, which potentially decreases the risk of reflux while increasing gastric emptying. Once again, a randomized, controlled trial failed to confirm the benefit of using this agent to decrease the risk of VAP.²⁹

Overwhelming Lower Respiratory Host Defenses

An underappreciated fact regarding nosocomial pneumonia is that despite the extremely common occurrence of aspiration of oropharyngeal secretions containing pathogenic bacteria, only a minority of colonized patients actually develop pneumonia. In the classic study by Johanson et al., only 23% of patients with gram-negative colonization of the oropharynx subsequently developed pneumonia.⁶¹ Others have shown that quantitative culture levels of microorganisms equivalent to those found in pneumonia can transiently appear in routine non-bronchoscopic BAL samples without causing clinical VAP.⁶² Thus, the two steps described earlier—colonization by pathogens and aspiration—are necessary but not sufficient causes of nosocomial pneumonia.

The third step in the pathogenesis of nosocomial pneumonia, overwhelming the lower respiratory tract defenses, is the least studied or understood. A major reason for this lack of understanding may be that the causes are heterogeneous and patient dependent, in contrast to the stereotypical steps of colonization and aspiration. As infection control and patient safety efforts become more effective, the remaining patients who develop VAP are even more likely to have significant defects in lower respiratory tract host defense. Patients who develop VAP should generally be considered to have a form of acquired immunosuppression. The more frequent occurrence of other nosocomial infections in patients with VAP supports this concept. In addition, some VAP patients develop multiple separate episodes of VAP, suggesting disproportionate compromise of lower respiratory tract defenses.

Many of the causes of compromised lower respiratory tract defenses involve underlying disease or critical illness, precipitating ICU

admission and the need for mechanical ventilation. However, several risks generic to most ICU patients may be targets for prevention.

Minimizing Antibiotic Use

Rather than being sterile, lung alveoli harbor a normal bacterial flora. This recognition raises important issues in understanding the development of HAP/VAP. The normal lung microbiome is similar to that of the normal oropharynx, predominantly streptococci but also anaerobes, *Hemophilus*, and *Mycoplasma*, but at significantly lower concentrations.⁶³ This normal alveolar flora therefore represents an important component of host defense that, similar to that of the oropharynx and the gastrointestinal tract, is adversely affected by systemic antibiotics. *Pseudomonas* pneumonia is virtually never seen without previous antibiotic exposure and develops with progressive monolithic replacement of the normal heterogeneous lung microbiome in response to antibiotic pressure.⁶⁴ Minimizing the effect of antibiotics on VAP may occur with enteral probiotics,⁶⁵ but lung-specific therapy is not available. Diagnostic strategies for VAP that result in less antibiotic treatment^{17,20} and earlier discontinuation in culture-negative patients⁶⁶ have consistently resulted in improved mortality and less superinfection.

Corticosteroids

Systemic corticosteroids have well-documented antiinflammatory effects that can influence immune function. The difficulty in determining the effect of corticosteroids on risk of VAP is the competing beneficial effect on other risk factors for VAP. An example is that the use of corticosteroids may allow earlier extubation of a patient intubated for an exacerbation of asthma, thereby lowering the risk of VAP. This dual effect probably holds true for most cases in which corticosteroids are used acutely for critically ill patients. The potential benefits begin to be outweighed by adverse consequences after more prolonged courses.

Transfusions

A common cause of immunosuppression is red blood cell transfusions. This effect of transfusions has been known for decades and was used therapeutically in the past for pretransplantation management of patients with end-stage renal disease. The transfusion trigger varies widely among institutions and even among individual practitioners. A conservative transfusion policy was reported to be associated with equivalent mortality to more liberal transfusions in most ICU patients⁶⁷ and decreased VAP rates in trauma patients.⁶⁸

KEY POINTS

1. A distinction should be made between the prevention of all nosocomial pneumonia and the prevention of **life-threatening nosocomial pneumonia, usually late-onset ventilator-associated pneumonia.**
2. **Pathogenesis of nosocomial pneumonia can be broken down into three basic steps:** colonization of the oropharynx with pathogenic microorganisms, aspiration, and overwhelming of the lower respiratory tract's host defense processes.
3. The most important factor in colonization of the oropharynx with pathogenic microorganisms and compromise of distal lung defenses is the suppression of normal flora at these sites **by systemic antibiotics, especially broad-spectrum antibiotics.**
4. The risk of ventilator-associated pneumonia is time dependent, so **any maneuver that decreases the duration of mechanical ventilation will decrease pneumonia rates.**
5. **Avoiding the supine position** as much as possible in ventilated patients **and maintaining adequate tracheal cuff pressure** are simple and effective measures to prevent microaspiration and should be practiced in all ICUs.
6. Several lines of evidence suggest that **minimizing the number of manipulations of the ventilator tubing** will decrease the incidence of ventilator-associated pneumonia.
7. **Causes of the relative immunocompromise** that allows bacteria to overwhelm local host defenses in the lung are heterogeneous and patient dependent, unlike the stereotypical steps of colonization and aspiration.

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In critical care settings, antibiotics commonly used to treat gram-negative infection include β -lactams (penicillin, cephalosporin, carbapenem, and monobactam), fluoroquinolones, and aminoglycosides. Combinations of a β -lactam with aminoglycoside or fluoroquinolone are used to overcome bacterial resistance and to provide synergistic activity. A short discussion of polymyxins is included for the treatment of resistant gram-negative pathogens.

■ β -LACTAMS

Mechanism of Action

β -lactam antibiotics exhibit their bactericidal effects by inhibiting cell wall synthesis. The primary function of the bacterial cell wall is to maintain cell shape and to protect the organism from osmotic rupture. Peptidoglycan, the essential component of the cell wall, is composed of alternating *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM) cross-linked by peptide side chains.¹ β -lactam antibiotics are structural analogs of D-alanyl-D-alanine of the peptide side chain. Acylation of penicillin binding protein transpeptidase enzymes (PBPs) results in inhibition of peptidoglycan formation and consequent bacteriolysis and death.^{1,2}

The efficacy of a β -lactam antibiotic is determined by its ability to reach the target PBPs and its binding affinity to various PBPs.³ In gram-negative bacteria, the peptidoglycan lies in the periplasmic space, and the outer membrane functions as a permeability barrier to substrates. β -lactams are hydrophilic molecules and must cross the outer membrane via porin channels to reach PBPs.⁴ Entry through the porin channels is determined by size, charge, and hydrophobicity.^{1,5} In contrast, in gram-positive bacteria, peptidoglycan is the outermost structure of the cell, conferring easier access to β -lactam antibiotics.

Resistance

Four primary mechanisms allow bacteria to resist the cytotoxic activity of β -lactams. First, modification of PBPs can decrease their binding affinity for β -lactams. This mechanism is largely used by gram-positive bacteria, although it is important in some gram-negative bacteria, including *Haemophilus influenzae* and *Neisseria meningitidis*.⁶⁻⁹ Second, deficiency or loss of outer membrane proteins in gram-negative bacteria can diminish the permeability of the membrane to β -lactam and thus restrict its access to PBPs. Down regulation of OprD is associated with *Pseudomonas aeruginosa* resistance to imipenem^{10,11} and the loss of CarO associated with carbapenem resistance in multidrug-resistant *Acinetobacter baumannii*.^{12,13} Third, active efflux systems, especially in conjunction with decreased outer membrane permeability, can result in multidrug resistance in gram-negative bacteria. Overexpression of the MexAB-OprM efflux pumps in *P. aeruginosa* confers intrinsic resistance to multidrugs, including β -lactams.^{14,15} *A. baumannii* showing upregulated AdeABC efflux pump is associated with a higher level of resistance to β -lactams including carbapenems.¹⁶ Finally, β -lactamase production is largely responsible for β -lactam antibiotic resistance among gram-negative bacteria in the critical care setting. β -lactamase contains either a serine residue or a metal ion to acylate

and hydrolyze the β -lactam ring, rendering the drug inactive.⁹ β -lactamase can be encoded either chromosomally or via plasmids or transposons. β -lactamase production may be constitutive or inducible, and β -lactam antibiotics vary in their ability to induce β -lactamase production.^{17,18}

Extended-spectrum β -lactamases (ESBLs) have been found in Enterobacteriaceae, most commonly in *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacter* species. These ESBLs hydrolyze third-generation cephalosporins and aztreonam but are inhibited by β -lactamase inhibitors.¹⁹ Numerous studies report outbreaks of ESBL-producing *Klebsiella* and *Enterobacter* infections in intensive care units (ICUs).¹⁹⁻²² AmpC β -lactamase resistance is another particular concern in ICUs. Exposure to β -lactam antibiotics can induce or lead to selection of spontaneous “depressed” mutants that constitutively hyperproduce AmpC.^{9,23,24} AmpC resistance has been demonstrated in many clinically important gram-negative bacteria, including *Acinetobacter* spp., *Citrobacter freundii*, *Enterobacter* spp., *E. coli*, *Morganella morganii*, *P. aeruginosa*, and *Serratia marcescens*.¹⁹ Emergence of AmpC resistance in *Enterobacter* spp. during third-generation cephalosporin therapy may be of particular significance. AmpC β -lactamase inactivates most cephalosporins and aztreonam and is not inhibited by β -lactamase inhibitors.²⁵

Most organisms producing ESBL and AmpC β -lactamase remain susceptible to carbapenems, but carbapenemase-producing gram-negative bacteria have been increasingly reported worldwide.^{26,27} These organisms often display multidrug resistance, with limited treatment options. The most concerning of the carbapenemases are those of *K. pneumoniae* (KPCs). They are mostly plasmid-encoded and hydrolyze all β -lactams, although cephamycins and ceftazidime are weakly hydrolyzed.²⁸ The hydrolytic activity of KPCs is not sufficient to produce resistance against carbapenems but increases the minimum inhibitory concentration (MIC) and potentially the risk of therapy failure. Carbapenemase-producing isolates are generally resistant to all β -lactams as well as aminoglycosides and fluoroquinolones. Colistin and tigecycline typically retain activity against these enzymes.²⁹⁻³¹ Combination therapies with different antibiotic classes³² or newer β -lactamase inhibitors such as avibactam may be alternatives based on in vitro data,³³⁻³⁴ but clinical data supporting such recommendations are lacking.

Spectrum of Activity

β -lactam antibiotics have a wide spectrum of activity against gram-positive and gram-negative aerobic and anaerobic bacteria. However, each individual class of β -lactams has a unique microbiological spectrum. Natural penicillins are seldom used in critical care settings because they lack activity against β -lactamase-producing bacteria. Their utility has been limited to treatment of meningococcal meningitis, streptococcal endocarditis, and streptococcal necrotizing fasciitis. Semi-synthetic penicillins (nafcillin, oxacillin) are usually reserved for infections caused by methicillin-susceptible *S. aureus* (MSSA).

One strategy for achieving β -lactamase stability is combination of β -lactams with β -lactamase inhibitors such as clavulanate, sulbactam, and tazobactam. β -lactamase inhibitors have weak antibacterial

activity but preserve and increase the antibacterial activity of the accompanying β -lactam against β -lactamase producing pathogens. Ampicillin/sulbactam is active against gram-positive bacteria including *Enterococcus* spp., gram-negative cocci, and certain strains of Enterobacteriaceae. Ampicillin/sulbactam does not possess activity against *P. aeruginosa* or ESBL-producing Enterobacteriaceae^{22,35,36} and consequently should not be used as an empiric monotherapy for critically ill patients. Ticarcillin/clavulanate and piperacillin/tazobactam have broader spectrum activity including *P. aeruginosa*, Enterobacteriaceae, and anaerobes such as *B. fragilis*, *Fusobacterium*, and *Prevotella* spp. Piperacillin has better antipseudomonal activity than ticarcillin.^{37,38} However, the susceptibility rates of *P. aeruginosa* to piperacillin/tazobactam in the ICU were reported to be only 70.6% in the United States and 64.7% in Europe,²² necessitating optimization of drug exposure or combination therapy to ensure the efficacy against *P. aeruginosa*. It should be noted that high doses of ampicillin/sulbactam and ticarcillin/clavulanate in combination therapy have demonstrated effectiveness against *A. baumannii* and *Stenotrophomonas maltophilia*, respectively, providing alternative options to treat these pathogens that often exhibit multidrug resistance in the ICU.³⁹⁻⁴¹

Cephalosporins have activity against gram-positive cocci, gram-negative bacilli, and anaerobes, depending on the agent. They are also stable against many β -lactamases. Cephalosporins are broadly divided into five generations. Cefazolin, a first-generation cephalosporin, has activity against MSSA and coagulase-negative staphylococci but may be susceptible to staphylococcal β -lactamase. Cefazolin is also active against most streptococci, but all cephalosporins lack adequate activity against the enterococci. Cefazolin activity against gram-negative bacteria is limited to *E. coli*, *P. mirabilis*, *K. pneumoniae*, *Moraxella catarrhalis*, *Salmonella* spp., and *Shigella* spp. The second-generation cephalosporins are divided into two groups based on their anaerobic activity. Cephamycins such as cefoxitin and cefotetan are active against most gram-negative anaerobic organisms, including *Prevotella* spp., *Fusobacterium* spp., and *B. fragilis*. Cephamycins have less activity against gram-positive bacteria than the first-generation cephalosporins but greater activity against Enterobacteriaceae such as *M. organii*, *P. vulgaris*, *Providencia* spp., and *S. marcescens*. Unfortunately, cefoxitin is a potent inducer of chromosomally mediated β -lactamases.⁴² The second group of second-generation cephalosporins includes cefuroxime. Cefuroxime is stable to most β -lactamases produced by gram-negative bacilli and is more active against methicillin-susceptible staphylococci and streptococci than is cefazolin. With excellent efficacy against *H. influenzae*, cefuroxime is effective against most typical community-acquired respiratory tract pathogens.

Third-generation parenteral cephalosporins include cefotaxime, ceftriaxone, and ceftazidime. These agents can be divided by their antipseudomonal activity, with cefoperazone and ceftazidime having clinically useful potency against *P. aeruginosa*. Cefoperazone possesses a methylthiotetrazole side chain that causes hypoprothrombinemia, limiting its use in the critically ill. Ceftazidime has the greatest potency of the third-generation agents against *S. aureus*. Third-generation cephalosporins have excellent clinical expanded activity against the Enterobacteriaceae and *Streptococcus pneumoniae* but lack activity against enterococci, MRSA, *Listeria monocytogenes*, *S. maltophilia*, and many *Acinetobacter* spp. Third-generation cephalosporins can be hydrolyzed by ESBL-producing Enterobacteriaceae such as *Klebsiella*, *Enterobacter*, and *E. coli*. Cefepime is a fourth-generation cephalosporin with activity similar to that of ceftazidime with better stability to ESBLs.⁴³ The latest marketed product is a combination of ceftazidime and avibactam. Avibactam is a non- β -lactam inhibitor that is able to inhibit Ambler class A, class C, and some class D serine β -lactamases.³⁴ The addition of avibactam improves the activity of ceftazidime against Enterobacteriaceae and *P. aeruginosa*. Avibactam does not improve the activity of ceftazidime against *Acinetobacter* spp., *Burkholderia* spp., or anaerobic gram-negative bacilli.⁴³ Ceftaroline, known as an anti-MRSA cephalosporin, is a fifth-generation cephalosporin with bactericidal activity against MRSA and penicillin-resistant *S. pneumoniae*. It also

has activity against gram-negative bacilli such as *H. influenzae*, *M. catarrhalis*, *E. coli*, and *K. pneumoniae* but lacks activity against ESBL-producing Enterobacteriaceae and *P. aeruginosa*.⁴⁴

The carbapenems are the broadest spectrum β -lactams and are typically reserved for severe nosocomial infections. They are active against most gram-positive bacteria (except MRSA and *Enterococcus faecium*) and gram-negative bacteria (except *S. maltophilia*), as well as anaerobes. Ertapenem is not active against important nonfermenting gram-negative bacilli such as *P. aeruginosa* and *A. baumannii*.⁴⁵ In general, doripenem has been demonstrated to have better activity than imipenem and similar or slightly better activity than meropenem against *P. aeruginosa*.⁴⁶⁻⁴⁷ Aztreonam, a monobactam, has broad aerobic gram-negative activity but lacks efficacy against gram-positive bacteria and anaerobes. Carbapenems are stable against ESBL and AmpC β -lactamase-producing gram-negative bacteria^{48,49} but are susceptible to carbapenemases and metallo- β -lactamases, although these resistance mechanisms are less common. Carbapenems are preferred empiric therapy over β -lactam/ β -lactamase inhibitors or cefepime that are associated with the inoculum effect and increasing resistance rates that can lead to unfavorable clinical outcomes.⁵⁰⁻⁵³ In general, the susceptibility rates of *P. aeruginosa* and *Acinetobacter* isolates to carbapenems in the ICU were 10% to 20% lower than those of non-ICU isolates.²² Only 71.6% and 72.7% of *P. aeruginosa* in the United States and 67% and 66.5% in Europe were susceptible to imipenem and meropenem, respectively. *Acinetobacter* spp. exhibited low susceptibility to imipenem and meropenem in both the United States (43%) and Europe (43%-45%), with increasing prevalence of resistance.²²

Pharmacokinetics and Pharmacodynamics

The pharmacokinetics of β -lactams has not been well investigated in critically ill patients. β -lactams are hydrophilic molecules with a low volume of distribution (Vd), similar to that of extracellular fluid (0.1-0.6 L/kg), with predominant renal clearance.⁵⁴ However, the Vd may be increased in critically ill patients because of sepsis and/or fluid resuscitation, with increased or decreased renal drug clearance.⁵⁵ In healthy volunteers, β -lactam/ β -lactamase inhibitors have a half-life of about 1 hour, and protein binding ranging from 20% to 50%. The primary elimination is by renal excretion, but biliary excretion may be also significant for piperacillin/tazobactam. Most cephalosporins have short half-lives (1-3 hours) and undergo extensive renal elimination. Ceftriaxone, with significant biliary excretion, does not require dosing adjustments in renal dysfunction. The half-life of cefotaxime is not significantly increased in patients with renal failure; however, its active metabolite, desacetylcefotaxime, accumulates significantly and thus requires dosing adjustments. With the exception of ertapenem, all carbapenems exhibit a similar half-life (~1 hour) and small protein binding (2%-20%). Ertapenem is highly protein bound (~95%) and has a 4-hour half-life, allowing once daily administration. Carbapenems are extensively eliminated by the kidney (70%-80%). Reconstituted imipenem and meropenem are stable at room temperature only for 1 to 4 hours, compared with doripenem that displays longer stability (4-12 hours).

β -lactams are time-dependent antibiotics for which the time of free serum concentration above the pathogen MIC ($T > \text{MIC}$) is the pharmacodynamic parameter associated with clinical efficacy.⁵⁶ Typically, bacterial killing occurs when $T > \text{MIC}$ is 50% of the dosing interval for penicillins, 60% to 70% for cephalosporins, and 40% for carbapenems. However, further improved clinical efficacy has been observed when a longer $T > \text{MIC}$ (~100%) is achieved in critically ill patients.^{54,57} In addition, a maximal killing effect and suppressed bacterial resistance have been demonstrated when antibiotic concentrations are maintained at four to five times the MIC, accounting for penetration into the infection sites.^{56,58}

Although therapeutic drug monitoring is not routinely available for β -lactam antibiotics, studies suggest that drug concentrations may be subtherapeutic in critically ill patients given conventional doses.^{59,60} Critically ill patients often have physiologic alterations, including

increased Vd and/or augmented renal clearance. Renal replacement therapy can efficiently eliminate most β -lactam antibiotics. Pathogens with reduced susceptibility and resistance are more common in critically ill patients. Together, these factors commonly observed in critically ill patients warrant aggressive dosing to minimize treatment failure and drug resistance. Prolonged β -lactam infusion—either extended (3–4 hours) or continuous—has been suggested as an alternative dosing strategy to optimize antibiotic exposure, particularly in critically ill patients with resistant gram-negative pathogens including *P. aeruginosa*.^{61–64} The randomized trials report conflicting data regarding the clinical benefits of prolonged β -lactam infusion compared to intermittent dosing.^{62,63,65} A recent meta-analysis found that continuous β -lactam infusion is associated with improved clinical cure and mortality compared with intermittent dosing in severely septic patients without renal replacement therapy. However, a definitive benefit of continuous infusion should be confirmed by a large randomized study.

Adverse Effects

The most common adverse event with penicillin is allergic or hypersensitivity reaction (~10%). The most common presentations of hypersensitivity reactions include maculopapular or urticarial rashes and angioedema, but severe reactions such as anaphylaxis can also occur. A history of penicillin allergy is known to be unreliable in predicting the risk of developing an immediate allergic reaction because hypersensitivity to penicillin can wane with time.^{66,67} Patients with a history of nonanaphylactic penicillin allergy who have a negative penicillin skin test are unlikely to experience hypersensitivity reactions^{67–69} and may be able to receive β -lactam therapy. However, patients who react to the skin test should avoid β -lactams or undergo desensitization.⁷⁰

Cephalosporins are generally well tolerated. Agents with the methylthiotetrazole (MTT) side chain may cause hypoprothrombinemia via inhibition of synthesis and absorption of vitamin K and competitive inhibition of vitamin K-dependent clotting factors. Agents bearing the MTT side chain are cefoperazone, cefotetan, and cefmetazole. Use of these agents may require vitamin K supplementation. The MTT side chain has also been associated with a disulfiram-like reaction.

A higher rate of seizures (1.5%–2%) has been reported when higher imipenem doses (≥ 4 g/day) are administered.^{71,72} Risk factors for imipenem-associated seizures include renal impairment, lower body weight, and history of seizures or other CNS diseases.^{71,73,74} Imipenem is metabolized extensively by renal dehydropeptidase-1 (DHP-1), producing nephrotoxic metabolites. Consequently, imipenem requires coadministration with cilastatin, a DHP-1 inhibitor, to increase the imipenem urine delivery and to prevent nephrotoxicity. Other carbapenems are intrinsically more stable to DHP-1.

Cross-Sensitivity

Approximately 8% of the U.S. population reports a history of penicillin allergy that ranges from mild cutaneous reactions to life-threatening Type 1 IgE-mediated hypersensitivity reactions. Fortunately, the incidence of anaphylaxis to penicillins is low ($\leq 0.02\%$).^{75,76} A history of cephalosporin allergy is only reported in about 1% of the U.S. population.⁷⁷ Cephalosporin-associated toxic epidermal necrolysis, Stevens-Johnson syndrome, severe hepatitis, interstitial nephritis, and hemolytic anemia are extremely rare. Clinically significant immunologic cross-reactivity between β -lactams is much lower than once believed. Cephalosporin allergy in penicillin-allergic patients is attributable to cross-reactive antibodies to side chains similar between cephalosporin and penicillins or amoxicillin. Based on side-chain similarity, first-generation cephalosporins are cross-reactive with penicillins, but cross-reactivity is negligible with second- and third-generation cephalosporins.⁷⁸ Attributable cross-reactivity is very unlikely or absent between penicillins-cephalosporins and carbapenems.⁷⁹ Monobactams

are not cross-reactive with penicillins but are so with ceftazidime because they have identical side chains.⁸⁰

FLUOROQUINOLONES

Mechanism of Action

The fluoroquinolones are another broad-spectrum antibiotic class used in the critical care setting. Ciprofloxacin, levofloxacin, and moxifloxacin are commonly used. Fluoroquinolones impair DNA replication and cause cell death by interfering with normal function of DNA gyrase (gyrA and gyrB) or topoisomerase IV (parC and parE), which condenses DNA into supercoils to allow large amounts of DNA to be packed into the cell.⁸¹ The widespread use of fluoroquinolones has caused an increase in bacterial resistance to these drugs. Resistance derives from mutations in gyrA, gyrB, parC, and parE with or without efflux pump. Multiple forms of resistance can be present simultaneously, further increasing their MIC.⁸²

Spectrum of Activity

Fluoroquinolones have activity against a wide range of both gram-positive and gram-negative organisms. Levofloxacin and moxifloxacin are potent against penicillin-sensitive or -resistant *S. pneumoniae* but inactive against MRSA. Over the years, increasing resistance has reduced the usefulness of fluoroquinolones against gram-negative bacteria. Ciprofloxacin is considered the most potent fluoroquinolone against gram-negative bacteria, with the lowest MIC values, but a higher levofloxacin dose can be used to achieve similar efficacy. Fluoroquinolones are typically stable against ESBL or carbapenemase-producing pathogens. For common resistant ICU pathogens such as *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*, fluoroquinolones are used in combination with β -lactams. The susceptibility of *P. aeruginosa* is approximately 70%, while that of *A. baumannii* is usually less than 50%.²² Although fluoroquinolones are not widely used for anaerobic infections, moxifloxacin does have an FDA indication for intra-abdominal infections.⁸³

Pharmacokinetics and Pharmacodynamics

The oral bioavailability of fluoroquinolones is high (70%–99%) and can be administered orally in patients who can tolerate it. The large Vd following rapid oral absorption suggests adequate tissue concentrations. The long half-lives (4–12 hours) allow once- or twice-daily dosing. Ciprofloxacin and levofloxacin are excreted renally as unmetabolized drug, necessitating dosing adjustments in renal insufficiency. Moxifloxacin, however, is highly metabolized and does not require dose adjustments in either renal or hepatic dysfunction. Fluoroquinolones display concentration-dependent bactericidal effect. The free area under the serum concentration time curve to MIC ratio (f-AUC/MIC) seems to be the best predictor of efficacy. An f-AUC/MIC ratio greater than or equal to 87.5/h best predicts clinical and microbiologic success for gram-negative infections; f-AUC/MIC greater than or equal to 33.7/h maximizes the efficacy against gram-positive infections. Treatment of infection with resistant pathogens such as *P. aeruginosa* and *A. baumannii* requires the maximum fluoroquinolone doses (i.e., intravenous ciprofloxacin 400 mg every 8 hours or levofloxacin 750 mg every 24 hours) in patients with normal renal function.⁸⁴

Adverse Effects

Fluoroquinolones have an acceptable safety profile. Prolongation of the QTc interval, which may predispose susceptible patients to potentially fatal torsades de pointes arrhythmias, has been observed and should be monitored in patients with uncorrected hypokalemia or receiving Class IA or III antiarrhythmics.⁸⁵ *Clostridium difficile*-associated colitis has been associated with fluoroquinolone use but remains

controversial.⁸⁶ Fluoroquinolones may alter the serum glucose concentration (hypo- or hyperglycemia), especially in those patients who have a history of diabetes and are on hypoglycemic agents. Oral absorption of fluoroquinolones is altered by di- or trivalent-cation-containing products (some tube feedings, antacids, multivitamins, ferrous sulfate, sucralfate), and their administration should be separated by at least 2 hours.⁸³

■ AMINOGLYCOSIDES

Aminoglycoside use in the critical care setting is mainly additive or synergistic with β -lactams or fluoroquinolones. Early combination therapy that includes aminoglycosides has shown survival benefit in patients with septic shock.⁸⁷⁻⁸⁹ Aminoglycosides should be given based on once-daily aminoglycoside dosing for a short period of time (5-7 days) to improve effectiveness and reduce nephrotoxicity. Commonly used aminoglycosides are gentamicin, tobramycin, and amikacin.

Mechanism of Action

Aminoglycosides are cations that bind passively to negatively charged portions of the outer membranes of gram-negative bacilli and competitively displace cell wall Mg^{2+} and Ca^{2+} that link lipopolysaccharides. Once inside the cell, aminoglycosides then bind to the 16S rRNA of 30S subunits of ribosomes, causing termination and miscoding of protein synthesis.⁹⁰ In gram-positive bacteria, aminoglycoside uptake is reduced by the thicker outer cell wall membranes; higher MICs are reported.

Spectrum of Activity

Aminoglycosides are active primarily against gram-negative bacteria and staphylococci. Gentamicin is a potent agent against Enterobacteriaceae. Tobramycin has slightly higher activity than gentamicin against *P. aeruginosa* and *Acinetobacter* spp. Amikacin is usually reserved for gram-negative pathogens that are resistant to gentamicin and tobramycin. Aminoglycosides are active against MSSA. For MRSA caused by *Streptococcus* spp. and *Enterococcus* spp., aminoglycosides are used to provide synergistic activity with β -lactam antibiotics.⁹¹ Bacterial resistance to aminoglycosides is caused by modifications of ribosomal binding sites and enzymes, decreased antibiotic uptake, and efflux of antibiotics.⁹²

Pharmacokinetics and Pharmacodynamics

All the aminoglycosides have similar pharmacokinetic properties. Distribution of the drug from the vascular to the extravascular space occurs rapidly, within 15 to 30 minutes post infusion. Aminoglycosides are primarily excreted by glomerular filtration and require dosage adjustments in renal insufficiency. In patients with normal renal function, the half-lives of all aminoglycosides range from 1.5 to 3.5 hours. More than 90% of a parenterally administered dose is recovered in urine unchanged during the first 24 hours. The remainder is slowly recycled into the tubular lumen, where accumulation of the drug causes nephrotoxicity.⁹³ Aminoglycoside concentrations are generally low in infected secretions and tissues.⁹⁴ Inhalation therapy has been used in ventilator-associated pneumonia with resistant organisms.⁹⁵

Pharmacodynamic principles associated with aminoglycosides include concentration-dependent bactericidal activity, postantibiotic effect (PAE), and synergism with other cell-wall-active agents. Rapid bacterial killing against Enterobacteriaceae correlates best with the 24-hour AUC/MIC ratio, while the peak/MIC ratio is better in *P. aeruginosa*. The PAE for *P. aeruginosa* may be as long as 10.2 hours and even longer for Enterobacteriaceae.⁹⁶ Synergy is frequently reported with the combination of an aminoglycoside and a cell wall-active antimicrobial (e.g., β -lactam), even against pathogens with higher MICs. Once-daily dosing employs these pharmacodynamics principles

and administers a larger dose less frequently to produce a rapid bactericidal effect and yet undetectable trough concentrations to reduce drug accumulation.

Adverse Effects

The most common adverse event with aminoglycosides is nephrotoxicity ranging from 5% to 25%.^{93,97} Risk factors for nephrotoxicity include older age, preexisting renal insufficiency, diabetes, concomitant vancomycin use, longer treatment duration (≥ 4 days), and shock/hypotension.⁹⁸ Aminoglycosides may cause ototoxicity that is manifested as auditory (cochlear) and vestibular toxicity. Risk factors include patient age, prolonged therapy of greater than 10 days, renal function, and additive effects of other ototoxic agents (loop diuretics).⁹⁹ The most life-threatening adverse reaction to aminoglycosides, although very rare, is neuromuscular blockade.¹⁰⁰ Blockade results from inhibition of the presynaptic release of acetylcholine and blockage of postsynaptic acetylcholine receptor sites. Risk factors include aminoglycoside given intravenously in patients with renal insufficiency and concomitant administration of a neuromuscular blocking or anesthetic agent.

Dosing and Monitoring

Aminoglycosides are administered in small doses multiple times per day or in large doses less frequently, as in a once-daily dosing, based on a patient's renal function. Once-daily dosing may have similar to better clinical efficacy and delay onset of nephrotoxicity if used in short duration.⁹⁶ Serum concentrations of aminoglycosides are essential for both efficacy and toxicity. For traditional multiple-dose daily regimens, peak and trough concentrations should be checked 1 hour after the start of infusion and right before the next dose, respectively. They should be measured during steady state, which is approximately after the third dose. The frequency of subsequent monitoring should be based on changes in renal function. For lower respiratory tract infections, the target peak concentration should range from 8 to 12 mg/L for gentamicin and tobramycin and 25 to 30 mg/L for amikacin. Trough concentrations should be less than 2 mg/L, although less than 1 mg/L is preferred. For once-daily dosing, the targeted peak concentration should be 20 mg/L or a C_{max}/MIC of 10, and the trough concentration should be undetectable (<0.5 mg/L) for approximately 4 hours at the end of the dosing interval.¹⁰¹ In gram-positive infections such as infective endocarditis, a synergistic effect is achieved with low-dose gentamicin to achieve a peak concentration of 3 μ g/mL and a trough concentration of less than 0.5 μ g/mL.

■ COLISTIN

Polymyxins include polymyxin B and polymyxin E (colistin); colistin has been used more commonly in clinical practice. Colistin use has increased as salvage therapy against multidrug-resistant gram-negative pathogens including *P. aeruginosa*, *A. baumannii*, *K. pneumoniae*, and *Enterobacter* spp.¹⁰² Polymyxins have no appreciable activity against gram-positive bacteria and most anaerobes. Colistin interacts with the lipid A component of lipopolysaccharide (LPS) and displaces the calcium and magnesium bridges that stabilize the LPS. Disruption of the integrity of the outer membrane may lead to increased permeability and improved uptake of colistin, but the ultimate mechanism of their bactericidal activity is not well understood. Currently, resistance to colistin is relatively low, and the mechanism of resistance is not well described.¹⁰³ Modification of the lipid A portion of LPS is associated with resistance in *P. aeruginosa* and *E. coli*, while increased production of capsule polysaccharide is thought to be responsible for *K. pneumoniae* resistance.¹⁰⁴ Further studies are needed to better elucidate the mechanisms of action and resistance.

Colistin is formulated as a prodrug, colistin methanesulfonate (CMS, also known as colistimethate) and available for parenteral or aerosol use. CMS slowly hydrolyzes to the active colistin, with the

TABLE 116-1 Recommended Adult Dosing Regimens Based on Renal Function*

| ANTIBIOTIC | ADULT DOSE [§] | DOSING ALTERATION FOR RENAL DYSFUNCTION | ANTIBIOTIC | ADULT DOSE [§] | DOSING ALTERATION FOR RENAL DYSFUNCTION |
|-------------------------|-------------------------|--|------------------------------------|---|---|
| B-LACTAMS | | | | | |
| Ampicillin/sulbactam | 1.5-3 g q 6 h | CrCl: 15-29 mL/min: 1.5-3 g q 12 h CrCl: 5-14 mL/min: 1.5-3 g q 24 h CRRT: 1.5-3 g q 8-12 h | Imipenem | 500 mg-1 g q 6-8 h | CrCl 41-70 mL/min: 500-750 mg q 8 h CrCl 21-40 mL/min: 250-500 mg q 6 h CrCl <20 mL/min: 250-500 mg q 12 h CRRT: 500 mg q 6 h |
| Ticarcillin/clavulanate | 3.1 g q 4-6 h | CrCl: 30-60 mL/min: 3.1 g LD, then 2 g q 4 h CrCl: 10-30 mL/min: 3.1 g LD, then 2 g q 8 h CrCl: <10 mL/min: 3.1 g LD, then 2 g q 12 h CRRT: 2-3.1 g q 6-8 h | Meropenem | 1 g q 8 h | CrCl 25-50 mL/min: 1 g q 12 h CrCl 10-25 mL/min: 500 mg q 12 h CrCl <10 mL/min: 500 mg q 24 h CRRT: 1 g q 12 h |
| Piperacillin/tazobactam | 2.25-4.5 g q 6 h | CrCl: 40-60 mL/min: 3.75-4.5 g q 6 h CrCl: 20-40 mL/min: 2.25-3.375 g q 6 h CrCl: <20 mL/min: 2.25 g q 6-8 h CRRT: 4.5 g q 6-8 h | Ertapenem | 1 g q 24 h | CrCl <30 mL/min: 500 mg q 24 h CRRT: 500 mg-1 g q 24 h |
| Cefazolin | 1-1.5 g q 6-8 h | CrCl: 11-34 mL/min: 500 mg q 12 h CrCl: ≤10 mL/min: 500 mg q 18-24 h CRRT: 1-2 g q 12 h | Doripenem | 500 mg q 8 h | CrCl 30-50 mL/min: 250 mg q 8 h CrCl 10-29 mL/min: 250 mg q 12 h CRRT: 500 mg q 8 h |
| Cefotetan | 2-3 g q 12 h | CrCl: >30 mL/min: 2-3 g q 12 h CrCl: 10-30 mL/min: 2-3 g q 24 h CrCl: <10 mL/min: 2-3 g q 48 h CRRT: 1-2 g q 12 h | Aztreonam | 1-2 g q 8 h | CrCl 10-29 mL/min: 500 mg to 1 g q 8 h CrCl <10 mL/min: 500 mg to 1 g q 12 h CRRT: 2 g q 12 h |
| Cefoxitin | 2 g q 4-6 h | CrCl: 30-50 mL/min: 1-2 g q 8-12 h CrCl: 10-29 mL/min: 1-2 g q 12-24 h CrCl: <10 mL/min: 0.5-1 g q 12-48 h CRRT: 1-2 g q 8-12 h | AMINOGLYCOSIDES[†] | | |
| Cefuroxime | 1.5 g q 8 h | CrCl: 10-20 mL/min: 750 mg q 12 h CrCl: <10 mL/min: 750 mg q 24 h CRRT: 1 g q 12 h | Gentamicin and tobramycin | 1.5-2.5 mg/kg q 8 h or 5 mg/kg q 24 h | CrCl 40-59 mL/min: 1.5-2.5 mg/kg q 12 h CrCl 20-39 mL/min: 1.5-2.5 mg/kg q 24 h CrCl <20 mL/min: Redose when trough levels <1 µg/mL CRRT: Redose when trough levels <1 µg/mL |
| Ceftazidime | 1-2 g q 8 h | CrCl: 31-50 mL/min: 1 g q 12 h CrCl: 16-30 mL/min: 1 g q 24 h CrCl: 6-15 mL/min: 0.5 g q 24 h CrCl: <5 mL/min: 0.5 g q 48 h CRRT: 2 g q 8-12 h | Amikacin | 7.5 mg/kg q 8 h or 15 mg/kg q 24 h | CrCl 40-59 mL/min: 5-7.5 mg/kg q 12 h CrCl 20-39 mL/min: 5-7.5 mg/kg q 24 h CrCl <20 mL/min: Redose when trough levels <5 µg/mL CRRT: Redose based on trough levels <5 µg/mL |
| Ceftriaxone | 1-2 g q 24 h | No adjustment CRRT: 1-2 g q 12 h | FLUOROQUINOLONES | | |
| Cefepime | 1-2 g q 8-12 h | CrCl: 11-29 mL/min: 1-2 g q 24 h CrCl: ≤10 mL/min: 1 g q 24 h CRRT: 2 h q 8-12 h | Ciprofloxacin | 400 mg q 8-12 h | CrCl 5-29 mL/min: 200-400 mg q 18-24 h CRRT: 400 mg q 12 h |
| Ceftaroline | 600 mg q 12 h | CrCl: 31-50 mL/min: 400 mg q 12 h CrCl: 15-30 mL/min: 300 mg q 12 h CrCl: <15 mL/min: 200 mg q 12 h CRRT: 400-600 mg q 12 h | Levofloxacin | 750 mg q 24 h | CrCl 20-49 mL/min: 750 mg q 48 h CrCl 10-19 mL/min: 750 mg initially, then 500 mg q 48 h CRRT: 750 mg initially, then 500-750 mg q 24 h |
| | | | MISCELLANEOUS | | |
| | | | Colistin [‡] | 2.5 mg CBA/kg q 12 h (Max 340 mg CBA/day) | CrCl 50-79 mL/min: 1.25-1.9 mg/kg q 12 h CrCl 30-49 mL/min: 1.25 mg/kg q 24 h CrCl 10-29 mL/min: 1.5 mg/kg q 36 h CRRT: 1.25-2.5 mg/kg q 12-24 h |

*Data compiled from package insert information.

[†]For aminoglycosides dosing, adjusted body weight should be used: $(0.45 \times [\text{total body weight} - \text{ideal body weight}] + \text{ideal body weight})$.

[‡]For colistin, dosing should be based on lower of actual or ideal body weight.

[§]All administration is intravenous; dosing is for serious, life-threatening infections.

q, every; h, hours; CrCl, creatinine clearance; CRRT, continuous renal replacement therapy.

maximum concentration occurring about 7 hours after administration. The half-life of colistin is 14 hours, delaying steady-state attainment to 2 to 3 days. The protein binding of colistin is approximately 60%. About two-thirds of CMS is eliminated renally within 24 hours, but elimination of active colistin is not renal. Colistin achieves adequate concentration in the liver, kidney, heart, and muscle, but is poorly distributed to the bones, cerebrospinal fluid, lung parenchyma, and pleural cavity, requiring nebulization to treat life-threatening respiratory infections.¹⁰⁵ Pharmacodynamic studies suggest that the $f\text{-AUC}/\text{MIC}$ ratio is the optimal parameter to predict the antibacterial effect, indicating that time-averaged exposure to colistin is important.¹⁰⁶⁻¹⁰⁸ A high dose (3 MU of CMS every 8 hours) of colistin does not yield sufficient serum concentrations, especially for resistant gram-negative pathogens showing higher MICs ($\geq 2 \mu\text{g/mL}$).¹⁰⁹ Consequently, a large loading dose and higher maintenance doses may be needed to achieve the target colistin serum concentrations more rapidly.¹¹⁰ However, neph-

rotoxicity is the major dose-limiting adverse effect. Colistin-associated nephrotoxicity is dose-dependent and has been observed in 15% to 25% of patients treated with colistin.^{111,112} Older age, concurrent use of other nephrotoxic agents, hypovolemia/shock, and severe illness may increase the risk of acute kidney injury.

Based on the current understanding of colistin, a CBA loading dose of 5 mg/kg (maximum, 300 mg) is recommended, followed by a maintenance dose starting 24 hours after the loading dose. The maintenance dose can be based on the package insert as presented in Table 116-1. Both the loading and maintenance doses should be based on the lower of the actual or ideal body weight.^{109,113} To improve effectiveness, colistin should be used in combination with other antimicrobial therapy. Synergistic activity was observed with carbapenems and to a lesser extent with fluoroquinolones.¹¹⁴ Ongoing randomized controlled trials comparing colistin-meropenem combinations may shed light on the future direction of colistin use.

KEY POINTS

1. Antibiotics commonly used to treat gram-negative infection in critical care settings include penicillin, cephalosporin, carbapenem, monobactam, fluoroquinolone, and aminoglycosides.
2. β -lactam antibiotics are combined with β -lactamase inhibitors, as in ampicillin/sulbactam, ticarcillin/clavulanate, piperacillin/tazobactam, and ceftazidime/avibactam, to overcome bacterial resistance.
3. Carbapenems and cefepime are more reliable against gram-negative bacteria expressing extended-spectrum β -lactamases.
4. Penicillin allergy is commonly reported, but true anaphylaxis is rare. Cross-reactivity between penicillins and other β -lactams is low, with the highest incidence in first-generation cephalosporins. Cross-reactivity is negligible with other β -lactams.
5. Fluoroquinolones should be combined with β -lactam antibiotics or aminoglycosides until susceptibility is documented.
6. Aminoglycosides should be combined with β -lactam antibiotics or fluoroquinolones for a short duration of 5 to 7 days in septic shock or hypotensive patients.
7. Colistin should be administered in combination with carbapenems for use against multi-drug resistant gram-negative pathogens.

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- Paul M, Sibiger I, Grozinsky S, et al. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev* 2006;1:CD003344.
- A total of 64 randomized and quasi-randomized trials were included in a meta-analysis to compare any β -lactam monotherapy to any combination of one β -lactam and one aminoglycoside for sepsis. The primary outcome of all-cause mortality did not differ between monotherapy and combination therapy in studies that compared the same β -lactams (RR 1.01; 95% CI, 0.75–1.35) and in studies that compared different β -lactams (RR 0.85; 95% CI, 0.71–1.01). Nephrotoxicity was significantly more frequent with combination therapy (RR 0.30; 95% CI, 0.23–0.39).
- Aarts MW, Hancock JN, Heyland D, et al. Empiric antibiotic therapy for suspected ventilator-associated pneumonia: a systematic review and meta-analysis of randomized trials. *Crit Care Med* 2008;36:108–117.
- Although a total of 41 randomized controlled trials were included in a meta-analysis comparing monotherapy to combination therapy for the empiric treatment of ventilator-associated pneumonia, only two trials evaluated a combination with an aminoglycoside therapy. In these two trials evaluating meropenem versus ceftazidime plus aminoglycoside, no difference in all-cause mortality was reported (RR 0.73; 95% CI, 0.47–1.18), but treatment failure was lower in the meropenem group (RR 0.70; 95% CI, 0.53–0.93).
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- A database of infective endocarditis patients from two tertiary university hospitals in Copenhagen, Denmark, was evaluated for nephrotoxic effects of gentamicin. Of 373 patients with infective endocarditis, 287 received gentamicin therapy that was adjusted according to serum creatinine and trough drug levels. Kidney function was evaluated using estimated endogenous creatinine clearance (EECC). The mean time on gentamicin therapy was 17 days (range, 1–69). The mean EECC decrease was 8.6%, with a 0.5% decrease noted per day of gentamicin treatment. This decrease in EECC did not correlate to postdischarge mortality. This study did not evaluate the use of other nephrotoxic agents or the gentamicin dose.

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Nosocomial infections continue to pose a significant burden on the healthcare system. A recent summary of data reported to the National Healthcare Safety Network (NHSN) showed that gram-positive organisms were leading causes of healthcare-associated infections (HAIs) between 2009 and 2010.¹ Similarly, the EPIC II study in 2007 demonstrated gram-positive organisms were associated with 47% of infections in the ICU.² The causative pathogen can vary depending on the type of ICU as well as the type of HAI. For example, nosocomial bacteremias are caused most often by coagulase-negative staphylococci and occur more commonly in the medical ICU.¹ *Staphylococcus aureus* is the most common pathogen associated with nosocomial pneumonia as well as surgical-site infections.¹ Along with the increase in prevalence of gram-positive cocci in the ICU, staphylococci are becoming multidrug resistant. This chapter addresses gram-positive organisms and resistance issues associated with each of the antimicrobials with activity against these pathogens.

VANCOMYCIN

Vancomycin was discovered in 1956 and marketed in 1958. Early preparations of the drug contained pyrogens and impurities that produced a brownish, muddy appearance that provided vancomycin's nickname, "Mississippi mud." In addition, these pyrogens and impurities caused high fevers, hypotension, severe phlebitis, and possibly nephrotoxicity.³

Mechanisms of Action and Resistance

Vancomycin is a glycopeptide that inhibits synthesis of the cell wall by binding to the D-alanyl-D-alanine terminus of cell wall precursor units and is bactericidal against most gram-positive organisms. In the past decade, the Clinical and Laboratory Standards Institute (CLSI) and the U.S. Food and Drug Administration (FDA) changed the vancomycin breakpoints against *S. aureus* from less than or equal to 4 µg/mL to less than or equal to 2 µg/mL for susceptible strains. Intermediate susceptibility is now 4 to 8 µg/mL, and resistance to vancomycin is greater than or equal to 16 µg/mL.⁴ The European Committee on Antimicrobial Susceptibility Testing (EUCAST) changed their vancomycin interpretations against *S. aureus* to less than or equal to 2 µg/mL as susceptible and greater than 2 µg/mL as resistant. These changes in breakpoints will alter how literature is interpreted with respect to the frequency or prevalence of vancomycin-intermediate or vancomycin-resistant *S. aureus* over the past 30 years.

Five types of resistance to vancomycin have been isolated from enterococci: VanA, VanB, VanC, VanD, and VanE. The VanA phenotype, inducible by vancomycin, confers high-level resistance to both teicoplanin (minimum inhibitory concentrations [MICs]: 16 to 512 µg/mL) and vancomycin (MICs: 64 to greater than 1000 µg/mL), whereas VanB confers low-level resistance primarily to vancomycin. Both have been identified in *Enterococcus faecium* and *Enterococcus faecalis*. VanA, B, D, and E are all transferable to other organisms. In contrast, the VanC phenotypes are endogenous (constitutively produced) and are components of *Enterococcus gallinarum*, *Enterococcus casseliflavus*, and *Enterococcus flavescens* and confer resistance to vancomycin alone.

Vancomycin-intermediate *S. aureus* (VISA), defined using the previous breakpoints of MIC 8 to 16 µg/mL, was first reported from

Japan in 1996; by June 2002, eight cases were confirmed in the United States.⁵ A precursor to VISA, known as heteroresistant vancomycin-intermediate *S. aureus* (hVISA), was described around the same time.⁶ Using the new breakpoints, a surveillance study of 42 U.S. medical centers in 2011 showed an increase in the prevalence of hVISA compared to 2009 (1.2% versus 0.4%), but no VISA was detected.⁷ In June 2002, the first case of vancomycin-resistant *S. aureus* (MIC greater than 32 µg/mL) was identified in Michigan, followed in September 2002 by a second case in Pennsylvania.^{5,8} While the exact mechanism leading to reduced susceptibility in VISA isolates has yet to be determined, many agree that a common element involves thickening of the cell wall. In addition, both strains of vancomycin-resistant *S. aureus* possessed the VanA gene.

Spectrum of Activity

Vancomycin is active primarily against aerobic gram-positive cocci, including *Corynebacterium* and methicillin-resistant *S. aureus* (MRSA). The MIC₉₀ is 1 µg/mL against methicillin-susceptible *S. aureus* (MSSA) and 1 to 2 µg/mL against MRSA.^{7,9} The present incidence of vancomycin-intermediate or vancomycin-resistant *S. aureus* is very low. The activity of vancomycin against enterococci varies greatly with the species. *E. faecium* is the most resistant species of enterococci to vancomycin, with the resistant rates ranging from 30% to 90% depending on the institution. For all enterococci the vancomycin resistance rates are now approximately 35%.¹⁰

Most streptococci are susceptible to vancomycin, although it is considered an agent of last resort against these organisms. Vancomycin has been shown to be inferior to nafcillin or oxacillin for the treatment of MSSA infections. Treatment failures, prolonged treatment, and higher mortality rates were demonstrated when vancomycin was used to treat MSSA infections compared with nafcillin or oxacillin.^{11,12}

Vancomycin is active against anaerobic gram-positive organisms such as *Peptostreptococcus* spp., *Propionibacterium* spp., *Eubacterium* spp., *Bifidobacterium* spp., and most *Clostridium* spp., including *C. difficile*.¹³

Pharmacokinetics/Pharmacodynamics

Vancomycin is administered orally and intravenously (IV). The drug is poorly absorbed after oral administration, and while the majority of the drug is excreted unchanged in feces, inflammation of the gastrointestinal tract may result in increased absorption.¹⁴ Intramuscular injections are extremely painful and should not be used. Vancomycin is approximately 55% bound to plasma proteins. The volume of distribution (*V_d*) corrected for weight ranges is 0.4 to 0.9 L/kg.¹⁵⁻¹⁸ Vancomycin does not penetrate well into aqueous humor or noninflamed meninges; however, penetration ranges from 1% to 37% of serum concentrations in the setting of meningeal inflammation.¹⁹⁻²¹ Penetration is greater than 75% serum concentrations into ascitic, pericardial, and synovial fluids, approximately 50% into pleural fluid, and 30% to 50% into bile.¹⁷ Elimination of vancomycin is 80% to 90% unchanged drug in the urine via glomerular filtration and the remaining via nonrenal elimination (up to 40 mL/min in healthy individuals).²² The half-life of the drug increases with decreased renal function; in patients with creatinine clearances (CrCl) greater than 80 mL/min, the half-life

TABLE 117-1 Dosages for Agents with Primary Activity Against Gram-Positive Bacteria

| DRUG | DOSAGE | ADVERSE EFFECTS | CONSIDERATIONS |
|---------------------------|--|--|--|
| Vancomycin | Oral (PO) and intravenous (IV) administration Dose based on actual body weight (ABW) PO: 125 mg q 6 h IV: 1 g (~15 mg/kg) q 12 h for average-weight adult IV: For morbidly obese adult, dose on ABW ~15 mg/kg/dose | Red man syndrome: erythema, pruritus, flushing of upper torso Thrombophlebitis Ototoxicity: rare Nephrotoxicity: rare Maculopapular or erythematous rashes | Intramuscular injections painful Poorly absorbed orally Half-life of drug increases with decreased renal function Moellering and Matzke methods for dosing guidelines For obese patients and patients on dialysis, consider drug clearance |
| Teicoplanin | PO and IV administration PO: 200 mg BID (<i>Clostridium difficile</i> -associated diarrhea) Moderate infections: 400 mg (6 mg/kg) once followed by maintenance dose 200 mg (3 mg/kg) q 24 h Severe infections: 400-800 mg (6-12 mg/kg) q 12 h for 2-3 doses, followed by 400-800 mg q 24 h | Nephrotoxicity: rare Ototoxicity: rare Hypersensitivity | Special dosage considerations for patients with renal failure, patients on dialysis Compassionate use only in the United States (not FDA approved) |
| Telavancin | IV: 10 mg/kg once daily | Nausea and vomiting Taste perversion Foamy urine Renal impairment | Teratogenic in animal models, further information needed in humans Interferes with common anticoagulation and urine protein dipstick testing |
| Daptomycin | IV: 4 mg/kg q 24 h for average-weight adult for skin and skin-structure infection 6 mg/kg q 24 h for bacteremia/endocarditis | Transient muscle weakness Myalgia | Contraindicated in pneumonia |
| Linezolid | Bioequivalence between PO and IV formulations Moderate infections: 600 mg twice daily Uncomplicated infections: 400 mg twice daily | Reversible myelosuppression Anemia Neutropenia Thrombocytopenia Diarrhea Headache Nausea and vomiting | Oral formulation is bioequivalent to IV formulation Caution with prolonged use and in patients on selective serotonin reuptake inhibitors (SSRIs) |
| Tedizolid | Bioequivalence between PO and IV formulations 200 mg daily for acute bacterial skin and skin structure infections | Nausea, vomiting, diarrhea Headache Dizziness | |
| Quinupristin/dalfopristin | IV: 7.5 mg/kg q 8-12 h infused over 1 h | Arthralgia Myalgia Infusion-related Nausea, vomiting, diarrhea, rash | Last line agent due to significant toxicities |

is 4 to 6 hours. The pharmacodynamic target predicting efficacy has received much attention and is suggested to be an area under the concentration time curve to MIC (AUC/MIC) ratio of 400.²³

Dosage Regimens and Therapeutic Monitoring

Oral Administration

Oral administration of vancomycin is only for treating *C. difficile* colitis. The dose is 125 to 500 mg orally every 6 hours and is not adjusted for renal dysfunction, owing to the poor absorption. Two oral formulations (capsules or liquid) can be used, or the IV solution can be administered orally to treat *C. difficile*. Table 117-1 lists dosing regimens for the antimicrobials discussed in this chapter.

Intravenous Administration in Adults

In nonobese adults with normal renal function, the usual dose of vancomycin is 1 g (~15 mg/kg actual body weight) every 12 hours. This dose results in peak serum concentrations of 25 to 40 µg/mL 1 hour after completion of the infusion and trough serum concentrations of 5 to 15 µg/mL. Several dosing guidelines have been developed to accurately and easily dose vancomycin. The most popular methods include the Moellering¹⁵ and Matzke¹⁶ nomograms. These methods use body weight and CrCl to calculate vancomycin dose. The weaknesses of these nomograms include the small number of patients used to develop and evaluate the nomogram and the fixed volume of distribution assumed for all patients (0.9 L/kg). The variance in volume of distribution (0.4 to 0.9 L/kg) affects the reproducibility of these nomograms when applied to different patient populations. The Cockcroft

and Gault and modified Cockcroft and Gault methods of estimating CrCl are relatively reliable and accurate methods in patients of normal body mass.²⁴

Dosing in the Setting of Obesity

Morbidly obese patients are difficult to dose given the lack of pharmacokinetic studies. Based on recent investigations, actual body weight and CrCl continue to be the best correlate to volume of distribution and vancomycin clearance in this population.²⁵ Additionally, the best prediction of CrCl estimation in the obese patient is via the Salazar-Corcoran method.²⁶ Young obese patients with no comorbid conditions have 2.3 to 2.5 times higher clearance compared with nonobese patients, thus often requiring a more frequent dosing interval to achieve a trough serum concentration of 5 to 15 µg/mL.^{27,28} On the other hand, there is a significant risk in overdosing older obese patients due to the decline in kidney function with age.²⁹

Dosing in Critically Ill Patients

Determination of appropriate dosing of vancomycin in critically ill patients can be challenging due to alterations in the volume of distribution and renal clearance.^{30,31} Pharmacokinetic parameters can vary widely, as was seen in a prospective, multicenter pharmacokinetic point-prevalence study in critically ill patients receiving contemporary dosing.³² Overall, the median (IQR) vancomycin trough was 17 µg/mL (range, 8-23), and 57.1% of patients achieved a trough greater than or equal to 15 µg/mL. Another pharmacokinetic study involving critically ill patients found that those with severe illness (SOFA score greater than or equal to 11), obesity, and unstable renal function had less

predictable pharmacokinetic modeling.³³ These studies highlight the high interpatient variability of vancomycin pharmacokinetics in critically ill patients and the need for individualized treatment regimens.

Dosing in Renal Failure/Dialysis

The removal of vancomycin during intradialytic administration has been studied using three types of cellulose membranes, with mean removal ranging from 13% with cellulose acetate (CA) up to 24% and 26% with CA high performance 210 (CAHP 210) and cellulose triacetate (CT).³⁴⁻³⁶ High-flux synthetic membranes such as polysulfone or polyacrylonitrile remove significantly more vancomycin than do the cellulose membranes, with 30% to 55% and 25% to 40% of vancomycin removed, respectively.^{34,37-41}

Of the most frequently used methods of continuous renal replacement therapy (CRRT), continuous venovenous hemodialysis (CVVHD) and continuous arteriovenous hemodialysis (CAVHD) result in a greater total body clearance of vancomycin than does continuous venovenous hemofiltration (CVVH). The total clearance of vancomycin with CVVHD or CAVHD is 31 to 39 mL/min, and high-volume hemofiltration (HVHF) increases vancomycin clearance to approximately 60 mL/min.⁴²⁻⁴⁶ Therefore, patients receiving CAVHD or CVVHD should receive vancomycin every 36 to 48 hours, and those undergoing HVHF should receive the drug every 12 to 24 hours.⁴⁷ Dosing in patients receiving extended daily dialysis (EDD), a newer modality combining intermittent hemodialysis and CRRT, is much more challenging given the paucity of data that exists in this arena.⁴⁸ Overall, a review of several pharmacokinetic studies in patients receiving various forms of CRRT showed an association between effluent flow rate and vancomycin clearance. However, these findings require additional validation.⁴⁸ Based on the variability in clearances achieved with each of these methods depending on blood flow rate, ultrafiltration rate, and the membranes used, therapeutic drug monitoring remains an effective method of ensuring appropriate vancomycin dosing when CRRT is used.

Dosing in Cardiopulmonary Bypass/Extracorporeal Membrane Oxygenation

Cardiopulmonary bypass (CPB) was found to significantly affect the pharmacokinetic parameters of vancomycin in several small studies over the past 20 years. For example, Ortega et al. observed an immediate decrease in vancomycin serum concentration by 7 µg/mL after initiation of CPB, followed by gradual and steady decreases over the next 30 minutes.⁴⁹ However, a recent prospective, comparative evaluation of vancomycin pharmacokinetics found no difference in maximum plasma concentration (C_{max}), area under the curve (AUC_{0-8}), V_d , and clearance (Cl) between patients undergoing cardiac surgery with and without CPB.⁵⁰

A study of 11 patients receiving extracorporeal membrane oxygenation (ECMO) and continuous infusion vancomycin found a median volume of distribution and total clearance similar to matched controls, reflecting vancomycin's relative stability in ECMO circuits.⁵¹

Therapeutic Drug Monitoring

Routine monitoring of vancomycin serum concentrations has become a highly debated issue over the years. Those who advocate routine monitoring cite the need to ensure therapeutic concentrations as well as minimize toxicities.

Studies have shown that peak concentrations of vancomycin are not associated with toxicities or clinical efficacy. Therefore, monitoring peak serum concentrations has largely fallen out of favor. On the other hand, vancomycin troughs have been heavily studied for their correlation with efficacy and toxicity. A few recent publications found improved outcomes when targeting vancomycin troughs of 15 to 20 µg/mL.^{52,53} In contrast, it has been suggested that vancomycin troughs of this magnitude (greater than or equal to 15 µg/mL) are associated with an increased risk of nephrotoxicity.⁵⁴ Given the lack of consensus, it may be prudent to measure serum trough concentrations until more definitive studies are conducted to address this issue.⁵⁵

Adverse Effects

Common toxicities that have been associated with vancomycin therapy include red man syndrome, thrombophlebitis, ototoxicity, and nephrotoxicity. Evidence establishing a clear relationship between these toxicities and vancomycin peak or trough concentrations or the incidence of these events is limited and contradictory.^{3,56-58}

Red man syndrome comprises erythema, pruritus, and flushing of the upper torso and is often associated with too rapid an infusion of the drug. In general, the infusion rate should not exceed 1 g/h. Less frequently, hypotension and angioedema can occur. It is thought that increased histamine release is the cause of this syndrome, and the effects can be relieved by antihistamines.^{3,57-61}

Ototoxicity rates range from 0% to 9% in patients receiving vancomycin.^{3,57} The definition of ototoxicity ranges from tinnitus to hearing loss. The evidence demonstrating any relationship between ototoxicity and high peak serum concentrations of vancomycin is limited. Reports have been associated with peak serum concentrations anywhere from 37.5 to 152 µg/mL.^{62,63} A trial comparing once-daily to twice-daily dosing of vancomycin demonstrated more frequent ototoxicity in the twice-daily dosed group (15.6% vs. 3.2%), which had a significantly lower peak concentration and similar trough concentration compared to the group receiving daily doses.⁵⁷ This lack of correlation between serum concentrations of vancomycin and ototoxicity suggests that the observed toxicity was caused by either another drug or the combination of another drug with vancomycin. In the majority of cases, ototoxicity symptoms disappear within a month of discontinuing vancomycin.

The issue of nephrotoxicity associated with vancomycin is complicated by several confounding factors. The original formulation was very impure, and the impurities were associated with toxicities, including nephrotoxicity. In addition, many definitions of nephrotoxicity have been used over the years, different patient populations have been studied, and different doses used, making it difficult to compare one study to another. In general, the rate of nephrotoxicity is 5% to 10% when vancomycin is not administered with other nephrotoxic agents, and trough concentrations are less than 10 µg/mL.^{57,64,65} Elting and colleagues identified older age, Acute Physiology and Chronic Health Evaluation (APACHE) score greater than 40, and duration of therapy of greater than 14 days to be the best predictors of a patient developing nephrotoxicity due to vancomycin therapy.³ A number of other studies have found an increased incidence of nephrotoxicity (21%-35%) when vancomycin serum trough concentrations are greater than 10 µg/mL.⁶⁵⁻⁶⁷ In addition, Lodise demonstrated an increased rate of nephrotoxicity (~35%) when the total daily dose is 4 grams or more compared to total doses less than 4 grams (~11%).⁶⁸ Studies have demonstrated higher rates of nephrotoxicity when vancomycin is used in combination with an aminoglycoside compared with either agent alone.^{65,69,70} Goetz performed a meta-analysis of eight studies and found the incidence of nephrotoxicity associated with combination therapy was 13% greater than with vancomycin alone and 4% greater than with an aminoglycoside alone.⁷⁰

Other toxicities associated with vancomycin include maculopapular or erythematous rashes (2%-8%)^{18,71,72} and anecdotal reports of neutropenia and thrombocytopenia.^{71,73}

TEICOPLANIN

Teicoplanin is a glycopeptide antibiotic and is not approved for use in the United States. It is available for use in Europe, some Asian countries, Mexico, New Zealand, and Australia. It has a more favorable adverse-effect profile than vancomycin; however, there is concern over teicoplanin's clinical efficacy in the treatment of severe gram-positive infections.

Mechanisms of Action and Resistance

Teicoplanin, like other glycopeptide antibiotics, inhibits synthesis of the cell wall by binding to the D-alanyl-D-alanine terminus of cell wall

precursor units. Resistance has been reported in both staphylococci and enterococci. The VanA phenotype confers high-level resistance to both teicoplanin (MIC: 16-512 µg/mL) and vancomycin (MIC: 64- >1000 µg/mL). The VanB phenotype has also been identified in both *E. faecium* and *E. faecalis* and usually confers low-level resistance to vancomycin but not to teicoplanin. This resistance may limit the utility of teicoplanin for some vancomycin-resistant enterococcal infections. Several reports of *S. aureus* resistance developing during therapy with teicoplanin have been reported.⁷⁴⁻⁷⁷ The mechanism of the resistance was determined in one patient to be constitutive and non-plasmid-mediated.⁷⁵ Most phenotypes of hVISA and VISA demonstrate cross-resistance to teicoplanin.⁷⁸

Spectrum of Activity

Teicoplanin is only active against gram-positive organisms. Activity against MSSA and MRSA is comparable to that of vancomycin. Coagulase-negative staphylococci have a varied pattern of susceptibility to teicoplanin. *Staphylococcus haemolyticus* is the most resistant species to teicoplanin (30%).⁷² These isolates are 25% more resistant to teicoplanin than to vancomycin. For methicillin-resistant coagulase-negative staphylococci, 39% of isolates have teicoplanin MICs greater than 8 µg/mL compared with 1% with vancomycin.^{72,79} Teicoplanin is similar in activity to vancomycin against enterococci, although its reliability in treating infections with VanB resistance to vancomycin may be limited. Teicoplanin is active against other aerobic and anaerobic gram-positive organisms such as *Corynebacterium* spp., *Clostridium* spp., including *C. difficile* and *C. perfringens*, *Peptostreptococcus* spp., and *Propionibacterium acnes*.

Pharmacokinetics/Pharmacodynamics

Teicoplanin is administered orally and intravenously. The drug is poorly absorbed after oral administration, and approximately 40% of the drug is excreted unchanged in feces. The pharmacokinetic model that best describes the elimination of teicoplanin is triexponential. IV administration of 400 mg (6 mg/kg) should provide a peak serum concentration of 20 to 50 µg/mL attained 1 hour after administration.⁸⁰ The volume of distribution is large, at 0.9 to 1.41 L/kg, and teicoplanin is 90% to 95% protein bound.⁸⁰ Tissue distribution is variable; most notably, penetration is poor into noninflamed meninges and fat but good into myocardium and pericardium.⁸¹ Teicoplanin is primarily eliminated via glomerular filtration, and only 3% is metabolized.⁸⁰ The half-life is approximately 150 hours in patients with normal renal function.⁸⁰ Because of the long half-life, it takes 14 days to reach steady state. In patients with mild to moderate renal dysfunction, the half-life was found to be 157 to 567 hours.^{81,82}

Dosage Regimens and Therapeutic Monitoring

Despite the long half-life in patients with normal renal function, teicoplanin should be administered daily, and the dose is dependent on the severity of infection. For less serious infections involving the urinary tract, skin, soft tissue, and lower respiratory tract, a loading dose of 400 mg (6 mg/kg) × 1 is administered, followed by a maintenance dose of 200 mg (3 mg/kg) every 24 hours. For severe infections such as septicemia, endocarditis, and osteomyelitis, 400 mg of teicoplanin is administered every 12 hours for 3 doses, followed by 400 mg every 24 hours. This dosage reasonably attains levels within the lower therapeutic range of 10 to 20 mg/L. For specific clinical scenarios such as *S. aureus* endocarditis, levels between 20 and 30 mg/L have been recommended. Therefore, higher doses (up to 12 mg/kg) are suggested.^{80,83}

Dosing in Renal Failure/Dialysis

Teicoplanin is not removed by hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).^{84,85} The amount removed by high-flux membranes such as CVVH, CVVHD, and CVVHDF can be

significant.⁸⁶⁻⁸⁸ For renal dysfunction, several dosing regimens exist, with doses even as high as 600 to 1800 mg/day during CVVH.⁸⁷ Even with such high doses, therapeutic drug monitoring is still recommended, given the variability in protein binding and ultrafiltration rates when using CRRT.

Adverse Effects

Nephrotoxicity associated with teicoplanin is much lower than with vancomycin. The incidence from published and unpublished studies found the nephrotoxic rate to be 4%.⁵⁸ Ototoxic rates with teicoplanin are similar to those with vancomycin.⁵⁸ Hypersensitivity reactions are the most common adverse reaction to teicoplanin (2%-15%).⁵⁸

■ TELAVANCIN

Telavancin was approved in the United States in 2009 for the treatment of complicated skin and skin structure infections and in 2013 for hospital-acquired and ventilator-associated pneumonia.

Mechanisms of Action and Resistance

Telavancin is a lipoglycopeptide derivative of vancomycin that has a dual mechanism of action. It binds to the D-alanyl-D-alanine terminus of the cell wall precursors as does vancomycin but additionally binds to bacterial membranes, resulting in depolarization and increased permeability of the membrane.^{89,90} This dual mode of action, in addition to structural differences, allows for enhanced activity against MRSA and some enterococci.⁹¹ The acquired VanA phenotype in enterococci confers resistance to telavancin. However, susceptibility is retained with the VanB phenotype.⁹² Van-mediated resistance in *S. aureus* leads to reduced telavancin activity but not as great as for vancomycin. In vitro studies have shown a low rate of de novo resistance development in both staphylococci and enterococci, even with previous vancomycin exposure, and currently only one case of elevated telavancin MIC has been reported with clinical use.⁹³⁻⁹⁹

Spectrum of Activity

Telavancin is active against MSSA, MRSA, coagulase-negative staphylococci, vancomycin-susceptible enterococci, *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus anginosus*. Breakpoints for susceptibility after changes in testing methods have been updated to less than or equal to 0.06 µg/mL against the *S. anginosus* group, less than or equal to 0.12 µg/mL for other streptococci and staphylococci, and ≤0.25 µg/mL for enterococci (vancomycin susceptible).^{100,101} No interpretations for defining *intermediate* or *resistant* exist at this time. The MIC₉₀ against both methicillin-susceptible and methicillin-resistant *S. aureus* is 0.06 µg/mL, and despite higher MICs, telavancin does have activity against vancomycin-intermediate and vancomycin-resistant strains (MIC ranges of 0.03-0.25 µg/mL, 0.06-0.5 µg/mL, and 0.25-8 µg/mL against hVISA, VISA, and VRSA, respectively).¹⁰²⁻¹⁰⁷ Against *Enterococcus* spp., telavancin is slightly less potent, and greater activity is seen against vancomycin-resistant strains with VanB over those with VanA.^{92,102-107} Telavancin is active against most anaerobic gram-positive organisms including *C. difficile* and *C. perfringens*.¹⁰⁸

Pharmacokinetics/Pharmacodynamics

Telavancin is administered IV and demonstrates linear pharmacokinetics over doses of 7.5 to 15 mg/kg. In healthy subjects, doses of 7.5 and 15 mg/kg at steady state resulted in mean C_{max} serum concentrations of 88 and 186 µg/mL and trough concentrations of 6 and 16 µg/mL, respectively.¹⁰⁹ Approximately 70% of telavancin is renally eliminated, and the half-life was dose dependent and ranged from 6 to 7.5 hours.¹⁰⁹ Telavancin is 90% protein bound to albumin and has a volume of distribution of approximately 0.14 L/kg.¹⁰⁰ Telavancin

penetrates lung epithelial lining fluid and alveolar macrophages well, and concentrations exceeded 0.5 µg/mL during the entire dosing interval.¹¹⁰ Penetration into blister fluid is approximately 40% of serum concentrations but only 1% to 2% into inflamed meninges.^{111,112}

Telavancin exhibits rapid concentration-dependent killing. The pharmacodynamic parameter identified in animal models as the best predictor of efficacy is the AUC/MIC ratio, with a target of 219 resulting in optimal killing.^{113,114}

Dosage Regimens and Therapeutic Monitoring

For both complicated skin and skin-structure infections and hospital-acquired/ventilator-associated pneumonia, telavancin is dosed 10 mg/kg IV every 24 hours when CrCl is over 50 mL/min.

Dosing in Renal Failure/Dialysis

Because of the high urinary elimination of telavancin, dosage reductions are required when the patient's CrCl falls below 50 mL/min. If CrCl is 30 to 50 mL/min, the dose of telavancin is 7.5 mg/kg every 24 hours; when less than 30 mL/min, the dose is further reduced to 10 mg/kg every 48 hours.^{100,114} Hemodialysis does not have a significant impact on telavancin removal.¹¹⁵ In vitro studies evaluated the effect of CRRT on telavancin elimination and found high ultrafiltrate or dialysate rates can remove a significant amount of telavancin, which could require supplemental dosing.¹¹⁶

Dosing in the Setting of Obesity

A linear relationship is seen between body weight and clearance, thus supporting the milligram per kilogram dosing strategy; however, further investigation is warranted given the potential overestimation of CrCl using total body weight.^{117,118}

Adverse Effects

Telavancin is a pregnancy category C drug with little information available in pregnant women. In three animal species, telavancin was found to have fetal effects including decreased birth weight and increased digit and limb malformations. A serum pregnancy test should be performed in women of childbearing age before starting telavancin. A pregnancy exposure registry is available should there be a need to use telavancin in a pregnant woman.¹⁰⁰

The most common adverse effects associated with telavancin are nausea, vomiting, diarrhea, taste disturbance, foamy urine, and renal impairment.^{100,119-122} An increase in mortality was seen in patients with moderate to severe renal dysfunction treated with telavancin for HABP/VABP.¹²² Telavancin interferes with urine protein qualitative dipstick tests, and several anticoagulation tests including PT, APTT, INR, ACT, and factor X activity assays.¹⁰⁰ For this reason, concomitant use with unfractionated heparin is contraindicated.^{100,123a} When measuring anticoagulation, these tests should be performed as close as possible prior to a patient's next dose or alternative monitoring methods considered.¹⁰⁰

DAPTOMYCIN

Daptomycin is a lipopeptide that was first discovered in the 1980s and was approved in 2003 by the FDA for complicated skin and skin structure infections and in 2006 for *S. aureus* bloodstream infections, including right-sided endocarditis.

Mechanisms of Action and Resistance

Daptomycin has a unique mechanism of action and has been found to inhibit lipoteichoic acid synthesis by binding to the membrane in the presence of calcium.^{124,125} To date, there have been several case series and case reports describing daptomycin resistance in patients with *S. aureus*.¹²⁶ The mechanism appears to be multifactorial, with cell wall changes being largely implicated. Development of resistance

in enterococcus has been observed as well.¹²⁷ However, in contrast to *S. aureus*, genetic pathways appear to be the key alterations explaining this phenomenon. Clinically, the development of resistance has led to treatment failures and the need for salvage therapy.

Spectrum of Activity

Daptomycin's antibacterial activity encompasses most gram-positive bacteria, including vancomycin-resistant isolates and penicillin-resistant pneumococci. The MICs of daptomycin are 8- to 16-fold lower in the presence of calcium. Therefore, all in vitro testing must be supplemented with physiologic concentrations of calcium.¹²⁸ The breakpoint for susceptibility is less than or equal to 1 µg/mL for staphylococci and β-hemolytic streptococci. Given the rare number of isolates not susceptible to daptomycin, a resistant breakpoint has yet to be determined. The MIC90 against MSSA, MRSA, *Staphylococcus epidermidis*, and *Staphylococcus saprophyticus* are all 0.5 µg/mL or less.^{128,129} In a recent surveillance study, 53 *S. aureus* and 41 coagulase-negative staphylococci were nonsusceptible to daptomycin.¹³⁰ Daptomycin initially appeared active against vancomycin-intermediate and vancomycin-resistant strains of *S. aureus*. However, a recent analysis of 33 VISA isolates found 70% resistance to daptomycin.¹³¹⁻¹³³ Interestingly, 100% of VRSA isolates were susceptible, possibly due to the difference in resistance mechanisms. The breakpoint for susceptibility against enterococci is less than or equal to 4 µg/mL, and again no resistant breakpoint has been established. Against *E. faecalis* and *E. faecium*, including vancomycin-resistant strains, the MIC90 is 2 µg/mL or less.^{128,129} Daptomycin resistance is higher among *E. faecium* than *E. faecalis*.¹³⁰ The MIC90 is 0.25 µg/mL against *S. pneumoniae* and β-hemolytic streptococci, and resistance has not been reported with these organisms.^{128,129}

Pharmacokinetics/Pharmacodynamics

Healthy volunteers who received 6 mg/kg of daptomycin given as either a 30- or 2-minute infusion achieved bioequivalent pharmacokinetic results. The C_{max} was about 94 and 88 µg/mL for the 2- and 30-minute infusions, respectively.¹³⁴ Daptomycin demonstrates linear kinetics at dosing from 4 to 12 mg/kg, and the half-life is 7 to 9 hours in patients with normal renal function.¹³⁵ The drug is 90% to 95% protein bound and is primarily eliminated by the renal route. In patients with CrCl less than 30 mL/min, end-stage renal disease/hemodialysis/peritoneal dialysis, a 4 mg/kg dose should provide peak serum concentrations around 25 to 30 µg/mL and half-life of about 30 hours.¹³⁵

Daptomycin is rapidly bactericidal and exhibits concentration-dependent killing against gram-positive organisms including enterococci.^{124,125} Daptomycin also exhibits a postantibiotic effect that allows for once-daily dosing.¹³⁶

Dosage Regimens and Therapeutic Monitoring

For complicated skin and skin-structure infections (cSSSIs), dosing of daptomycin is 4 mg/kg every 24 hours. Dosing for bacteremia or right-sided endocarditis is 6 mg/kg every 24 hours.¹³⁵ Limited clinical evidence suggests consideration of higher doses (8-12 mg/kg) in specific scenarios such as MRSA bacteremia after vancomycin failure and deep-seated enterococcal infections.

Dosing in Renal Failure/Dialysis

In patients with CrCl less than 30 mL/min or undergoing hemodialysis or chronic peritoneal dialysis, the dose should be reduced to 4 mg/kg every 48 hours and 6 mg/kg every 48 hours for bacteremia or endocarditis.¹³⁵ In patients undergoing continuous renal replacement therapy (CRRT), the amount of daptomycin removed is dependent upon the type of filter and the flow rates.¹³⁷ Dosing recommendations for patients undergoing CRRT are 4 to 6 mg/kg every 48 hours, and there is some speculation that doses may need to be increased to 8 to 10 mg/kg every 48 hours or 4 to 6 mg/kg every 24 hours.¹³⁸⁻¹⁴³ Similarly,

a dose of 6 mg/kg every 24 hours has been proposed for patients receiving extended daily dialysis (EDD).¹⁴⁴

Dosing in the Setting of Obesity

Two single-dose studies using 4 mg/kg total body weight have been performed in moderately and morbidly obese patients. The C_{\max} was increased 25% to 60% compared to normal-weight patients, and the area under the curve (AUC) increased 30% to 60% in the obese patients.^{145,146} Based on this, recommendations have been to base daptomycin dosage on total body weight. However, a subset analysis of patients receiving daptomycin 6 mg/kg for bacteremia and endocarditis found that patients over 111 kg were more at risk for creatinine phosphokinase (CPK) elevations.¹⁴⁷ Despite this, there is currently insufficient evidence to routinely use other weight measurements, such as ideal body weight or adjusted body weight, when determining daptomycin dosage.

Dosing in Burn Patients

One study evaluated single-dose pharmacokinetics (4 mg/kg) in burn patients and found the C_{\max} was 44% lower, with 47% lower AUC and an increase in volume of distribution and clearance.¹⁴⁸ The authors suggest a dose of 10 to 12 mg/kg in burn patients should provide the same drug exposure as 6 mg/kg in healthy volunteers.

Adverse Effects

Creatine phosphokinase (CPK) concentrations increased in 2.8% of patients treated with daptomycin in the cSSSI studies, and 9.2% in the bacteremia/endocarditis trial.^{125,135} Elevations in CPK can occur 2 to 3 days before clinical signs or symptoms of myopathy present.¹³⁶

LINEZOLID

Linezolid was approved in 2000 by the FDA for several indications involving susceptible gram-positive organisms, including skin and skin structure infections, community-acquired and nosocomial pneumonia, and vancomycin-resistant *Enterococcus faecium* infections (including those with concomitant bacteremia).

Mechanisms of Action and Resistance

Linezolid is an oxazolidinone antibiotic, a new class of synthetic agents. Linezolid binds to the 50S ribosome and inhibits the binding of mRNA, thereby preventing protein synthesis.¹⁴⁹ Clinical isolates of *S. aureus*, *E. faecium*, and *E. faecalis* resistant to linezolid have been identified but rates are low (<1.0%) and have remained relatively stable over the past decade.¹⁵⁰ The most common mechanism of resistance is alteration of the 23S rRNA.¹⁵¹ A second mechanism of resistance involves acquisition of the natural resistance gene, *cfr*, and has been increasing in linezolid nonsusceptible isolates in recent years.^{150,152,153} This finding is worrisome because the *cfr* gene confers resistance to other antimicrobial classes, including chloramphenicol and clindamycin. Additionally, this gene may become transmissible, and the first human acquisition of a clinical isolate with this gene on a transferable plasmid was described in 2012.¹⁵⁴ These resistance issues, although rare, do raise concern and emphasize the importance of appropriate use of linezolid.

Spectrum of Activity

The breakpoint for susceptibility to linezolid is less than or equal to 4 µg/mL for staphylococci and less than or equal to 2 µg/mL for enterococci and streptococci. It is active against both methicillin-susceptible and methicillin-resistant staphylococci. The MIC₉₀ against *S. aureus* and coagulase-negative staphylococci is 1 and 0.5 µg/mL, respectively.¹⁵⁰ Against vancomycin-intermediate and vancomycin-resistant *S. aureus*, the drug is active with MIC₉₀ of 4 and 2 µg/mL, respectively.^{123b,123c} Linezolid is equally active against both vancomycin-susceptible and

vancomycin-resistant enterococci, with an MIC₉₀ of 1 µg/mL.¹⁵⁶⁻¹⁵⁹ Against both penicillin-susceptible and penicillin-resistant *S. pneumoniae*, the MIC₉₀ is 1 µg/mL.^{150,156,157} Linezolid is also active against a variety of other organisms, including *Pasteurella multocida*, *Peptostreptococcus* spp., *Fusobacterium* spp., and *Prevotella* spp.

Pharmacokinetics/Pharmacodynamics

Linezolid is available in both oral and IV formulations. Oral absorption is over 90%, making the oral formulation bioequivalent to the IV formulation. The peak serum concentration and half-life at steady state after 600 mg twice daily is 14 to 18 µg/mL and 5 to 6 hours.¹⁶⁰⁻¹⁶² Linezolid is approximately 30% protein bound and penetrates quickly into bone, fat, and muscle, achieving 50% to 60% of serum concentrations in bone and 90% to 95% in muscle.¹⁶³ Cerebrospinal penetration has been documented in patients with meningitis at a fluid/plasma ratio around 1.¹⁶⁴⁻¹⁶⁷ Elimination of linezolid is 30% renal and 70% metabolized, with essentially no linezolid eliminated in feces as unchanged drug.¹⁶² Linezolid is not an inducer of the cytochrome P450 enzyme system.

Linezolid is bacteriostatic against staphylococci and enterococci and is bactericidal against streptococci. It appears that the pharmacodynamic parameter that best models the killing activity is the AUC/MIC ratio.¹⁶⁸ The AUC/MIC ratio required to produce a bacteriostatic effect varied from 22 to 97 (mean 48) for pneumococci and 39 to 167 (mean 83) for staphylococci. A dosage regimen of 600 mg twice daily achieves these values for organisms with MICs as high as 4 µg/mL.

Dosage Regimens and Therapeutic Monitoring

The usual dose of linezolid is 600 mg twice daily, and for uncomplicated skin and skin structure infections, the dose is 400 mg twice daily.

Dosing in Critically Ill Patients

A handful of studies have evaluated the pharmacokinetics of linezolid in critically ill patients.¹⁶⁹⁻¹⁷² Most recently, Zoller and colleagues found significant variability in linezolid serum concentrations in those receiving standard dosing, with 63% of their critically ill patients achieving insufficient levels based on an AUC₂₄/MIC₉₀ target of 100.¹⁷³ To improve drug delivery, a few studies utilizing continuous infusion have been performed and did demonstrate higher rates of target attainment.^{169,172} Thus, continuous infusion, in conjunction with therapeutic drug monitoring, may provide an option for optimizing the pharmacodynamic parameters, but further studies are needed to assess the efficacy and safety of these strategies.

Dosing in Renal Failure/Dialysis

Hemodialysis removes approximately 30% of linezolid during a 3- to 4-hour session, and limited data exist on peritoneal dialysis removal. However, no dosage adjustment is needed in patients with renal dysfunction or end-stage renal disease. During different modalities of CRRT, linezolid removal is variable and has the potential to lead to subtherapeutic levels; however, further studies are warranted to determine the true impact that RRT has on linezolid pharmacokinetics.¹⁷⁴

Dosing in Burn Patients

In a small study of severe burn patients, the volume of distribution and renal clearance were similar to healthy controls; however, total clearance was higher, likely the result of increased nonrenal clearance in those with thermal injuries (323 + 191 vs. 80.4 + 27.5 mL/min, $P = 0.063$).¹⁷⁵

Adverse Effects

Reversible myelosuppression is the most significant adverse effect associated with linezolid therapy. Anemia, neutropenia, and thrombocytopenia have all been reported, and the incidence increases with

durations of therapy exceeding 14 days.^{176,177} The decrease in hemoglobin when linezolid therapy is greater than 2 weeks is 18% compared with 13% for comparator agents and linezolid therapy less than 2 weeks' duration.¹⁷⁶ The thrombocytopenia rate is 8%, with the longer duration of therapy compared with 5% to 6% in all durations of therapy compared with 3% with comparator agents. Rates of neutropenia also increase to about 10% with extended durations of therapy. Complete blood cell counts should be monitored weekly, especially in patients in whom the duration of therapy is likely to exceed 2 weeks.

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase; therefore, the potential for interaction with adrenergic and serotonergic agents exists. Several case reports of serotonin syndrome (fever, agitation, tremors, and mental status changes) secondary to an interaction between linezolid and selective serotonin reuptake inhibitors (SSRIs) have been identified.¹⁷⁸

Serious reactions, including optic or peripheral neuropathy, have been increasingly reported and are generally seen after longer durations of linezolid therapy.¹⁷⁸ Optic neuropathy tends to be reversible upon discontinuation of linezolid, but peripheral neuropathy tends to be permanent.¹⁷⁸ The mechanism underlying this neuropathy is thought to involve the inhibition of mitochondrial protein synthesis.^{178,179} Lactic acidosis, another potentially fatal effect, is also thought to be caused by prolonged therapy and mitochondrial disruption.¹⁸⁰

Other adverse reactions to linezolid include diarrhea (8%), headache (7%), nausea and vomiting (6% and 4%), dizziness, rash, fever, constipation (2%), and abnormal liver function tests (1%).

TEDIZOLID

FDA-approved in 2014, tedizolid is currently indicated only for the treatment of acute bacterial skin and skin-structure infections (ABSSSIs). This new definition of skin and skin-structure infection is based on the 2013 FDA Guidance for Industry, which seeks to assist clinical development of drugs for this specific indication.

Mechanisms of Action and Resistance

Tedizolid phosphate, the prodrug of the active moiety tedizolid, is a second-generation oxazolidinone. It acts via a mechanism similar to linezolid in preventing protein synthesis by binding to the 50S ribosome.¹⁸¹ Owing to the incorporation of a D-ring substituent and a hydroxymethyl group, however, tedizolid exhibits 4- to 8-fold greater potency against staphylococcal, streptococcal, and enterococcal isolates.^{182,183} These structural changes are also responsible for tedizolid's ability to maintain activity against some oxazolidinone-resistant organisms. Specifically, tedizolid was shown to have MIC values between 0.5 and 1 mg/L against MRSA possessing the *cfr* gene, compared to a 4- to 8-fold elevation in MIC seen with linezolid.^{184,185} Cross-resistance to tedizolid can occur, however, and is likely mediated by a combination of alterations in 23S rRNA or ribosomal proteins L3 and L4.^{185,186} Overall, the spontaneous development of resistance to tedizolid is low.¹⁸⁷

Spectrum of Activity

The breakpoint for susceptibility to tedizolid is less than or equal to 0.25 µg/mL for streptococci in the *Streptococcus anginosus* group and less than or equal to 0.5 µg/mL for other streptococci, enterococci, and staphylococci (including both methicillin-resistant and methicillin-susceptible isolates). The MIC₉₀ against *S. aureus*, and coagulase-negative staphylococci is 0.5 µg/mL.¹⁸⁸ Against hVISA, VISA and daptomycin-nonsusceptible (DNS) *S. aureus*, tedizolid demonstrates activity with an MIC₉₀ value of 0.5 µg/mL against all pathogens.¹⁸⁹ Higher MICs were seen when tedizolid was tested against linezolid-resistant isolates of *S. aureus* (range 1 to 8 µg/mL), albeit much lower than the MICs to linezolid (range, 8-64 µg/mL).¹⁹⁰ Tedizolid is equally active against both vancomycin-susceptible and vancomycin-resistant enterococci with an MIC₉₀ of 0.5 µg/mL, and against

linezolid-resistant enterococci, the MIC ranged from 1 to 4 µg/mL.^{188,190} Tedizolid exhibited similar potency against penicillin-susceptible and penicillin-resistant *S. pneumoniae* with an MIC₉₀ of 0.25 µg/mL.¹⁸⁸

Pharmacokinetics/Pharmacodynamics

Tedizolid is available in both oral and IV formulations as tedizolid phosphate, a prodrug that is rapidly converted by serum phosphatases to the active tedizolid compound. Oral absorption is approximately 90%.^{191,192} The mean maximum plasma concentration ranged from 1.8 to 2.4 µg/mL at 2 to 3 hours after oral administration, with a mean half-life of approximately 11 hours.¹⁹¹ Tedizolid is 90% protein bound and is widely distributed into soft tissues ($V_d = 108$ L), including significant accumulation in epithelial lining fluid (ELF).^{193,194} Elimination of tedizolid is 20% renal and 80% via the liver as an inactive sulfate conjugate.^{195,196} Tedizolid has low affinity for cytochrome P450 enzymes, and weak, reversible inhibition of MAO was seen in vitro.^{181,197} Clinically, however, this did not translate into a significant increase in head twitch response in a 5-hydroxytryptophan murine head twitch model, in contrast to linezolid, which did.

Tedizolid is bacteriostatic and early models suggest that the free AUC to MIC ratio ($fAUC/MIC$) is the pharmacodynamic parameter most reflective of tedizolid killing of staphylococci.^{198,199} The AUC/MIC ratio required to produce bacteriostasis and a 1 log₁₀ reduction in CFU in neutropenic models was 20 and 35, respectively. A 25-fold increase in activity is seen in the presence of granulocytes; therefore, a 200-mg once-daily regimen effectively achieves target attainment against *S. aureus* with MIC less than or equal to 0.5 µg/mL.²⁰⁰⁻²⁰²

Dosage Regimens and Therapeutic Monitoring

The usual dose of tedizolid is 200 mg once daily for the treatment of acute bacterial skin and skin-structure infections (ABSSSIs). This FDA approval is based on one phase II and two phase III clinical trials that evaluated the efficacy and safety of tedizolid.²⁰²⁻²⁰⁴ At this time, there have been no completed studies exclusively in critically ill patients. However, a phase III study is currently ongoing comparing tedizolid versus linezolid for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilated nosocomial pneumonia (VNP).²⁰⁵

Study of patients with extensive renal (estimated glomerular filtration rate <30 mL/min/1.73 m²) and hepatic impairment (Child Pugh 7-9 and Child Pugh 10-15) suggest that no adjustment of tedizolid dosage is required for these populations, as their pharmacokinetics were not significantly altered versus healthy controls.¹⁹⁶ Additionally, hemodialysis does not influence the pharmacokinetics of tedizolid, nor does it significantly remove the drug.¹⁹⁶

Adverse Effects

The potential for myelosuppression, similar to that observed with linezolid, exists with tedizolid and was studied in healthy adults receiving 200 to 400 mg of tedizolid daily for 21 days.²⁰⁶ Significant hematologic changes were not observed at any point in those receiving 200 mg daily; however, changes were seen between days 8 and 21 in those receiving 400 mg daily. In phase II studies of shorter durations (5 to 7 days), hematologic parameters remained stable.²⁰⁷ A pooled analysis of two phase III trials in patients receiving tedizolid for ABSSSI found a lower incidence of thrombocytopenia (platelet count <150,000 cells/mm³) compared to those receiving linezolid (3.2% vs. 5.6%, day 7-9 visit).²⁰⁸ These results suggest that tedizolid may have less harmful hematologic effects than linezolid.

Monoamine oxidase inhibition by tedizolid was also evaluated in human and animal studies. No significant rise in blood pressure was seen with pseudoephedrine or tyramine administration in either rats or humans, nor was there a significant increase in serotonergic response in mice.^{197,209,210} Despite these findings, the true impact of this interaction remains to be seen as more widespread use of tedizolid takes place.

The potential for neurotoxicity was evaluated in rats receiving tedizolid for up to 9 months. No evidence of neuropathy was found, even at exposures sixfold higher than those used in humans.²¹¹ Similarly, no reports of optic or peripheral neuropathy were seen after a 10-day course of tedizolid in healthy adults.²¹²

Overall, the most common adverse reactions seen with tedizolid include nausea (8%), headache (6%), diarrhea (4%), vomiting (3%), and dizziness (2%).¹⁸¹

■ QUINUPRISTIN/DALFOPRISTIN

Mechanisms of Action and Resistance

Quinupristin/dalfopristin is a streptogramin antibiotic and is a mix of two different streptogramin components from groups A and B. The individual components are bacteriostatic, but the combination is often bactericidal. Each component binds to different sites on the 50S subunit of the ribosome, inhibiting translation of mRNA at the elongation step.²¹³ The resulting complex of drug and ribosome inhibits protein synthesis.

Streptogramins share similar sites of action with macrolide and lincomycin antibiotics. As a result, mechanisms of resistance are also shared. The most common type of resistance to streptogramins involves the erythromycin resistance methylase (*erm*) genes, termed *MLS_B*.²¹⁴ These genes decrease the binding of antibiotics such as streptogramins group B, erythromycin, and clindamycin by dimethylating a residue on the 23S ribosome. Group A streptogramins are not affected, and the combination often retains its synergistic activity.²¹⁴ Enzymatic modification of both components is another mechanism of resistance to the drug.^{215,216} The third mechanism involves efflux pumps: one that pumps out both macrolides and streptogramins and one specific for streptogramins.^{215,217,218}

Spectrum of Activity

Quinupristin/dalfopristin is active against a wide variety of gram-positive organisms as well as many anaerobes and oral flora organisms. An MIC of 2 µg/mL or less indicates susceptibility. The MIC₉₀ of most MSSA, MRSA, and coagulase-negative staphylococci is 1 to 2 µg/mL.^{129,219} Against vancomycin-intermediate and vancomycin-resistant *S. aureus*, the drug is active with MICs of 0.25 to 1 µg/mL.^{132,220} Both vancomycin-susceptible and vancomycin-resistant *E. faecium* are susceptible to quinupristin/dalfopristin (MIC₉₀: 1–4 µg/mL); however, *E. faecalis* is resistant to quinupristin/dalfopristin (MIC₉₀: 4–32 µg/mL).^{219–221} Against a variety of streptococcal organisms, including penicillin-resistant pneumococci, the MIC₉₀ ranges from 0.5 to 2 µg/

mL. Quinupristin/dalfopristin is also active against a variety of other organisms including *Chlamydia* spp., *Mycoplasma pneumoniae*, *Legionella* spp., *Peptostreptococcus* spp., *Fusobacterium* spp., *Prevotella* spp., *Actinomyces* spp., and *Clostridium* spp.

Pharmacokinetics/Pharmacodynamics

Quinupristin/dalfopristin infusions should be administered over 1 hour, and the drug is incompatible with saline. In healthy volunteers and in patients undergoing CAPD, the mean peak serum concentration of quinupristin was 2.6 and 2.9 µg/mL, respectively, and for dalfopristin it was 7.1 and 8.5 µg/mL, respectively, following a single 7.5-mg/kg dose.²²² Quinupristin/dalfopristin is hepatically metabolized to several active metabolites, and both the parent components and the metabolites are primarily eliminated via bile into feces.²²³ Urinary excretion of quinupristin/dalfopristin and metabolites is 15% to 19%. The mean half-life ranges from 1.2 to 1.5 hours. The drug is 90% protein bound.²²⁴

Quinupristin/dalfopristin is bactericidal against staphylococci and streptococci, but it is bacteriostatic against *E. faecium*. The pharmacodynamic parameters that best predict efficacy have not been well characterized.

Dosage Regimens and Therapeutic Monitoring

The normal dose of quinupristin/dalfopristin is 7.5 mg/kg every 8 to 12 hours and infused over 1 hour. Dosage reduction is likely required in patients with severe liver dysfunction, although specific recommendations are not available.

Dosing in Renal Failure/Dialysis

Neither hemodialysis nor peritoneal dialysis removes any appreciable amount of quinupristin/dalfopristin.^{222,225} Penetration into the peritoneal cavity is negligible in CAPD patients. No dosage adjustment is needed in patients with renal insufficiency or on dialysis.

Adverse Effects

Myalgias (6%–7%) and arthralgias (9%–9.5%) are the most severe adverse effects and are often the reason for discontinuation of the drug.^{226,227} Elevations in direct and conjugated bilirubin and γ-glutamyl transferase are common. Infusion-related adverse effects occur in 30% to 45% of patients with peripheral lines used for the infusion.²²⁶ The reactions include pain, burning, inflammation, and thrombophlebitis. Other toxicities include nausea, diarrhea, vomiting, and rash.

KEY POINTS

Vancomycin

1. Vancomycin is bactericidal against most gram-positive organisms. Vancomycin resistance of the VanA phenotype confers high-level resistance to both teicoplanin and vancomycin. Resistance is relatively common within *Enterococcus*. In 2002, this resistance gene was passed to two different *Staphylococcus aureus* isolates and for the first time conferred high-level resistance to vancomycin within the *Staphylococcus* genus.
2. The pharmacodynamic effect of vancomycin is time-dependent killing or time above the minimum inhibitory concentration (MIC). There is no documented correlation between serum peak concentrations and clinical outcomes, whereas vancomycin troughs have been heavily studied.

3. Ototoxicity rates range from 0% to 9%, and these numbers have not changed from initial studies conducted in the 1960s through studies conducted in the 2000s. There is no correlation between serum concentration and ototoxicity. The rate of nephrotoxicity when vancomycin is not administered with other nephrotoxic agents or when trough concentrations are less than 10 µg/mL is 5% to 10%. Trough concentrations of more than 10 µg/mL result in nephrotoxicity rates of 20% to 35%.

Teicoplanin

1. Teicoplanin is a glycopeptide antibiotic with similar activity to vancomycin, approved in several countries outside the United States. There is concern over teicoplanin's clinical efficacy in

KEY POINTS—cont'd

severe gram-positive infections compared to vancomycin, despite a more favorable side-effect profile.

Telavancin

1. Telavancin was approved by the FDA in September 2009 for treating complicated skin and skin-structure infections and 2013 for hospital-acquired and ventilator-associated pneumonia. The drug is categorized as pregnancy category C; however, teratogenicity in animals has been observed (digit and limb malformation and decreased birth weight).
2. Telavancin interferes with anticoagulation tests including INR, PT, APTT, and ACT, and therefore use with unfractionated heparin is contraindicated. These tests should be performed when telavancin concentrations are lowest in the blood.

Daptomycin

1. Approved for bacteremia, right-sided endocarditis, and complicated skin and skin-structure infections. It is contraindicated for lung infections, as surfactant breaks down the drug. Creatine phosphokinase concentrations increase 2 to 3 days before clinical manifestation of symptoms and are derived 100% from the MM isoenzyme.

Linezolid

1. Oral absorption is over 90%, making the oral drug bioequivalent to the intravenous formulation. Linezolid is bacteriostatic against staphylococci and enterococci.

2. Reversible myelosuppression is the most significant adverse effect associated with linezolid therapy. Anemia, neutropenia, and thrombocytopenia have all been reported, and the incidence of these complications increases with duration of therapy exceeding 14 days.
3. Linezolid is a reversible nonselective inhibitor of monoamine oxidase; therefore, the potential for interaction with adrenergic and serotonergic agents exists. Case reports of serotonin syndrome secondary to an interaction between linezolid and selective serotonin reuptake inhibitors have been reported.

Tedizolid

1. Tedizolid is a second-generation oxazolidinone approved for treatment of acute bacterial skin and skin structure infections. Tedizolid is thought to have a lower potential for myelosuppression, neurotoxicity, and monoamine oxidase inhibition compared with its predecessor linezolid; however, the impact of these factors remains to be seen with further clinical use.

Quinupristin/Dalfopristin

1. This drug is active against vancomycin-resistant *Enterococcus faecium*, methicillin-resistant *S. aureus*, vancomycin-intermediate *S. aureus*, and vancomycin-resistant *S. aureus*. It has no activity against *Enterococcus faecalis*. Myalgias (6%-7%) and arthralgias (9%-9.5%) are the most severe adverse effects and are reasons for discontinuation of the drug.

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A small pharmacokinetic study performed in two different healthy adult populations was conducted to assess the pharmacokinetics and safety of rapid bolus administration of daptomycin. The 2-minute infusion was bioequivalent to the standard 30-minute infusion with regard to C_{max} and AUC. The 2-minute infusion was well tolerated.

Gotfried MH, Shaw JP, Benton BM, Krause KM, Goldberg MR, Kitt MM, et al. Intrapulmonary distribution of intravenous telavancin in healthy subjects and effect of pulmonary surfactant on in vitro activities of telavancin and other antibiotics. *Antimicrob Agents Chemother* 2008;52:92-97.

Small study in healthy volunteers evaluating the penetration of telavancin into ELF and alveolar macrophages. Over the entire dosing interval, concentrations in the ELF and macrophages was greater than 0.5 µg/mL. Telavancin is stable in the presence of pulmonary surfactant.

Zhan G, Love R, Adam H, et al. Tedizolid: a novel oxazolidinone with potent activity against multidrug-resistant gram-positive pathogens. *Drugs* 2015;75:253-270.

Comprehensive review of chemical structure, mechanism of action and resistance, and efficacy and safety profile based on studies leading to the approval of tedizolid.

References for this chapter can be found at expertconsult.com.

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Infections caused by anaerobic bacteria are common and may be serious and life-threatening. Anaerobes are predominant components of the bacterial flora of the normal human skin and mucous membranes¹ and are a common cause of endogenous bacterial infections. Because of their fastidious nature, they are difficult to isolate and are often overlooked. Their isolation requires appropriate methods of collection, transportation, and cultivation.²⁻⁵ Treatment of anaerobic bacterial infections is complicated by the relatively slow growth of these organisms, frequent polymicrobial nature, and growing resistance to antimicrobials.

Antimicrobial resistance among anaerobes has increased in the past three decades, and their susceptibility has become less predictable.⁶⁻¹³ The most commonly isolated antibiotic-resistant anaerobes are those that belong to the *Bacteroides fragilis* group.¹⁴ This increase makes the choice of appropriate empiric therapy more difficult. Resistance patterns have been monitored through national and local surveys, but susceptibility testing of anaerobic bacteria at individual hospitals is rarely done.¹⁰ This chapter describes the antimicrobials effective against anaerobic bacteria and the resistance of these organisms against them.

ANTIMICROBIAL AGENTS EFFECTIVE AGAINST ANAEROBIC BACTERIA

Table 118-1 illustrates the antimicrobials effective against anaerobic bacteria and their efficacy against both aerobic and anaerobic bacteria. Table 118-2 illustrates the resistance of bacteria from the *B. fragilis* group and other anaerobes to antimicrobials.

Beta-Lactam Antibiotics

Penicillin G is the classical drug of choice when the infecting strains are susceptible. Most *Clostridium* strains (except some *Clostridium ramosum*, *C. clostridioforme*, and *C. innocuum*) and *Peptostreptococcus* spp. remain susceptible to penicillin. Most *B. fragilis* groups are resistant to penicillin. Other strains that may show resistance are growing numbers of anaerobic gram-negative bacilli (AGNB), such as pigmented *Prevotella* and *Porphyromonas* spp., *Prevotella oralis*, *P. bivia*, *B. disiens*, strains of *Clostridia*, *Fusobacterium* spp. (*Fusobacterium varium* and *Fusobacterium mortiferum*), and microaerophilic streptococci. Some of these strains show minimum inhibitory concentration (MIC) of 8 to 32 units/mL of penicillin G. In these instances, administration of very high dosages of penicillin G (for non-beta-lactamase producers) may eradicate the infection.

Ampicillin, **amoxicillin**, and penicillin are generally equal in activity to penicillin G, but the semisynthetic penicillins are less active. **Methicillin**, **nafcillin**, and the isoxazolyl penicillins (**oxacillin**, **cloxacillin**, and **dicloxacillin**) are ineffective against the *B. fragilis* group, have unpredictable activity, and are frequently inferior to penicillin G against anaerobes.¹⁵

Penicillin and ampicillin/amoxicillin are of limited utility due to the production of beta-lactamases by many oral and most intra-abdominal anaerobes. Clavulanate, sulbactam, and tazobactam irreversibly inhibit beta-lactamase enzymes produced by beta-lactamase-producing *Fusobacterium* spp. and AGNB.¹⁵⁻¹⁷ When used in combination with a beta-lactam antibiotic (e.g., **ampicillin-sulbactam**, **amoxicillin-**

clavulanate, and **piperacillin-tazobactam**), they are effective in treating anaerobic infections caused by beta-lactamase-producing bacteria (BLPB).

Beta-lactam/beta-lactamase inhibitor combinations (BL-BLICs) are appropriate choices for mixed aerobic-anaerobic infections. They have maintained good activity against most anaerobes. While 89% of *B. fragilis* are susceptible to ampicillin-sulbactam, 98% are susceptible to piperacillin-tazobactam⁸ compared to 86% and 92%, respectively, for *B. thetaiotaomicron* isolates. Recently, the Infectious Diseases Society of America (IDSA) removed ampicillin-sulbactam from the recommended list of drugs for intra-abdominal infections due to increased *Escherichia coli* resistance.¹⁸ Amoxicillin-clavulanate remains the agent of choice for human and animal bite wound infections,¹⁹ especially when anaerobes may be involved. Piperacillin-tazobactam is also a frequently and appropriately prescribed agent for serious intra-abdominal infections. It has also maintained good activity against most anaerobes.⁸

The semisynthetic penicillins, the carboxy-penicillins (**carbenicillin** and **ticarcillin**), and ureidopenicillins (**piperacillin**, **azlocillin**, and **mezlocillin**), generally are administered in large quantities to achieve high serum concentration. These drugs are effective against Enterobacteriaceae and have good activity against most anaerobes at these concentrations. However, up to 30% of the bacteria in the *B. fragilis* group is resistant.²⁰

Many anaerobes possess cephalosporinases, and therefore cephalosporins have limited utility.²¹ The activity of **cephalosporins** against the beta-lactamase-producing AGNB varies. The antimicrobial spectrum of the first-generation cephalosporins against anaerobes is similar to penicillin G, although on a weight basis, they are less active. Most strains of the *B. fragilis* group and many *Prevotella*, *Porphyromonas*, and *Fusobacterium* spp. are resistant to these agents.²² Cephalosporinases have little or no hydrolytic activity against the second-generation **cefoxitin** (a cephamycin), which is the most effective cephalosporin against the *B. fragilis* group. However, susceptibility may vary by geographic location and is generally directly related to its clinical use. Cefoxitin is relatively inactive against most species of *Clostridium*, including *C. difficile*, with the exception of *C. perfringens*.²²⁻²⁴

Cefoxitin is often used for surgical prophylaxis at most body sites that involve mucous membranes. With the exception of moxalactam, the third-generation cephalosporins are not as active against *B. fragilis*.

Currently, approximately 85% of *B. fragilis* isolates are susceptible to cefoxitin, but the other *B. fragilis* group species are more resistant.⁸ Cefotetan is less effective than cefoxitin against *B. fragilis* and other members of the *B. fragilis* group. Recently, the IDSA removed cefotetan from the recommended list of drugs against intra-abdominal infections due to poor *B. fragilis* group activity and resultant clinical failures.²⁵⁻²⁷

The carbapenems (imipenem, meropenem, doripenem, and ertapenem) have excellent activity against anaerobes.²⁸ **Imipenem**, a thienamycin, is a beta-lactam antibiotic that is effective against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms, including *B. fragilis*.^{29,30} It is also effective against most Enterobacteriaceae, with about 5% to 15% of *Pseudomonas* spp. resistance.³¹ To overcome the problem of renal metabolism of imipenem, it is combined at a 1:1 ratio with an inhibitor of the renal dipeptidase, ciliastatin.

TABLE 118-1 Antimicrobial Agents Effective Against Mixed Infections

| ANTIMICROBIAL AGENT | ANAEROBIC BACTERIA | | AEROBIC BACTERIA | |
|--|-------------------------------|-----------------|---------------------|--------------------|
| | BETA-LACTAMASE-PRODUCING AGNB | OTHER ANAEROBES | GRAM-POSITIVE COCCI | ENTEROBACTERIACEAE |
| Penicillin ^a | 0 | +++ | + | 0 |
| Chloramphenicol ^a | +++ | +++ | + | + |
| Cephalothin | 0 | + | ++ | + / - |
| Cefoxitin | ++ | +++ | ++ | ++ |
| Carbapenems | +++ | +++ | +++ | +++ |
| Clindamycin ^a | ++ | +++ | +++ | 0 |
| Ticarcillin | + | +++ | + | ++ |
| Amoxicillin + clavulanate ^a | +++ | +++ | ++ | ++ |
| Piperacillin + tazobactam | +++ | +++ | ++ | ++ |
| Metronidazole ^a | +++ | +++ | 0 | 0 |
| Moxifloxacin | ++ | ++ | ++ | +++ |
| Tigecycline | ++ | +++ | +++ | ++ |

Degrees of activity: 0 to +++; a, available also in oral form.

TABLE 118-2 Percent Resistance of *Bacteroides fragilis* Group and Other Anaerobes to Antimicrobial Agents (Includes Intermediate-Resistant Strains) (Adapted from Reference 78)

| | AMP-SULB | AMX-CLAV | PIP-TAZO | FOX | ERTA | IMI | MERO | DORI | CLINDA | MOXI | TIGE |
|-------------------------------|----------|----------|----------|--------|--------|-------|--------|--------|---------|---------|-------|
| Suscept. breakpoint | <8/4 | <4/2 | <32/4 | <16 | <4 | <4 | <4 | <4 | <2 | <2 | <4 |
| Resistant | >32/16 | >16/8 | >128/4 | >64 | >16 | >16 | >16 | >16 | >8 | >8 | >16 |
| ORGANISM | | | | | | | | | | | |
| <i>B. fragilis</i> | 2.8-11 | 4-37 | 0-5 | 4-25 | 1.4-10 | 0.3-7 | 1.2-22 | 1.3-12 | 10-42 | 10-41 | 2-11 |
| <i>B. thetaiotaomicron</i> | 4.9-15 | 12-37 | 0-12 | 6.8-68 | 1.3-3 | 0-7 | 0-3 | 0-3 | 39.8-60 | 13-75 | 0-5.8 |
| <i>P. distasonis</i> | 15-20.6 | 21 | 0-14 | 11-60 | 0-6 | 0-1 | 0-1 | 0 | 14.3-64 | 12.5-52 | 0-3.2 |
| <i>B. ovatus</i> | 2-8 | 18 | 0 | 18-59 | 2-2.2 | 0 | 0 | 0 | 36-45.5 | 8-87 | 2-5.2 |
| <i>B. vulgatus</i> | 3-25 | 14 | 1.1-7 | 11-20 | 0-2 | 0-7 | 0 | 0 | 40-54 | 21-74 | 0-5 |
| <i>B. fragilis</i> group | | 10-20 | 0-8 | 17-33 | | <1-1 | | | 32-52 | 14-57 | 2-13 |
| <i>Prevotella</i> spp. | 0 | 0-19 | 0-1 | 0-3 | 0 | 0-6 | | | 13-33 | 11-42 | 0 |
| <i>Fusobacterium</i> spp. | | 0-11 | 0 | 0 | 0 | 4 | 8 | 0 | 8-31 | 10-25 | 0 |
| <i>Clostridium</i> spp. | 0 | 0-5 | 0 | 16-35 | 0-4 | 15 | 0-5 | 0 | 16-25 | 7-53 | 14 |
| Anaerobic gram-positive cocci | 0 | 0-6 | 0-3 | 0-2 | 0 | 0 | 0 | 0 | 5-27 | 3-36 | 0 |

Amp-Sulb, ampicillin/sulbactam; Amx-Clav, amoxicillin/clavulanate; Pip-Tazo, piperacillin/tazobactam; Fox, cefoxitin; Ert, ertapenem; Imi, imipenem; Mero, meropenem; Dori, doripenem; Clinda, clindamycin; Moxi, moxifloxacin; Tige, tigecycline.

Metronidazole is not included since >99% of gram-negative strains are susceptible.

This agent is an effective single agent for the treatment of mixed aerobic-anaerobic infections.

Meropenem antibacterial activity is similar to imipenem. However, it is less active against staphylococci and enterococci and provides better coverage of aerobic and facultative gram-negative bacteria.³² Meropenem has been effective in abdominal infections, meningitis in children and adults, community-acquired and nosocomial pneumonia, and neutropenic fever.³³

Ertapenem, a newer 1-beta-methyl carbapenem, is stable to dehydropeptidase and has a broad antibacterial spectrum for aerobic and anaerobic bacteria, including *C. perfringens*, *Fusobacterium* spp., *Peptostreptococcus* spp., and AGNB.³⁴ Compared to other available carbapenems, ertapenem has a long half-life of 4.5 h and is given as a single daily dose. It is not active against *Pseudomonas aeruginosa*, *Enterococcus* spp., and *Acinetobacter* spp.

Doripenem, a synthetic 1-beta-methyl carbapenem, possesses a similar antimicrobial spectrum to meropenem and imipenem.³⁰ It has significant in vitro activity against aerobic and anaerobic bacteria including the *B. fragilis* group. In vitro, resistant *P. aeruginosa* mutants appear to be harder to select with doripenem than with other carbapenems.

Carbapenems are generally employed in more serious anaerobic infections such as intra-abdominal and skin and soft tissue infections.²⁵⁻²⁷ Recent reports have noted the development of some carbapenem resistance among anaerobes,¹² ranging from 1.1% to 2.5% in a multicenter U.S. survey but higher in a small number of isolates from Taiwan.³⁵

Resistance to β -Lactam Antibiotics

Anaerobes manifest three major resistance mechanisms to β -lactam antibiotics: inactivating enzymes, mainly beta-lactamases (BLAs), which include penicillinases and cephalosporinases, low-affinity penicillin binding proteins (PBPs), and decreased permeability through alterations in the porin channel.³⁶ The production of BLAs is the most common mechanism of resistance to β -lactam antibiotics in anaerobes, especially among the *B. fragilis* group and *Prevotella* spp.³⁷ Typically, the cephalosporinases belong to the 2e class type and can be inhibited by three beta-lactamase inhibitors, clavulanic acid, sulbactam, and tazobactam. Each individual cephalosporin may have either a class or specific inhibitor enzyme that is able to inactivate it.

Carbapenemases are active against the carbapenems as well as all β -lactam antibiotics. Carbapenem resistance occurs in <1% of U.S. isolates, and up to 3% of *Bacteroides* strains harbor one of the genes that is expressed at a very low level.

With a few exceptions among some *Clostridium* spp., strains of *Clostridium*, *Porphyromonas*, and *Fusobacterium* have also been found to express resistance by one or more of the BLAs. BLA producing *Fusobacterium* and *Clostridium* spp. express enzymes that are generally inhibited by clavulanic acid.³⁸ Resistance to β -lactam antibiotics through changes in the OMP/porin channels, decreased PBP affinity, and efflux pumps³⁹ is less well studied. The bacteria in the *B. fragilis* group are generally resistant to penicillins (average 90%), piperacillin (25%), cefoxitin (25%), cefotetan (30%-85%), and third-generation cephalosporins.^{40,41} The combinations of BL/BLICs inhibitors and carbapenems have maintained their excellent antibacterial activity. The combination of ampicillin-sulbactam, amoxicillin clavulanate, ticarcillin-clavulanate, and piperacillin-tazobactam is generally very active against members of the *B. fragilis* group.⁴⁰ However, species-to-species variation in susceptibility occurs.⁴² *B. fragilis* group resistance rates for piperacillin-tazobactam is generally <1%.⁴⁰ However, resistance of *Parabacteroides distasonis* to ampicillin-sulbactam has risen to 20% in 2002-2004 but continued to be low for the other *B. fragilis* group species.

The carbapenems (imipenem, meropenem, doripenem, and ertapenem), are very effective against all members of the *B. fragilis* group, and resistance is rare at <0.1%.^{39,42,43} Geometric mean MICs for imipenem and meropenem for *P. distasonis*, *B. thetaiotaomicron*, and *B. ovatus* have been reported to be one-fold dilution lower than those for ertapenem⁴⁰ in 2004.

β -lactams are generally effective against non-*B. fragilis* group species, and resistance to them is generally low except that more than half of *Prevotella* spp. may also produce BLAs. A multicenter survey²⁹ found penicillin resistance for *Fusobacterium* spp., *Porphyromonas* spp., and *Peptostreptococcus* spp. at 9%, 21%, and 6%, respectively. No resistance was found to cefoxitin, cefotetan, β -lactam/BLA inhibitor combinations, and carbapenems in that survey, with the exception of *Peptostreptococcus* spp. and *Porphyromonas* spp. (4% and 5% resistance to ampicillin-sulbactam, respectively). Beta-lactamases were identified in several *Prevotella* and *Porphyromonas* spp. recovered from pediatric intra-abdominal infections.

Chloramphenicol

Chloramphenicol, a bacteriostatic agent, is active against most anaerobic bacteria but is rarely used in the United States.^{3,22} Resistance is rare. Although several failures to eradicate anaerobic infections with chloramphenicol have been reported,⁴⁴ this agent has been used for over 65 years for treatment of anaerobic infections. In the past, it was the drug of choice for the treatment of serious anaerobic infections including the central nervous system (CNS). However, the drug has potential significant toxicity. The risk of fatal aplastic anemia with chloramphenicol is estimated to be approximately one per 25,000-40,000 patients treated. This serious complication is unrelated to the reversible, dosage-dependent leukopenia. Other side effects include the production of the potentially fatal "gray baby syndrome" when given to neonates, hemolytic anemia in patients with G6PD deficiency, and optic neuritis in those who take the drug for a prolonged time.⁴⁵

Chloramphenicol has a unique property of lipid solubility to permit penetration across lipid barriers. Levels in the cerebrospinal fluid, with or without meningitis, usually are one-third to three-fourths the serum concentrations. Levels in brain tissue may be substantially higher than serum levels.⁴⁶

Macrolides: Erythromycin, Azithromycin, Clarithromycin

The macrolides, which possess low human or animal toxicity, have moderate to good in vitro activity against anaerobic bacteria other than

the *B. fragilis* group and *Fusobacterium*.²² Macrolides are active against pigmented *Prevotella* and *Porphyromonas* and microaerophilic streptococci, gram-positive non-spore-forming anaerobic bacilli, and certain clostridia. They are less effective against *Fusobacterium* and *Peptostreptococcus* spp.⁴⁷ They show relatively good activity against *C. perfringens* and poor or inconsistent activity against AGNB.

Clarithromycin is the most active of the macrolides against gram-positive oral cavity anaerobes, including *Actinomyces* spp., *Propionibacterium* spp., *Lactobacillus* spp., and *Bifidobacterium dentium*. Azithromycin is slightly less active than erythromycin against these species.⁴⁷ Azithromycin is the most active macrolide against AGNB: *Fusobacterium* spp., *Bacteroides* spp., *Wolinella* spp., and *Actinobacillus actinomycetemcomitans*, including those resistant to erythromycin. Clarithromycin showed similar activity to erythromycin against most AGNB.⁴⁸

Erythromycin resistance during therapy can occur.^{49,50} Erythromycin is effective in the treatment of mild to moderately severe anaerobic soft tissue and pleuropulmonary infections when combined with adequate débridement or drainage of infected tissue. Phlebitis is reported to develop in one-third of the patients receiving intravenous erythromycin, but the oral preparation is well tolerated.

Clindamycin

Clindamycin has a broad range of activity against anaerobes. It is used to treat dental infections, especially in patients allergic to penicillin and to treat aspiration pneumonia. Clindamycin hydrochloride is rapidly absorbed from the gastrointestinal tract.⁵¹⁻⁵³ It rapidly penetrates into body tissues and fluids, including saliva, sputum, respiratory tissue, pleural fluid, soft tissues, prostate, semen, bones, and joints,⁵⁴ as well as into fetal blood and tissues. Clindamycin does not efficiently cross the blood-brain barrier or eye and should not be administered in CNS infections.

The side effect of most concern is *C. difficile*-associated colitis.^{55,56} Colitis has also been associated with a number of other antimicrobials, such as ampicillin, cephalosporins, and quinolones, and occasionally also in the absence of previous antimicrobial therapy.

Because *B. fragilis* resistance to clindamycin is increasing, it is no longer recommended as an empiric therapy for intra-abdominal infections.^{12,40,43,57} An 8-year study revealed that 19.3% of 2721 *B. fragilis* group isolates, 29.6% of *P. distasonis*, 33.4% of *B. ovatus*, 33.3% of *B. thetaiotaomicron*, and 35.6% of *Bacteroides vulgatus* strains were clindamycin resistant. This is a significant increase compared to only 3% clindamycin resistance in 1987.⁴¹

Resistance has also increased, for many non-*Bacteroides* anaerobes. Up to 10% resistance was noted in *Prevotella* spp., *Fusobacterium* spp., *Porphyromonas* spp., and *Peptostreptococcus* spp., with higher rates for some *Clostridium* spp. (especially *C. difficile*).²⁹ *Propionibacterium acnes* isolates have also become more resistant to clindamycin, and this has been associated with prior therapy for acne.⁵⁸

Clindamycin has lost some of its activity against anaerobic gram-positive cocci (*Finegoldia magna*, 30% resistant, *Peptoniphilus* spp., etc.) and *Prevotella* spp. (*P. bivia*, 70% resistant; *P. oralis* and *P. melaninogenica*, both 40% resistant), although its activity against *Fusobacterium* and *Porphyromonas* spp. remains good.

Among the other resistant anaerobes are various species of *Clostridium*, especially *C. difficile*. Approximately 20% of *C. ramosum* are resistant to clindamycin, as are a smaller number of *C. perfringens*.

Metronidazole and Tinidazole

Metronidazole and tinidazole have excellent in vitro activity against most obligate anaerobic bacteria, such as the *B. fragilis* group, other species of *Bacteroides*, *Fusobacterium*, and *Clostridium*.³⁴ Only six strains of the *B. fragilis* group were ever reported to be clinically resistant and associated with therapeutic failure.²

Resistance of anaerobic gram-positive cocci is rare, and nonsporulating bacilli are common. Microaerophilic streptococci, *P. acnes*, and

Actinomyces spp. are almost uniformly resistant.⁵⁹ Aerobic and facultative anaerobes are usually highly resistant. Because of its lack of activity against aerobic bacteria, an antimicrobial effective against these organisms (e.g., a cephalosporin, a fluoroquinolone) needs to be added when treating a polymicrobial infection.

Adverse reactions to metronidazole are rare and include CNS toxicity, ataxia, vertigo, headaches, convulsions, and peripheral neuropathy. Peripheral neuropathy is associated with prolonged metronidazole use. Gastrointestinal side effects are common and include nausea, vomiting, metallic taste, anorexia, and diarrhea. Other adverse reactions include reversible neutropenia, phlebitis at intravenous infusion sites, and drug fever.

Some studies in mice^{60,61} have shown possible mutagenic activity associated with administration of large doses of metronidazole. Other experiments⁶¹ in rats and hamsters did not show any pathology. In addition, no evidence of mutagenicity was found in humans.⁶²

Metronidazole is effective in the treatment of anaerobic infections, including those of the CNS.^{63,64} Valid data on the safety of metronidazole in pregnancy is still needed. The nonteratogenicity of metronidazole is difficult to prove, but the existing data indicate no major risks.⁶⁵

Resistance to metronidazole among the *B. fragilis* group is rare.^{33,66} Half of the resistant *B. fragilis* group isolates carry one of nine known *nim* genes [*nim* A-I] on either a chromosome or a mobilizable plasmid. This gene encodes a nitroimidazole reductase that converts 4- or 5-nitroimidazole to 4- or 5-aminoimidazole, preventing the formation of toxic nitroso residues necessary for the agents' activity. Resistance among gram-positive organisms that are not strict anaerobes is frequent, especially for *P. acnes* and *Actinomyces* spp.

Tetracyclines

Tetracycline is of limited use because of the development of resistance to it by most anaerobes. Resistance to *P. acnes* has been related to previous use.⁵⁸ Only about 45% of all *B. fragilis* strains presently are susceptible to this drug.²² The tetracycline analogues, doxycycline and minocycline, are more active than the parent compound. Because of significant resistance to these drugs, they are useful only when susceptibility tests can be performed or in less severe infections in which a therapeutic trial is feasible. The use of tetracycline is not recommended before 8 years of age because of its adverse effect on teeth.

Tygecycline is a glycylcycline, a direct analog of minocycline with a 9-glyclamide moiety. It has activity against both aerobic gram-negative and gram-positive bacteria, anaerobes,^{67,68} and certain drug-resistant pathogens.⁶⁹ It is active against the *Streptococcus anginosus* group (which includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *B. fragilis*, *B. thetaiotaomicron*, *B. uniformis*, *B. vulgatus*, *C. perfringens*, *C. difficile*, and *Parvimonas micra* (*Peptostreptococcus micros*).⁶⁷ Resistance of tygecycline for members of the *B. fragilis* group varied from 3.3% to 7.2%.^{12,40}

Fluoroquinolones

Quinolones with low activity against anaerobes include ciprofloxacin, ofloxacin, levofloxacin, fleroxacin, pefloxacin, enoxacin, and lomefloxacin. Compounds with intermediate antianaerobic activity include sparflaxacin and grepafloxacin.⁷⁰ **Trovaflaxacin**, **gatifloxacin**, and **moxifloxacin** yield low MICs against most groups of anaerobes.⁷¹ The use of trovaflaxacin has been limited because of hepatotoxicity. Quinolones with the greatest in vitro activity against anaerobes include clinafloxacin and sitafloxacin.⁷²

Moxifloxacin has been studied as monotherapy in intra-abdominal infections in adults^{25,57} and has shown activity against intra-abdominal anaerobic isolates.^{73,74} However, the increasing fluoroquinolone resistance in both the *E. coli* and *B. fragilis* groups has reduced its use in intra-abdominal infections.^{9,12,57,74}

The use of quinolones is restricted in growing children because of their possible adverse effects on cartilage. The major concerns with the use of fluoroquinolones to treat anaerobic infections have been the increasing resistance in the *B. fragilis* group as well as anaerobic gram-positive cocci and the impact of these antibiotics on the growing incidence of *C. difficile*-associated disease.⁷²

Bacteroides spp. resistance to fluoroquinolone has been attributed to either an alteration in efflux of the antibiotic or a mutation in the quinolone resistance determining region (QRDR) of the gyrase A gene (*gyrA*) from either single or multiple mutations.⁷⁵ High-level resistance can be caused by both mechanisms.

Other Agents

Bacitracin was active in vitro against pigmented *Prevotella* and *Porphyromonas* spp. but is inactive against *B. fragilis* and *Fusobacterium nucleatum*.²² Vancomycin and daptomycin are effective against all gram-positive anaerobes but are inactive against AGNB.⁷⁶ Quinupristin/dalfopristin shows antibacterial activity against some anaerobic organisms that were tested, including *C. perfringens*, *Lactobacillus* spp., and *Peptostreptococcus* spp.⁷⁷ Linezolid is active against *Fusobacterium nucleatum*, and other *Fusobacterium* spp., and *Porphyromonas* spp., *Prevotella* spp., *Peptostreptococcus* spp.⁴⁸ Little clinical experience has, however, been gained in the treatment of anaerobic infections using these agents.

GENERAL CONSIDERATION OF ANTIMICROBIAL SELECTION

Because anaerobic infection is often polymicrobial, antimicrobials effective against both aerobic and anaerobic components of the infection should be administered. When such therapy is not given, the infection may persist, and serious complications may occur.^{2,3,78} A number of factors should be considered when choosing appropriate antimicrobial agents: they should be effective against all target organism(s), induce little or no resistance, achieve sufficient levels in the infected site, have minimal toxicity, and have maximum stability and longevity.

When selecting antimicrobials for the therapy of mixed infections, their antibacterial spectrum and their availability in oral or parenteral form should be considered (see Table 118-1). Some antimicrobials have a limited range of activity. For example metronidazole is only active against anaerobes and therefore cannot be administered as a single agent for the therapy of mixed infections. Other antimicrobials, such as carbapenems, tigecycline, and BL-BLICs, possess a broader spectrum of activity against aerobic and anaerobic bacteria.

Selecting antimicrobials is simplified when a reliable culture result is available. However, this may be particularly difficult in anaerobic infections because of the difficulties in obtaining appropriate specimens. For this reason, many patients are treated empirically on the basis of suspected, rather than established, pathogens. Fortunately, the types of anaerobes involved in many anaerobic infections and their antimicrobial susceptibility patterns tend to be predictable.^{2,3} However, some anaerobes have become resistant to antimicrobials, and many can develop resistance during therapy.^{39,79}

Aside from susceptibility patterns, other factors influencing the choice of antimicrobial therapy include the pharmacologic characteristics of the various drugs, their toxicity, their effect on the normal flora, and bactericidal activity.^{2,3} Although identification of the infecting organisms and their antimicrobial susceptibility may be needed for selection of optimal therapy, the clinical setting and Gram stain preparation of the specimen may indicate the types of anaerobes present in the infection as well as the nature of the infectious process.

Typically, antimicrobial therapy for anaerobic infections should be given for prolonged periods because of their tendency to relapse. This may range from 3 weeks to 3 months, depending on the site and severity of the infection.

KEY POINTS

1. Because anaerobic infection is often polymicrobial, antimicrobials effective against both aerobic and anaerobic components of the infection should be administered. When such therapy is not given, the infection may persist, and serious complications may occur.
2. Anaerobes are often involved in mixed infections, which present unique situations for antimicrobial use. The interactions between the different bacteria and the various antibiotics can be difficult to distinguish and/or predict.
3. Selecting antimicrobials is simplified when a reliable culture result is available. However, this may be particularly difficult in anaerobic infections because of the difficulties in obtaining appropriate specimens.
4. Susceptibility patterns of anaerobes have been changing over the years, and susceptibility to metronidazole cannot be assumed. Although susceptibility testing of anaerobes is difficult, clinicians must realize the importance of performing and analyzing the susceptibility tests.
5. Several β -lactam antibiotics, fluoroquinolones, clindamycin, and tigecycline possess activity against anaerobic organisms. However, resistance is a concern with all of these classes of antibiotics. A few investigational agents have the potential for use in anaerobic infections, but clinical data are needed.

ANNOTATED REFERENCES

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This paper presents susceptibility data on 542 blood isolates of the B. fragilis group tested over a 12-year period. Metronidazole, β -lactam/ β -lactamase combinations, and carbapenems were consistently the most active agents. These data show the importance of susceptibility testing of the B. fragilis group and serve as a guide in the choice of empiric antimicrobial therapy.

Lamp KC, Freeman CD, Klutman NE, et al. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet* 1999;36:353–373.

This review presents a comprehensive overview of the pharmacokinetics, pharmacodynamics, and use of metronidazole and nitroimidazole antimicrobials.

Pelaez T, Alcalá L, Alonso R, et al. Reassessment of *Clostridium difficile* susceptibility to metronidazole and vancomycin. *Antimicrob Agents Chemother* 2002;46:1647–1650.

C. difficile is generally assumed to be sensitive to metronidazole and vancomycin. However, this manuscript shows that some isolates are either resistant (6.3% for metronidazole) or have intermediate resistance (3.1% to vancomycin) to these agents.

Snydman DR, Jacobus NV, McDermott LA, et al. Lessons learned from the anaerobe survey: historical perspective and review of the most recent data (2005–2007). *Clin Infect Dis* 2010;50:S26–S33.

This report affirms the findings of Aldridge and colleagues and documents the first report of metronidazole resistance among Bacteroides spp. in the United States. Trends in susceptibility testing showed increasing resistance to clindamycin, moxifloxacin, and ampicillin/sulbactam, with relatively stable resistance rates to carbapenems, and piperacillin/tazobactam.

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Infections acquired in the intensive care unit (ICU) often occur during the treatment of critically ill patients, increasing their morbidity, mortality, and health care costs.^{1,2} Several studies suggest that the use of prophylactic antibiotic regimens such as selective decontamination of the digestive tract (SDD)³⁻⁶ and selective oropharyngeal decontamination (SOD) can reduce the incidence of respiratory tract infections and mortality in ICU patients.^{5,7,8} The SDD approach^{9,10} is directed toward the following: prevention of secondary colonization with gram-negative bacteria, *Staphylococcus aureus*, and yeasts through application of nonabsorbable antimicrobial agents in the oropharynx and gastrointestinal tract; preemptive treatment of possible infections due to commensal respiratory tract bacteria through systemic administration of cephalosporins during the patient's first 4 days in the ICU; and maintenance of anaerobic intestinal flora through selective use of antibiotics (administered both topically and systemically) without anti-anaerobic activity.¹⁰

BACKGROUND

The intestinal flora is highly diverse and consists primarily of anaerobic bacteria. Intact anaerobic flora is considered an important defense mechanism against intestinal colonization by potentially pathogenic microorganisms. The commensal flora of the oropharynx consists of hundreds of bacterial species, including enterococci and anaerobic bacteria, which are replaced by gram-negative bacteria during the first week of hospitalization in the ICU. Gastric acidity usually prevents bacterial overgrowth in the stomach. Yet, in ICU patients, reduced acid production due to underlying diseases, use of acid-modifying medication (stress ulcer prophylaxis), and intragastric administration of enteral nutrition (with a pH of 6) leads to a gastric environment that favors bacterial growth, especially of gram-negative bacteria.

Anaerobic bacteria grow well on the mucosa of the gut and actively line the epithelium.¹¹ Disruption of this layer by antibiotics that destroy the anaerobic flora may create a portal of entry for pathogenic microorganisms.

Combinations of nonabsorbable antibiotics have been used to selectively decontaminate the digestive tract and reduce the load of pathogenic aerobic microorganisms while maintaining the anaerobic flora. This concept was first investigated in mice⁹ and later developed into an infection prevention strategy for neutropenic leukemia patients, which the investigators called *selective decontamination of the digestive tract*, or SDD.^{12,13}

From Concept to Practice in the ICU

The earlier experience with SDD in leukemia patients suggested that some infections in ICU patients might have an endogenous source and could be prevented in the same way. After a 2-year observational microbiological study of trauma patients, an infection classification was proposed (Table 119-1) that included definitions for colonization and the use of SDD for infection prevention in trauma patients in the ICU.^{10,14,15} These studies resulted in the establishment of an SDD regimen consisting of the application of nonabsorbable antimicrobial agents in the oropharynx and gastrointestinal tract to prevent acquired colonization with gram-negative bacteria, *Staphylococcus aureus*, and yeasts, in combination with 4 days of intravenous administration of a third-generation cephalosporin to preemptively treat incubating respiratory tract infections with gram-positive and gram-negative bacteria. Topical and systemic antibiotics were selected based on their antibacte-

rial spectrum and presumed absence of activity on the anaerobic intestinal flora.^{14,15}

CLINICAL RESULTS

Earlier Studies

The first study of SDD in ICU patients was performed in 63 trauma patients, using a historical control group of 59 trauma patients.¹⁰ Because of its design and use of a historical control group, this study not only triggered many critical comments and editorials but also led to additional studies in more heterogeneous ICU patient populations, with different combinations of absorbable and nonabsorbable antibiotics, with or without parenteral antibiotics.^{3,16-18} The conflicting results of these clinical trials led to the conclusion that there was insufficient scientific evidence to recommend SDD as a routine infection control measure in ICU patients.¹⁹

Recent Studies

A single-center, prospective, controlled, randomized, unblinded study in 2003 reported significantly lower ICU and hospital-mortality rates (35% and 22%, respectively), shorter length of stay, and a lower incidence of antibiotic resistance in patients with an expected duration of mechanical ventilation of ≥ 2 days and/or expected length of stay in the ICU of ≥ 3 days and receiving SDD.^{4,20} A subsequent multicenter, controlled, crossover study using cluster randomization and identical inclusion criteria that compared SDD with SOD was performed in the Netherlands. SOD was included because of the hypothesis that the main effect of SDD—a reduction in the incidence of ventilator-associated pneumonia (VAP)—could be achieved by oropharyngeal decontamination only, without intestinal decontamination and without the routine prophylactic use of systemic antibiotics during the first 4 days of ventilation.^{7,8} The results of this first Dutch multicenter trial (DMT-I) with almost 6000 patients showed that SDD and SOD groups were associated with a reduction in mortality at day 28 of 13% and 11% relative to controls, respectively, corresponding to an absolute reduction of 3.5% and 2.9%.⁵ There were several noteworthy limitations to this study; in particular, as with most SDD studies, it was not blinded, so all physicians were aware of the treatment patient participants would receive. Because inclusion was based on several criteria, this created the possibility of selection bias. To minimize the occurrence of selection bias, patient eligibility and inclusion rates were monitored frequently and immediately followed by feedback to the participating investigators. Yet despite the use of these measures next to the objective inclusion criteria, there were baseline differences between the control and the two intervention groups. Patients in the intervention groups (SDD and SOD) were more frequently intubated, less likely to be surgical patients, and had a higher baseline APACHE score. Further, SDD patients were older compared to SOD and control patients.⁵

A second Dutch open cluster, randomized, crossover, multicenter trial (DMT-II: 12,000 patients) compared 12 months of SDD to 12 months of SOD. Again, there was a baseline difference, and there was no day-28 mortality difference between SDD (24.1%) and SOD (25.4%) (SDD vs. SOD: adjusted OR 0.96, 95% CI 0.88-1.06) and no difference in the length of stay.²¹ A Cochrane meta-analysis was published in 2009 on the effects of topical antibiotics (with or without systemic antibiotics) and its effects on mortality and the incidence of respiratory tract infections (RTI).⁶ This meta-analysis included 36 trials, with a total of

TABLE 119-1 Definitions

| | |
|---------------------------------|--|
| Colonization resistance | The strong protective effect of the endogenous anaerobic fraction of the intestinal microflora in resisting colonization by aerobe microorganisms along the alimentary canal. Suppression of the anaerobic flora increases the risk of overgrowth by gram-negative bacteria. |
| PPM | Potentially pathogenic microorganisms |
| SDD | Selective decontamination of the digestive tract is the selective elimination of PPM from the oral and intestinal flora by topical, nonabsorbable, antibiotics. |
| SOD | Selective oropharyngeal decontamination is the selective elimination of PPM from the oral flora by topical, nonabsorbable, antibiotics. |
| Primary endogenous infections | Caused by PPM with which the oropharynx and/or digestive tract of the patient was colonized at admission. These PPM are part of the "normal" flora of the patient. |
| Secondary endogenous infections | Caused by PPM with which the oropharynx and/or digestive tract of the patient was not colonized at admission but acquired during ICU stay |
| Exogenous infections | Caused by PPM not present at admission and developing without preceding colonization |
| Colonization | Presence of the same species of PPM in an organ system for more than 3 days (≥ 2 positive cultures) without signs of infection |

6914 patients (without DMT-I for the reasons described). The authors concluded the following:

1. In trials comparing a combination of topical and systemic antibiotics to controls, there was a significant reduction in both RTIs (16 studies; OR, 0.28; 95% CI 0.20-0.38) and mortality (17 studies; OR, 0.75; 95% CI, 0.65-0.87).
2. In trials comparing topical antibiotics alone to controls or comparing topical plus systemic to systemic alone, there was a significant reduction in RTIs (17 studies; OR, 0.44; 95% CI, 0.31-0.63) but not in mortality (19 studies; OR 0.97, 95% CI, 0.82-1.16).

This last conclusion contrasts the results of the DMT-I, which showed a significant reduction in mortality with the use of topical antibiotics in the oropharynx only.⁵

Another systematic review and meta-analysis published in 2014 compared SDD, SOD, and oropharyngeal chlorhexidine for the prevention of death and concluded that SDD had a favorable effect on mortality, with a less certain effect of SOD. Both were superior to chlorhexidine, with a remark that chlorhexidine might be associated with increased mortality.²²

The "what, when, and why" of the different parts of the SDD regimen as it is used in the latest studies are shown in Table 119-2.

MICROBIOLOGICAL EFFECTS OF SELECTIVE DECONTAMINATION

Decontaminating Effect

The DMT-I showed that the proportion of SDD patients colonized with gram-negative bacteria isolated from rectal swabs decreased from 56% at day 3 to 25% at day 8 and 15% at day 14. Oropharyngeal colonization rates with gram-negative bacteria decreased from 18% at day 2 to 4% at day 8 among SDD patients. The same trial showed a comparable decrease in oropharyngeal colonization rates with gram-negative bacteria in SOD patients from 20% at day 2 to 7% at day 8.⁵ These results are comparable to those reported in other studies.^{10,23,24} Further, it was shown that SDD could eradicate cephalosporin-resistant Enterobacteriaceae from the intestinal tract.²⁵

The positive effects of SDD (and SOD) on respiratory tract colonization and infection have been described extensively.^{4,6-8} The DMT-I showed significantly a lower incidence of ICU-acquired bacteremia during SOD and SDD for *S. aureus*, glucose-nonfermenting gram-negative rods (mainly *Pseudomonas aeruginosa*), and Enterobacteriaceae as compared to controls. The incidence of ICU-acquired candidemia was lower in the SDD group compared to either SOD or control groups.⁵ Patients receiving SDD had a lower incidence of ICU-acquired bacteremia with Enterobacteriaceae than those receiving SOD,^{5,26} a result that was confirmed by the DMT-II.²¹

Emergence and Selection of Antibiotic Resistance in Gram-Negative and Gram-Positive Microorganisms During Selective Decontamination

Enhanced selection of antibiotic-resistant microorganisms has been considered an important threat of SDD and SOD.²⁷ Consistent use of surveillance cultures as part of SDD and SOD protocols makes it possible to assess the efficacy of enteral decontamination and to detect the emergence of antibiotic-resistant pathogens early.

Gram-Negative Microorganisms

Several studies showed an overall decrease in antibiotic-resistant gram-negative microorganisms in patients receiving SDD, including a significant beneficial effect on colonization with resistant gram-negative bacteria such as *P. aeruginosa* resistant to ceftazidime, imipenem, and ciprofloxacin and other aerobic gram-negatives resistant to imipenem, ciprofloxacin, and tobramycin.^{4,18} Patients receiving SDD during the DMT-I had a lower incidence of ICU-acquired candidemia, bacteremia with Enterobacteriaceae, and bacteremia with highly resistant microorganisms (HRMO; according to Dutch guidelines²⁸) than those receiving SOD, all confirmed by the DMT-II except for candidemia.²⁹ Analysis of the rates of colistin resistance during SDD and SOD in DMT-I showed that during persistent intestinal carriage of gram-negative bacteria and during intestinal colonization with tobramycin-resistant gram-negative bacteria, the risk of acquisition of colistin resistant gram-negative bacteria and conversion rates to colistin resistance increased. The overall risk of acquisition of colistin-resistant gram-negative bacteria and conversion rates to colistin resistance were low.³⁰ A post hoc analysis in five Dutch ICUs using SDD or SOD over 7 years showed no increase in the prevalence of resistance against colistin or tobramycin.³¹ On the other hand, an increase in colistin resistance in extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* was reported when SDD was used to control an outbreak.³²

The incidence of candidemia and bacteremia caused by HRMO was low in both the DMT-I and -II, so whether the difference between SDD and SOD will translate into a difference in clinical outcome depends on the overall incidence of candidemia and bacteremia caused by HRMO, the appropriateness of empiric antimicrobial therapy in such patients, and the attributable effects of such events on the outcome and length of stay. These findings do not support the concern that the use of topical antibiotics, with or without systemic prophylaxis with third-generation cephalosporins, increases the prevalence levels of antibiotic resistance in gram-negative bacteria. This conclusion is supported by two 5-year prospective studies and a recent meta-analysis.³³⁻³⁵

Gram-Positive Microorganisms

Methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) are highly prevalent in ICUs in many countries, unlike the Netherlands, where the last three major studies were carried out. The use of topical antibiotics for SDD or SOD is generally considered to be contraindicated in such settings, as such regimens may increase colonization and infection rates with these bacteria. More data are available on the effects of SDD or SOD in settings with high levels of MRSA.³³ In one study, a shift toward gram-positive organisms was detected after the introduction of SDD in trauma patients, including

TABLE 119-2 Selective Decontamination of the Digestive Tract Regimen

| WHAT | WHEN | WHY |
|---|--|---|
| BASELINE | | |
| Oropharyngeal application of 0.5 g of a paste containing polymyxin E, tobramycin, and amphotericin B, each in a 2% concentration* | 4 times daily until ICU discharge | Selective decontamination of the oropharynx |
| Administration of 10 mL of a suspension containing 100 mg polymyxin E, 80 mg tobramycin, and 500 mg amphotericin B via the nasogastric tube | 4 times daily until ICU discharge | Selective decontamination of the gut from stomach to rectum |
| Cefotaxime 1 g intravenously during the first 4 days of study (or other third-generation cephalosporins) | 4 times daily during the first 4 days | Preemptive treatment of primary endogenous infections |
| Avoidance of (systemic) antibiotics that might impair the colonization resistance (i.e., antibiotics with antianaerobic activity) | During treatment with SDD, until ICU discharge | Avoidance of penicillins, carbapenems, etc. No addition of antibiotics for patients with colonization without clinical signs suggestive of infection |
| Cultures of endotracheal* aspirates, oropharyngeal* and rectal swabs | On admission and surveillance cultures twice weekly | Determination of colonization pattern at admission and during treatment, including monitoring of effectiveness of SDD Detection of infection |
| Oropharyngeal care* | 4 times daily using sterile water or chlorhexidine† mouthwash, preceding application of oropharyngeal paste; includes brushing of teeth twice daily Clean visually contaminated oropharyngeal cavity with swab moistened with 1.5% hydrogen peroxide | Cleansing of mouth and teeth Removing residue of paste Preparing mouth for (next) application of paste |
| Use of normal hygiene guidelines* | Always | Preventing transmission of pathogens in the patient Prevention of (exogenous) cross-contamination and infections from and to other patients Control of outbreak |
| MODIFICATIONS FOR PATIENTS WITH | | |
| Tracheostomy* | 0.5 g of paste applied around the tracheostomy 4 times daily | Selective decontamination of the oropharynx |
| Duodenal tube or jejunostomy | Divide the 10 mL of suspension into 5 mL suspension via the gastric tube and 5 mL via the duodenal tube or jejunostomy | Selective decontamination of the gut from stomach to rectum |
| Colostoma or ileostoma | SDD suppositories (containing 100 mg polymyxin E, 40 mg tobramycin, and 500 mg amphotericin B) twice daily in the distal part of the gut | Selective decontamination of the gut from stomach to rectum |
| Documented cephalosporin allergy | Cefotaxime can be replaced by ciprofloxacin (twice daily 400 mg). | Avoidance of allergic reaction |
| MODIFICATIONS FOR PATIENTS WITH PERSISTENT RESPIRATORY TRACT COLONIZATION WITH YEASTS OR GRAM-NEGATIVE BACTERIA | | |
| If a surveillance culture (>48 h after admission culture) of the throat yields yeasts and/or gram-negative bacteria* | Increase application of oropharyngeal paste to 8 times daily until 2 surveillance cultures are negative. | Decolonization |
| If a sputum surveillance (>48 h after admission culture) culture yields yeasts* | Nebulize 5 mL (5 mg) amphotericin B 4 times daily until 2 sputum cultures are negative. | Decolonization |
| If a sputum surveillance culture (>48 h after admission culture) yields gram-negative bacteria* | Nebulize 5 mL (80 mg) polymyxin E 4 times daily until 2 sputum cultures are negative. | Decolonization |

*The SDD regimen from de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in intensive care patients. *N Engl J Med* 2009;360:20–31.

†Chlorhexidine was not used in the Dutch SDD-SOD trial (*N Engl J Med* 2009;360:20–31).

an outbreak and increased carriage rates with MRSA 2 years after the introduction of SDD.^{36,37} This shift was successfully addressed by implementation of control measures.³⁶ To prevent infections with MRSA, some investigators add vancomycin to the SOD or SDD regimen.^{7,38} When applied topically, vancomycin is not absorbed and reaches high concentrations in the intestinal tract. In a Spanish burn unit, SDD with topical vancomycin was associated with improved patient outcome and lower colonization rates with MRSA.³⁸ A disadvantage of such an approach might be the selection of VRE in ICUs where both pathogens are prevalent; however, such reports have not been published yet.

The results of the DMT-I indicate that both SDD and SOD are associated with higher rates of acquired respiratory tract colonization but not with higher rates of bacteremia caused by enterococci.

In ICU patients, enterococci will colonize all body sites (especially the skin) and contaminate the inanimate environment. Enterococci are now among the most frequent causes of hospital-acquired infections worldwide, and the proportion of infections caused by ampicillin-resistant enterococci (ARE) has increased substantially in Western countries, including the Netherlands.³⁹ In the United States, approximately 35% of all ICU-acquired enterococcal bacteremias are caused by VRE. The clinical relevance of ARE and VRE infections is unclear.

Widespread use of topical vancomycin in units with high levels of MRSA will increase the selective pressure for VRE. This factor should be carefully balanced against the benefits of treating SDD or SOD with vancomycin. In the United States, ICUs with high levels of MRSA frequently also have high endemic levels of VRE. In such settings,

the addition of oropharyngeal chlorhexidine oral washings and/or chlorhexidine body washings may help to control spread and bloodstream infections caused by VRE and MRSA.^{40,41}

Ecological Effects

During the DMT-I, surveillance cultures from the respiratory and intestinal tract were obtained each month on a fixed day from all patients present in the ICU, regardless of whether they were included in the study.⁵ These 18 point-prevalence studies in 13 ICUs allowed analysis of the effects of SDD and SOD on the bacterial ecology in these ICUs together. The effect of SDD (over a 6-month period) and SDD/SOD (combined over a 12-month period) on intestinal and respiratory tract carriage with gram-negative bacteria was determined by comparing results from consecutive point-prevalence surveys using intervention to consecutive point-prevalence data in the pre- and post-intervention periods.⁴² The average proportion of patients colonized with ceftazidime, tobramycin, or ciprofloxacin-resistant gram-negative bacteria in the intestinal tract decreased during the use of SDD in the ICU and increased again after discontinuation. During combined SDD/SOD, resistance levels in the respiratory tract were low ($\leq 6\%$) for all three antibiotics but seemed to increase gradually, with a significant increase only for ceftazidime resistance ($P < 0.05$). After discontinuation of SDD/SOD, the resistance levels increased to 10% or higher. Clearly, both SDD and SOD have marked ecological effects that are supported by the results of a 4-year ecological study published in 2014.⁴³ According to the DMT-II, SDD showed significantly lower rectal carriage of antibiotic-resistant gram-negative bacteria than did SOD.²¹ Further, a gradual increase in tobramycin resistance was observed during both the SOD and SDD periods, but more clearly during SDD; however, the incidence of acquired bacteremia with aminoglycoside-resistant GNB was lower in the SDD group than in the SOD group.²¹ Of note, some of these patients were in the ICU only briefly (and not receiving SOD or SDD), and the incidence of resistance in other hospital wards was unknown. An increasing incidence of resistance in the participating hospitals might have influenced these results.

Overall, the ecological effects (i.e., lowest resistance levels during interventions) corroborate the positive effects of SOD and even more of SDD on antibiotic resistance in individual patients.^{4,29}

Other Issues

Effectiveness of SDD in Specific Patient Groups

Evidence suggests that SDD might not be equally effective in all ICU-patient groups. In one meta-analysis, increased SDD efficacy was observed in surgical patients.¹⁷ Further, studies on the preoperative use of SDD suspension and other oral antibiotics in patients undergoing gastrointestinal surgery report lower rates of surgical site infections and anastomotic leakage.⁴⁴⁻⁴⁶ In a post hoc subgroup analysis of the Dutch multicenter study, different effects of SDD and SOD were found for surgical and nonsurgical patients.⁴⁷ Compared to controls, SDD was equally effective in decreasing 28-day mortality in surgical and nonsurgical patients and significantly decreased the duration of mechanical ventilation, ICU stay, and hospital stay among surgical patients. On the other hand, SOD appeared to be even more effective in reducing mortality in nonsurgical patients but was not associated with a decrease in day-28 mortality in surgical patients or in the duration of mechanical ventilation or length of stay in the ICU or hospital. These findings suggest that surgical patients benefit from the addition of the enteric and/or systemic component of the SDD regimen. However, the DMT-II did not show comparable effects between the SOD and SDD groups, possibly because of a different definition of “the surgical patient.”²¹ All in all, these results should be considered as hypothesis generating. Further studies are needed to confirm such observations. If confirmed, the results may help elucidate the mechanisms of the protective action of SDD and SOD in specific groups of ICU and other patients.

Hospital-Acquired Infections After Treatment with SOD and SDD

In the SDD study by De Jonge et al., the relative risk reduction in ICU mortality of 35% decreased to 22% at hospital discharge.⁴ Triggered by these findings, it was hypothesized that this reduction in survival benefit after ICU discharge might be related to an increased incidence of hospital-acquired infections (HAI) in patients who had received SDD in the ICU. Nested within the DMT-I, the incidence of HAI was prospectively monitored during the first 14 days after ICU discharge in all patients transferred to regular wards in two university hospitals.⁴⁸ Most HAI were in the respiratory tract, with a similar incidence and duration of infection in all three posttreatment study groups. The incidence of bloodstream infections was also similar in the three post-treatment groups, but the time until infection tended to be longer in the post SOD and post SDD groups compared to the post control group. On the other hand, the incidence of surgical site infections (SSI) increased in the postintervention groups. Considering the low rates of HAI, the overall low mortality rates after ICU discharge and the low prevalence of infections among those who succumbed after ICU discharge refute the hypothesis that discontinuation of SDD and SOD post ICU increases the infection rate and thus affects clinical outcomes.⁴⁸

Antibiotic Use and Cost-Effectiveness

De Jonge determined that the total cost of antibiotics, topical and systemic, was 11% lower in the SDD group than in the control group. This difference was primarily attributed to the decrease in the use of antibiotics such as ciprofloxacin, ceftazidime, imipenem, and antifungal treatment.⁴ These results were confirmed by the DMT-I, with a decrease of 12% and 10% in the use of daily defined doses of systemic antibiotics in the SDD and SOD groups, respectively, as compared to controls.⁵ The post hoc cost-effectiveness evaluation showed that both SDD and SOD were effective and cost saving in Dutch ICUs.⁴⁹

Adverse Events

Three patients are reported to have suffered large clots from accumulation of the buccally applied oral SDD/SOD paste, causing obstruction of the esophagus or jejunum. This complication can be prevented by regular and appropriate oral care.⁵⁰

KEY POINTS

1. Selective decontamination of the oropharynx (SOD) and the digestive tract (SDD) improves survival in ICU patients.
2. Both SDD and SOD lower the incidence of bacteremia, respiratory tract infection (RTI), and the use of systemic antibiotics. SDD reduces the incidence of bacteremia compared to that of SOD. Only SDD lowers the incidence of candidemia compared to controls.
3. No evidence supports the concern that the use of topical antibiotics with or without systemic prophylaxis increases the prevalence of antibiotic resistance to gram-negative bacteria. In particular, SDD decreases the rate of antibiotic resistance to gram-negative bacteria.
4. Both SDD and SOD are cost effective.
5. Larger and longer longitudinal studies are needed to determine the long-term effects of SOD and SDD on antibiotic resistance, with special attention to the changes in antibiotic resistance among gram-negative bacteria in surroundings with high antibiotic resistance levels and in combination with other topical agents such as chlorhexidine.

ANNOTATED REFERENCES

Stoutenbeek CP, van Saene HKF, Miranda DR, Zandstra DF. The effect of selective decontamination of the digestive tract on colonization and infection rate in multiple trauma patients. *Intensive Care Med* 1984;10:185–192.

First study on SDD in ICU patients. Good description and overview of theoretical background.

Liberati A, D'Amico R, Piffieri S, Torri V, Brazzi L, Parmelli E. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. *The Cochrane Library* 2009, Issue 4. Available at <http://www.thecochranelibrary.com>

State-of-the-art meta-analysis. Provides a very good and thorough overview of SDD studies, concluding that a combination of topical and systemic antibiotics causes a significant decrease in RTIs (16 studies; OR, 0.28) and mortality (17 studies; OR, 0.75) compared to controls. Comparing topical antibiotics alone to control or topical plus systemic to systemic alone, there was a significant reduction in RTIs (17 studies; OR, 0.44) but not in mortality (19 studies; OR, 0.97).

de Jonge E, Schultz M, Spanjaard L, et al. Effects of selective decontamination of the digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet* 2003;362:1011–1016.

Prospective, randomized, controlled, single-center study on SDD in 934 ICU patients with an expected length of stay more than 72 hours and/or expected duration of mechanical ventilation more than

48 hours. The most important finding was a remarkable 34.7% relative reduction in ICU mortality for patients treated in the SDD ward. For these patients, the relative reduction in hospital mortality was 22.6%. In addition, SDD-treated patients had a shorter duration of ventilation, and total antibiotic costs were less for these patients. Furthermore, isolation of antibiotic-resistant gram-negative bacteria occurred more frequently among non-SDD patients.

de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in intensive care patients. *N Engl J Med* 2009;360:20–31.

First multicenter, cluster-randomized trial comparing SDD with SOD and control in groups (2000 patients per group). Both interventions significantly improved survival (absolute mortality reduction of 3.5% and 2.9%, respectively) and decreased the rate of bacteremia (ORs SDD versus control, 0.44; SOD versus control, 0.68; SDD versus SOD, 0.65).

Bergmans DC, Bonten MJ, Gaillard CA, et al. Prevention of ventilator-associated pneumonia by oral decontamination: a prospective, randomized, double-blind, placebo-controlled study. *Am J Respir Crit Care Med* 2001;164:382–388.

Prospective, randomized, double-blind, placebo-controlled study showing that oropharyngeal decontamination prevented acquired oropharyngeal colonization and significantly lowered the incidence of VAP but was not associated with better survival or shorter duration of ventilation or ICU stay.

■ References for this chapter can be found at expertconsult.com.

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Central venous catheters (CVCs) are inserted into about half of the ICU patients and are present for 65% of the patient-days. In Europe, the incidence density of CVC-related bloodstream infections (BSIs) ranges from 1 to 3.1 per 1000 patient-days.¹ In the United States, 15 million CVC-days are estimated to occur each year in ICU patients, as well as about 40,000 CVC-related BSIs, leading to a rate of more than 2 for 1000 CVC-days.² The attributable mortality of CVC-related BSIs ranges from 0% to 11.5%,³ and the excess ICU length of stay was estimated at 9-12 days.^{4,5}

In contrast to other nosocomial infections, a large fraction of the risk factors are device-related, suggesting that CR-BSI is largely preventable if rigorous policies are adopted. The education and training of healthcare workers and continuous unit-based improvement programs are essential.^{6,7} New technical developments will be discussed and put into perspective according to the available recommendations.

■ PATHOPHYSIOLOGY

Colonization of the catheter occurs by two main pathways: the extraluminal route and the intra-luminal route. The cutaneous entry site of the catheter is the predominant route of colonization for short-term CVCs (<15-20 days), whereas colonization via the endoluminal route resulting from hub contamination predominates for long-term CVCs.⁸ These main differences should be kept in mind when choosing between different diagnostic options and preventive strategies.

The occurrence of bacteremia caused by common skin organisms is a major criterion for the diagnosis of CR-BSI, although gram-negative *Enterobacteriaceae* and *P. aeruginosa* are often encountered, especially in case of femoral site of insertion.⁹

■ DEFINITIONS

Published guidelines for the diagnosis of CR-BSI are used worldwide. It is important to keep in mind available definitions to better interpret clinical evidence. Related definitions are summarized in Table 120-1.

■ DIAGNOSIS OF CATHETER INFECTIONS

Fever or erythema at the catheter entry site is nonspecific and usually of little help in diagnosing CR-BSI. Usually, when CR-BSI is suspected, the common practice in the ICU is to remove the CVC and to replace it at a new site. However, only about 15 to 25 percent of CVCs removed as such indeed proved to be infected upon quantitative tip culture.

Diagnostic Tests Performed After Catheter Removal

Qualitative broth culture has a high sensitivity but a very low specificity and is unable to distinguish contamination from infection. Quantitative culture techniques have been developed for investigating either the extraluminal part of the catheter (semiquantitative Maki's technique) or the extra- and intraluminal catheter.¹⁰⁻¹³ Overall, quantitative culture techniques appear more accurate than the semiquantitative ones.¹⁴

One clinical and one experimental study showed that the sensitivity of catheter culture^{15,16} might be decreased by the previous use of antimicrobials. This point should be kept in mind when interpreting nega-

tive or borderline culture results and emphasize the need for diagnostic tests (blood and catheter cultures) before starting new antimicrobials.

Diagnosis of CR-BSI with the Catheter in Place

In case of severe sepsis, the catheter should be systematically removed.¹⁴ The diagnosis of catheter-related BSI is then performed as described above. However, most of the suspected catheter-related infections are not life threatening. Diagnostic techniques that allow an accurate diagnosis while keeping the catheter in place are attractive options in these cases.

Quantitative Culture of the Catheter Exit Site

Quantitative culture of the catheter exit site reflects the extraluminal contamination pathway. Bouza et al.¹⁷ have confirmed the good negative predictive value of negative skin surface culture for predicting catheter colonization (NPV, 90.6%) or CR-BSI (NPV, 99.2%).

In case of suspicion of CRI, such culture tests rule out this diagnosis, thereby preventing unnecessary catheter replacement. However, routine surveillance culture is useless, as positive cutaneous culture is closely related to cutaneous clinical signs at the insertion site.¹⁸

Quantitative Blood Culture

Simultaneous samples drawn through the catheter and through a peripheral vein without removal or exchange of the catheter are more accurate in predicting CR-BSI. The time to positivity of a blood culture is highly related to the bacterial concentration in the milieu. Therefore, measuring differences in the time to positivity of hub blood as compared to peripheral blood cultures has been proposed.¹⁹ Using a cutoff of 120 minutes, sensitivity and specificity were greater than 90%.¹⁹ Theoretically, this technique only explores the intraluminal route of infection, but recent reports suggest that it should be used for both short- and long-term CR-BSI.¹⁹⁻²¹ Aspiration is technically impossible in one-fourth of the cases.²² Furthermore, each lumen may represent a source of infection. One study reported that sampling one out of three lumens of the catheters missed 37.3% of the CR-BSI.²³

■ PREVENTION

Guidelines for CR-BSI prevention have been recently updated.^{7,24} Such guidelines are based on two categories of studies: those applying multi-module programs to improve general infection control measures when using catheters, such as surveillance, education, quality management strategies, and those testing new biomaterials, antiseptic dressings, and catheter locks. Key points are summarized in Table 120-2.

Catheter Insertion

One important part of prevention concerns catheter insertion.

Sterile Barrier Precautions and Skin Antisepsis

Full barrier precautions using sterile gloves, a long-sleeved sterile gown, mask, cap, and large sterile sheath drape during catheter

TABLE 120-1 Definitions

| | DEFINITION | COMMENTS |
|---|--|---|
| Catheter tip colonization | Positive culture of the catheter tip that grew to ≥ 15 cfu/mL (semiquantitative), 10^2 cfu/mL (quantitative sonication), or 10^3 cfu/mL quantitative vortexing. | Qualitative culture should no longer be used. |
| Exit-site infection | Tenderness, erythema of site induration >2 cm | Positive culture of exudate confirms the exit-site infection microbiologically |
| Catheter-related bloodstream infection (CR-BSI) | One positive blood culture obtained from a peripheral vein and clinical manifestation of infection and (1) catheter tip colonization or (2) a differential time to positivity of more than 120 min and no obvious source of bacteremia except the catheter | Simultaneous quantitative culture from a peripheral vein and the catheter of 5:1 ratio is rarely used. NB: exclusion of other sources of infection reveals important variability in the final classification in ICU patients. Purulence of the catheter exit site strongly implicates the catheter as the source of infection. |
| Central line–associated bloodstream infection (CLA-BSI) | One positive blood culture and clinical manifestation of infection in a patient with a catheter in place with no other source of bacteremia except the catheter | Easy-to-collect definitions for epidemiologic purposes. Exposed to an overestimation of the BSI due to catheter infection, especially in ICU and oncohematological patients |
| Catheter-related clinical sepsis | Clinical manifestation of infection that disappears within 48 h of catheter removal and a positive catheter tip culture and no other obvious treated source of infection | Represent 30%-50% of catheter-related infections with general manifestations. Not easy to collect routinely but may need antimicrobial treatment (see text). |

TABLE 120-2 Main Recommended Strategies for Prevention of CR-BSI in ICU**STRUCTURE AND PROCESS OF CARE**

Adequate nurse-to-patient ratio
 Use only trained personnel who demonstrate competence for catheter insertion and maintenance
 Educate, assess knowledge, and audit adherence to guidelines of ICU HCWs
 Conduct a continuous quality-improvement program based on recommendations and adapted locally
 Organize a follow-up of the institution's process of care and CRBSI rate
 Participate in a surveillance network

CATHETER INSERTION

Hand hygiene
 Full barrier precautions for CVC insertion
 Preparation of cutaneous site with chlorhexidine
 Subclavian rather than jugular or femoral access (should be weighed against the risk of mechanical complications)
 Avoid subclavian access for dialysis catheters
 Subcutaneous tunnelling for internal jugular or femoral short-term CVCs*
 Ultrasound guidance to reduce number of cannulation attempts and mechanical complications for jugular and femoral access
 Use a sterile sleeve for all pulmonary artery catheters
 Do not routinely replace CVCs (even using guidewire exchange procedure)
 Chlorhexidine-sulfadiazine impregnated for short-term CVCs only if the level of CR-BSI is high despite implementation of a comprehensive strategy to reduce the rate of CR-BSI

CATHETER MAINTENANCE

Immediate dressing change if loosened, soiled, or moistened
 Remove catheters as soon as possible after intended use
 Daily visual inspection of the catheter site
 Sterile transparent or gauze dressings for CVCs
 Gauze when blood is oozing from the insertion site
 Chlorhexidine-impregnated gels or chlorhexidine sponge dressings should be used to reduce CRBSI from arterial catheters and CVCs
 Replace tubing used to administer blood products and lipid emulsions (including propofol) within 24 hours of initiating the infusion
 Replace administration sets no more frequently than at 4-day intervals, but at least every 7 days

insertion is an essential measure for preventing CR-BSI and must be a standard method during central venous and pulmonary catheter insertion. The potential of hand rubs with aqueous alcoholic solution to improve the compliance and tolerance of hand cleansing in the operating room has been reported, and its use could be extended to CVC insertion precautions.²⁵

Chlorhexidine solution is superior to aqueous povidone iodine (PVI) solution for cutaneous antisepsis. However, most studies compared 2% chlorhexidine or chlorhexidine-alcohol preparation to the regular PVI solution.²⁶ Alcohol acts in synergy with both chlorhexidine and PVI. It should be kept in mind that PVI possesses broad-spectrum activity and very rare intrinsic or acquired resistance of bacteria or fungi,²⁷ but its maximal efficacy is only reached after 2 minutes of application. A cluster-randomized study compared 5% povidone/70% ethanol to the regular 10% PVI. This study showed that alcoholic povidone decreased catheter colonization (OR, 0.38; 95% CI, 0.22-0.65) and catheter-related infection (OR, 0.34; 95% CI, 0.13-0.91) but failed to demonstrate a significant decrease in CR-BSI.²⁸

One monocenter randomized trial and one before-after study found that an alcoholic-CHG antiseptic is superior to 5% alcoholic-PVI in terms of catheter colonization.^{29,30}

One prospective cohort study found no difference in catheter colonization by CR-BSI between 0.5% alcoholic chlorhexidine and 2% aqueous chlorhexidine.³¹ A 2% alcoholic chlorhexidine solution is now available, but, considering its high cost as compared to that of the 0.5% alcoholic solution, the potential benefit of the 2% alcoholic chlorhexidine should be further demonstrated. A large RCT comparing 5% alcoholic-povidone iodine and 2% alcoholic-CHG will be available soon (CLEAN study; Clinicaltrial.gov NCT 01629550).³²

The suggested CHG superiority is probably based on its rapid bactericidal activity. The spectrum of CHG is narrower than the spectrum of PVI (particularly for sporulated microorganisms, *Mycobacterium* sp., and viruses). Increases in MIC to CHG have been shown for gram-negative bacteria (*Pseudomonas*, *Proteus*, and *Providencia* spp.), especially after CHG skin preexposure.³³ Less susceptible *Acinetobacter*, *Klebsiella pneumoniae*, and *Enterobacter* have also been recovered in hospital gram-negative flora.³⁴ Finally, acquired resistance has been found in methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum beta-lactamases Enterobacteriaceae (ESBLE).²⁷ In vitro resistance profiles are not presently associated with clinical consequences, but we should be concerned about the extensive use of CHG and the absence of available alternatives.

Other solutions have been tested recently. Octenidine, a 0.1%-propanolol solution, is superior to ethanol in reducing catheter colonization (7.9 vs. 17.8%; $P = 0.009$).³⁵ Data comparing octenidine and CHG are not available.

Catheter Insertion Site

Central venous catheter insertion is required in many critically ill patients. Selection of the insertion site should be based on both the

ease and the risks of the procedure. These latter include infection, thrombosis, and mechanical complications. The choice of the best central venous access for a particular patient is based on the rate and severity of failures and complications.

Subclavian access should be preferred for infection control purposes,³⁶ although other factors (potential mechanical complications, thrombosis, operator experience) should be considered. Internal jugular and femoral access are associated with similar rates of infection, although the femoral route is associated with a higher colonization rate if the catheter is maintained for more than 5 days.³⁷

The use of femoral catheters is associated with a higher rate of thrombosis and should probably be restricted to thin patients for whom the mechanical complication of other access (i.e., pneumothorax or hemorrhage) would be unacceptable.

In the ICU, if femoral or internal jugular access is unavoidable, it should be kept in mind that catheter tunneling decreases the risk of CR-BSI.^{38,39}

Ultrasound-Guided Placement

The use of US guidance has been promoted to decrease the risks of failure and immediate complications of catheter insertion. This technique may confer advantages for jugular internal insertion.⁴⁰ This method decreased the rate of internal-jugular failed insertion and mechanical complications.⁴¹ The impact of US guidance on infection is uncertain.⁴² In hospitals where ultrasound equipment is available and physicians have sufficient training, the use of US guidance should be routinely considered before internal jugular CVC placement. Data concerning femoral and subclavian access are insufficient to draw definite conclusions.

Antithrombotic Prophylaxis

A close relationship has been demonstrated between catheter thrombosis and infection.^{43,44} A fibrin sheath surrounding the catheter enhances catheter colonization.⁴⁵ Recently conducted clinical trials suggest that heparin use reduces catheter-related infections. A randomized, double-blind study of critically ill children reported that heparin-bonded catheters reduce thrombosis (0 vs. 8%; $P = 0.006$) and the rate of positive blood cultures (drawn through the catheter) (4 vs. 33%; $P = 0.0005$).⁴⁶ Although heparin may be beneficial for decreasing the risk of catheter infection in bone marrow transplant patients,⁴⁷ its impact on ICU patients remains to be evaluated. The potential benefits of heparin or heparin-coated catheters might be balanced by the risk of heparin-induced thrombocytopenia.

Catheter Care: Replacement, Dressings, and Tubing

Repeated catheterization increases the risk of catheter infection.⁴⁸ This finding, together with randomized studies, argues in favor of avoiding any routine replacement of CVCs for catheters that are functioning and have no evidence of local or systemic complications. This conclusion is probably different for Swan-Ganz catheters and arterial catheters, where the daily risk of infection might increase with the duration of catheter maintenance.⁴⁹

Physicians and nurses should assess a patient's need for an intravascular catheter on a daily basis. Semipermeable transparent dressings are widely used and allow continuous observation of the skin insertion site and reduce the risk of extrinsic colonization. Gauze dressing is preferred if blood is oozing from the catheter insertion site. Catheter dressings should be changed immediately if the dressing becomes damp, loose, or soiled. We found that two-thirds of the dressings in the ICU have come loose before the planned removal date. Dressing disruption occurs more frequently if subclavian access is not used. The risk of CRI and CR-BSI increased more than threefold after the second dressing disruption and more than tenfold if the final dressing was disrupted.⁵⁰ The rhythm of scheduled dressing changes in the

ICU could be safely increased to 7 days provided soiled or nonadhered dressings are changed immediately.⁵¹

Systematic regrowth of cutaneous flora occurs under the transparent dressing, even after careful disinfection, because bacteria migrate from the derma to the epiderma. Epidermal regrowth of microorganisms is prevented by chlorhexidine-impregnated dressings. Both CHG-impregnated sponges and CHG-gel dressings are associated with a 60% decrease in the risk of catheter infections, including CR-BSIs.^{51,52} These findings were confirmed by a recent meta-analysis.⁵³ CHG-impregnated sponges and CHG-gel dressings were responsible for contact dermatitis in adults, with a rate of less than 10/1000 catheters without any recovered systemic reactions, but are discouraged for use in low-birth-weight infants (≤ 1000 g), where the rate of contact dermatitis was 15.3%.⁵⁴

It is recommended that tubings be replaced at least no more frequently than 96 hours but at least every 7 days.⁵⁵ A large, randomized study comparing tubing replacement every 4 versus every 7 days is ongoing in Australia.⁵⁶ Nevertheless, tubings used to administer blood, blood products, or lipid emulsions (including propofol infusions) should be replaced within 24 hours.⁵⁷

Many needless intravascular connector valves have been introduced into clinical practice to minimize the risk of needlestick injury. After disinfection of the connections, the microbial contamination of these systems is lower than that of the three-way stopcocks with caps.⁵⁸ However, in cohort studies, these systems are frequently shown to be contaminated after the common 3- to 5-second alcohol disinfection and therefore are frequently inadequately disinfected. Moreover, the devices are most often opaque, making it impossible to verify whether they have been properly flushed. These points explain why these devices have been repeatedly associated with outbreaks of bloodstream infections.⁵⁹⁻⁶¹ A large epidemiologic study involving five hospitals strongly suggested that these systems increase the risk of central line-associated infections.⁶² Overall, any excessive manipulation of CVCs independently increases the risk for CR-BSI and must be avoided.⁷

Antimicrobial-Coated or -Impregnated Catheters

The efficacy of catheters impregnated with chlorhexidine and silver sulfadiazine was tested in many randomized studies in the 90s. New chlorhexidine-sulfadiazine-impregnated catheters are now available that have a long half-life impregnation at the internal and the external surface. A meta-analysis of five randomized controlled trials has shown this catheter to halve the risk of CR-BSI (OR, 0.51; 95% CI, 0.56-1.00).⁶³ However, this study found significant heterogeneity between study results. More important, the pooled level of CR-BSI in the control groups was unacceptably high in two studies (7.2% and 14%). Therefore, the use of chlorhexidine-silver-sulfadiazine catheters should be proposed when the rate of infection is high despite adherence to other strategies such as maximal barrier precautions and implementation of an educational program. As acceptable incidence rates are below 1 CR-BSI per 1000 catheter-days, the use of such impregnated catheters is not standard practice. Other catheters impregnated with oligon, silver zeolite, carbon, and platinum have been tested, but their efficacy has not been proven.⁶³

Catheters impregnated intraluminally and extraluminally with minocycline-rifampin reduce the risk of CR-BSI as compared to polyurethane catheters and to externally coated chlorhexidine-silver sulfadiazine-impregnated catheters (OR, 0.23; 95% CI, 0.14-0.40).⁶⁴ Its use decreases the risk of CR-BSI as compared to controls (five studies in ICU; OR, 0.26; 95% CI, 0.15-0.47).⁶³ However, despite eight randomized, controlled trials, no clear conclusion could be drawn regarding the effect of the use of rifampin-minocycline-impregnated catheters on the development of antimicrobial resistance or on the selection of resistant flora and *Candida* spp.^{65,66} A large, monocenter, prospective 7-year follow-up of 9200 catheters (more than 500,000 catheter-days) failed to reveal the emergence of bacterial resistance among staphylococcal species.⁶⁷

Antibiotic or Antiseptic Lock Solutions

The prophylactic use of systemic antibiotic at the time of catheter insertion has not proven to be effective in reducing the incidence of CR-BSI and is strongly discouraged.

Use of an antiinfective lock requires that the catheter not be used during a certain period of time. This method is effective in preventing the endoluminal route of contamination, theoretically achieving antiinfective concentrations sufficient to kill organisms embedded in the biofilm, although its role in preventing short-term CR-BSI in the ICU is limited to catheters not used continuously (such as hemodialysis catheters⁶⁸ or PICCs in neonates). In a recent meta-analysis, the use of antimicrobial lock solutions led to a 69% reduction in the CLABSI rate (RR, 0.31; 95% CI, 0.24-0.40) and a 32% reduction in exit-site infection rate (RR, 0.68; 95% CI, 0.49-0.95) compared to heparin.⁶⁹ However, a significant publication bias was observed. Chelators such as citrate have an anticoagulant activity similar to heparin, increase the activity of antimicrobial drugs against organisms embedded in biofilm, and are superior to heparin in hemodialysis catheters.⁷⁰

Many antimicrobials, including vancomycin, teicoplanin, daptomycin, gentamycin, cephalosporins, and minocycline, have been tested for lock therapy with interesting results. However, in my opinion, to prevent CR-BSI, use of an antibiotic-antiseptic lock should be limited to the administration of substances that cannot be administered parenterally.

Ethanol lock solutions were also evaluated.⁷¹ They were found to be effective at concentrations greater than 20% and to inhibit biofilm formation even if left in place only 2 minutes (>50% ethanol).⁷² No interactions with catheter structures have been observed with concentrations below 90%. Recent RCTs performed outside the ICU provide conflicting results.^{73,74} The flush of the ethanol lock was associated with facial flushing (40%), altered taste (40%), and dizziness (50%) and should be strongly discouraged. Souweine et al. recently found that a 2-minute 60% ethanol lock does not decrease the rate of CR-BSI in hemodialysis catheters of ICU patients.⁷⁵

Impact of Continuous Quality-Improvement Programs

A comprehensive unit-based safety program that includes staff education, identification of and learning from defects, assignment of a manager to lead the program, and implementation of teamwork tools is essential to all general safety programs.^{76,77} Evidence must be translated into practice by creating a checklist, identifying local barriers to implementation, measuring performance, participating in a global network,⁷⁸ and ensuring that all health care workers (HCWs) receive the data. The general components of a unit-based safety program should easily be applied to control CR-BSI. The designation of a program leader is also a key factor for success.

Prevention and control of the spread of multiresistant bacteria, hand hygiene, and surveillance of nosocomial infections should be implemented at first. HCWs should then focus on several established methods directed at preventing contamination of the catheter. Proposed categories of practice should be developed using available recommendations and adapted locally: (1) improve hand hygiene compliance; (2) preferential use of subclavian access if possible; (3) use antiseptic solution containing alcohol; (4) inspect the insertion site daily; (5) immediately change unstuck soiled or moistened catheter dressings; (6) remove catheters immediately when no longer prescribed. These clear recommendations must be constantly reinforced to prevent frequent violations in routine practice.^{79,80}

Importantly, the positive effects of educational programs can be sustained if staff members are involved in designing the measures included in the program and all new nurses, residents, and fellows undergo an introductory in-service training program.⁸¹

Many success stories were published from 2002 to 2010 using these recommendations, most of which were observed in ICUs.⁸²⁻⁸⁶ While I personally believe that a zero-level infection rate could not be reached

and is a dangerous and counterproductive goal,⁸⁷ the implementation of bundles of care (adapted locally) combined with reinforcement of a safety culture is the necessary first step for improvement.

MANAGEMENT OF CATHETER-RELATED INFECTIONS

Catheter Removal or a More Conservative Attitude?

If catheter infection is suspected, the diagnostic strategy must be to change the catheter or use a more conservative strategy. The physician's attitude must be guided by the ease of a new catheter insertion, the immune status, the severity of the underlying illness of the patient, and the severity of the clinical sepsis. In this field, relevant data are very rare, as there are very few randomized studies and there are uncontrolled biases in most of the reported cohort studies. Cautious decisions about catheter removal and the type and length of antibiotic therapy should be made after each case is examined in light of these variables.

In case of septic shock or severe sepsis of undetermined origin or when frank local signs of infection are found, the catheter should be removed. In the absence of severe sepsis or local signs, two conservative strategies might be proposed, especially when a new catheter insertion is hazardous: (1) to change the catheter over a guidewire (GWX) or (2) to perform the watchful waiting strategy,⁸⁸ preferentially with catheter exit site culture (high negative predictive value) with paired blood cultures (high positive predictive value).

When conservative strategies have been initially decided, the decision of catheter removal mainly depends on microorganisms and on the evolution of the patient's state during the first 48 hours.

If blood cultures recover *S. aureus*, enterococci, gram-negative bacilli, or fungi, the catheter should be removed.^{14,89} For coagulase-negative staphylococci, catheters should generally be removed if blood culture contamination is ruled out on the basis of multiple positive culture results with at least one blood culture drawn from a peripheral vein.

Overall, conservative strategies are always risky in critically ill patients. After a decision is made, patients must be cautiously monitored. The catheter must be removed in case of a complicated course suggested by persistent fever or bacteremia longer than 3 days. If GWX occurs in the setting of an infection, the newly placed catheter should be removed. The timing of antimicrobial therapy in such cases has not been studied. Antimicrobial therapy instituted just before GWX might decrease the risk of infection at the new CVC.

Antimicrobial Therapy

When catheter BSI is associated with severe sepsis or shock, antimicrobial therapy must be administered immediately, together with catheter replacement. Probabilistic treatment should include vancomycin, a broad-spectrum β -lactamin with activity against *P. aeruginosa*, and an aminoglycoside. In case of previous *Candida* colonization or high risk thereof, antifungal therapy should be started, preferably with an echinocandin.

Treatment must be deescalated according to the results of catheter-tip cultures and blood cultures. In case of catheter-related BSI with positive blood cultures, the duration of treatment should be at least 14 days for uncomplicated (regression of septic signs and bacteremia <3 days, no persistent infectious site) infections with *S. aureus*, *Pseudomonas* spp., *A. baumannii*, and *Candida* spp. For uncomplicated CRI caused by other microorganisms, antimicrobial therapy should not exceed 7 days if the catheter has been removed. *Staphylococcus lugdunensis* should be treated in a similar manner to *S. aureus*.

In some rare circumstances, catheter salvage therapy might be proposed in the ICU, especially for long-term catheters inserted before the ICU stay. This treatment should only be considered in the absence of

severe sepsis and when *Candida* spp. and *S. aureus* (and probably *Pseudomonas* spp. or *A. baumannii*) are not the responsible microorganisms. Compared with parenteral therapy alone, antibiotic lock therapy was significantly more likely to result in catheter salvage. The fact that the catheter needs to be unused during the antibiotic lock process limits its potential usefulness in the ICU.

There are few reports in the literature to guide clinicians regarding the use of antimicrobial therapy for patients whose catheter tip cultures reveal significant growth in the absence of culture-proven bacteremia or fungemia. In case of clinical catheter-related sepsis, available data suggest that patients with a positive tip culture with *S. aureus* but without demonstrated bacteremia within 24 h after intravascular catheter removal had a 10% to 39% chance of subsequent *S. aureus* bacteremia if they did not receive immediate antistaphylococcal antibiotics. Similar results have been found for *P. aeruginosa*⁹⁰ and extensively resistant *A. baumannii*⁹¹ and to a lesser extent for *Enterococcus* spp. and *Candida* spp.⁹² Treatment within 24 h after intravascular catheter removal led to an important decrease in the incidence of subsequent bacteremia. All these retrospective studies suffer from important methodologic flaws and do not demonstrate that subsequent BSI is directly related to the positive catheter tip culture. While awaiting new studies, it seems reasonable to prescribe a short (7 days) course of antimicrobials to critically ill patient with sepsis whose catheters reveal significant growth of *S. aureus*, *P. aeruginosa*, *A. baumannii* or *Candida* spp., especially in immunocompromised patients or patients with heart valve disease. If the catheter tip culture grows coagulase-negative staphylococci or *Enterobacteriaceae*, catheter removal with no antimicrobial treatment might be sufficient. On the contrary, when a conservative approach has been chosen and the blood culture drawn through the catheter is positive, antimicrobial therapy should probably be given.

Complicated Courses

Relapse, continuous fever, or bacteremia despite removal of the catheter is consistent with a persistent focus of infection. This condition implies the need for prolonged or modified antimicrobial treatment and an active search for a catheter-related infection of another vascular line infection, metastatic abscess, septic thrombophlebitis, or endocarditis.¹⁴

Failure caused by poor pharmacokinetic-pharmacodynamic properties of the antimicrobial are mainly encountered when treating methicillin-resistant staphylococci with glycopeptides.

The volume of distribution of hydrophilic antimicrobials is always elevated in cases of septic shock and might explain the failure of treatment with β -lactams or vancomycin.⁹³ Therefore, therapeutic drug monitoring for the pharmacokinetic optimization of antimicrobials doses, particularly vancomycin, is strongly recommended in these situations.⁹⁴ Through level of vancomycin of 15 to 20 mg/L (or even 20 to 25 mg/L with *S. aureus* endocarditis) should be reached to obtain a C_{min}/MIC ratio of more than 5. Daptomycin might be an alternative of choice,⁹⁵ particularly when the MIC to vancomycin reaches 1.5 mg/mL.⁹⁶

In patients with *S. aureus* CR-BSI and persisting fever or bacteremia, transesophageal echocardiography should be used to rule out an endocarditis, and the treatment duration should be extended to at least 4 weeks of intravenous therapy with an active agent.

An infected intravascular thrombus after catheter removal may explain the persistence of severe sepsis despite adequate antibiotic therapy. In general, the most common infecting organism is *S. aureus*; less common pathogens includes *Candida* spp. and gram-negative bacilli.

The optimal choice and duration of therapy are based on retrospective studies and expert recommendations. A 4- to 6-week antibiotic treatment should be given. Although data from comparative trials are required to draw definitive conclusions, the available evidence suggests that the administration of heparin should be considered early in the management of patients with septic thrombophlebitis.⁹⁷ Surgical excision of the vein is rarely needed and should be limited to patients with purulent superficial veins or patients in whom the infection extends beyond the vessel wall, as well as cases in which conservative therapy has failed.

CONCLUSION

Catheter-related bloodstream infection is a leading type of nosocomial infection, particularly in ICUs, and the most frequent cause of hospital bacteremia. Although CR-BSI has milder consequences than other bacteremic infections, it is a typical device-associated iatrogenic infection and therefore highly preventable if rigorous policies are adopted. CR-BSI should be one of the main targets of a quality improvement program. The management of CR-BSI in the ICU most often requires catheter removal, although a more conservative strategy should be attempted in the absence of severe sepsis or septic shock.

KEY POINTS

1. Catheters are the leading source of bloodstream infections in critically ill patients.
2. Such infections are oversuspected because diagnostic signs are not specific enough, resulting in unnecessary catheter removal.
3. A conservative approach might be attempted in mild infections, while the catheter should always be removed in cases of severe sepsis or septic shock.
4. Comprehensive, unit-based improvement programs are now effective in decreasing the rate of CR-BSI. Rates of CR-BSI higher than 1 per 1000 catheter days are no longer acceptable.
5. A locally adapted checklist of preventive measures should include cutaneous antisepsis with alcoholic preparation, maximal barrier precautions, a strict policy of catheter maintenance, and ablation of useless catheters.
6. Antiseptic dressings and, to a lesser extent, antimicrobial-coated catheters, can be added to the prevention strategies if the level of infections remains high despite implementation of a prevention program.
7. In case of persistence of fever or positive blood culture after 3 days despite adequate antimicrobial therapy and catheter removal, endocarditis or thrombophlebitis should be ruled out.

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INCIDENCE

Septic shock is a form of acute circulatory shock that occurs secondary to severe infection. The incidence of septic shock may be rising, partly related to medical progress that allows individuals to survive longer, resulting in increased numbers of older, debilitated, or immunocompromised patients passing through the intensive care unit (ICU). Some 15% of ICU patients develop septic shock at one time or another, and the mortality rate is close to 50%.^{1,2} Somewhat lower mortality rates have been reported in some trials evaluating the effects of new therapeutic interventions, but such studies include a number of exclusion criteria that are often associated with high mortality rates—cirrhosis, immunosuppression, and “do-not-resuscitate orders,” for example—so it is perhaps not surprising that mortality rates are lower in these therapeutic trials than in “real life.”

ETIOLOGY OF SEPTIC SHOCK

Septic shock is most often bacterial, but it can also be caused by a fungal or parasitic infection. In one-third of patients, no infectious agent is identified.^{1,2} About half of the infections are nosocomial in origin. Although an infection can arise anywhere, the lung is the most common source of infection (40%), followed by the abdomen (20%), indwelling venous and arterial catheters and primary bacteremias (15%), and the urinary tract (10%).^{1,2}

PATHOPHYSIOLOGY OF SEPTIC SHOCK

The pathophysiology of septic shock is complex. Essentially, the systemic sepsis response starts with the recognition of an invading organism or its toxins. Among the bacterial factors, one of the best known toxins is lipopolysaccharide, which is part of the outer gram-negative bacterial membrane, but other bacterial-derived factors include lipoteichoic acid and peptidoglycan. In certain cases, essentially infections involving *Staphylococcus aureus* or β -hemolytic group A *Streptococcus*, the formation of superantigens results in toxic shock syndrome.

The early humoral response involves the complement and contact (kinin-kallikrein) systems. Immune cells, principally monocytes/macrophages and polymorphonuclear neutrophils (PMNs), are not only able to recognize pathogenic agents and their products so they can phagocytose and destroy them but also release a series of mediators that can activate other cells. Among cell membrane receptors implicated in the recognition of pathogenic agents are the so-called Toll-like receptors. In response to cellular stimulation, intracellular signaling is activated, resulting largely in the activation of transcriptional factors, including nuclear factor kappa B, which in turn are responsible for the initiation of proinflammatory reactions. A number of cytokines, two of the key players being tumor necrosis factor alpha (TNF- α) and interleukin (IL)-1 that interact synergistically, are released by macrophages and other cells. TNF- α and IL-1 are particularly important proinflammatory cytokines whose administration in animals can reproduce all features of septic shock including hypotension and development of multiple organ failure. A host of secondary mediators including lipid mediators, oxygen free radicals, proteases, and arachidonic acid metabolites are also released by macrophages, PMNs, and other cells. Vasodilator substances such as nitric oxide (NO) and prostaglandins are released by endothelial cells and are responsible for the early hemodynamic changes of sepsis. NO, in particular, is a

powerful vasodilator acting on vascular smooth muscle. Increased NO production is essentially due to the induction of inducible NO synthase by proinflammatory cytokines. The formation of large quantities of NO can also have secondary toxic effects on cells. NO can block mitochondrial respiration, directly by inhibiting cytochrome a,a3 and reacting with superoxide radicals, resulting in the production of peroxynitrite, which inhibits various phases of mitochondrial respiration.³ These effects result in depletion of cellular adenosine triphosphate and potentially have detrimental effects on cell function. It is important to note that the inflammatory response also causes release of vasoconstrictor substances including thromboxane and endothelins.

Other effects of the inflammatory reaction that accompanies septic shock include expression of adhesion molecules on vascular endothelium and circulating cells (platelets, PMNs, and monocytes), allowing adhesion of activated leukocytes and their migration to subendothelial tissues. Alterations in intercellular endothelial junctions result in increased capillary permeability and generalized edema. Alterations in coagulation and fibrinolysis complete the picture, with proinflammatory mediators creating a procoagulant state. Briefly, the activation of tissue factor on the surface of various cells, particularly monocytes and endothelial cells, initiates the coagulation system.⁴ In addition, sepsis causes a significant reduction in plasma levels of natural anticoagulants such as protein C, protein S, and antithrombin by reducing their synthesis and increasing their consumption and clearance. Thrombolysis is also stimulated with an increase in the levels of plasminogen activator inhibitor-1. The net result is a balance in favor of procoagulant processes, often leading to disseminated intravascular coagulation and participating in the microcirculatory disorder that leads to multiple organ failure and death in many patients with severe sepsis.

During the sepsis response, antiinflammatory mediators including IL-4 and IL-10 are also released, which limit the effects of proinflammatory mediators and can lead to a state of relative immunosuppression sometimes called *immunoparalysis*.⁵ Many patients are already immunosuppressed when sepsis is diagnosed.⁶

CLASSIFICATION

Patients with septic shock may be classified according to the letters *PIRO*⁷:

P = Predisposing Factors

Each patient has specific characteristics. For example, an individual receiving long-term immunosuppressant therapy requires a different approach than someone who was previously healthy. Factors associated with lifestyle, such as alcoholism, may influence the course of septic shock.⁸ Patient age and sex may also be important. Increasingly, genetics is being considered, and studies are discovering the genetic factors that can influence the development of and survival from sepsis.⁹⁻¹¹ Improved understanding of these aspects should help better direct therapeutic strategies.

I = Infectious Insult

This refers to the specific characteristics of the infection, that is, the agent or pathogen involved (e.g., gram-positive vs. gram-negative, bacteria vs. fungus), the source of sepsis (e.g., urinary tract vs.

respiratory tract), and the degree of extension of the infection (e.g., pneumonia confined to one lobe of one lung vs. generalized bilateral lung involvement, appendicitis vs. generalized peritonitis). All these factors can influence the severity of sepsis response and the patient's likely response to therapy.

R = Host Response

This refers to factors involved in the inflammatory response of the host to the infection and is assessed largely by the presence or absence of the signs and symptoms of sepsis (e.g., degree of elevation of white blood cell count, C-reactive protein [CRP], or procalcitonin). Each patient mounts a different response dependent on various factors including those previously discussed, and a patient's response will vary with his or her clinical course and treatment.

O = Organ Dysfunction

This refers to the degree of organ dysfunction related to sepsis and can be evaluated using various scoring systems, including the SOFA (sequential organ failure assessment) score,¹² which uses objective, readily available measures to quantify the dysfunction of six organ systems (Table 121-1). Dysfunction of each organ is rated according to a scale (0 [normal function] to 4 [organ failure]), and individual scores can then be summed to provide a total. Individual organ function as well as a composite score can thus be followed during the course of the disease and treatment.

CLINICAL PRESENTATION

It has been suggested that sepsis progresses in a continuum through to septic shock, but in the clinical situation, such a progression is not always so clear-cut or constant, and it is difficult to predict which patients are going to develop septic shock and when. Septic shock can develop very abruptly, without evidence of signs of sepsis in the preceding hours.

Septic shock is characterized by the persistence of severe arterial hypotension requiring vasopressor support, despite adequate fluid resuscitation, and the presence of perfusion abnormalities manifest by oliguria, reduced peripheral perfusion, and altered mental status. Septic shock is typically associated with hyperlactatemia (blood lactate concentrations above 2 mEq/L).¹³

One may anticipate that patients with septic shock will have fever, leukocytosis, and other typical features of sepsis, but this is not always true. Fever may be an important clue, but moderate fever can be found in other types of shock. More important, fever is often absent in patients with septic shock; in fact, hypothermia may be present in 10% to 15% of cases, and this feature is associated with higher mortality rates.¹⁴ Tachycardia can be the result of circulatory alterations associated with any type of shock. Leukocytosis is also nonspecific and can be found in other types of circulatory failure; moreover, acute leukopenia may occur in sepsis due to peripheral trapping of activated leukocytes and is also associated with a worse prognosis. Lactic acidosis, a hallmark of all types of circulatory failure, is usually compensated by hyperventilation, so tachypnea is not specific for septic shock.

A more typical characteristic of septic shock is the hyperkinetic pattern characterized by high cardiac output. Although such a hemodynamic pattern is not entirely specific—it can be found in other inflammatory states such as polytrauma or pancreatitis or even anaphylactic shock—it should alert the attending physician to a likely diagnosis of septic shock.

HEMODYNAMIC CHANGES

The inflammatory reaction causes intense vasodilation that increases vascular capacity and results in a fall in arterial blood pressure. Hypovolemia due to fluid loss (e.g., diarrhea, vomiting, or sweating) and alterations in capillary permeability contributes to hypotension, and reduced myocardial contractility can further aggravate the hemodynamic situation, although it is completely reversible when the septic shock resolves. The pathophysiology of reduced myocardial contractility includes alterations in endothelial function, alterations in β -adrenergic receptors, and alterations in myocardial calcium metabolism. These effects are caused largely by sepsis mediators such as TNF- α and IL-1, oxygen free radicals, platelet activating factor, and NO, which all have negative inotropic effects.

After vascular filling as a result of volume resuscitation, the hemodynamic status in septic shock is characterized by a fall in vascular tone associated with reduced systemic vascular resistance and a raised cardiac output. In addition, reduced myocardial contractility causes a fall in the ventricular ejection fraction. Ejection volume and, particularly, cardiac output may be maintained by an increase in diastolic volumes. Hence, there is myocardial depression or dysfunction without

TABLE 121-1 The Sequential Organ Failure Assessment Score

| SOFA SCORE | 0 | 1 | 2 | 3 | 4 |
|--|----------------|-------------------|---------------------------------------|---|--|
| RESPIRATION PaO ₂ /FiO ₂ , mm Hg | >400 | ≤400 | ≤300 | ≤200 with respiratory support | ≤100 with respiratory support |
| COAGULATION Platelets × 10 ³ /mm ³ | >150 | ≤150 | ≤100 | ≤50 | ≤20 |
| LIVER Bilirubin, mg/dL (μmol/L) | <1.2 (<20) | 1.2-1.9 (20-32) | 2.0-5.9 (33-101) | 6.0-11.9 (102-204) | >12.0 (>204) |
| CARDIOVASCULAR Hypotension | No hypotension | MAP < 70 mm Hg | Dopamine ≤5 or dobutamine (any dose)* | Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1* | Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1* |
| CENTRAL NERVOUS SYSTEM Glasgow Coma Score | 15 | 13-14 | 10-12 | 6-9 | <6 |
| RENAL Creatinine, mg/dL (μmol/L) or urine output | <1.2 (<110) | 1.2-1.9 (110-170) | 2.0-3.4 (171-299) | 3.5-4.9 (300-440) or <500 mL/d | >5.0 (>440) or <200 mL/d |

Data from Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units. Results of a multicenter, prospective study. Crit Care Med 1998;26:1793-800.

*Adrenergic agents administered for at least 1 hour (doses given are in μg/kg/min).

any true cardiac failure (which would be associated with reduced cardiac output).

MONITORING

Any patient with septic shock requires monitoring with an arterial catheter to enable reliable and continuous assessment of arterial pressure. Changes in systolic and pulse pressures in mechanically ventilated patients during the respiratory cycle may also indicate a greater likelihood of response to a fluid challenge; however, this sign is not reliable when the patient triggers the ventilator.¹⁵ The arterial catheter also facilitates blood sampling, notably for blood gas analysis.

Invasive Versus Less Invasive Monitoring

The role of the pulmonary artery catheter (PAC) in critically ill patients has been questioned. However, although no study has conclusively demonstrated positive effects of this type of monitoring on outcome,¹⁶ information obtained from the PAC may help in guiding patient management in complex cases.¹⁷ The PAC is useful not only for monitoring pulmonary artery occlusion pressure (PAOP) and cardiac output but also for assessment of mixed venous oxygen saturation (SvO_2), a highly useful parameter because a fall in SvO_2 is generally indicative of inadequate oxygen transport.

Less invasive monitoring techniques are increasingly being used. Echocardiography can provide useful additional information, largely to visualize the degree of ventricular filling and ejection volume. However, echocardiography requires an experienced operator, gives no information on the adequacy of cardiac output for the patient's needs, and is difficult to perform continuously, so information is usually intermittent. Other less invasive methods of monitoring cardiac output include PiCCO, LidCO, transesophageal Doppler techniques, and even bioimpedance or bioreactance techniques.¹⁸ However, measurement of cardiac output in isolation is not very helpful in most critically ill patients.

Blood Lactate Levels

The blood lactate level is an important biological variable in determining the adequacy of perfusion and oxygenation. The normal blood lactate level is around 1 mEq/L, and hyperlactatemia becomes clearly pathologic above a level of 2 mEq/L. Although hyperlactatemia is due to cellular hypoxia in other forms of circulatory shock, in septic shock, additional mechanisms may play an important role in raising blood lactate levels. In sepsis, blood lactate levels may be raised by an increase in cellular metabolism, by inhibition of pyruvate dehydrogenase, and by reduced clearance. Repeated measurements enable one to assess the efficacy of treatment¹⁹ and have a predictive value superior to derived oxygenation parameters. The evolution of blood lactate levels enables a global evaluation of the state of shock in response to treatment, although in view of the relatively slow rate of change, blood lactate levels cannot be used to guide resuscitation.

Peripheral Perfusion Parameters

Measurement of the gastric intramucosal pH or its derivatives (mucosal PCO_2 or the difference between the mucosal and arterial PCO_2 [the PCO_2 gap]) is considered to reflect splanchnic perfusion and hence provide an idea of the adequacy of regional oxygenation. However, these techniques may be influenced by technical considerations, including the influence of gastric acid and enteral nutrition, and are not used clinically.

Other techniques for monitoring peripheral perfusion have been developed. While the sublingual region is not a region that would immediately seem to be of most interest, it is easily accessible, and using techniques of orthogonal polarization spectral or sidestream darkfield imaging, heterogeneity of microcirculatory flow and reduced perfused vessel density and proportion of perfused vessels can be

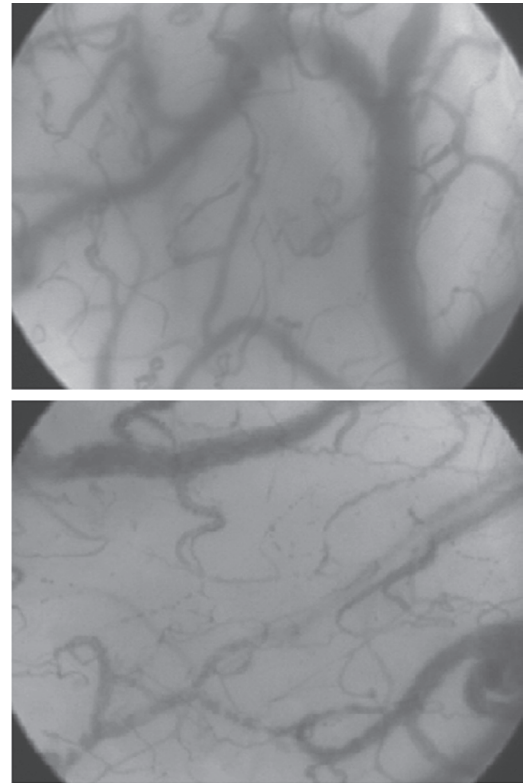


FIGURE 121-1 ■ Representative examples of sublingual microvasculature in a healthy volunteer (*top panel*) and in a patient with septic shock (*lower panel*). Note decrease in density of small vessels in sepsis. (From De Backer D, Creteur J, Preiser JC, et al. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med* 2002;166:98–104, with permission.)

observed (Fig. 121-1) and quantified in patients with sepsis.²⁰ Moreover, the impact of therapeutic interventions on such changes can be monitored,^{21,22} opening the possibility that monitoring the microcirculation could be used to guide treatment.

Near-infrared spectroscopy is a technique that uses the differential absorption properties of oxygenated and deoxygenated hemoglobin to evaluate tissue oxygenation (StO_2). Analysis of changes in StO_2 during a circulatory stress test, such as a brief episode of forearm ischemia (venous or arterial occlusion), may be more useful to quantify sepsis-induced microvascular dysfunction than an isolated StO_2 value.²³

Although these techniques have demonstrated clearly the presence of alterations in the microcirculation in patients with sepsis, which are associated with prognosis,²⁴ further research is needed to fully evaluate the relevance of these values to the early resuscitation and care of critically ill patients.

MANAGEMENT

Septic shock, which systematically causes dysfunction of other organs, is a serious condition, and patients must be stabilized as a matter of urgency. Management of the patient with septic shock involves three inseparable components: treatment of the infection, cardiovascular resuscitation, and modulation of the host response (Fig. 121-2).²⁵

Treatment of Infection

Infection must be treated effectively and rapidly. Antibiotics must be started quickly and must cover all likely organisms.²⁶ The choice of antibiotics may depend on local microbiological flora and resistance

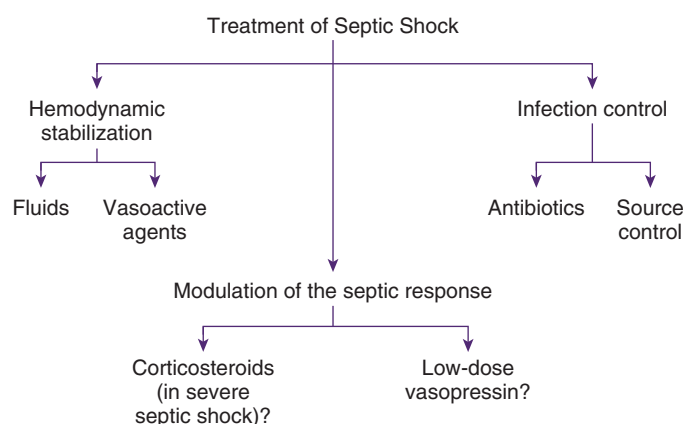


FIGURE 121-2 ■ The three aspects of the treatment of septic shock.

patterns. Often, the microorganism(s) responsible for sepsis in an individual patient is not known for sure, and empiric broad-spectrum antibiotics must be given to ensure adequate coverage. Such empiric therapy must then be modified as soon as microbiology culture results become available.

In addition to antibiotic treatment, any focus of infection must be removed or drained by emergency surgery if necessary. If no source is identified, a systematic search should be made based on the “big five”: lungs, abdomen, urine, wounds, and catheters.

Cardiovascular Resuscitation

The VIP rule proposed by Weil and Shubin²⁷ should be followed. Each patient is in fact a VIP, but the letters refer here to *Ventilation, Infusion, and Pump*.

V = Ventilation

All patients with septic shock must be generously oxygenated with the aim of correcting any hypoxemia, regardless of whether it is due to inadequate cardiac output, pulmonary edema, or pulmonary disease. Severe cases need endotracheal intubation and mechanical ventilation. Noninvasive ventilation is not recommended in such hemodynamically unstable patients. Even though it may represent a temporary support rather than a treatment per se, mechanical ventilation allows not only an improvement in gaseous exchange but also has beneficial hemodynamic effects, notably by reducing the oxygen requirement of the respiratory muscles.

I = Infusion

Septic shock is accompanied by absolute and relative hypovolemia, the result of various mechanisms:

- External losses, which may be obvious, such as vomiting and diarrhea, or less apparent, such as sweating
- Internal losses via an increase in capillary permeability with development of edema and sometimes liquid effusions (peritoneal, pleural effusion)
- Increase in plasma volume associated with arterial and venous dilatation

Hypovolemia needs to be corrected rapidly as it causes hemodynamic instability both at the level of cardiac output and in terms of peripheral perfusion.

Assessment of an adequate volume state is essentially clinical: restoration of arterial pressure, improvement of cutaneous perfusion, improved urine output, and improved mental state. The central venous pressure (CVP) can be a useful guide, but it is not possible to define in advance the CVP that should be reached in any individual patient. Measurements of CVP or PAOP are primarily used as a limit

TABLE 121-2

The Fluid Challenge Technique (with the TROL Mnemonic)

| DEFINE | EXAMPLE |
|------------------|----------------------------------|
| Type of fluid | Ringer's lactate |
| Rate of infusion | 200 mL in 10 min |
| Objective | Mean arterial pressure >75 mm Hg |
| Limits | Central venous pressure 16 mm Hg |

to fluid administration in order to minimize the risk of pulmonary edema. In fluid replacement, it is preferable to use a fluid challenge technique, in which filling pressures are measured at regular intervals during fluid administration (Table 121-2).²⁸ If cardiac output is monitored, one should ensure that it increases with fluid boluses, and such fluid administration should be stopped when cardiac output reaches a plateau.

There has been considerable debate as to which fluid should be used in sepsis, but it is the quantity of fluid rather than the type of fluid per se that is of greatest importance. Because of their propensity for leakage into the extravascular space, greater volumes of crystalloids are needed to achieve the same effect as colloids,²⁹ thus potentially increasing the risk of edema, but colloids are more expensive and carry their own risks. In particular, there has been considerable controversy about the use of albumin in critically ill patients, but the SAFE study suggested a decrease in mortality associated with albumin administration in patients with sepsis.³⁰ Most clinicians would use some albumin in septic patients with significant hypoalbuminemia.

P = Pump (Vasoactive Agents)

If fluid administration alone is unable to restore an adequate perfusion pressure, vasoactive agents are required. Catecholamines are preferred for their rapid action and efficacy and their short half-lives. Adrenergic agents stimulate β_1 - (positive inotropes), β_2 - (essentially vasodilators and bronchodilators), and α - (essentially vasoconstrictors) receptors to varying degrees. Dopamine also stimulates dopaminergic receptors, causing vasodilation primarily in the splanchnic and renal regions, but the clinical relevance of this effect is doubtful.

A randomized controlled study showed that dopamine use is associated with increased adverse effects, notably arrhythmias, in patients with shock,³¹ and a meta-analysis indicated that dopamine administration is associated with higher mortality rates than norepinephrine in septic shock.³² Norepinephrine is, therefore, the preferred first-line vasopressor in patients with septic shock. Epinephrine should not be used as a first-line vasopressor in patients with septic shock; it can have deleterious effects on splanchnic circulation and increase cellular metabolism. Dobutamine is often added to vasopressor therapy, particularly when using norepinephrine, to increase cardiac output by its positive inotropic effects.

The place of vasopressin derivatives is not well defined. Patients with septic shock usually have a degree of relative vasopressin deficiency so that vasopressin supplementation may be warranted. Recent studies have suggested that vasopressin is involved in endothelial protection so that early administration of vasopressin derivatives may limit edema formation.³³ This hypothesis is presently being tested in clinical trials.

Immunomodulation

Clinical trials assessing drugs that limit the effects of proinflammatory cytokines such as TNF- α (anti-TNF antibodies, TNF receptors) and IL-1 (IL-1 receptor antagonist inhibitors) have not given convincing results on beneficial effects of these agents on outcome, probably largely because such cytokines have multiple effects, beneficial as well as harmful. Administration of activated protein C (drotrecogin alfa [activated]) early in septic shock reduced mortality and morbidity in

initial studies,³⁴ but the drug was withdrawn from the market after a later negative placebo-controlled study.³⁵

The administration of large doses of corticosteroids for patients with septic shock was proposed many years ago. More recently, the concept of relative adrenal insufficiency has emerged, and administration of moderate doses of corticosteroids (200 mg hydrocortisone in 24 hours) in patients with septic shock has been proposed, but this is also debated.^{36,37}

The treatment of fever is controversial. Increased body temperature increases oxygen requirements, but the increased cellular metabolism may form part of the body's natural defense. Animal studies have suggested that control of fever is detrimental³⁸ and that the release of heat shock proteins in fever may have important protective effects.³⁹ A multicenter study of acetaminophen in febrile ICU patients with suspected infection showed that the drug was well tolerated but did not reduce mortality.⁴⁰

High-flow hemofiltration techniques can remove a range of bacterial products and mediators but are not without risk, notably because this process can remove beneficial products such as hormones and medications, including antibiotics, as well as potentially harmful substances.⁴¹ Clinical studies have provided conflicting data regarding the effects of these techniques on outcomes.⁴²

Nutritional Support

Malnutrition can prolong the course of sepsis and increase the risk of complications. When considering nutritional support in patients with septic shock, several factors should be remembered:

- There is no urgency to start nutritional support, unless the patient is malnourished.
- The enteral route is preferable to the parenteral route.
- Enteral nutrition should not be started during the initial phase of resuscitation. Although studies are limited, increasing the oxygen requirements of the gut is probably unwise in circulatory shock. However, as soon as the patient has achieved a degree of hemodynamic stability (after a maximum of 24–48 hours), enteral nutrition should be started.
- There is no urgency to start parenteral nutrition. Waiting a few days is acceptable.
- Careful control of blood glucose levels is recommended. Control of blood glucose levels has been shown to be associated with improved outcomes,⁴³ but hypoglycemia can be a problem with very strict blood glucose protocols. A suggested target glucose concentration is, therefore, 110 to 150 mg/dL.^{25,44} Variability in glucose levels should also be avoided.⁴⁵

Organ Support

Organ dysfunction can involve any organ and can be quantified using the SOFA score (see Table 121-1). Techniques for individual organ support are covered in separate chapters, but an overview is given here.

Respiratory Alterations

Respiratory failure is a common complication of sepsis and is usually characterized by hypoxemia. The diagnosis of acute respiratory distress syndrome is made when the $\text{PaO}_2/\text{FiO}_2$ ratio is less than 300 mm Hg in the presence of bilateral infiltrates on a chest radiograph, with no evidence of left heart failure.⁴⁶

When starting a patient on mechanical ventilation, several factors need particular attention:

- Worsening of arterial hypotension when starting mechanical ventilation suggests the presence of hypovolemia due to a reduction in venous return (and hence in cardiac output) when intrathoracic pressures are increased.

- Tidal volume should be limited, not only for hemodynamic reasons but also to avoid a major inflammatory reaction.
- Sedation must be avoided whenever possible. Administration of sedative drugs and analgesics should be titrated with respect to the needs of the individual patient. Reduced administration of sedative agents can shorten the duration of mechanical ventilation and ICU stay.^{47,48}

Renal Alterations

Sepsis is the leading cause of acute renal failure in the ICU.⁴⁹ Renal function can worsen as a result of combined circulatory changes and inflammation. In addition, management of septic patients often involves administration of nephrotoxic agents—for example, aminoglycosides or contrast material for radiologic examinations.

Unfortunately, there is no prophylactic approach to renal failure other than to try to maintain adequate renal perfusion and overall volume state. Administration of low (renal)-dose dopamine is ineffective at preventing renal failure,⁵⁰ and diuretics may be harmful.⁵¹

Renal replacement therapy is frequently necessary in septic patients. In septic shock, continuous venovenous techniques, with or without dialysis, are generally preferred over intermittent techniques to facilitate control of fluid balance.

Coagulation Alterations

Coagulopathy is common in septic shock. A low platelet count is common and may be associated with a prolonged prothrombin time and an activated partial thromboplastin time. Treatment of these alterations revolves primarily around the cause, and there is no indication for heparin therapy. In severe cases associated with significant bleeding, administration of fresh frozen plasma or platelet infusions may be indicated.

Hepatic Alterations

Circulatory shock of any cause frequently results in the elevation of liver-associated enzyme levels, but the contribution of various organs (e.g., muscles) to increased enzyme levels is difficult to quantify. Often there is a rise in bilirubin levels after several days, without evidence of hemolysis, major hematomas, or biliary pathology. Supplementary examinations such as ultrasound may be indicated to exclude any associated biliary pathology.

Cerebral Function Alterations

Circulatory shock is typically accompanied by an alteration in intellectual function, initially manifested as confusion without real coma. Cerebral alterations can be prolonged, and the patient is then said to have septic encephalopathy. The exact cause of the encephalopathy is unclear, although various mediators of sepsis have been implicated. Investigations are of little use except to exclude other causes. The electroencephalogram generally shows a slow diffuse slowing,⁵² whereas cerebral computed tomography and cerebrospinal fluid examination are normal. These alterations are usually fully reversible with the resolution of shock.

CONCLUSION

Optimal treatment of a patient with septic shock requires a rapid and effective management plan with the assistance of the full ICU team. Infection control and achieving hemodynamic stability must be tackled simultaneously. Other interventions are currently undergoing clinical trials, with the hope that they will improve the microcirculatory changes of sepsis or beneficially modulate the host response. A better characterization of patients with septic shock—for example, by using the PIRO system—is necessary to appropriately titrate therapeutic interventions to individual patients.

KEY POINTS

1. Septic shock affects about 15% of ICU patients and has a mortality rate of close to 50%.
2. Septic shock is most commonly caused by a bacterial infection, although fungi, viruses, and parasites can all be implicated. The most common source of infection is the lung, followed by the abdomen.
3. Patients with sepsis can be classified according to their predisposing factors, the nature of the infection, degree of immune response, and associated organ dysfunction.
4. *Septic shock* is defined as sepsis with organ dysfunction with persistent arterial hypotension requiring vasopressor administration despite adequate fluid resuscitation, in the presence of perfusion abnormalities manifested by oliguria, reduced peripheral perfusion, and/or altered mental status.
5. Blood lactate levels are typically raised in septic shock, and persistently raised levels are a poor prognostic sign.
6. Management of septic shock includes infection control, hemodynamic stabilization, and modulation of the host response.

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CHANGING OUTCOMES AND EPIDEMIOLOGY

The mortality rate due to neonatal and pediatric severe sepsis has improved from 97% in 1963 to 9% in 1999 to 4% in 2003.¹⁻⁴ Previously healthy children have better outcomes than children with chronic illness. The randomized controlled trial of bactericidal permeability-increasing protein⁵ for children with purpura fulminans/presumed meningococcal septic shock showed 10% mortality rates in the placebo groups. The reported outcomes in children with septic shock when using therapeutic approaches similar to those recommended in the 2002 American College of Critical Care Medicine *Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Patients in Septic Shock*⁶ show a decreasing tendency. In children with meningococcal septic shock in the United Kingdom, a 5% mortality rate was reported,⁷ and in the Netherlands, a decreasing mortality was shown in the same patient group.⁸ Ngo and colleagues⁹ observed a 0% mortality rate in a randomized dengue shock fluid resuscitation trial. The U.S. KIDS database showed an overall 4.2% severe sepsis mortality, with 2% in previously healthy and 8% in chronically ill children.³ The most recent implementation of the AAP-CHA septic shock initiative in 22 pediatric emergency departments showed a reduction in hospital mortality from 11% to 3%, with the use of an identification trigger tool and administration of fluids and antibiotics within the first hour of presentation.¹⁰ This timely administration of antibiotics and fluids also decreases the incidence of organ dysfunction and multiple organ failure.¹¹

Although outcomes are improving, the burden of newborn and pediatric sepsis is increasing in the United States. More children die with severe sepsis than with cancer, with an estimated yearly healthcare cost of \$4 billion in the United States for patients with this condition.⁴ Half are newborns, with most of these having a low birth weight. Half of the children with severe sepsis have underlying chronic illness. Neurologic and cardiovascular chronic illnesses are most common in infants with severe sepsis and cancer, whereas immune deficiency is most common in children with severe sepsis. Medical advances have affected etiology and epidemiology. In 1990, Jacobs and coworkers¹² reported that the most common causes of septic shock in children were, in descending order, *Haemophilus influenzae* b, *Neisseria meningitidis*, and *Streptococcus pneumoniae*. The 1995 and 1999 U.S. estimates suggest a change. *H. influenzae* type b is all but nonexistent; *N. meningitidis* is prevalent in only a few regions of the United States, and group B *Streptococcus* is decreasing. The more recent use of the *S. pneumoniae* vaccine is reducing the incidence of this infection. The Canadian government has implemented nationwide immunization in children younger than 2 years for *N. meningitidis* serotype C.¹³ The most prevalent causes of severe sepsis and septic shock in the United States now seem to be staphylococcal and fungal infections.⁴ Methicillin-resistant *Staphylococcus aureus* (MRSA) is an emerging disease.¹⁴ Influenza vaccines are now universal for both endemic and pandemic forms (H1N1). While mortality rates in the United States are decreasing in all other organisms, they are doubling in children with *S. aureus* infection, underlining the need for first-line MRSA coverage in children with severe sepsis.^{4,14}

PATHOPHYSIOLOGY AND DEVELOPMENTAL EFFECTS

Molecular Pathogenesis

Controlled Inflammation with Eradication of Infection

Endotoxin, mannose, and other glycoprotein moieties on the cell walls of yeast and fungi, superantigens, toxins associated with some gram-positive bacteria, mycobacteria, and viruses, also called *pathogen-associated molecular patterns*, activate the innate immune system after recognition by pathogen recognition receptors. The innate immune system comprises polymorphonuclear neutrophils, monocytes, and macrophages, in part through Toll-like receptors, CD14 receptors (endotoxin), and other costimulatory molecules. These innate immune cells internalize microorganisms and kill them. Monocytes and macrophages present processed antigens from these killed microorganisms to circulating T lymphocytes and coordinate the adaptive immune response. This second wave of immune response includes B-cell activation and antibody production and generation of cytotoxic T cells and natural killer (NK) cells (particularly in viral and fungal infection). Opsonization with antibodies allows the more efficient recognition, killing, and clearing of microorganisms by resident macrophages in the reticuloendothelial system.^{15,16}

The activated inflammatory cells also initiate a series of biochemical cascades that result in phospholipase A₂, platelet-activating factor, cyclooxygenase, complement, and cytokine release that orchestrate an efficient and controlled inflammatory/immune response. The cytokines tumor necrosis factor (TNF) and interleukin (IL)-1 β synergistically interact to promote positive feedback cascades that result in fever and vasodilation. These cytokines stimulate the production of many important effector molecules, including proinflammatory cytokines (e.g., IL-6, IL-8, and interferon [IFN]-gamma), which promote immune cell-mediated killing and antiinflammatory cytokines (e.g., soluble TNF receptor, IL-1 receptor antagonist protein, IL-4, and IL-10), which turn off the immune response when the infection has been cleared. These cytokines stimulate nitric oxide (NO) production, which leads to vasodilation. NO combines with superoxide radicals to form peroxynitrite radicals (ONOO⁻), which participate in the intracellular killing of microorganisms. Cytokines increase the expression of endothelial-derived adhesion molecules, including E-selectin, which facilitates white blood cell rolling, and intercellular adhesion molecule and vascular adhesion molecule, which facilitate white blood cell adhesion and diapedesis. This activity guides activated inflammatory cells to the site of infection. The cytokines induce a change in the endothelium to a prothrombotic and antifibrinolytic state. Expression of thrombomodulin is possibly decreased, and expression of the prothrombotic molecule tissue factor and the antifibrinolytic molecule plasminogen activator inhibitor-1 (PAI-1) is increased. The ensuing thrombus "walls off" the infection and allows vascular remodeling until antiinflammatory cytokines turn off the proinflammatory cytokine response and restore the antithrombotic profibrinolytic milieu after the infection is cleared.

Uncontrolled Inflammation and Persistent Infection Lead to Septic Shock and Multiple Organ Failure

If the controlled activated immune cell response is ineffective in killing the infectious agent and clearing the antigen or if inflammation is uncontrolled, systemic organ injury ensues. Increased TNF and NO production in cardiac cells and circulating myocardial depressant substances can lead to cardiac dysfunction and cardiovascular collapse. Peroxynitrite can cause DNA damage, and subsequent polyadenosyl ribose synthase activation depletes cells of oxidized nicotinamide adenine dinucleotide and adenosine triphosphate (ATP), leading to secondary energy failure. Thrombosis and antifibrinolysis become systemic. Antithrombotic molecules, including protein C and antithrombin III, are consumed, and ongoing systemic release of tissue factor and PAI-1 results in unremitting thrombosis. At some point, the consumption of procoagulant factors leads to a precarious state in which thrombosis is accompanied by bleeding because there are insufficient clotting factors. The antiinflammatory response becomes deleterious. IL-10 induces a T_H2 response and reduces the ability of monocytes/macrophages to kill the infection. Overactivated immune cells release Fas and Fas ligand. Circulating Fas prevents activated immune cell apoptosis and ensures ongoing inflammation, and the Fas ligand can induce liver injury. In patients with NK cell dysfunction, activated immune cell death is further hampered. Ineffective and unresolving inflammation leads to systemic organ failure.

Clinical Pathologic Correlates

On the basis of in vivo biochemical analyses and an autopsy histology, several forms of multiple organ failure could be characterized.¹⁷⁻²⁷ *Thrombocytopenia-associated multiple organ failure* (platelet count < 100,000/ μ L or a 50% decrease in platelet count from baseline) was attributable to purpura fulminans and disseminated intravascular coagulation (DIC) with increased tissue factor activity in vivo and fibrin thrombi at autopsy in only 20% of patients. Of these patients, 80% showed thrombotic thrombocytopenic purpura pathophysiology with increased thrombogenic ultralarge von Willebrand factor (vWF) multimers, absent vWF cleaving protease (ADAMTS 13), increased PAI-1 activity in vivo, and platelet/fibrin thrombi at autopsy. This phenotype responds well to daily plasma exchange, which removes ultralarge vWF multimers and restores ADAMTS13 activity.²¹ The monoclonal C5A antibody eculizumab is FDA approved for children with this syndrome and atypical TTP-HUS.²²

Sequential or liver dysfunction-associated multiple organ failure (shock/acute respiratory distress syndrome followed sequentially by liver and renal failure) was associated with viral sepsis and lymphoproliferative disease.²³ Patients were found to have unremitting Epstein-Barr virus (EBV) infection, with lymphocyte Fas ligand-mediated destruction of liver and high circulating Fas and Fas ligand levels. This syndrome is also found in patients with defects in NK cell activity. Absent NK cell activity is found in primary hemophagocytic lymphohistiocytosis (HLH), and decreased NK cell activity is found in secondary HLH. NK cells are responsible for killing viruses and stopping lymphoproliferation. Posttransplant-related lymphoproliferative disease is treated with the CD20 monoclonal antibody rituximab, which eradicates the EBV reservoir.²⁴

Unresolving multiple organ failure with prolonged monocyte deactivation (monocyte HLA-DR expression <30% or ex vivo TNF response to lipopolysaccharide <200 pg/mL for >5 days) was associated with secondary bacterial, fungal, or herpesvirus family infection. These patients had elevated IL-10 and IL-6 levels. Patients who died had infection at autopsy.²⁵ This was associated with *lymphoid depletion syndrome* (lymphocyte depletion of the lymph nodes and spleen) at autopsy.²⁶ All these children had fungal, bacterial, or herpesvirus family infection at the time of death. Risk factors (odds ratio >10) for this process included lymphocytopenia (<1000/ mm^3) or hypoprolactinemia or both for more than 7 days. Phagocytosis of these apoptotic bodies by monocytes/macrophages leads to immunoparalysis. Daily

GM-CSF can reverse this process and prevent secondary infections.²⁵

Sepsis with features of *macrophage activation syndrome* is defined clinically by the presence of DIC, and hepatobiliary dysfunction with hyperferritinemia (>500 ng/mL) can be a manifestation of macrophage-driven hyperinflammation related to uncontrolled inflammation secondary to an uneradicated source or to an inflammation phenotype left untreated. Histology shows hemophagocytic histiocytosis in the presence or absence of increased CD8 T cells and reduced NK cells. Treatment of this syndrome with IL1RAP was associated with a reduction in mortality from 60% to 31% in adult patients with severe sepsis.²⁷

These clinical pathologic correlates support the following hypotheses: (1) uncontrolled inflammation contributes to organ failure after septic shock, (2) uncontrolled inflammation contributes to systemic thrombosis, (3) uncontrolled inflammation leads to adrenal dysfunction not only through thrombosis but also potentially through NO-mediated inhibition of cytochrome P450 activity, (4) uncontrolled inflammation is commonly associated with uneradicated infection, and (5) it is likely that genetic and environmental factors increase a patient's risk of systemic thrombosis and uneradicated infection and the development of inflammation phenotypes that can respond to personalized therapies.

Coagulation System

As is generally accepted and explained in many reviews, coagulation and fibrinolysis are integral parts of the immune system.²⁸ There are important physiologic differences in the hemostatic system in children compared with adults. The decreased levels of several crucial coagulants and increased levels of α_2 -macroglobulin may contribute, in part, to the lower risk of thrombotic events in childhood during physiologic conditions.^{29,30} In pathologic conditions, these physiologic differences might lead to an earlier exhaustion of coagulation factors and DIC in infants and young children.³¹ ADAMTS 13 is decreased in infancy; therefore, there may be an increased susceptibility to systemic fibrin and platelet thrombosis. The coagulation system is a marker of organ dysfunction in sepsis. It is associated with subsequent endothelium activation and systemic clotting and finally antifibrinolysis.

Cardiovascular System

Ceneviva and associates³² found that in contrast to adults, who predominantly have high cardiac output/low vascular resistance shock, children with fluid-refractory/inotropic-resistant shock have varied hemodynamic states, including low cardiac output/high systemic vascular resistance (60%), low cardiac output/low vascular resistance (20%), and high cardiac output/low vascular resistance (20%), which can change with time and depend on age. In contrast to adults, death from shock is most commonly associated with progressive cardiac failure, not vascular failure. Infants and children are frequently insensitive to dopamine or dobutamine and respond to epinephrine (cold shock) or norepinephrine (warm shock).³²⁻³⁴ Newborns are different as well. Adults can double their heart rate to improve cardiac output, but newborns cannot. Newborns, although tachycardic, depend on increased vascular tone to maintain blood pressure. Persistent pulmonary hypertension and right ventricular failure complicate newborn septic shock.^{35,36}

PREDISPOSING FACTORS AND PREVENTION STRATEGIES

Environmental and genetic factors associated with reduced immune function predispose children to the development of sepsis and septic shock. These factors include age (prematurity, neonate, and age <1 year), cancer and immunosuppressive chemotherapeutic agents, transplantation and immunosuppressive agents, primary immunodeficiency disorders (e.g., hypocomplementemia, hypogammaglobulinemia, or chronic granulomatous disease), acquired immunodeficiency

disorders (neutropenia, lymphocytopenia, or monocyte deactivation), and malnutrition. Prolonged use of invasive catheters, muscle relaxants, and broad-spectrum antibiotics also predisposes to infection.

Among the community-acquired causes of sepsis, *N. meningitidis* has a diverse clinical picture, ranging from a self-limiting bacteremia to meningitis to a severe rapidly fatal sepsis. After invasion of the bloodstream by the bacteria, three main cascade pathways are activated: the complement system, the inflammatory response, and the coagulation and fibrinolysis pathway. These pathways do not act independently but are able to interact with each other. Genetic polymorphisms among components of these pathways have been shown to be involved in the susceptibility, severity, and outcome of meningococcal disease. Knowledge of genetic variations associated with susceptibility to and severity of meningococcal infection has been reviewed.³⁷

Complement deficiencies and defects in sensing or opsonophagocytic pathways, such as the rare Toll-like receptor 4 single nucleotide polymorphisms and combinations of inefficient variants of Fcγ-receptors, seem to have the most important role in genetically established susceptibility. The most recent and largest study on susceptibility is a genome-wide analysis of DNA from 1600 children with meningococcal sepsis. The results of this study showed the significant influence of genetic variants in the complement factor H in the susceptibility.³⁸ This deficiency has been associated with atypical TTP-HUS, which manifests as *thrombocytopenia-associated MOF*. Plasma exchange and the C5a monoclonal antibody eculizumab have been used to treat these children and adults.²⁷ The effect on severity has repeatedly been reported for FcγRIIa and PAI-1 polymorphisms. Angiotensin-converting enzyme is associated with a proinflammatory response. The absence of a 284-base pair marker in the angiotensin-converting enzyme gene (D allele) is associated with higher circulating angiotensin-converting enzyme activity than the presence of an I allele. The DD genotype is associated with increased disease severity, and although not significant, a twofold increase in mortality rate has been reported. Outcome effects have been confirmed for single nucleotide polymorphisms in properdin deficiencies, PAI-1 and combination of the -511C/T single nucleotide polymorphisms in IL-1β, and +2018C/T single nucleotide polymorphisms in IL RN. Conflicting results are reported for the effect of the -308G/A promoter polymorphism in TNF. These differences may reflect discrepancies in group definitions among studies or the influence of additional single nucleotide polymorphisms in the TNF promoter, which can form haplotypes representing different cytokine production capacity. For several single nucleotide polymorphisms, the potential effect on susceptibility, severity, or outcome has not yet been confirmed in an independent study.

The hallmark of pediatric medicine is prevention. Public health programs that reduce prematurity could be expected to have the greatest impact on the incidence of sepsis. The use of group B streptococcal prophylaxis in at-risk mothers has reduced the incidence of septic shock in premature and term infants. Immunization programs for diphtheria, pertussis, tetanus, measles, mumps, rubella, *H. influenzae* type b, *S. pneumoniae*, *N. meningitidis* (type C for infants and types C, A, and Y for college students), and influenza effectively reduce the incidence of sepsis in newborns and children. The primary immunodeficiency initiative is an important physician education program. Children with frequent pneumonia, sinus infections, or skin infections can benefit from early immunodeficiency workups, including quantitative immunoglobulins, complement levels, nitroblue toluene testing of polymorphonuclear neutrophil function, and antibody titer response to immunization. Early identification of these children can lead to the use of therapies that reduce the incidence of sepsis.

DIAGNOSTIC APPROACH AND SCORING SYSTEMS

The following prognostic factors are related to severity and nonsurvival:

- Increased levels of endotoxin, cytokines, lactate, PAI-1, adhesion molecules, procalcitonin, elastase, troponin, adrenocorticotrophic hormone, and ferritin.³⁹
- Decreased levels of C-reactive protein (or increased), glucose, fibrinogen, coagulation factors, protein C, ADAMTS 13, leukocytes, and platelets
- Many scoring systems in use are specific for pediatric patients, including pediatric risk of mortality⁴⁰ and pediatric organ failure and are specific for certain categories of patients, including Rotterdam score,⁴¹ Glasgow Meningococcal Septicaemia Prognostic Score,⁴² DIC,^{43,44} PELOD,⁴⁵ and adapted adult scores (e.g., organ failure score).⁴⁶

THERAPY

Early Recognition and Goal-Directed Therapy to Improve Outcome

Early recognition, adequate resuscitation, appropriate therapeutic response, removal of the nidus of infection, and effective antibiotic therapy are crucial to optimal outcome.⁴⁷ In June 2007, the American College of Critical Care Medicine published its evidence-based *Clinical Practice Parameters for Hemodynamic Support of Newborns and Children with Septic Shock* based, in part, on the concept that early recognition and resuscitation improve outcome (Fig. 122-1). The major new recommendations include the use of epinephrine through a peripheral intravenous (IV) or intraosseous catheter until a central catheter is available and administration of antibiotics in the first hour.⁴⁸

Immediate Resuscitation (First Hour)

Airway and Breathing

Newborns and children usually have an adequate airway, but mechanical ventilation is required in 80% in shock. Intubation should be performed according to pediatric advanced life support and Neonatal Resuscitation Program guidelines on the basis of clinical diagnosis of respiratory distress or hemodynamic instability, not blood gas analysis. Volume resuscitation and the use of the noncardiac depressant drug ketamine as an induction agent are recommended to prevent worsening positive-pressure ventilation-associated hypotension. It is clinical practice to intubate pediatric patients in an early stage of the disease, generally when they need more than 60 mL/kg of fluid resuscitation.

Volume Resuscitation

Virtually all children with shock require volume resuscitation^{49,50}; this should be given as 20-mL/kg boluses of normal saline or colloid as IV pushes to as much as 40 to 60 mL/kg in the first 10 to 20 minutes. If the liver edge becomes palpable, rales are heard, or the perfusion pressure (mean arterial pressure – central venous pressure) narrows, more fluid is not advised and diuretics should be considered. Many clinicians use crystalloid as the first fluid and follow with colloid when more fluids are required. Serum glucose levels should be checked because hypoglycemia can have devastating neurologic consequences. Glucose should be administered rapidly in this condition.

Cardiovascular Therapy

Children in shock can present with low cardiac output and high systemic vascular resistance, high cardiac output and low systemic vascular resistance, or low cardiac output and low systemic vascular resistance. Depending on which situation exists, inotropic support should be started in case of fluid-refractory shock or a combination of an inotrope with a vasopressor or vasodilator. Peripheral epinephrine is probably the first choice of support for a pediatric patient with hypotension refractory to fluid resuscitation until central access can be attained. Dobutamine-refractory or dopamine-refractory shock can often be reversed with epinephrine or norepinephrine infusion. Pediatric patients requiring inotropic support are in a state of low cardiac output,

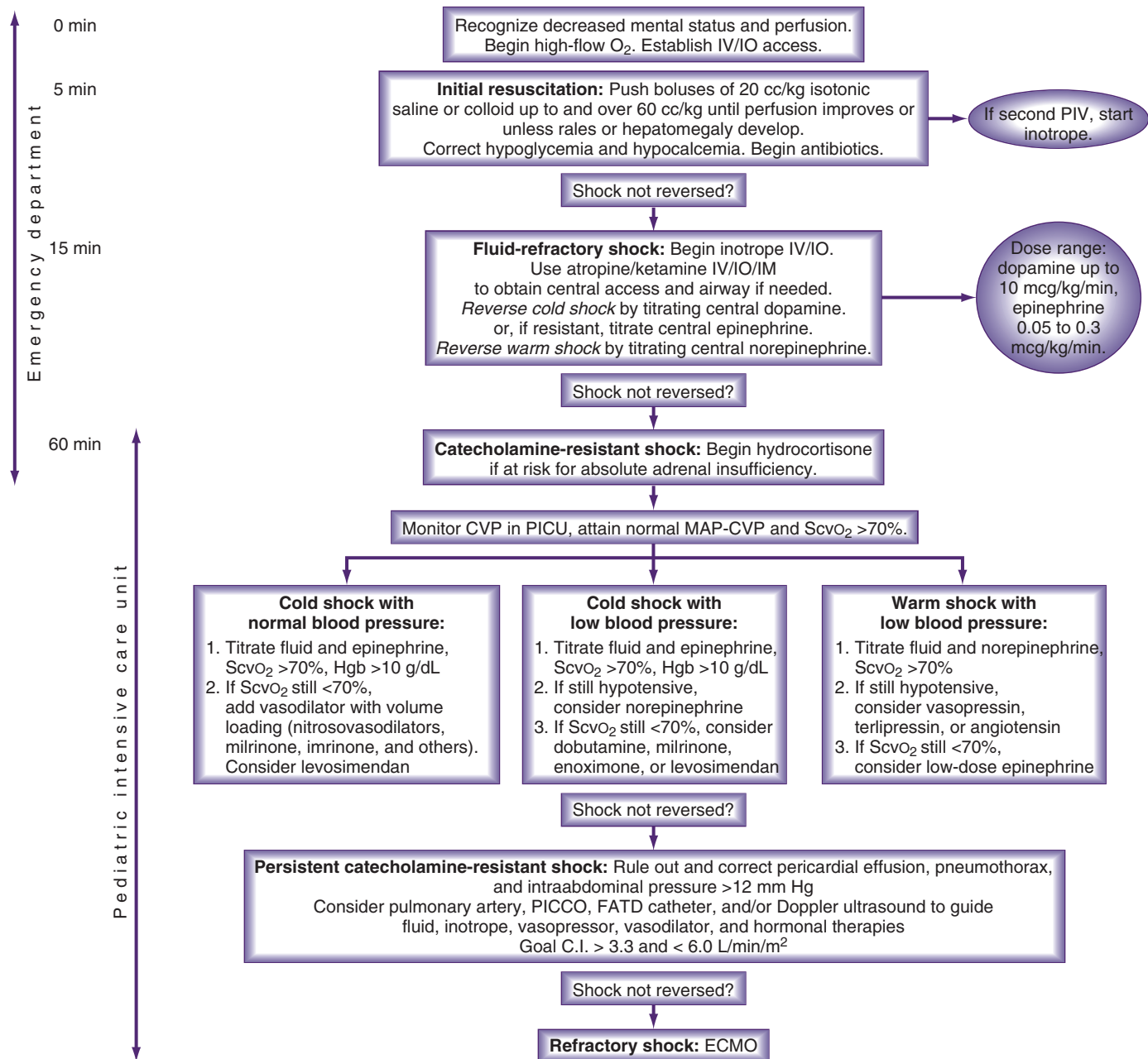


FIGURE 122-1 ■ Clinical practice parameters for hemodynamic support of newborns and children with septic shock. This evidence-based treatment algorithm is based on early recognition and resuscitation to improve outcome. ACTH, adrenocorticotropic hormone; APLS/PALS, advanced pediatric life support/pediatric advanced life support; CI, cardiac index; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; FATD, femoral artery thermodilution; MAP, mean arterial pressure; PDE, phosphodiesterase; PICCO, pulse index contour cardiac output; PICU, pediatric intensive care unit; ScvO₂, central venous oxygen saturation. (From Brierly J, Carcillo JA, Choong J, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med 2009;37: 666–688.)

not high cardiac output. The use of vasodilators can reverse shock in pediatric patients who remain hypodynamic with a high systemic vascular resistance state, despite fluid resuscitation and inotropic support implementation. Milrinone or nitrovasodilators (nitroprusside or nitroglycerin have a short half-life) are used as first-line therapy for children with epinephrine-resistant low cardiac output and elevated systemic vascular resistance shock.

Adrenal Insufficiency

Lack of response to epinephrine (cold shock) or norepinephrine (warm shock) can be caused by adrenal insufficiency or thyroid deficiency.⁵¹⁻⁵³ Children at risk of this condition (e.g., purpura fulminans, prior steroid exposure, or central nervous system disease) should be treated with hydrocortisone. The proper dose has been poorly investigated and

ranges from a stress dose (2 mg/kg) to a shock dose (50 mg/kg of hydrocortisone), followed by the same dose over 24 hours as a continuous infusion. The dose that is better in catecholamine-resistant shock has not been determined.

Antibiotics

Antibiotics and antifungal therapies should be administered according to age, setting, and resistance patterns (empiric therapy) after proper cultures have been performed. The emergence of resistant organisms mandates that antibiotics be specific to regional practice. Some investigators advocate antibiotic cycling in the ICU.⁵⁴

Stabilization of Sepsis and Septic Shock (After First Hour of Resuscitation)

Cardiovascular

The first hour of resuscitation is directed toward restoration of normal perfusion pressure; however, ensuing therapies should be directed toward obtaining normal central venous oxygen saturation. Children with persistent warm shock can respond to norepinephrine. In selected children with norepinephrine-resistant shock, vasopressin (at a physiologic dose) or angiotensin can bypass alpha receptor desensitization and restore vascular tone; however, this can increase afterload and decrease cardiac output.⁵⁵⁻⁵⁷ In a large study in pediatric patients with vasodilatory shock (majority being post cardiac surgery), vasopressin was useful, with limitations regarding its adverse effects on the renal system and platelet counts.⁵⁸ Children with cold shock and normal blood pressure respond to afterload reduction and volume loading. When pediatric patients remain in a normotensive low-cardiac output and high-vascular resistance state despite epinephrine and nitrovasodilator therapy, the use of milrinone should be strongly considered.⁵⁹ This type III phosphodiesterase inhibitor can bypass β -adrenergic receptor desensitization.⁵⁹⁻⁶¹ Children with cold shock and hypotension are most worrisome. They can respond to more volume and epinephrine. Neonates and children with pulmonary hypertension and right ventricular failure can respond to inhaled NO.⁶² These therapies should be titrated to obtain a superior vena cava oxygen saturation above 70%.⁶³

Extracorporeal membrane oxygenation (ECMO) is an effective therapy in refractory neonatal shock (80% survival) and should be considered as a possible therapy in refractory pediatric shock (50% survival).^{64,65} This success is likely due to the fact that refractory shock in newborns and children is usually cardiac, not vascular, failure. Adults with refractory shock from *Hantavirus* (a low-cardiac output/high-vascular resistance state) have similar ECMO outcomes to newborns with refractory shock.⁶⁶

Respiratory

Lung “protection” ventilation strategies reduced mortality rates in adults with acute respiratory distress syndrome (many who had sepsis).⁶⁷ Effective tidal volumes of 6 mL/kg are a reasonable compromise when ventilating septic children with acute respiratory distress syndrome. Positive end-expiratory pressure protects against volutrauma by maintaining functional residual capacity and optimal compliance. Optimal positive end-expiratory pressure can be determined using partial pressure of oxygen in the arterial blood-to-inspired oxygen fraction ratio or compliance.

Renal Failure

Renal failure occurs if ischemia continues for longer than 60 minutes, thrombosis prevents perfusion, or myoglobin and uric acid obstruct tubular flow. During the first 60 minutes of ischemia, the neurohormonal system releases aldosterone, angiotensin, and the antidiuretic hormone (vasopressin), which prevent natriuresis and diuresis; this manifests clinically with oliguria. Rapid resuscitation reverses ischemia, and because 20% of the blood flow goes to renal perfusion, it manifests as return of urine output greater than 1 mL/kg/h. If ischemia lasts more than 1 hour, ATP depletion causes epithelial cells to separate

from and obstruct tubules, leading to tubulobstructive renal failure (also called *acute tubular necrosis*). Tubular regeneration requires 6 weeks to 3 months.

Blood flow to the kidney is autoregulated by pre- and postglomerular constriction and dilation. The ability of the preglomerular arterioles to dilate is impaired during endotoxemia and cirrhosis. Blood flow to the kidney depends on perfusion pressure (measured as mean arterial pressure – central venous pressure or, in the case of abdominal compartment syndrome, mean arterial pressure – intraabdominal pressure) in children with sepsis.⁶⁸ Perfusion pressure should be maintained with volume, inotropes, and in some cases, vasopressor therapies. Creatinine clearance should be measured daily to assess function. Diuretics are recommended to prevent fluid overload. Patients with myoglobinuria or uric aciduria should be treated with mannitol, alkalization, and allopurinol (uric aciduria). Severe oliguria or anuria, despite the use of diuretics, should be managed with daily or continuous hemofiltration/hemodialysis or peritoneal dialysis.

Purpura Fulminans and Disseminated Intravascular Coagulation

DIC is recognized clinically as a prolonged prothrombin time/partial thromboplastin time, reduced fibrinogen, increased fibrin degradation products or D-dimers, and thrombocytopenia. When patients present with purpura fulminans/DIC with genetic proclivity (thrombophilias) or with rapidly growing organisms (meningococcus), the process is deadly, unless reversed. Tissue factor is exposed by endothelial injury and is released into the bloodstream. If tissue factor is unmatched by tissue factor pathway inhibitor, it activates factor VII-mediated coagulation. Ongoing coagulation consumes clotting factors (including fibrinogen), antithrombotic factors (antithrombin III and protein C), and platelets; this leads to a state of massive clotting and sometimes bleeding. Therapeutic strategies must restore a homeostatic milieu by removing or inhibiting tissue factor activity and replacing anticoagulant factors, procoagulant factors, and platelets. If systemic clotting is limb-threatening or life-threatening, fibrinolytic therapies may be required for reperfusion. Debate continues on whether specific therapies (e.g., antithrombin III, protein C, heparin, or tissue plasminogen activator), nonspecific therapies (fresh frozen plasma and platelet replacement or plasma exchange), or a combination of both (plasma exchange plus antithrombin III or protein C), with tissue plasminogen activator added for limb- or life-threatening thrombosis) is best. Some investigators think that patients with meningococcemia cannot activate protein C,⁶⁹ whereas others have shown that these children can activate protein C.⁷⁰ Thus far, there is no evidence on the benefit of either product. Studies using intensive plasma exchange therapy appears to be of benefit because plasma exchange reverses both fibrin and platelet-vWF multimer-mediated thrombosis.⁷¹⁻⁷³

Nutrition, Electrolytes, Endocrine, and Metabolism

It is debated whether one should feed patients enterally when in shock; however, there is agreement that the enteral route is best when shock resolves. Total parenteral nutrition should be considered in patients not tolerating enteral feeds and “calories given” directed to “calories expended” if a metabolic monitor is available. If a monitor is not available, calorie needs can be overestimated when using classic formulas in critically ill children. Hypoglycemia should be rigorously avoided and treated. Hypoglycemia is associated with devastating neurologic outcomes. Strict control of hyperglycemia with insulin infusion substantially reduced mortality in a pediatric ICU by reducing deaths from multiple organ dysfunction syndrome/multiple organ failure.⁷⁴ In general, infants are at risk of developing hypoglycemia when they depend on IV fluids; a glucose intake of 4 to 6 mg/kg/min or maintenance fluid intake with glucose 10% and sodium chloride 0.45% is advised.

Immunomodulation

Children whose system cannot kill invading organisms die from sepsis. Primary and acquired immunodeficiency states must be treated. Children with chronic granulomatous disease require white blood cell transfusions and interferons. Patients with hypogammaglobulinemia require treatment with IV immunoglobulin. Granulocyte macrophage colony-stimulating factor was shown to improve survival in newborn neutropenic septic shock in randomized controlled trials.^{75,76} Transplant and nontransplant patients who develop septic shock while receiving immunosuppression die unless the immunosuppressants are rapidly tapered. Polyclonal IV immunoglobulin has been reported to reduce mortality rate and is a promising adjuvant in the treatment of sepsis and septic shock. The number of trials with children has been small, however, and the totality of the evidence is insufficient to support a robust conclusion of benefit. Adjunctive therapy with monoclonal IV immunoglobulin is experimental.⁷⁷

Drug Dosing

Decreased cytochrome P450 activity is manifested in impaired steroid synthesis and impaired drug metabolism is present in children with

sepsis, septic shock, or multiple organ failure. Patients with multiple organ failure are at particular risk of toxicity with drugs that are metabolized by the cytochrome P450 system. Renal function is also impaired. Creatinine clearance-directed drug dosing of renally eliminated drugs is necessary in these patients. Drugs should be administered according to pharmacodynamic and pharmacokinetic goals.

SOME MULTICENTER RANDOMIZED CONTROLLED TRIALS FOR PEDIATRIC SEPTIC SHOCK

deOliveira and colleagues observed a greater than threefold reduction in mortality when using ACCM-PALS therapies directed to RA/SVC or RA/IVC oxygen saturations over 70%.⁶³ The intervention arm received more fluids, blood, and inotrope/vasodilators than the non-intervention arm. In two trials, neither vasopressin nor terlipressin was effective in improving outcomes in refractory vasodilated shock.^{78,79}

Ventura and colleagues demonstrated that peripheral epinephrine is superior to peripheral dopamine in children with fluid refractory shock without central access (mortality rate 20% with dopamine, 7% with epinephrine).⁴⁸

KEY POINTS

1. The mortality by severe sepsis in neonatal and pediatric patients has improved from 97% in 1963 to 9% in 1999 to about 4% in 2003. Previously healthy children have better outcomes than children with chronic illness.
2. Although outcomes are improving, the burden of newborn and pediatric sepsis is increasing in the United States. More children die with severe sepsis than with cancer, with an estimated yearly healthcare cost of \$4 billion in the United States for patients with this condition.
3. The physiologic differences in coagulation and fibrinolysis between adults and children might lead to an earlier exhaustion of coagulation factors and disseminated intravascular coagulation in infants and young children.
4. In contrast to adults, death from shock in children is most commonly associated with progressive cardiac failure, not vascular failure. Pediatric patients have low cardiac output/high systemic vascular resistance (60%), low cardiac output/low vascular resistance (20%), or high cardiac output/low vascular resistance (20%).
5. Genetic polymorphisms in components of the inflammatory pathways have been shown to be involved in the susceptibility, severity, and outcome of pediatric sepsis.
6. Published in 2007, the American College of Critical Care Medicine evidence-based *Clinical Practice Parameters for Hemodynamic Support of Newborns and Children with Septic Shock* were based, in part, on the concept that early recognition and resuscitation improve outcome.
7. The moment of intubation should be estimated on the basis of clinical diagnosis of respiratory distress or hemodynamic instability, not on blood gas analysis.
8. Many children with shock require aggressive volume resuscitation. Unless hepatomegaly, cardiomegaly, or crackles are present, this should be given as 20-mL/kg boluses of normal saline or colloid to a total of 60 mL/kg in the first 10 to 20 minutes, while peripheral epinephrine is being started and the airway is being managed.
9. Development of multiple organ failure is observed with delayed resuscitation and source control. Patients with multiple organ failure commonly have inflammation phenotypes that can respond to personalized therapies.

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Infections in the intensive care unit (ICU) contribute significantly to patient morbidity. Depending on the type of ICU, nosocomial infections may account for 70% of infections.¹ Nosocomial infections of the urogenital tract are frequent and sometimes underestimated in the ICU.²

DEFINITION

Urinary tract infection (UTI) can be the primary cause for admission to the ICU or can be acquired after intensive care procedures. Because patients are frequently sedated in the ICU, clinical diagnosis of UTI is often difficult. Nevertheless, UTI is an important cause of morbidity and antibiotic resistance in the ICU. Complicated UTI is a very heterogeneous entity, with a common pattern of the following factors^{3,4}:

- Anatomic, structural, or functional alterations of the urinary tract, which significantly impede urodynamic properties (e.g., stents, urine transport disturbances, instrumentation of the urinary tract, stones, tumors, or neurologic disorders)
- Impaired renal function due to parenchymal diseases or pre-, intra-, or postrenal nephropathies (e.g., acute and chronic renal insufficiencies, cardiac insufficiency)
- Accompanying diseases impairing the patient's immune status (e.g., diabetes mellitus, liver insufficiency, use of immunosuppressive agents such as corticosteroids, acquired immunodeficiency syndrome (AIDS), or hypothermia)

ETIOLOGY

Causative pathogens of UTI are almost exclusively bacteria and yeast. Viral pathogens are only found in patients with severe immunosuppression, such as after bone marrow transplantation. High antibiotic pressure and special circumstances in the ICU modulate the microbial spectrum. *Escherichia coli* is the most frequent pathogen but occurs less frequently than in uncomplicated community-acquired UTI. Other Enterobacteriaceae may also be uropathogens (e.g., *Klebsiella*, *Proteus*, *Enterobacter*, *Serratia*, *Citrobacter*, or *Morganella* species). Nonfermenters such as *Pseudomonas aeruginosa*, gram-positive cocci such as staphylococci and enterococci, and *Candida* species may also play an important role. The microbial spectrum is likely to differ over time and from one institution to the other. To follow the spectrum and development of antibiotic resistance, each ICU has to update its own analyses (Table 123-1, Fig. 123-1).

EPIDEMIOLOGY

The Extended Prevalence of Infection in Intensive Care (EPIC II) study¹ revealed that 51% of patients were infected on the study day and that 71% of all patients were receiving antibiotics. The most frequent types of ICU-acquired infections with their total occurrence were respiratory tract infections, 63.5%; abdominal infections, 19.6%; bloodstream infections, 15.1%; and renal or UTIs, 14.3%.¹ The true incidence of UTI, however, may be even higher if meticulously looked for. In a prospective study specifically evaluating nosocomial UTI, nosocomial UTIs accounted for 28% of nosocomial infections, lower respiratory tract infections for 21%, pneumonia for 12%, and bloodstream infections for 11%. The rates of urinary catheter-associated

UTIs varied between 4.2% (symptomatic UTI) and 14.0% (asymptomatic UTI), which shows that asymptomatic bacteriuria is frequent in ICU patients, although symptoms of UTIs in intensive care patients are frequently difficult to assess.² In the global one-day point prevalence study in urologic hospitalized patients (GPIU study), asymptomatic bacteriuria accounted for 27% of health care-associated (HA) UTIs, followed by cystitis (26%), pyelonephritis (20%), urosepsis (11%), and other urogenital infections (16%),⁷ showing that HA UTI is present in high frequency in certain patient groups.

UTIs in the ICU are divided into two groups:

1. UTIs with nonurologic complicating causes: diabetes mellitus, renal insufficiency, immunodeficiency, infectious foci contiguous to the urogenital tract, or trauma patients
2. UTIs with urologic complicating causes: renal transplantation, neurogenic bladder dysfunction, procedures in the urogenital tract, urinary stones or foreign bodies in the urogenital tract

In UTIs with primary nonurologic complicating causes, antimicrobial therapy is generally sufficient. However, in UTIs with primary urologic causes, the complicating factors must be identified and treated. In such cases, antimicrobial therapy is only one component of the treatment.

Urinary Tract Infections with Nonurologic Complicating Causes

Individuals with diabetes are at higher risk of UTIs.^{8,9} Increased susceptibility in patients with diabetes is positively associated with the increased duration and severity of diabetes as a result of impaired granulocyte function, decreased excretion of the Tamm-Horsfall protein, low levels of interleukin (IL)-6 and IL-8 in the urine that lead to lower "cidality" of the urine, and altered microflora in the genital region. In addition, diabetic cystopathy and nephropathy may be complicating factors in the urinary tract. In addition to antibiotics, treatment must address the metabolic situation. In pyelonephritis, usually, a switch to insulin or insulin-analogous therapy is necessary.

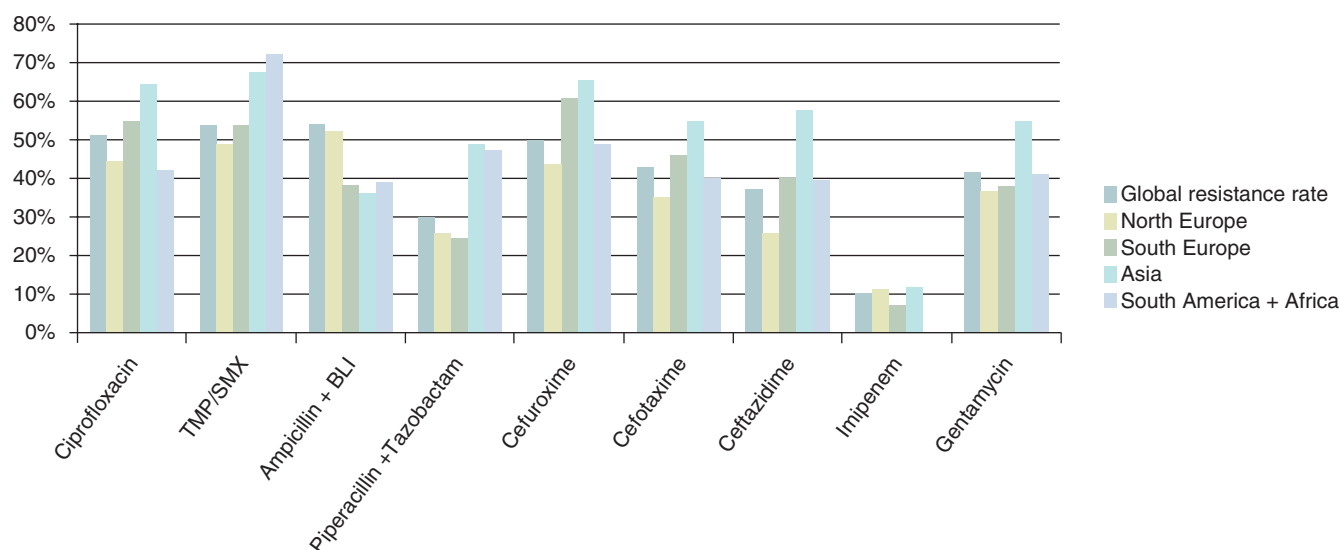
The place of immunosuppression per se in the development of UTI remains unresolved.¹⁰ Patients with end-stage renal failure are generally not particularly susceptible to the usual gram-negative urinary pathogens, although they may acquire unusual and granulomatous infections. Patients have evidence of reduced cellular and humoral immunity. However, the situation is a little clearer in male patients with HIV and AIDS, where there is a close relationship between CD4 counts and the risk of bacteriuria, particularly in those whose counts are less than 200 cells/mL.¹¹

Pathogens may be translocated into the urinary tract from contiguous infectious foci (e.g., appendicitis, sigmoid diverticulitis, or translocation by ileus). Symptoms and localization of pain can be misleading and may delay the diagnosis. Operations or trauma may cause hypothermia, tissue hypoxia, and hemodynamic alterations that result in kidney dysfunction and impaired mucosal perfusion. The use of latex catheters in these critical situations (e.g., operations with heart-lung machine) can also lead to urethral strictures. Silicone catheters or suprapubic catheters are recommended in these patients.¹² Suprapubic catheters cannot prevent UTIs. They can, however, lower the rate of UTIs from 40% to 18%.¹³

TABLE 123-1 Bacterial Spectrum of Health Care–Associated Uropathogens ($\geq 2\%$) from Distinct Surveillance Studies

| NAME OF STUDY | SENTRY ⁵ | SENTRY ⁵ | SENTRY ⁵ | ESGNI-003 ⁶ | GPIU-Study ⁷ |
|---|---------------------------|---------------------------|---------------------------|---------------------------------------|-------------------------|
| Regions of the world | North America | Latin America | Europe | Europe | Global |
| Year of surveillance | 2000 | 2000 | 2000 | 2000 | 2003-2010 |
| Type of surveillance | Longitudinal | Longitudinal | Longitudinal | Cross-section | Cross-section |
| Origin of samples | Microbiology laboratories | Microbiology laboratories | Microbiology laboratories | Different departments in the hospital | Urology departments |
| Number of pathogens | n = 1466 | n = 531 | n = 783 | n = 607 | n = 1371 |
| Species, % | | | | | |
| <i>Escherichia coli</i> | 43% | 60% | 46% | 36% | 40% |
| <i>Klebsiella</i> spp. | 12% | 12% | 9% | 8% | 11% |
| <i>Pseudomonas</i> spp. | 7% | 6% | 9% | 7% | 11% |
| <i>Proteus</i> spp. | 6% | 7% | 10% | 8% | 6% |
| <i>Enterobacter</i> spp. | 3% | 4% | 4% | 4% | 5% |
| <i>Citrobacter</i> spp. | 4% | 2% | 2% | 2% | n.r. |
| <i>Enterococcus</i> spp. | 16% | 4% | 13% | 16% | 12% |
| <i>Staphylococcus</i> spp. | 6% | 3% | 3% | 4% | 6% |
| RESISTANCE RATES OF ANTIBIOTICS FOR THE TOTAL BACTERIAL SPECTRUM TESTED, % | | | | | |
| Ampicillin | 59% ^[a] | 62% ^[a] | 65% ^[a] | 66% ^[a] | n.r. |
| Ampicillin + BLI | 31% ^[a] | 36% ^[a] | 36% ^[a] | 29% ^[a] | 53% |
| TMP/SMZ | 43% ^[a] | 38% ^[a] | 48% ^[a] | 32% ^[a] | 53% |
| Ciprofloxacin | 29% ^[a] | 32% ^[a] | 29% ^[a] | 17% ^[b] | 51% |
| Gentamicin | n.r. | n.r. | n.r. | 18% | 42% |
| Ceftazidime | n.r. | n.r. | n.r. | 13% ^[c] | 38% |
| Amikacin | n.r. | n.r. | n.r. | 19% ^[c] | n.r. |
| Piperacillin/tazobactam | n.r. | n.r. | n.r. | n.r. | 30% |
| Imipenem | n.r. | n.r. | n.r. | 14% ^[c] | 10% |
| Vancomycin | n.r. | n.r. | n.r. | 1% ^[d] | n.r. |

^a, gram-negative bacteria excluding *Pseudomonas aeruginosa*; ^b, gram-negative bacteria; ^c, *P. aeruginosa*; ^d, enterococci.; ^e, *E. coli*, *Klebsiella* spp., *P. aeruginosa*, enterococci. BLI, β -lactamase-inhibitor; n.r., not reported; TMP-SMZ, trimethoprim-sulfamethoxazole.

**FIGURE 123-1** ■ Global and regional resistance rates of the total bacterial spectrum from health care–associated UTI.⁷

Urinary Tract Infections with Urologic Complicating Causes

Patients show a high risk of developing bacteriuria after renal transplantation, threatening clinical outcomes for both the patient and

transplant. Early infections (up to 3 months after transplantation) are differentiated from late infections (more than 3 months after transplantation). Early infections may present with no symptoms. In this phase, occult bacteremia (60% of bacteremias after renal transplantation originate from the urinary tract), allograft dysfunction, and recurrent

UTIs after antibiotic therapy are frequently seen.⁴ Sometimes, it can be very difficult to distinguish rejection from infection. Patients must also be investigated for surgical complications.

UTIs caused by *Candida* species are frequently asymptomatic. There is, however, a risk of obstructive fungal balls leading to candidemia or invasion of the anastomosis in renal transplant recipients. Asymptomatic candiduria should therefore be treated in these patients.⁴ Urine transport disturbances (e.g., from an obstructive ureteral stone) require specific urologic therapy such as percutaneous nephrostomy or stenting. In case of bladder obstruction, an indwelling urinary catheter (suprapubic or transurethral) will be the primary therapy in the ICU. Long-term indwelling catheters (more than 30 days) are associated with a selected microbial spectrum of difficult-to-treat uropathogens (e.g., *Providencia* spp., *Proteus* spp., or *Pseudomonas* spp.).¹⁴ After initiation of antimicrobial therapy, the catheter should be replaced to remove the biofilm material.⁴

■ PATHOPHYSIOLOGY

UTIs generally occur from organisms invading the urinary tract via the urethra. Pathogens originate from endogenous or exogenous nosocomial flora. Hematogenous spread to the urinary tract is rare.

In uncomplicated UTIs, pathogens need to have very specific virulence factors enabling them to initiate an infection after the invasion of the urinary tract. The medical conditions of an ICU patient may weaken physiologic barriers and defenses, thus facilitating the entry of pathogens. In addition, the nosocomial environment in the ICU, including antibiotic pressure and decreased supply of oxygen or nutrients (e.g., iron) to tissues, can select pathogens with specific resistance patterns. A general adaptation strategy is the formation of hypermutator strains, which show 100- to 1000-fold increased mutation frequencies, enabling the pathogens to rapidly adapt to challenging environments and thus develop effective mechanisms for antibiotic resistance.^{15,16}

An important mechanism contributing to UTI is the formation of biofilms, which is associated with the increased number of biomaterials used in medical practice. Biofilm infections develop not only around foreign bodies such as urinary catheters or stents but also in urinary stones, scar or necrotic tissue, obstructive uropathies, or even chronic bacterial prostatitis. A biofilm has been defined as an accumulation of microorganisms and their extracellular products, forming a structured community on a surface. The formation of a biofilm generally consists of three steps:

1. Deposition of a host conditioning film
2. Attachment of microorganisms followed by microbial adhesion and anchorage to the surface by exopolymer production
3. Growth, multiplication, and dissemination of the organisms

The basic structural unit of a biofilm is a microcolony—that is, a discrete matrix-enclosed community consisting of bacteria of one or more species. The biofilm is usually built up of three layers.^{12,13}

1. Linking film that attaches to the surface of a tissue or biomaterial
2. Base film of compact microorganisms
3. Surface film as an outer layer, where planktonic organisms can be released to float freely and spread on the surface

Bacteria within biofilms differ both in behavior and phenotypic form from the planktonic, free-floating bacteria. The failure of antimicrobial agents to treat biofilms has been attributed to a variety of mechanisms:

- Organisms encapsulated in biofilms grow more slowly than planktonic ones, probably because encapsulated bacteria have a decreased nutrient and oxygen supply, leading to a decreased metabolic rate and antimicrobial susceptibility. This may select a less susceptible genotype, forming a resistant population. Furthermore, antimicrobial binding proteins are poorly expressed in these slow-growing bacteria.
- The biofilm matrix delays or impedes the diffusion of antibiotic molecules into the deeper layer of the film (extrinsic resistance).

- Bacteria within the biofilm are phenotypically so different from their planktonic counterparts that antimicrobial agents fail to eradicate them. Bacteria within a biofilm activate many genes that alter the cell envelope and molecular targets by altering the susceptibility to antimicrobial agents (intrinsic resistance). These phenotypic changes are likely to play a more important role in the development of antimicrobial resistance than external resistance (biofilm matrix, glycocalyx).
- Bacteria within a biofilm can sense the external environment, communicate with each other, and transfer genetic information and plasmids within biofilms.
- Bacteria in biofilms can usually survive antibacterial concentrations 100 to 150 times higher than those needed to kill planktonic bacteria of the same species.¹⁷⁻¹⁹

Antimicrobial treatment can be effective in only “young” biofilms (<24 hours). At present, combination therapy with fluoroquinolones and macrolides or fosfomycin seems to be most effective against biofilm infections. During an acute febrile phase of biofilm infection, antimicrobial therapy is essential and can be effective because the planktonic bacteria are responsible for the febrile reactions and not the bacteria covered in the biofilm. However, to eradicate pathogens from the biofilm, the biofilm itself has to be removed (e.g., catheter change or extraction of infectious stones).

■ DIAGNOSIS

Medical History and Physical Examination

Sedated intubated patients are often difficult to evaluate regarding their signs and symptoms of UTIs. The patient or a family member should be asked about previous episodes of UTIs as well as urologic diseases (e.g., stones or tumors) or operations.

The physical examination should include inspection and palpation of the costophrenic area, lower abdomen, pubic region, inguinal lymph nodes, and genitals and a digital transvaginal or transrectal examination. Ultrasound is an important diagnostic device, and its use should be frequently considered because of the close proximity of the urogenital organs to the intestine, spleen, liver, pancreas, gallbladder, ovary, or uterus.

Urinary Examinations

Urine specimens in ICU patients are almost exclusively collected from catheters. Because urine from catheters has to be collected into a closed system, the urine specimen should be taken from the puncture site at the catheter after disinfection, without opening the closed system. There are different complementary methods for laboratory examination of the urine specimen.

Dipstick Test

The dipstick test is performed with undiluted urine and investigates the following infection-related parameters²⁰:

- pH: an alkaline urine (pH > 8.0) points to urease-producing organisms such as *Proteus* or *Providencia* spp. and is associated with magnesium-ammonium-phosphate stones.
- Nitrate: most Enterobacteriaceae harbor a nitrate reductase that reduces nitrate to nitrite. Some common uropathogens such as *Enterococcus* and *Staphylococcus* lack nitrate reductase and will therefore not be detected using this parameter, independent of their urinary concentration. The positive detection of nitrate requires its inclusion in the patient's diet.
- Leukocytes (positive leukocyte esterase): granulocytes are the most frequently detected leukocytes in the urine of UTI patients. Macrophages appear fairly often in patients with UTIs, but their significance remains unknown.
- Erythrocytes (positive hemoglobin): hematuria remains a major sign of urinary tract and renal disease.
- Specific gravity/osmolality (degree of urine dilution)

TABLE 123-2

Division and Dosage of Distinct Antibiotics Recommended for Treatment of Urinary Tract Infections

| ANTIBIOTIC GROUP | SUBSTANCE | DOSAGE | |
|----------------------------|-----------------------------|---|--|
| | | ORAL | IV |
| Aminopenicillin + BLI | Ampicillin/sulbactam | 0.750 g twice daily | 0.75-3 g 3 times daily |
| | Amoxicillin/clavulanic acid | 1 g twice daily <i>or</i> 0.625 g 3 times daily | 1.2-2.2 g 3 times daily |
| Acylureidopenicillin + BLI | Piperacillin/tazobactam | — | 2.5-4.5 g 3 times daily |
| | Piperacillin/sulbactam | — | 5 g 3 times daily |
| Cephalosporin Gr. 1 | Cephalexin | Prophylaxis only | — |
| Cephalosporin Gr. 2 | Cefuroxime axetil | 500 mg twice daily | — |
| | Cefuroxime | — | 0.75-1.5 g 3 times daily |
| | Cefotiam | — | 1-2 g 2-3 times daily |
| Cephalosporin Gr. 3 | Cefpodoxime proxetil | 200 mg twice daily | — |
| | Ceftibuten | 200-400 mg daily | — |
| Cephalosporin Gr. 3a | Cefotaxime | — | 1-2 g 2-3 times daily |
| | Ceftriaxone | — | 1-2 g daily |
| Cephalosporin Gr. 3b | Ceftazidime | — | 1-2 g 2-3 times daily |
| Cephalosporin Gr. 4 | Cefepime | — | 2 g twice daily |
| Cephalosporin + BLI | Ceftolozane/tazobactam | — | Ceftolozane/tazobactam 1.5 g 3 times daily |
| | Ceftazidime/avibactam | — | Ceftazidime/avibactam 2.5 g 3 times daily |
| Carbapenem Gr. 1 | Imipenem | — | 0.5-1 g q 6-8 h |
| | Meropenem | — | 0.5-1 g 3 times daily |
| | Doripenem | — | 0.5 g 3 times daily |
| Carbapenem Gr. 2 | Ertapenem | — | 1 g daily |
| Fluoroquinolone Gr. 2 | Ciprofloxacin | 500-750 mg twice daily | 400 mg twice daily |
| | Ciprofloxacin XR | 1000 mg daily | — |
| Fluoroquinolone Gr. 3 | Levofloxacin | 500-750 mg daily | 500-750 mg |
| ANTIMYCOTIC GROUP | | | |
| Azole derivatives | Fluconazole | 400-800 mg daily | 400-800 mg daily |
| | Voriconazole | 4-6 mg/kg BW daily | 4-6 mg/kg BW daily |
| Pyrimidine analog | Flucytosine | — | 100-150 mg/kg BW 4 times daily |
| Echinocandin | Caspofungin | — | 50-70 mg daily |

BLI, β -lactamase-inhibitor; BW, body weight; IV, intravenous.

Data from (4).

- Protein; total protein in urine is a mixture of high- and low-molecular-weight plasma proteins from the kidney and urinary tract or bacteria.
- Glucose (metabolic condition of the patient)

Microscopy

There are two possibilities of a microscopic evaluation²⁰:

1. Chamber counting of uncentrifuged urine (standard values for urine shown in Table 123-2).
2. Urinary sediment findings; at least 10 fields of vision at 400 \times magnification are counted, and the mean value of particles is registered. However, centrifugation methods are never quantitative in counting erythrocytes and leukocytes because of variable loss during centrifugation.

Microbiology

To differentiate contamination in urine from significant bacteriuria, quantitative microbiology is needed. The microbial count has to be interpreted in relation to the urinary dilution.

Clinical Diagnosis

To survey and compare infection rates in different institutions, UTIs should be classified according to widely accepted definitions, such as the definitions of the U.S. Centers for Disease Control and Prevention (CDC). The CDC/National Healthcare Safety Network definitions²¹ stratify HA UTIs into symptomatic, asymptomatic, and other infec-

tions of the urinary tract. To be of value in determining a nosocomial infection, urine specimens must be obtained aseptically using an appropriate technique such as clean catch collection, bladder catheterization, or suprapubic aspiration.

THERAPY

General Principles

Not all bacteriuric patients in the ICU need to be treated. In general, asymptomatic bacteriuria does not have to be treated.²² Therapy should only be started in patients with significant symptoms and morbidity and in whom asymptomatic bacteriuria may be deleterious (e.g., before traumatizing intervention of the urinary tract and in pregnant women). In the ICU, indications for treatment of asymptomatic UTIs might include some other circumstances such as renal transplant, severe diabetes mellitus, or severe immunosuppression. In complicated UTIs, antibiotic therapy can only be successful when complicating factors can be eliminated or urodynamic functions restored. Treatment of complicated UTIs therefore comprises adequate antibiotic treatment and successful urologic intervention.

Antibiotic Therapy

For therapy of complicated UTI, antibiotics must possess appropriate pharmacodynamic and pharmacokinetic prerequisites: high renal

unmetabolized clearance with good antibacterial activity, both in acidic and alkaline urine. Moreover, microbial resistance patterns must be considered in the choice of antibiotics. Increasing antibiotic resistance, especially among Enterobacteriaceae, makes prudent antibiotic therapy increasingly difficult. The increasing appearance of quinolone-resistant and extended-spectrum β -lactamase (ESBL)-forming enterobacteria will inevitably lead to the increased use of carbapenems in the empiric therapy, thus increasing the antibiotic pressure on these highly potent antibiotics. To diminish the selection pressure for resistant pathogens, antibiotics from different classes should be used. Multiple antimicrobial agents are available for therapy for complicated UTIs (see Table 123-2): second- or third-generation cephalosporins, broad-spectrum penicillins with β -lactamase inhibitors, monobactams, and carbapenems. For empiric therapy for severe UTIs, broad-spectrum antibiotics should be used (e.g., broad-spectrum penicillins with β -lactamase inhibitors, third-generation cephalosporins, fluoroquinolones, or carbapenems). Synergism with aminoglycosides, which inhibit protein synthesis and thus block the formation of toxins or virulence factors, might be useful for initial therapy, but side effects have to be considered.

Candiduria is a common problem in ICUs. It may represent harmless colonization, but it can also be an early sign of systemic candidosis.²³ A second urine culture after replacing the urethral catheter can rule out contamination. In critically ill patients, systemic therapy for *Candida* species should be started according to susceptibility testing or species differentiation (see Table 123-2). Complicating factors such as diabetes mellitus or urologic abnormalities should be treated concomitantly. Systemic antimycotic therapy is preferred to local instillation therapy because of the potentially systemic nature of candiduria in ICU patients.

Urologic Therapy

Urologic interventional therapy of complicated UTIs is divided into acute therapy and delayed drainage therapy. The primary aim of acute therapy is improved urinary flow, with minimal patient contamination by infected urine. In primary therapy, catheters, stents, or drains are frequently used. Delayed drainage therapy of the urinary tract (e.g., lithotomy, prostatic resection, or ureter reimplantation) is frequently performed after days or weeks of stabilization.

Prophylaxis of Catheter-Associated Urinary Tract Infections

Some 80% to 90% of nosocomial UTIs are associated with urinary catheters or instrumentation of the urinary tract. The best prophylaxis is to avoid a catheter or, if catheterization is necessary, to minimize catheter duration. Various techniques have been used to avoid catheter-related infections.

Silver coating of catheters may exert a bactericidal effect, but the concentration of free silver ions must be high, whereas the exposure to albumin and chloride ions has to be low because silver-chloride complexes can precipitate.²⁴ A multicenter randomized controlled trial using silver alloy- or nitrofurantoin-coated catheters in adults requiring short-term catheterization in hospital could not demonstrate a sufficiently high reduction in symptomatic UTIs to recommend routine use of antimicrobial-impregnated catheters.²⁵ Suprapubic catheterization can initially decrease the rate of UTIs from 40% to 18% because the proximity to the anal region and the irritation of the urethral mucosa with ensuing mucopurulent discharge are avoided.¹³ Urinary drainage should be performed with a closed system that should not be opened either for emptying or for urinary sampling. The sites used for urinary sampling must be adequately sterilized. General hygienic procedures such as aseptic catheter insertion, wearing of disposable gloves, and hygienic hand disinfection to prevent cross-contamination or cross-infection are mandatory. International consensus recommendations for the use of urinary catheters to prevent HA infections have recently been described.²⁶

Recommended Evidence-Based Measurements for Preventing Catheter-Associated Urinary Tract Infections

The primary methodologies for preventing catheter-associated UTIs²⁶ include:

- Limiting unnecessary catheterization and discontinuing the use of the catheter as early as possible
- Policies and procedures for recommended catheter insertion indications, insertion and maintenance techniques, discontinuation strategies, and replacement indications should be developed and closely followed.
- Alternatives to indwelling urethral catheterization should be considered, such as condom catheterization, intermittent catheterization, or suprapubic catheterization, although data are insufficient to recommend one alternative over another.
- Closed catheter drainage systems should be used.
- Most other measures for the prevention of catheter-associated UTIs, such as prophylaxis with systemic antimicrobials, methenamine salts, cranberry products, enhanced meatal care, and catheter irrigation with either antimicrobials or saline, are not recommended.²⁶
- It is also unclear whether routine catheter changes reduce the risk of catheter-associated bacteriuria or UTIs.

SPECIAL CLINICAL ISSUES

Infections of the Upper Urinary Tract and Contiguous Organs

Pyelonephritis

The high osmolality of the renal medulla has a negative effect on leukocyte function. For this reason, the interstitium of the renal medulla is more affected in pyelonephritis than the cortex. Clinical symptoms are unilateral or bilateral flank pain, painful micturition, dysuria, and fever ($>38^{\circ}\text{C}$). Focal nephritis is limited to one or more renal lobules, which is comparable to that in lobular pneumonia. Ultrasonographic findings are circumscribed lesion with interrupted echoes that breaks through the normal cortex/medulla organization. A computed tomography (CT) scan shows typical wedge-shaped, poorly limited areas of diminished sonographic density. As differential diagnoses, renal abscess, tumor, and renal infarction must be taken into account. Emphysematous pyelonephritis characteristically shows gas formation in the renal parenchyma and perirenal space. Diabetes mellitus or obstructive renal disease is the predisposing factor. The most frequently isolated organisms are *E. coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*. Fermentation of glucose in Enterobacteriaceae occurs via two different metabolic pathways: mixed acid fermentation and the butylene glycol pathway. Organisms of the *Klebsiella-Enterobacter-Hafnia-Serratia* group and, to a lesser extent, *E. coli*, use the butylene glycol pathway and produce copious amounts of CO_2 , which appears clinically as gas formation.²⁷ Aggravated by diminished tissue perfusion, the contralateral side is often affected as well.

Renal and Perirenal Abscess

Clinical symptoms are rigor, fever, back or abdominal pain, flank tenderness, mass lesion and redness of the flank, and tenderness of the upper lumbar and paraspinal muscles. Respiratory insufficiency, hemodynamic instability, or reflexory paralytic ileus occurs frequently. Frequent signs of renal abscess formation are fever and leukocytosis for more than 72 hours, despite antibiotic therapy. The urinary culture may be negative in 14% to 20% of cases.²⁸ Frequently isolated organisms are *E. coli*, *K. pneumoniae*, *Proteus* spp., and *Staphylococcus aureus* from hematogenous spread. The fascial limitations are open toward the pelvis, and the perirenal fat is in close contact with the pelvic fat tissue. A perinephritic abscess may therefore point to the groin or perivesical

tissue or to the contralateral side, thus penetrating the peritoneum. Inflammation of the flank, thigh, back, buttocks, and lower abdomen may occur. Because of the late diagnosis, the mortality can be as high as 57%. Blood cultures are positive in 10% to 40% of cases, and urinary cultures are positive in 50% to 80%.²⁹

Infections of the Lower Urinary Tract and Contiguous Organs

Cystitis

Cystitis is frequently limited to the bladder mucosa and hence shows no systemic signs or symptoms. An ascending infection can, however, clinically result. Cystitis in the ICU is almost exclusively catheter-associated and can cause hematuria. Spontaneous elimination is frequently found after removal of the indwelling catheter but is less frequent in elderly patients.⁴

Epididymitis/Orchitis

Epididymitis in the ICU is usually an ascending infection and can also involve the testis. Possible causes are subvesical obstruction, transurethral resection of the prostate, or an indwelling transurethral urinary catheter, in which case the pathogens are identical with the pathogens in the urine. Of note, epididymitis is frequently involved in urogenital tuberculosis. Orchitis with the formation of a sterile hydrocele can appear during the course of polyserositis or cardiac failure and may point to a generalized systemic disease.

Cavernitis

Cavernitis of the penis is a rare phlegmonous infection of the cavernous bodies. Possible causes are indwelling transurethral urinary catheters, penile operations, autoinjection for erectile dysfunction, pelvic operations, or trauma. Pathogens may represent skin flora or uropathogens. Treatment consists of suprapubic catheterization, broad-spectrum antibiotic therapy, and, if needed, operative débridement.

Acute Prostatitis and Prostatic Abscess

Acute prostatitis and prostatic abscess are bacterial infections of the prostate gland. The bacterial spectrum consists of 53% to 80% *E. coli* and other enterobacteria, 19% gram-positive bacteria, and 17% anaerobic bacteria.³⁰ In regions with a high incidence of *Neisseria gonorrhoeae*, the prostate may be involved. Symptoms are high fever, rigor, dysuria, urinary retention, and perineal pain. Rectal palpation reveals an enlarged, tender prostate. Prostate massage is contraindicated. In acute prostatitis, the pathogens are usually detected in the urine. However, the urine may be sterile in prostatic abscess formation. Therapy consists of a combination of antibiotic therapy with broad-spectrum antibiotics

as well as the insertion of a suprapubic catheter. In case of a prostatic abscess, urologic drainage is necessary.³⁰

Fournier's Gangrene

Fournier's gangrene is a necrotizing fasciitis of the dartos and Colles fascias. It is mainly seen in men in the fourth to seventh decades but also occurs in women or newborns. Causes are operations or trauma in the genital or perineal region, including microlesions, or infectious processes from the rectal or urethral areas. Important predisposing factors are diabetes mellitus, liver insufficiency, chronic alcoholism, hematologic diseases, or malnutrition. Patient-related predictors of mortality are increasing age, increased Charlson comorbidity index, preexisting conditions such as congestive heart failure, renal failure or coagulopathy, and hospital admission via transfer.³¹ Fatality rates were 7.5% in one large study.³² The infectious process follows anatomically preformed spaces. The superficial perineal fascia is fixed dorsally at the transverse deep perineal muscle and laterally at the iliac bone and merges ventrally in the superficial abdominal fascia. Hence, a ventrally open and craniodorsally and laterally closed space is formed (Colles space), which facilitates the spread of infection. In contrast to gas gangrene, the fascial borders are respected in Fournier's gangrene. A mixed bacterial flora is seen, consisting of gram-positive cocci, enterobacteria, and anaerobic bacteria. The released toxins facilitate platelet aggregation and complement activation, which, in conjunction with the release of heparinase by anaerobic bacteria, lead to small vessel thrombosis and tissue necrosis. The destruction of tissue enhances the potential of acute renal failure. Fournier's gangrene is a rapidly progressing infection that leads to septic shock if not treated in time.

Therapy for Fournier's gangrene consists of immediate operative débridement, followed by subsequent operations until the infectious process has been controlled. A suprapubic catheter is advisable, and colostomy may have to be performed in cases where fecal contamination of the wound is inevitable. A combination of antibiotic therapy with broad-spectrum β -lactam antibiotics, fluoroquinolones, and clindamycin is recommended.

Urosepsis

In 20% to 30% of all septic patients, the initial infectious focus is in the urogenital tract. The most frequent causes for urosepsis are obstructive diseases of the urinary tract such as ureteral stones, anomalies, stenosis, or tumor. Early relief from the obstruction controls the infectious focus and improves organ perfusion. This is one reason why mortality in urosepsis is usually lower than that in other septic forms (Fig. 123-2).³³

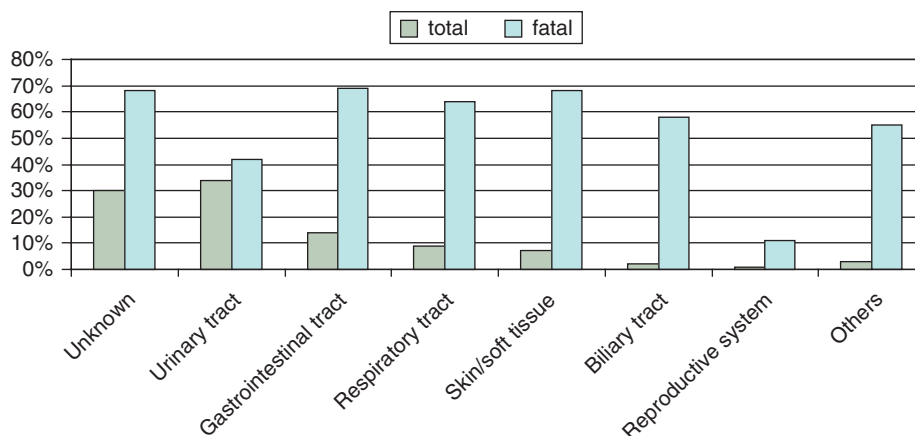


FIGURE 123-2 ■ 612 Episodes of gram-negative bacteremia 1965-1974.³³

Immediately after microbiological sampling of urine and blood, empiric broad-spectrum antibiotic therapy should be started parenterally. Adequate initial (e.g., in the first hour) antibiotic therapy ensures improved outcome in septic shock.^{34,35} Inappropriate antimicrobial therapy in severe UTIs is linked to a higher mortality rate.³⁶ Empiric antibiotic therapy is based upon the expected bacterial spectrum, institution-specific resistance rates, specific pharmacokinetic and pharmacodynamic factors in UTIs, and individual patient characteristics.

The bacterial spectrum in urosepsis predominantly consists of Enterobacteriaceae such as *E. coli*, *Proteus* spp., *Enterobacter* and *Klebsiella* spp., nonfermenting organisms such as *P. aeruginosa*, and gram-positive organisms.³⁷⁻³⁸ *Candida* spp. and *Pseudomonas* spp. occur as causative agents in urosepsis mainly if the host defense is impaired. Patients with candiduria show frequently invasive candidiasis and candidemia.^{39,40} Candiduria at any time in an ICU is associated with higher mortality rates (OR, 2.86).⁴⁰ Viruses are not common causes of urosepsis.

Although urosepsis is a systemic disease, the activity of an antibiotic at the site of the infection is critical. A variety of studies have shown that inflammatory mediators such as IL-6, CXC chemokines, endotoxin, or HMGB1 are produced and released in the urinary tract.⁴¹⁻⁴³ Therefore, predominantly antimicrobial substances with high activities in the urogenital tract are recommended.^{44,45}

The increasing antibiotic resistance rates of pathogens causing urosepsis significantly diminish the choice of antibiotics available for adequate empiric initial therapy in urosepsis. In particular, the increasing rates of Enterobacteriaceae producing ESBL pose clinically relevant problems.^{5,46-48} Other recent developments of concern include increased rates of fluoroquinolone-resistant enterobacteria and vancomycin-resistant enterococci.^{49,50} Currently, there are no specific pharmacokinetic/pharmacodynamic parameters available for the treatment of patients with urosepsis.

Correct dosing in urosepsis has to consider the altered systemic and especially renal pathophysiology that exists in patients with urosepsis. Sepsis and the treatment thereof result in higher clearances of antibacterial drugs.⁵¹ The increased volume of distribution as a result of peripheral edema in sepsis will lead to underexposure, especially of hydrophilic antimicrobials such as β -lactams and aminoglycosides, which exhibit a volume of distribution mainly restricted to the extracellular space.⁵² Increased dosing is therefore necessary. On the other hand, urosepsis may also cause multiple organ dysfunction such as hepatic or renal dysfunction, resulting in decreased clearance of antibacterial drugs. In such a case, dosing adjustment has to be considered. As β -lactams are time-dependent antibacterials, optimal administration would be by continuous infusion. Fluoroquinolones, on the other hand, display largely concentration-dependent activity. The volume of distribution of fluoroquinolones in sepsis is not greatly influenced by fluid shifts, and therefore, no alterations of standard doses are necessary, unless renal dysfunction occurs.^{51,52}

Depending on local susceptibility patterns, a third-generation cephalosporin, piperacillin, in combination with a β -lactamase inhibitor or a carbapenem may be appropriate for empiric therapy.^{4,53-56} In areas with

a high (>10%) rate of Enterobacteriaceae producing ESBL, initial treatment with a carbapenem might be advisable.⁵³⁻⁵⁷ Aminoglycosides as monotherapy might be an alternative; however, data supporting monotherapy in patients with urosepsis are not sufficient. In case of candiduria with signs of sepsis, antifungal treatment is recommended.^{39,40}

KEY POINTS

1. Complicated urinary tract infection (UTI) is a very heterogeneous entity with a common pattern of complicating factors.
2. The bacterial spectrum of complicated UTIs is much broader than that of uncomplicated UTIs, comprising a variety of gram-negative and gram-positive pathogens and, among these, frequently multiresistant pathogens.
3. UTIs are frequent in intensive care units (ICUs). It would be pragmatic to stratify UTIs into those with nonurologic complicating causes, in which antimicrobial therapy is the primary therapy, and those with urologic complicating causes, in which the complicating urologic anomaly has to be effectively treated.
4. Pathogens of nosocomial complicated UTIs may be characterized by certain properties such as adaptation strategies to changing environments (i.e., hypermutator strains) or propensity to biofilm formation.
5. The diagnosis of UTIs is based on medical history and a thorough physical examination, including bedside ultrasound as well as investigations of urine (dipstick test, microscopy, and microbiology). For clinical diagnosis, general accepted criteria should be employed. Symptomatic UTIs in ICU patients are especially difficult to evaluate.
6. Not all bacteriuric patients in ICUs need to be treated. Therapy should, however, be started early in those with significant symptoms and morbidity. Management of complicated UTIs comprises adequate antibiotic therapy and successful treatment of complicating factors.
7. Prophylaxis of UTIs is important. However, the percentage of infections that can be prevented is not known. Important points in prophylaxis encompass training of staff, hygiene measures, type of catheter and drainage, and patient care.
8. Special clinical pictures of UTIs and infections of contiguous organs are seen in the ICU. UTIs of the upper urinary tract are distinguished from those of the lower urinary tract and infections of the male adnexal glands and fasciitis of the perineum and scrotum. All these pictures can potentially merge into urosepsis if the UTI is not treated adequately. The urogenital tract is the source of sepsis in 20% to 30% of cases.

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Central nervous system (CNS) infections represent life-threatening conditions that frequently require treatment in a critical care unit. These infections may be challenging to recognize as numerous noninfectious conditions may mimic CNS infections. For example, a necrotic brain tumor may be clinically and radiologically indistinct from a brain abscess. Similarly, distinguishing between viral and autoimmune encephalitis can be challenging. Even when an infectious syndrome is suspected, it may take several days before a specific microorganism is identified, necessitating the use of broad empiric therapy directed against the most likely causative pathogens based on clinical, epidemiologic, and demographic clues. Pharmacologic considerations in selecting appropriate antimicrobials include the ability of the agent to cross the blood-brain barrier and achieve bactericidal levels at the site of infection. Clinical outcomes associated with CNS infections are directly related to the rapidity with which appropriate medical or surgical interventions can be provided, adding urgency to the diagnostic and therapeutic evaluation.¹

CNS infections may be caused by bacteria, fungi, viruses, protozoa, and prions. The risk of infection with these pathogens varies based on the host immune status (e.g., human immunodeficiency virus [HIV] infection, organ transplantation), epidemiology (e.g., time of year, travel to endemic regions), and acquisition site (e.g., community acquired vs. health care acquired). The microbiology and pathophysiology of CNS infections differ based on the specific anatomic site of infection. The major CNS syndromes covered in this chapter include meningitis, brain abscess, encephalitis, and myelitis. These syndromes may occur in isolation or may be found as overlapping conditions (e.g., meningoencephalitis or encephalomyelitis). Localizing the site of infection is often the first step in guiding the diagnostic evaluation and initiating empiric therapy.

MENINGITIS

Infections of the meninges can be subclassified by the acuity of onset of symptoms. Bacterial infections almost exclusively cause an acute meningitis syndrome, characterized by rapid (<48 hours) progression of fever, headache, and meningismus. In contrast, subacute meningitis syndrome, which occurs frequently due to viruses, fungi, or mycobacteria, is more slowly evolving, with symptoms developing over several days to weeks (Box 124-1). The following sections outline approaches to acute meningitis and subacute CNS infection syndromes. These approaches prioritize the competing needs of obtaining a precise microbiological diagnosis versus instituting early antimicrobial therapy.

Anatomy

Bacterial meningitis is a pyogenic infection of the cerebral ventricles and the subarachnoid space, with bacteria usually confined to the nutrient-rich cerebrospinal fluid (CSF). In adults, CSF is produced at a rate of approximately 500 mL/day, yet the CSF space averages only 140 mL in volume; therefore, there is rapid production and reabsorption. CSF is formed in the choroid plexus of the ventricles, flows into the subarachnoid space at the cisterna magna and around the cerebral hemispheres, and is reabsorbed by the arachnoid villi (Fig. 124-1). The cerebral and spinal subarachnoid spaces connect at the cisterna magna

and the flow of CSF through the spinal subarachnoid space are of variable velocity and direction.

There are numerous potential and actual spaces among the layers of the meninges (Fig. 124-2). Meningitis involves the actual space (i.e., the subarachnoid space), which consists of multiple interconnected compartments. The small size of the foramina of Luschka and Magendie allows for a unidirectional caudal flow toward the cisterna magna, where the CSF then moves either cephalad or caudally into the spinal canal. This compartmentalization has implications in therapy because the movement of medications and infectious agents is influenced by the rate and direction of CSF flow. A blockage at any of these levels may restrict the entry of antibiotics into sites of ongoing infection.

Infectious agents can invade the CSF by at least three routes (Box 124-2). First, the vascular structures of the choroid plexus and pia and the vessels that traverse the subarachnoid space may serve as conduits during systemic bacteremia. A second less common route is by direct invasion across the protective meninges. Physical disruption of the dura by trauma or surgery allows for the direct invasion of the subarachnoid space and should be considered in patients with a history of CSF leakage or rhinorrhea, in addition to those who have undergone recent neurosurgical interventions. Emissary veins provide another pathway for bacteria to spread from contiguous foci into the subarachnoid space. These veins traverse the skull and dura, directly connecting the soft tissues of the head and neck with the venous system of the brain and meninges, including the arachnoid villi. Although blood in the emissary veins usually flows away from the brain, the CNS veins and dural sinuses do not contain valves, and retrograde flow of bacteria is possible. Rarely, organisms may reach the ventricles or subarachnoid space from within the neural tissue; for example, rupture of a brain abscess into the ventricles may have disastrous effects. Until recently, it was thought that the brain has no lymphatic drainage and that these recently identified vessels may prove to be another route of infectious contamination of the CNS.^{2,3}

Pathophysiology

A number of virulence factors contribute to the development of bacterial meningitis.⁴ Despite complex host-cellular and anatomic defense mechanisms including immune surveillance of the CSF,⁵ microorganisms have evolved a number of virulence factors to overcome these. Once in the CSF, bacteria induce leukocyte migration into the subarachnoid space, which can cause occlusion of cortical blood vessels, damage to nerve roots that traverse the subarachnoid space (see Fig. 124-2), and impaired CSF flow (see Fig. 124-1). The activation of leukocytes leads to an inflammatory cascade, with the release of cytokines, oxidants, and proteolytic enzymes, which contribute to the damage caused by the infection. The resultant edema can lead to increased intracranial pressure and a risk of herniation.⁶

Epidemiology

Prior to the availability of antibiotics, bacterial meningitis was universally fatal. However, even with the availability of effective antimicrobial therapy, the case fatality of bacterial meningitis remains roughly 25%, with a high incidence of neurologic sequelae among survivors.^{7,8}

BOX 124-1

Causes of Acute and Subacute Central Nervous System Infection Syndromes

ACUTE MENINGITIS SYNDROME

Rapid onset (<24–48 h) of fever, headache, or meningismus, with early cognitive impairment

Common

Pyogenic meningitis (pneumococcal, meningococcal, *Listeria*, other)

Uncommon

Viral encephalitis (especially herpes simplex), subarachnoid bleed, brain abscess (with rupture)

Rare

Viral meningitis, granulomatous meningitis (cryptococcal, mycobacterial), carcinomatous meningitis, brain tumor

SUBACUTE CENTRAL NERVOUS SYSTEM INFECTION SYNDROME

Subacute onset (>24–48 h) of fever, headache, or meningismus, with no or gradual cognitive impairment

Common

Viral meningitis, viral encephalitis, rickettsial infection

Uncommon

Brain abscess, brain tumor, granulomatous meningitis

Rare

Cerebrovascular accident, carcinomatous meningitis

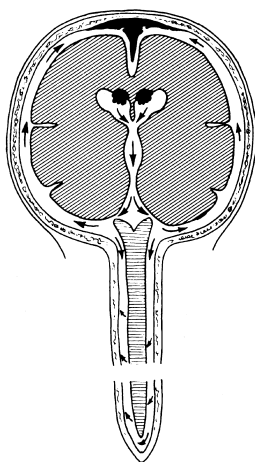


FIGURE 124-1 ■ Cerebrospinal fluid (CSF) flow within the central nervous system. CSF that forms at the choroid plexus of the cerebral ventricles rapidly enters the subarachnoid space at the foramina of Luschka and Magendie. From the cisterna magna, an organized flow of CSF occurs around the convexities of the brain to the arachnoid villi. There are multiple pathways of bidirectional flow around the spinal cord.

The epidemiology of bacterial meningitis in the United States has evolved in the past 20 years due to the widespread use of vaccines active against *Haemophilus influenzae* type B, *Neisseria meningitidis*, and *Streptococcus pneumoniae*.⁹ Simultaneously, the incidence of nosocomial bacterial meningitis caused by increasingly resistant strains of Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* is increasing.¹⁰ Meningococcal meningitis presents unique public health and infection control challenges. This diagnosis is suggested by the presence of a petechial or purpuric rash; however, this finding is neither sensitive nor specific.¹¹ To prevent secondary cases among healthcare workers, all patients with presumed bacterial meningitis should initially be placed in isolation to prevent the spread of infection by droplet transmission.

BOX 124-2

Routes by Which Bacteria May Enter the Subarachnoid Space

VASCULAR (BLOOD-BRAIN BARRIER)

Mostly likely pathogens: pneumococci, meningococci, *Listeria*, *Escherichia coli* (neonates), group B streptococci (neonates), *Haemophilus influenzae*

Choroid plexus: may be common site of invasion for *H. influenzae*

Meningeal blood vessels: throughout the subarachnoid space; may be usual route for pneumococci

Arachnoid villi: possible route of invasion, located between the sagittal sinus and subarachnoid space

TRANSDURAL

Most likely pathogens: pneumococci, gram-negative enteric bacilli, staphylococci (including coagulase-negative), *H. influenzae*

Surgery: including ventriculoatrial or ventriculoperitoneal shunts

Trauma: especially when cribriform plate or petrous bone is fractured

Parameningeal infective focus: including sinusitis, mastoiditis, otitis, or osteomyelitis; emissary veins may serve as conduit

Congenital defects: including myelomeningocele and spinal dermal sinus

TRANSPARENCHYMAL

Mostly likely pathogens: anaerobic bacteria, enteric gram-negative bacilli

Occurs when brain abscess ruptures directly into ventricles or subarachnoid space

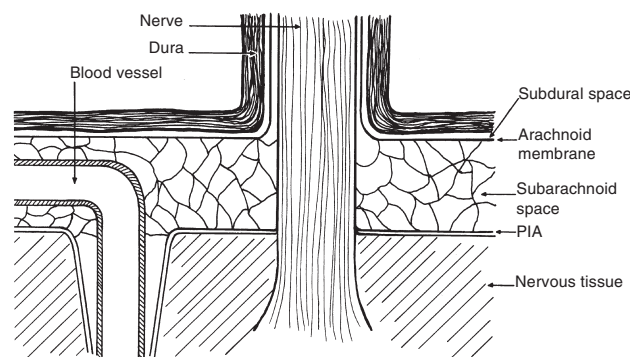


FIGURE 124-2 ■ This diagram of the potential and actual spaces between the layers of the meninges shows the relationship of blood vessels and nerve roots to the subarachnoid space.

Clinical Manifestations**Bacterial Meningitis**

Bacterial meningitis is a medical emergency, and patients with complications such as seizures or decreased level of consciousness are best managed in the intensive care setting.¹² The initial manifestations may be subtle, with a low-grade headache, nausea, and fever. However, once meningeal signs and symptoms (vomiting, severe headache, and stiff neck) develop, the clinical course is often dramatic. The classic clinical triad associated with bacterial meningitis (fever, neck stiffness, and altered mental status) is present in only 44% of cases.¹³ The signs of meningeal inflammation, including nuchal rigidity, Kernig's sign, or Brudzinski's sign, are neither sensitive nor specific for bacterial meningitis.¹⁴ A purpuric skin eruption is suggestive of meningococcal infections; however, skin lesions may be absent at the time of presentation.¹¹ Bacterial meningitis may present atypically in the elderly or immunocompromised patients, with minimal focal findings.^{15,16} In addition, these populations have a higher incidence of noninfectious conditions that may mimic acute meningitis (e.g., subarachnoid bleeding and malignancies involving the CNS) complicating the initial evaluation.

The diagnosis of meningitis is confirmed through the evaluation of CSF, assuming that there is no contraindication to lumbar puncture

TABLE 124-1 Empiric Antimicrobial Therapy for Adult Patients with Presumed Bacterial Meningitis

| SITE OF ACQUISITION | PREDISPOSITION | ORGANISM(S) | ANTIMICROBIAL AGENT(S) |
|---------------------|-------------------|--|--|
| COMMUNITY | Age 16-50 years | <i>Streptococcus pneumoniae</i> <i>Neisseria meningitidis</i> | Vancomycin plus 3rd-generation cephalosporin* |
| | T-cell deficiency | <i>S. pneumoniae</i> , <i>N. meningitidis</i> <i>Listeria monocytogenes</i> | Vancomycin plus 3rd-generation cephalosporin* plus ampicillin |
| | Age > 50 years | <i>S. pneumoniae</i> , <i>N. meningitidis</i> <i>L. monocytogenes</i> | Vancomycin plus 3rd-generation cephalosporin* plus ampicillin |
| | | Staphylococcal species Gram-negative bacilli (including <i>Pseudomonas aeruginosa</i>) | Vancomycin plus 4th-generation cephalosporin† or meropenem |
| NOSOCOMIAL | | | |

*Ceftriaxone or cefotaxime.

†Cefepime, ceftazidime.

(see below). Prompt transportation and processing of CSF is important to maximize specimen integrity as concentrations of neutrophils degrade by up to 50% after an hour post lumbar puncture.¹⁷ Findings suggestive of bacterial meningitis include neutrophilic pleocytosis, low glucose, and elevated protein levels. A positive Gram stain is diagnostic of bacterial meningitis, with a specificity of more than 99%, although the sensitivity varies based on bacterial burden and the antecedent use of antibiotics.^{18,19}

Management

Delay in antibiotic therapy increases the risk of an adverse outcome or death, particularly when progressive neurologic impairment occurs before receiving therapy.^{8,20} For this reason, guidelines recommend the expedited administration of empiric antibiotics to patients with a presumptive diagnosis of bacterial meningitis.²¹ Even in patients with profoundly abnormal Glasgow Coma Scale scores at presentation, complete recovery may be seen with directed therapy and intensive supportive care.²²

Coupled with the need for emergent treatment is the need for diagnosis. Identification of a pathogen allows a clinician to tailor the antibiotic regimen based on susceptibility patterns and has prognostic and therapeutic implications. However, in some cases, lumbar puncture is unavoidably delayed. When this is the case, antibiotics should be given immediately after peripheral blood cultures are obtained. The yield of CSF culture decreases within as little as 15 minutes following the administration of antibiotics.²³ Nevertheless, the risk of delaying antibiotic treatment outweighs the benefits of making a microbiological diagnosis. Despite the inhibitory effect of prior antibiotics on bacterial culture and Gram stain, the absolute neutrophil count and neutrophilic pleocytosis remain suggestive of bacterial meningitis,^{24,25} and a full course of empiric therapy should be completed if CSF parameters and the clinical presentation are consistent with this diagnosis.

Historically, neuroimaging has been recommended prior to lumbar puncture to exclude the presence of a mass lesion or any other risk factor for brain herniation. Studies have challenged this practice, citing the potential deleterious effect of computed tomography (CT) scan-related delays in the initiation of therapy or the compromising effect of premature sterilization of CSF cultures.^{8,20,23,26} Even among patients with an abnormal CT scan, only a minority of patients have radiographic findings precluding lumbar puncture.²⁷ For this reason, neuroimaging prior to lumbar puncture should be reserved for patients with compromised immune systems (e.g., HIV infection), use of immunosuppressive medications, or organ transplantation), history of an intracranial mass lesion, abnormal level of consciousness, papilledema, or focal neurologic deficits.²¹ In the absence of one of these features, it is generally safe to proceed directly to lumbar puncture, followed by immediate administration of empiric antibiotics.²¹

TABLE 124-2

Antimicrobial Dosages for Central Nervous System Infections

| DRUG | DOSAGE (BY TOTAL BODY WEIGHT) | USUAL DOSAGE (FOR 70-KG ADULT) |
|-------------------------------|--|---------------------------------------|
| Acyclovir | 10 mg/kg IV q 8 h | 700 mg IV q 8 h |
| Ampicillin | 30 mg/kg IV q 4 h | 2 g IV q 4 h |
| Cefotaxime | 30 mg/kg IV q 6 h | 2 g IV q 6 h |
| Ceftazidime | 30 mg/kg IV q 8 h | 2 g IV q 8 h |
| Cefepime | 30 mg/kg IV q 8 h | 2 g IV q 8 h |
| Ceftriaxone | 30 mg/kg IV q 12 h | 2 g IV q 12 h |
| Meropenem | 40 mg/kg IV q 8 h* | 2 g IV q 8 h |
| Metronidazole | 7.5 mg/kg IV q 6 h | 500 mg IV q 6 h |
| Nafcillin | 30 mg/kg IV q 4 h | 2 g IV q 4 h |
| Penicillin G | 60,000-70,000 units/kg IV q 4 h | 4 million units IV q 4 h |
| Tobramycin or gentamicin† | 2-mg/kg IV load, then 1.7 mg/kg q 8 h‡ | 140 mg IV load, then 120 mg IV q 8 h‡ |
| Intrathecal | 0.1 mg/kg/d | 5-10 mg/d |
| Intraventricular | 0.1 mg/kg/d | 5-10 mg/d |
| Trimethoprim-sulfamethoxazole | 5 mg/kg IV q 6 h | 350 mg IV q 6 h§ |
| Vancomycin | 15 mg/kg IV q 6 h | 500 mg IV q 6 h‡ or 1 g IV q 12 h |

*Pediatric dosage. Adults should receive usual dosage.

†Regardless of which aminoglycoside is used, only preservative-free preparations should be used.

‡Adjust dosage based on serum levels, with goal trough 15-20 mcg/mL.

§Dosage indicates trimethoprim component.

Antibiotics

The choice of empiric antibiotics is based on the assessment of the most likely causative agents. Recommendations for empiric therapy are listed in Table 124-1, with dosages commonly used for the treatment of CNS infections listed in Table 124-2.^{21,28} Pneumococci and meningococci remain the most common causes of community-acquired meningitis in immunocompetent adults younger than 50 years.^{28,29} Strains of *S. pneumoniae* that are increasingly resistant to penicillin have emerged as important pathogens; however, many isolates remain sensitive to third-generation cephalosporins, and all are susceptible to vancomycin.³⁰

Antimicrobial therapy should be directed against the most common causes of bacterial meningitis. In the absence of a positive CSF Gram

stain, initial empiric therapy for adults with community-acquired meningitis should include a third-generation cephalosporin such as cefotaxime or ceftriaxone, in combination with vancomycin. Vancomycin should never be used alone as initial therapy because of its marginal CNS penetration and lack of activity against gram-negative organisms. Empiric therapy for *Listeria monocytogenes* should be added for adults aged 50 years or older, patients with T-cell immunocompromise (e.g., on chronic steroid therapy), pregnant women, or patients with significant use of alcohol.^{21,28} If the CSF Gram stain shows gram-positive rods suggestive of *Listeria*, intravenous (IV) gentamicin should be given in addition to ampicillin. For patients intolerant to penicillins, trimethoprim-sulfamethoxazole is an acceptable alternative for treatment of *Listeria* meningitis.

In contrast to community-acquired meningitis, organisms causing nosocomial meningitis reflect the highly resistant strains endemic to the hospital. Empiric therapy for patients suspected to have nosocomial meningitis must therefore be directed against staphylococcal species (both coagulase-positive and -negative strains) and multidrug-resistant strains of gram-negative bacilli, including *P. aeruginosa* and *Acinetobacter baumannii*. Empiric therapy in this population should therefore include vancomycin in addition to an antipseudomonal cephalosporin (ceftazidime or cefepime) or an antipseudomonal carbapenem. Imipenem is active against *Pseudomonas* and achieves therapeutic levels in the CSF; however, because this agent lowers the seizure threshold, it is relatively contraindicated for meningitis. Meropenem, a related carbapenem, is less epileptogenic and is therefore preferred for this indication.³¹

Initial antibiotic choices can be refined when sensitivity patterns become available, typically in 2 to 3 days. The duration of therapy in bacterial meningitis varies with the pathogen and clinical response. Although there have been few randomized studies evaluating the optimal duration of therapy, 7 days of treatment for *H. influenzae* and *N. meningitidis* meningitis is typically sufficient,³² whereas *S. pneumoniae* requires 10 to 14 days of therapy.^{21,33} Adults with pneumococcal meningitis may have predisposing infections including pneumonia, sinusitis, otitis, or rarely, endocarditis, in which case prolonged therapy with bactericidal antibiotics is indicated.

Abnormalities of the CSF (e.g., pleocytosis and elevated protein) may persist for days to weeks following the eradication of infection. The resolution of infectious signs and symptoms (e.g., fever, meningismus, and leukocytosis) should serve as adequate evidence of successful therapy. In a patient who fails to respond to 48–72 hours of empiric therapy, lumbar puncture may be repeated, and head imaging, preferably an MRI with and without contrast, is indicated. A repeat lumbar puncture is particularly important for detecting clearance of bacteria from the CSF in patients with cephalosporin-resistant pneumococcal meningitis who demonstrate a slow clinical response.³⁴ Patients with culture-negative pyogenic meningitis and suboptimal clinical response should also have repeat lumbar puncture to ensure response to empiric antibiotics. Ongoing or worsening CSF parameters suggest infection with either resistant bacteria or with a pathogen more typically associated with a subacute meningitis syndrome (see Box 124-1).

Corticosteroids

Much of the morbidity from bacterial meningitis is caused by the host inflammatory response. Corticosteroids decrease inflammation, and animal studies have shown an improvement in outcome when corticosteroids are given as adjuvant therapy with antibiotics; whether this holds true in humans is less clear. A Cochrane Database review from 2013 evaluated 25 randomized controlled clinical studies on the effect of adjuvant corticosteroids for bacterial meningitis.³⁵ There was no reduction in overall mortality; however, there was a significant decrease in mortality among the subgroup of patients infected with *S. pneumoniae* meningitis. Administration of steroids was associated with a lower incidence of hearing loss and neurologic sequelae as well. Treatment guidelines recommend adjuvant dexamethasone (0.15 mg/kg IV every 6 hours for 2–4 days) given concomitantly with the first dose of

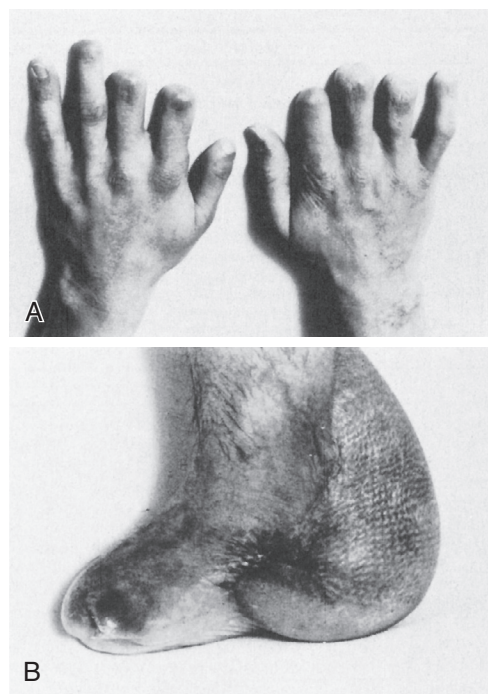


FIGURE 124-3 ■ Extremities—hands (A) and foot (B)—of a 14-year-old boy observed by two physicians as his petechial rash progressed to “bruises” (purpura fulminans). Purpura were not recognized as the hallmarks of *Neisseria meningitidis*-induced sepsis. In addition to the loss of extremities from the necrotizing vasculitis of meningococcemia, the patient rapidly developed signs and symptoms characteristic of the acute meningitis syndrome.

antibiotics for adult patients with suspected or proven pneumococcal meningitis.²¹ Whether steroids are beneficial for other causes of bacterial meningitis remains unclear.

Complications

Complications specific to meningococcal meningitis include purpura fulminans and necrotizing vasculitis leading to skin necrosis and digital gangrene (Fig. 124-3). Nonspecific complications associated with meningococcal as well as other forms of meningitis include adrenal insufficiency due to infarction (Waterhouse-Friderichsen syndrome), renal failure (due to acute tubular necrosis in the setting of hypotension), deafness, hydrocephalus, seizures, and cognitive impairment.

Other Causes of Meningitis

Other organisms including viruses, fastidious bacteria (e.g., *Rickettsia rickettsii*, *Treponema pallidum*), fungi (e.g., *Cryptococcus*), or mycobacteria may also infect the meninges (see Box 124-1). These organisms are often classified as causes of aseptic meningitis to differentiate them from the more fulminant syndrome of bacterial meningitis. In contrast to acute bacterial meningitis, patients with other forms of meningitis are less likely to require admission to the intensive care unit, and in the case of viral meningitis, usually improve spontaneously without antimicrobial therapy.

Differentiating bacterial and nonbacterial etiologies of meningitis may be challenging at the time of presentation, and laboratory data play an important role in making this distinction. Peripheral blood leukocytosis ($>10,000/\text{mm}^3$), CSF white blood cell counts over $1000/\text{mm}^3$, CSF protein concentration over 100 mg/dL , and CSF glucose concentrations below 40 mg/dL favor a bacterial cause. Patients with

these findings should be given empiric antibiotics until a specific diagnosis is made or bacterial cultures return negative. A lymphocytic predominance in the CSF, particularly in the absence of prior antibiotic therapy, argues against a bacterial etiology. Several models incorporating these variables have been developed to predict the likelihood of bacterial meningitis, although these have been best studied in pediatric patients.¹⁴ The measurement of CSF lactate levels has been shown to discriminate bacterial and aseptic meningitis; however, the sensitivity is decreased with prior receipt of antibiotics.³⁶⁻³⁸ Clinical judgment supersedes results from prediction models or biomarkers, particularly given the possibility of a fatal outcome when antibiotic therapy is deferred.

Viruses are the most common cause of aseptic meningitis, with enteroviruses predominating.^{33,39} Other viral causes of meningitis include arboviruses (including West Nile virus), herpesviruses (especially herpes simplex virus [HSV] type 2, which when recurrent is often referred to as *Mollaret's meningitis*), acute HIV infection, and lymphocytic choriomeningitis virus. Viral meningitis is typically a self-limited syndrome and does not require treatment. Laboratory testing may be useful if there is diagnostic uncertainty or to aid in epidemiologic evaluations.

Other causes of culture-negative meningitis may be more aggressive or require directed therapy. These include tickborne infections (such as with *Borrelia*, *Ehrlichia*, or *Rickettsia*), secondary syphilis, mycobacterial or fungal infections, irritation from a parameningeal focus, or partially treated bacterial infections. In these cases, additional diagnostic studies are indicated but should be individualized based on epidemiologic risk factors and clinical findings. Despite intensive diagnostic testing, a pathogen is identified in only two-thirds of patients with subacute meningitis syndrome.³³

BRAIN ABSCESS

A pyogenic brain abscess is a localized suppurative infection of the brain parenchymal tissue and may be caused by infection with bacteria, fungi, mycobacteria, or parasites. Differentiating a brain abscess from other CNS infections or brain tumors may be challenging as there is significant overlap in the clinical and radiologic presentations (Table 124-3). Optimal treatment often requires biopsy to identify the causative organism and obtain susceptibility testing. Even with a combined medical and surgical approach, mortality is significant. Rapid progression of symptoms and impaired mental status at presentation are predictors of an adverse outcome, with rupture of the abscess into the ventricles associated with significant mortality.⁴⁰

Pathophysiology

A brain abscess begins as a localized area of parenchymal infection (cerebritis) that evolves to necrosis and frank suppuration. As cerebritis progresses, a capsule-like hyperemic zone surrounding the area of inflammation develops. In time, liquefactive necrosis leads to abscess formation, with the capsule typically appearing as a ring-enhancing lesion on contrast MRI. In relatively avascular areas such as the cerebral white matter of the brain, capsule formation is delayed, and these sites have higher rates of spontaneous rupture.

Brain abscesses arise through a number of different mechanisms. The most frequent cause is the extension of infection from a contiguous focus (middle ear, mastoids, or sinuses). In approximately one-third of cases, seeding arises through hematogenous spread, and microabscesses typically develop in the distribution of the middle cerebral artery.⁴¹ Filtration of bacteria by the pulmonary vasculature provides some protection for the brain from hematogenous seeding. Therefore, when cardiac shunts or pulmonary arteriovenous fistulae are present, the risk of brain abscess is increased. In patients with endocarditis, multiple microabscesses are often detected clinically and on MRI. Direct inoculation may occur following neurosurgery or intracranial trauma.⁴² In approximately 20% of patients, no obvious source of infection is identified.^{43,44}

The pathogens causing brain abscesses differ according to the route of infection. Abscesses that arise from contiguous sites are frequently polymicrobial. In contrast, brain abscesses associated with hematogenous spread are usually due to a single pathogen. Infections following neurosurgery reflect nosocomial flora and often include multidrug-resistant organisms such as methicillin-resistant *S. aureus* (MRSA) or *Acinetobacter*. The bacteria most often isolated from brain abscesses include Enterobacteriaceae, streptococci, staphylococci, and pneumococci.⁴¹ Fastidious bacteria such as *Nocardia*, fungi such as *Aspergillus*, and even protozoa such as *Toxoplasma* can also be etiologic agents, particularly in immunosuppressed patients.

Clinical Manifestations

The signs and symptoms of a brain abscess relate to variations in location, size, and rapidity of development. At one extreme, the course may span weeks, with few constitutional symptoms. In this setting, signs and symptoms of a space-occupying lesion predominate, and the neoplasm itself is often the primary diagnostic concern. In contrast, a previously asymptomatic brain abscess may rupture into the subarachnoid space, causing death within hours. The differential diagnosis in

TABLE 124-3 Differential Diagnosis of Central Nervous System Infection and Tumor

| | BRAIN ABSCESS | BACTERIAL MENINGITIS | HERPETIC ENCEPHALITIS | BRAIN TUMOR |
|-----------------------------|---------------------|----------------------|-----------------------|------------------|
| HISTORY | | | | |
| Headache | Severe, often focal | Severe, generalized | Mild to severe | Absent to severe |
| Focal defect | Often | Occasional | Occasional | Often |
| Progression | Days to weeks | Hours to days | Days | Days to months |
| PHYSICAL EXAMINATION | | | | |
| Fever | Variable | >90% | >90% | Rare |
| Early focal signs | Often | Occasional | Occasional | Often |
| Pressure signs | Often | Rare | Occasional | Often |
| Extra-CNS infection | Often | Often | No | No |
| CT OR MRI SCAN | | | | |
| Focal | Always* | No | Often | Always |
| Ring effect/onset | Often/late† | No | No | Often/early |

*May be negative or nonspecific during first 48 hours of illness.

†Development of abscess wall may be delayed by steroid therapy.

CT, computed tomography; MRI, magnetic resonance imaging.

this setting includes an acute cerebrovascular event and pyogenic meningitis. However, brain abscesses usually progress subacutely over 7 to 14 days, which is temporally atypical for malignancy and inconsistent with stroke. The most common symptom is headache, which is present in approximately 70% of cases. Other signs and symptoms are less common and include fever (53%), focal neurologic deficits (48%), nausea or vomiting (47%), altered mentation (43%), papilledema (35%), nuchal rigidity (32%) and seizures (25%), and focal neurologic signs (48%).^{43,44} Notably, fever may be absent in as many as 50% of cases, which may lead to a missed or delayed diagnosis. CSF findings are often nonspecific and may be normal in approximately 15% of cases. Lumbar puncture may be contraindicated if there is clinical or radiographic evidence of increased intracranial pressure, given the risk of herniation.

Imaging

Neuroimaging plays a role in both diagnosis and in monitoring response to therapy. Maturation of a brain abscess is associated with encapsulation, and this is visualized as ring enhancement on CT or MRI.⁴⁵ MRI is superior to CT in assessing brain abscesses as the latter may miss small lesions or those localized to the brainstem or cerebellum. Misinterpretation can occur, particularly when the abscess is in the white matter, where decreased vascularity may result in delayed encapsulation with minimal ring enhancement. Similarly, steroid therapy may decrease local inflammation, resulting in the resolution of the ring enhancement. Furthermore, ring enhancement is not specific for bacterial abscesses and may be seen with other infections or brain tumors. Diffusion-weighted imaging is useful for differentiation of a brain abscess from other cystic brain lesions.⁴⁶ Ring-enhancing neoplasms often exhibit facilitated diffusion in the central, non-enhancing area, while abscesses typically demonstrate diffusion restriction.⁴⁵ When differentiating abscess from other pathologies, diffusion-weighted imaging has a sensitivity of 72% to 95% and a reported specificity of 96% to 100%.^{47,48}

Management

In general, a combination approach of antimicrobials coupled with surgical drainage remains the standard approach for the management of pyogenic brain abscesses. The choice of antimicrobials should be guided by culture results, given the diversity of potential pathogens and the need for prolonged therapy (e.g., 6–8 weeks). Because of the difficulty in achieving therapeutic concentrations of antibiotics across the blood-brain barrier, CNS penetration should be considered when selecting an agent. Empiric therapy should be guided by the most likely microbiology based on origin of the infection. In cases in which the source is unknown or a metastatic spread from a distant focus is likely, empiric therapy with vancomycin, metronidazole, and a third-generation cephalosporin is suggested.⁴⁴ An antipseudomonal cephalosporin should be substituted for postneurosurgical infections or for an abscess arising from an otogenic site. Meropenem may be substituted for cephalosporins and metronidazole when there is a contraindication to one of these agents.

Neurosurgical aspiration is invaluable in identifying specific pathogens, and sensitivity testing is crucial for narrowing therapy. Use of stereotactic biopsy allows minimally invasive drainage for both diagnostic and therapeutic purposes. Fungal and mycobacterial cultures should be obtained on all aspirates. Positive cultures from blood or extra-CNS suppurative foci can occasionally establish a presumptive etiologic agent. Ancillary testing for a culture-negative brain abscess includes HIV serology, serum cryptococcal antigen, and toxoplasma titers.

Medical management without drainage may be necessary when the lesion is inaccessible or surgical intervention poses unacceptable risks. However, open or stereotactic drainage is indicated when deterioration from increased intracranial pressure occurs or there is no improvement on medical therapy.⁴⁴ Patients treated without drainage

may require a longer duration (e.g., 12 weeks) of parenteral antibiotics and should be followed closely for clinical and radiographic improvement. Steroids should be reserved for cases in which significant edema is present.

ENCEPHALITIS

Encephalitis is inflammation of the brain parenchyma accompanied by neurologic dysfunction.⁴⁹ Clinical findings include altered mental status (such as disorientation, confusion, and behavioral and cognitive changes), seizures, fever, and focal neurologic signs. The worldwide incidence of encephalitis is estimated at 0.07 to 12.6 cases/100,000 persons,⁵⁰ with mortality in the range of 7% to 18% and severe disability reported in approximately half of all survivors.^{51–53}

Encephalitis presents a diagnostic challenge to the clinician, and a specific etiology is only identified in approximately 50% of all cases.⁵⁴ A myriad of causes may lead to encephalitis, including direct parenchymal infection, postinfectious syndromes such as acute disseminated encephalomyelitis (ADEM) and other immune-mediated etiologies such as neuronal cell surface and synaptic peptide specific autoantibodies (most commonly anti-N-methyl-D-aspartate receptor [NMDAR] autoantibody encephalitis), neuro-Behçet, and others.⁵⁵

Infection is the most common cause of encephalitis and constitutes approximately 50% of identifiable etiologies.⁵⁵ Among the infectious causes of encephalitis, viral infections are the most common. HSV-1 is the single most common cause of sporadic encephalitis worldwide; this pathogen is of particular importance as specific treatment is available. Varicella zoster virus (VZV) is another important cause of encephalitis that is associated with high mortality and treated similarly to HSV. In the United States, West Nile virus neuroinvasive disease is the leading cause of epidemic encephalitis during the summer and early fall. Among the immune-mediated etiologies, we will discuss postinfectious encephalitis such as ADEM and antibody-mediated encephalitis such as anti-GQ1b autoantibody syndrome (eponymously known as Fisher-Bickerstaff encephalitis) and anti-NMDAR encephalitis and will briefly address other antibody-mediated encephalitis.

Infectious Encephalitis

Pathophysiology

The blood-brain and brain-CSF barriers help protect the CNS from the free diffusion of potentially harmful biological and chemical agents.⁵⁶ Most vascular endothelial cells in the CNS are sealed by tight junctions and are unfenestrated. These contribute to the protection afforded by the basement membrane, which functions as an acellular barrier to CNS penetration. Within the CNS, astrocytic foot processes form a dense basal lamina surrounding the brain and spinal cord that contributes to the blood-brain barrier.⁵⁷ Juxtavascular microglial cells and perivascular macrophages within the brain parenchyma surveil the perivascular spaces. Nonfenestrated vascular endothelial cells in the meninges form the brain-CSF barrier. In the choroid plexus, endothelial cells are fenestrated but supported by a second layer of epithelial cells.

Inhaled viruses such as VZV or measles and ingested viruses such as enteroviruses penetrate the mucosal membranes and establish infection in the local lymphoid tissue. Viruses that are inoculated into subcutaneous tissue (e.g., arboviruses) are transported by Langerhans cells to the draining lymph nodes. From the secondary lymphoid tissues, the viruses are shed into the bloodstream and thereby disseminate. Many viruses (including West Nile virus, human T-lymphotropic virus type-1 [HTLV1]), and some bacteria such as *R. rickettsii*, have been shown to directly infect microvascular endothelial cells in vitro.^{58,59} Some viruses are capable of entering vascular endothelial cells by binding to endothelial cell-expressed molecules—for example, HTLV1 can utilize glucose transporter 1 in order to enter the endothelial cell.⁵⁸ Once within the endothelial cell, some agents can alter cellular physiology (e.g. promoting chemokine expression and

altering expression of adhesion molecules), leading to increased vascular permeability and allowing the agent to bypass the first layer of CNS protection.⁵⁷

While the brain is protected by both the blood-brain and brain-CSF barriers, many neurotropic infectious agents have developed mechanisms for gaining entry into the CNS.⁶⁰ Infection of host leukocytes, which are capable of entering the CNS, can serve as a “Trojan horse” neuroinvasive mechanism for viruses such as HIV.⁶¹ Another means of entry is direct neuronal invasion through peripheral nerves.⁶² Rabies virus and some enteroviruses, such as poliovirus, are examples of agents that reach the CNS through this mechanism. Poliovirus initially infects mucosal epithelial cells before gaining access to the CNS via retrograde transport in motor neurons,⁶³ while rabies infects epithelial cells and myocytes at the site of inoculation before gaining access to the nervous system. Once in the motor neurons, rabies virus is transported to the CNS by retrograde axonal transport and through synapses until it reaches the CNS.⁶⁴ HSV-1 infects keratinocytes before entering peripheral sensory nerves and may also gain access to the CNS through olfactory sensory neurons (as may several other viruses).⁶⁵

Individual infectious agents demonstrate variable affinities for different anatomic areas of the CNS. Those with a tropism for the meninges cause meningitis, while those capable of infecting the brain parenchyma can cause meningoencephalitis or encephalitis. Many agents can affect the spinal cord, causing myelitis (discussed below) as well. In older children and adults, HSV-1 characteristically causes temporal lobe encephalitis, whereas HSV-2 more typically causes meningitis. A number of infectious agents have a tropism for the brainstem and can cause a syndrome of brainstem encephalitis. Findings of brainstem encephalitis include cranial nerve palsies, crossed hemiparesis (ipsilateral face/contralateral body from corticospinal tract lesions) or anesthesia (medial lemniscus or spinothalamic tracts), ataxia (cerebellum/cerebellar peduncles), decreased alertness (reticular activating system in the pons), and unusual symptoms such as recalcitrant nausea/vomiting (area postrema). Infectious etiologies that have been associated with brainstem encephalitis include *L. monocytogenes*,⁶⁶ tuberculosis, Whipple's disease,⁶⁷ herpes group viruses,^{68,69} enteroviruses (particularly enterovirus 71), and flaviviruses (especially Japanese encephalitis virus and West Nile virus). There are a number of immune-mediated causes of brainstem encephalitis as well, such as neuro-Behçet, neuro-lupus, neuro-Sjögren, neuro-sarcoidosis, multiple sclerosis, neuromyelitis optica (NMO), chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids, Fisher-Bickerstaff encephalitis, and others.⁷⁰

Clinical Manifestations

In the approach to assessing a patient with possible encephalitis, it is important to first distinguish between encephalitis and encephalopathy without brain inflammation. Encephalopathy without inflammation can result from a number of etiologies—for example, metabolic derangements (hypoglycemia, hypoxia, electrolyte disturbances, renal, and liver disease) and toxin exposure (alcohol, illicit drugs, prescription medications, and environmental contaminants). A clinical case definition for encephalitis that has been proposed by an international working group⁴⁹ includes a major criterion of altered mental status for longer than 24 hours and at least two of the following: fever, seizures not attributable to a previously identified seizure disorder, new focal neurologic findings, CSF white cell count more than 5/mm³, and abnormalities on neuroimaging or EEG. This definition was designed for research and epidemiologic purposes but also provides case definition for a clinician.

Management

The history and physical examination are critically important in the diagnostic evaluation of the patient with encephalitis. Particular attention should be given to recent infectious symptoms, risk factors for tuberculosis or other infectious agents, unusual insect or toxin exposures, travel, rash, and neuropsychiatric symptoms. Full neurologic

and general examinations are important in guiding the diagnostic approach. Given the broad differential diagnosis, a diagnostic algorithm has been proposed that emphasizes the most common causes, those that benefit from targeted therapies, and those that pose a particular public health threat.^{49,71} Once a clinical diagnosis of encephalitis is suspected, empiric therapy with antiviral agents should be initiated while the diagnostic evaluation is under way.

Serum laboratory studies that should be obtained on all adults include CBC with differential, electrolytes, measures of renal and liver function, blood cultures, HIV testing, and treponemal testing. *Mycoplasma pneumoniae* IgM and IgG, EBV serologies (VCA IgG and IgM and EBNA IgG) should be obtained in children with encephalitis. Serum should be reserved from presentation, and convalescent serum should be collected 10 to 14 days later for paired antibody testing as indicated. Lumbar puncture should be obtained in all patients with encephalitis with opening pressure, cell count and differential, protein, glucose, Gram stain, oligoclonal bands, IgG index, bacterial cultures, HSV-1/2 PCR, VZV PCR and if available, VZV IgG and IgM, enterovirus PCR, cryptococcal antigen, or India ink staining and VDRL.

Neuroimaging, preferably MRI with and without contrast, should be obtained in all patients and may reveal an abscess, meningeal enhancement, limbic edema, ADEM, or other important diagnostic clues. EEG should be obtained in all patients with encephalitis and continuous EEG monitoring may be warranted in some patients as nonconvulsive status epilepticus is a common mimic and complication of encephalitis.⁷²

Patients with depressed consciousness, increased intracranial pressure, or seizures are best managed in an intensive care setting. All patients with encephalitis should be treated with IV acyclovir pending CSF PCR result for HSV. Empiric antibiotics should be given if there is concern for meningoencephalitis or a bacterial etiology such as *Listeria* rhomboencephalitis. Anticonvulsant therapy should be initiated in patients with clinical or subclinical seizures but not prophylactically. With the exception of encephalitis due to herpes group viruses and a few other agents (see below), the management of most viral encephalitides revolves around supportive care including control of seizures.⁷³

Herpesvirus Encephalitis

Herpes Simplex Virus Encephalitis

HSV-1 and -2 are two of eight human herpesviruses (HHVs), which also include VZV (HHV-3), Epstein-Barr virus (HHV-4), cytomegalovirus (HHV-5), HHV-6, HHV-7, and HHV-8. HSV-1 and -2 infections are common, with HSV-1 seropositivity at 80% to 90% worldwide.⁷⁴ HSV-1 is the most common cause of sporadic encephalitis in the United States, responsible for approximately 90% of HSV encephalitis in adults and children (with HSV-2 responsible for the remainder).⁷⁵ The mortality due to untreated HSV-1 encephalitis is roughly about 70%, and neurologic sequelae are almost universal in the absence of treatment.⁷⁵ However, timely administration of acyclovir has been shown to significantly improve survival and improve outcomes, particularly when initiated early in the course of infection.^{76,77}

HSV-1 encephalitis may be due to reactivation of the dormant virus or may occur in the setting of primary infection.⁷⁸ The virus has a tropism for the orbitofrontal and temporal lobes; however, no combination of clinical, laboratory, or radiographic findings is sufficiently sensitive to confirm the diagnosis, and an empiric acyclovir therapy should be given to all patients until all definitive diagnostic studies are completed.⁷³

Signs and symptoms typical of HSV-1 encephalitis reflect virus replication and inflammation in the medial temporal and orbitofrontal lobes and include personality change, aphasia, and seizures, in addition to other features of encephalitis.⁷⁹ Progressive temporal lobe edema can lead to uncal herniation with mydriasis (usually ipsilateral), which can progress to further herniation and death. When HSV-2 affects the CNS, it primarily causes meningitis, which may be recurrent

(Mollaret's meningitis) but may rarely cause encephalitis as well. HSV-2 can also cause brainstem encephalitis and myelitis.

The MRI is abnormal in most cases and may disclose unilateral or bilateral abnormalities within the mesial temporal and orbitofrontal lobes, the two most commonly affected structures.⁸⁰ Diffusion-weighted imaging may be more sensitive for HSV-1 encephalitis, particularly early in the course of the illness.⁸⁰ In one recent study, EEG was significantly more likely to demonstrate periodic discharges or focal slowing in frontotemporal leads in patients with HSV encephalitis compared to those with encephalitis from other causes.⁸¹

The CSF exhibits lymphocytic pleocytosis in over 90% of patients but may appear normal early in the course and is nonspecific. The CSF protein is usually elevated, and glucose level is generally normal. CSF PCR for HSV-1 and -2 DNA remains the diagnostic test of choice with a high sensitivity (96%) and specificity (99%).^{82,83} Empiric acyclovir therapy can usually be discontinued if the PCR result is negative, although there have been reports of false negative results early in the course of the disease; therefore, if the clinical suspicion for HSV encephalitis is high, repeat lumbar puncture and PCR for HSV should be performed after 48 hours while empiric acyclovir therapy is continued.⁸⁴

IV acyclovir 10 mg/kg every 8 hours is the treatment of choice for HSV-1 and -2 encephalitis and should be continued for a minimum of 14 to 21 days.⁸⁵ Caution should be used in renal impairment. The safety and efficacy of adjunctive corticosteroids have not been rigorously investigated, and these are typically reserved for use in patients with significant edema or a mass effect.⁸⁶ Cognitive deficits and seizures are significant sequelae among survivors. A recent trial of long-term valacyclovir after standard treatment for HSV encephalitis, while well tolerated, did not improve long-term outcomes.⁸⁷

While the illness is typically monophasic, 12% to 27% of patients will suffer an apparent clinical relapse days to months after the initial illness. Most affected are children who develop encephalopathy with choreoathetosis,⁸⁸ but many adults experience apparent relapse as well.⁸⁹ Recent evidence indicates that many of these patients have developed autoantibodies targeting neural peptides that are responsible for the clinical relapse.⁹⁰ HSV has been associated with a number of autoantibodies, including NMDA receptor, dopamine-2 receptor,⁹¹ and voltage-gated calcium channel⁹² autoantibodies as well as antibodies to unidentified neuronal antigens.⁹³ Patients with clinical relapse after viral encephalitis should be evaluated for autoimmune antibodies and consideration given to empiric immunosuppression once infectious etiologies have been excluded.

Varicella Zoster Virus Encephalitis

VZV is an important cause of encephalitis and was responsible for 5% of cases of encephalitis in one recent study, with a high case-fatality rate.⁵¹ VZV can also cause meningitis, myelitis, and vasculopathy that may lead to multifocal ischemic infarction, which may be recurrent (VZV has also been implicated in the pathogenesis of giant cell arteritis).⁹⁴ The diagnosis is confirmed by demonstrating VZV PCR positivity or elevated VZV IgG levels in the CSF. Treatment is similar to that for HSV encephalitis and consists of IV acyclovir for 10 to 14 days. Cutaneous zoster in the setting of encephalitis warrants empiric therapy while diagnostic evaluation is under way.

Immune-Mediated Encephalitides

While viral infections constitute the most commonly identified causes of encephalitis, it is increasingly recognized that immune-mediated encephalitis accounts for a substantial burden of disease and is the second most common cause of encephalitis.^{55,95} In particular, the autoimmune encephalitides associated with antibodies targeting neuronal cell-surface or synaptic antigens warrant discussion. In 2005, six patients with encephalitis were reported, all of whom had unidentified neural cell surface antibodies and improved with immunotherapy and/or tumor removal.⁹⁶ This small case series ushered in the study and characterization of a number of autoimmune antibody syndromes, a

growing area of interest that has had a significant impact in the fields of medicine, neurology, and psychiatry and has profoundly impacted many patients' lives. Since the discovery of anti-NMDAR encephalitis in 2007,⁹⁷ one to two novel pathogenic autoantibody syndromes have been identified yearly. Among these, anti-NMDAR encephalitis is the most common and is relatively frequently identified as a cause of encephalitis.⁵¹ In one large-scale study, anti-NMDAR encephalitis was the most commonly identified cause of encephalitis in patients who were 30 years or younger.⁹⁵

Pathophysiology

Binding of autoantibodies to their target extracellular epitopes on neural cell surface or synaptic proteins can lead to alteration of the structure or function of the target antigen.⁹⁸ Anti-NMDAR encephalitis is the best studied of the autoimmune encephalitides. The NMDAR is localized to the postsynaptic membrane and clustered at the postsynaptic density. In cultured neurons, the binding of patient IgG antibodies to the GluN1 subunit of the NMDAR leads to selective crosslinking and internalization of the NMDAR in a titer-dependent, reversible manner.^{99,100} Anti-GABA_BR and anti-AMPA_R antibodies have also been shown to cause selective internalization of their respective receptors in cultured neurons.^{101,102} More recently, Planaguma and colleagues demonstrated *in vivo* pathogenicity of anti-NMDAR antibodies by continuously infusing CSF from patients with anti-NMDAR encephalitis into the ventricles of mice, which caused memory and behavioral deficits.¹⁰³ Hippocampal analysis demonstrated accumulation of bound antibodies over time with a decrease in the number of synaptic NMDARs. Both the clinical and pathologic consequences improved with the cessation of antibody infusion.

Clinical Manifestations

The importance of the clinical history and examination cannot be overstated and there has been a tendency to be overreliant on antibody testing in autoimmune encephalitis (AIE). A recent position paper from experts in the field outlines a clinical approach to AIE.¹⁰⁴ The criteria for possible AIE include subacute, progressive deficits in memory, altered mental status or psychiatric symptoms with new focal CNS findings, unexplained seizures, CSF pleocytosis, or MRI suggesting encephalitis in patients in whom reasonable alternative causes have been excluded. Here we will briefly discuss anti-NMDAR encephalitis, but interested readers are referred to several recently published reviews of immune-mediated encephalitides.¹⁰⁵⁻¹⁰⁸

Anti-NMDAR encephalitis most commonly occurs among young females with a median age of 21 years (0.6-85 years). The syndrome develops over stages with approximately 70% experiencing a viral prodrome consisting of headaches, fevers, vomiting, diarrhea, and/or upper respiratory tract symptoms.¹⁰⁹⁻¹¹¹ Within 2 weeks, behavioral and neuropsychiatric manifestations develop and can easily be misinterpreted as evidence of a primary psychiatric condition. This is followed by a depressed level of consciousness that may alternate with episodes of agitation and catatonia. Dissociative responses such as resistance to eyelid opening and no reaction to noxious stimulation may be observed, similar to findings in pharmacologic NMDAR antagonism such as ketamine.¹¹² In this stage, patients develop a variety of abnormal movements and autonomic dysfunction that may lead to respiratory failure requiring mechanical ventilation.

Seizures are common throughout the illness, and EEG is abnormal in most patients. The extreme delta brush pattern, which consists of 1- to 3-Hz delta activity with superimposed 20- to 30-Hz beta activity, may be observed in 33% of patients and is relatively unique to NMDAR encephalitis.¹¹³ Brain MRI is abnormal in only 23% to 50% of patients and may reveal nonspecific T2 hyperintense lesions in the frontal, parietal, medial temporal, or posterior fossa and occasionally, the basal ganglia.¹¹⁴ A PET scan may demonstrate frontotemporal hypermetabolism with occipital hypometabolism.¹¹⁵ The detection of anti-NMDAR antibodies confirms the diagnosis, and autoantibodies should be sought in both the serum and CSF as 6% to 13% of patients will only have autoantibodies detectable in the CSF, depending on the method

used for antibody detection.¹¹⁶ There is also a risk of false positive results if testing is limited to the serum.¹¹⁷

Management

Management includes immunotherapy and the removal of any underlying antigenic stimulus. With treatment, 70% to 80% of patients with anti-NMDAR encephalitis will attain complete or near-complete recovery, and signs and symptoms of the disease generally abate in reverse order.¹¹⁸ Any mass lesion should be promptly removed, particularly ovarian or testicular masses, as neurologic symptoms often resolve following surgery. A retrospective analysis of 501 patients treated for anti-NMDAR encephalitis provides the most comprehensive data regarding outcomes.¹¹⁹ Treatment varied among patients and included first-line regimens consisting of tumor removal (when present), corticosteroids, IV immunoglobulin, or plasmapheresis and second-line treatment with rituximab (anti-CD20 monoclonal antibody) and/or cyclophosphamide. For patients who received first-line therapy, 53% improved within 4 weeks. Among patients who did not respond to first-line therapy, 57% were given second-line therapy, which was associated with improved outcomes compared to those who were continued on first-line therapy alone. Patients may require hospitalization for months while undergoing evaluation and treatment.

Although no data have demonstrated the superiority of one regimen over another, some authors have suggested first-line therapy with IV immunoglobulin (0.4 g/kg per day for 5 days) and methylprednisolone (1 g/day for 5 days) over plasmapheresis.¹¹¹ If improvement is not noted within 10 days, second-line therapy with rituximab (375 mg/m² every week for 4 weeks) or cyclophosphamide (750 mg/m² monthly for 3 to 6 months) should be considered. There are a few case reports of intrathecal methotrexate in place of cyclophosphamide.¹²⁰ Once substantial clinical improvement is noted, treatment can be discontinued in most patients; however, 20% to 25% of patients (usually those without a teratoma) may relapse, and longer term immunosuppression should be considered in these patients.

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory demyelinating disease of the CNS that is generally monophasic and can be difficult to prospectively distinguish from other causes of encephalitis. ADEM can occur in adults but most often affects children, with an annual incidence of 0.07 to 0.6/100,000 people.¹²¹⁻¹²³ ADEM generally presents within 2 to 4 weeks of an infectious illness or, occasionally, vaccination, but antecedent exposure may be absent in 26% of patients.¹²⁴ This observation, combined with data from an animal model of demyelination (experimental autoimmune encephalomyelitis) has led to the postulate that the pathogenesis is related to molecular mimicry in which antigenic epitopes are shared between pathogens or vaccines and host myelin. Alternatively, CNS infection with the subsequent inflammatory cascade may lead to disruption of the blood-brain barrier, exposing CNS antigens to the host immune system, which may lead to breakdown of tolerance.

The syndrome is clinically indistinguishable from encephalitis, with fever, encephalopathy (42%-83%),¹²⁵ headache with or without vomiting (15%-37%), meningeal signs (13%-43%), seizures (4%-48%), focal weakness (17%-77%), ataxia (10%-52%), cranial nerve palsies (11%-48%), and/or visual impairment (7%-23%).^{126,127} CSF analysis may disclose a variable degree of lymphocytic pleocytosis with mildly to moderately elevated protein levels, normal glucose levels, normal Gram stain with sterile cultures, and transient oligoclonal bands in 0% to 29%.¹²⁷

The MRI findings in ADEM typically include multiple large (>1-2 cm) asymmetric T2 and FLAIR hyperintense lesions randomly distributed in the cerebral hemispheres, cerebellum, brainstem, and spinal cord.¹²⁸⁻¹³⁰ Lesions classically involve the white matter but commonly develop in the deep gray matter as well, particularly the thalamus and basal ganglia, where they tend to be more symmetric.¹²⁴ The frequency and patterns of gadolinium enhancement are highly variable in ADEM (8%-100%), depending on the stage of inflammation,

although all lesions tend to be at the same stage at the same time (in contrast to the lesions seen with multiple sclerosis). ADEM is classically a monophasic illness, and signs and symptoms generally resolve over time; however, multiphasic ADEM has been reported. There is no standard treatment for ADEM, and the current suggested therapy is based on level IV evidence. After infectious and other causes of encephalitis have been excluded, most authors suggest high-dose IV methylprednisolone (20-30 mg/kg/day to maximum of 1 g/day) for 3 to 5 days followed by oral prednisone tapered over 4 to 6 weeks.^{127,129,131,132} For patients who are not responding to steroids, IV immunoglobulin has been reported to be successful in several case studies and can be considered. A reasonable regimen is 2 g/kg IV divided into doses given daily over 2 to 5 days (e.g., 0.4 mg/kg given daily for 5 days). In cases of fulminant ADEM unresponsive to steroids, plasma exchange can be considered and has been shown to be effective in aggressive CNS demyelination.¹³³

MYELITIS AND MYELOPATHY

Myelopathy refers to any pathology of the spinal cord with associated neurologic dysfunction and includes noninflammatory etiologies such as nutritional deficiency and malignancy. Myelitis is an inflammatory cause of myelopathy and may occur in isolation (e.g., poliovirus myelitis or herpesvirus myelitis) or coexist with encephalitis as an overlap syndrome (e.g., acute flaccid paralysis associated with West Nile virus encephalomyelitis, progressive encephalomyelitis with rigidity and myoclonus, or ADEM). The differential diagnosis of myelitis includes infectious and immune-mediated etiologies in addition to noninflammatory causes of myelopathy such as vitamin deficiencies (e.g., B12, copper), vascular myelopathies, and neurodegenerative conditions.

The differential diagnosis for myelitis is shown in [Box 124-3](#). Some causes, such as ADEM and other postinfectious myelitides, are monophasic, while others, such as multiple sclerosis, neuromyelitis optica, lupus myelitis (now recognized to be often associated with neuromyelitis optica), and neurosarcoidosis can be progressive and/or relapsing.

A thorough history and neurologic examination are critical for defining the temporal profile and localization. Back or neck pain (especially funicular pain), bowel or bladder dysfunction, saddle anesthesia, and bilateral upper or lower extremity weakness are historic features that suggest a spinal localization. The temporal profile is helpful in determining etiologic probabilities. For example, a hyperacute presentation is suggestive of a vascular or traumatic etiology,

BOX 124-3 Differential Diagnosis of Myelitis

VIRAL

HIV
HSV-1 and -2
VZV
CMV
EBV
WNV
HTLV

BACTERIAL

Mycoplasma pneumoniae
Borrelia burgdorferi
Treponema pallidum
Pyogenic bacteria
Mycobacterium tuberculosis

FUNGAL

Coccidioides immitis
Actinomyces
Aspergillus
Blastomyces dermatitidis
Histoplasmosis

IMMUNE-MEDIATED

Multiple sclerosis
Neuromyelitis optica
Connective tissue disorders
(neuro-lupus, neuro-Sjögren)
Neurosarcoidosis
Paraneoplastic

NONINFLAMMATORY MYELOPATHIES

Vitamin B12 deficiency
Folic acid deficiency
Copper deficiency
Vitamin E deficiency
Nitrous oxide toxicity
Heroin
Radiation myelopathy
Traumatic/compressive myelopathy
Vascular myelopathy

while an acute-subacute temporal profile suggests inflammatory or infectious etiologies and a subacute-chronic course implies nutritional deficiency or malignancy.

Identifying a spinal level is a key step in localizing a lesion to the spinal cord, and the pattern of localization may assist in determining the etiology (e.g., weakness and loss of pain/temperature with preserved vibration and proprioception in cases of anterior spinal artery occlusion or loss of vibration and proprioception with preserved pain/temperature and motor function in tertiary syphilis). In the acute setting, patients may present with hyporeflexia that can mimic Guillain-Barré syndrome, a finding that can mislead the diagnostician to a peripheral localization. While a localization can usually be identified, none of the features on the examination or history is sufficiently sensitive or specific to differentiate between inflammatory, vascular, or compressive causes. Therefore, all patients with myelitis should be managed as true emergencies utilizing a standardized approach.

The first step in the diagnostic approach to possible myelitis is to exclude extrinsic cord compression that might warrant surgical intervention.¹³⁴ Emergent imaging is indicated if cord compression is suspected as early decompression dramatically improves functional outcomes. The preferred modality is spinal MRI with and without contrast, although CT myelography is a reasonable alternative if MRI is contraindicated. Once compression is excluded, lumbar puncture with cell count and differential, total protein, glucose, Gram stain/cultures, IgG index, and oligoclonal bands should be obtained with an extra sample reserved for future studies. In addition, antiaquaporin-4 autoantibodies, SSA/SSB, ANA, anticardiolipin antibodies, copper, B12, treponemal antibody, CSF varicella zoster PCR and IgG, and enterovirus PCR should be considered. Inflammation of the spinal cord is supported by contrast enhancement on MRI, CSF pleocytosis, or elevated CSF IgG index.

There are four key steps in the management of myelitis: (1) recognition of the syndrome, (2) extinguishing acute inflammation, (3) determining the etiology, and (4) long-term management. While the diagnostic evaluation is under way, high-dose steroids (typically with 1 g IV methylprednisolone daily for 3–7 days) should be given in order to decrease the acute inflammation.¹³⁵

When infectious etiologies are suspected or confirmed, appropriate antimicrobial agents should be given. Patients with longitudinally extensive myelitis associated with lupus may benefit from the addition of cyclophosphamide to corticosteroids and plasma exchange.^{136,137} Those with myelitis as a result of neuromyelitis optica should be treated with steroids and plasma exchange, a regimen associated with improved outcomes.^{138–140} When neurosarcoidosis presents with myelitis, corticosteroids are usually effective,¹⁴¹ and refractory cases may respond to TNF- α antagonism (such as with infliximab).^{142,143} No specific regimen for infliximab in this setting has been validated as only small case series exist, but doses range from 3 to 5 mg/kg, including induction with doses at 0, 2, and 6 weeks and maintenance dosing every 4 to 6 weeks thereafter. Notably, TNF- α antagonism can worsen multiple sclerosis and is contraindicated in these patients.¹⁴⁴ In managing patients with severe myelitis of unknown etiology, consideration should be given to concomitant steroids and plasma exchange, which was associated with improved outcomes in at least one retrospective review.¹³⁷

Myelopathy from B12 deficiency should be treated with 1000 μ g intramuscular B12 daily for a week, weekly for a month, and then monthly thereafter. Depending on the cause of deficiency, some patients can eventually be treated with oral B12.¹⁴⁵ Hypocupremic myeloneuropathy should be treated with oral elemental copper 8 mg by mouth daily for a week, then 6 mg daily for a week, then 4 mg daily for a week, followed by 2 mg daily thereafter.¹⁴⁶ The underlying cause of deficiency should be identified (often associated with excessive zinc consumption, gastrointestinal surgeries, or malabsorption syndromes). Nitrous oxide toxicity may present with subacute-acute myelopathy and has been reported after a single exposure.¹⁴⁷ Nitrous oxide inactivates B12 by oxidizing the cobalt center of the molecule; therefore,

treatment is with vitamin B12. Heroin use may cause an acute myelopathy, the treatment of which is supportive.

Ischemic myelopathy secondary to spinal cord infarction is managed with lumbar drainage and hemodynamic augmentation with vasopressors in order to increase perfusion of the spinal cord.¹⁴⁸ Recent guidelines from the Congress of Neurological Surgeons recommend against the use of steroids in acute spinal cord infarction,¹⁴⁹ unless caused by vasculitis. Physical and occupational therapy are important interventions in the care of all patients with myelopathy. Long-term medical management is contingent upon the etiology of the myelitis.

CENTRAL NERVOUS SYSTEM INFECTION AND THE ACQUIRED IMMUNODEFICIENCY SYNDROME PATIENT

Patients with HIV/AIDS are susceptible to an array of opportunistic infections in addition to the more common causes of CNS infection. Those who present with altered mental status or an abnormal neurologic examination represent a diagnostic challenge. Differentiating baseline neurocognitive dysfunction associated with HIV from neurologic dysfunction related to malignancy or opportunistic infections requires a thoughtful and systematic diagnostic approach to allow rapid and appropriate treatment of what are frequently life-threatening infections.

Pathophysiology

It has long been recognized that opportunistic infections of the CNS are common in patients with HIV, including cryptococcus, toxoplasmosis, and tuberculosis.¹⁵⁰ More recently, the neurocognitive effects of HIV itself have become more widely recognized and are broadly termed *HIV-associated neurocognitive disorders* with HIV-associated dementia reserved for the most severe cases of cognitive dysfunction.¹⁵¹ Before the availability of highly active antiretroviral therapy, it was estimated that 20% to 30% of patients with uncontrolled HIV suffered from HIV-associated dementia.¹⁵² Over 40% of patients with HIV will present with neurologic manifestations, either related to the direct involvement of HIV itself or related to opportunistic infections over the course of their lives.¹⁵⁰ The neuropathogenesis of HIV has recently been reviewed, to which interested readers are referred.¹⁵³ Here we will focus on opportunistic infections associated with HIV.

Clinical Manifestations

The most important factor in approaching a patient with HIV and neurocognitive changes is the degree of immunosuppression of the patient. This framework can be used to establish the most likely etiologies in the differential diagnosis. Patients with CD4 counts higher than 500/ μ L are more likely to present with benign or malignant brain tumors, stroke, and other conditions common to immunocompetent patients. Those with CD4 counts between 200 and 500/ μ L are more likely to present with HIV-associated cognitive and motor disorders, while patients with CD4 counts lower than 200/ μ L are more likely to have CNS mass lesions, HIV-associated malignancy (such as CNS lymphoma), and opportunistic infections.

Management

In approaching a patient with HIV who presents with neurologic manifestations, a systematic approach is important. We recommend imaging prior to lumbar puncture in all patients in whom there is concern for increased intracranial pressure or a mass lesion. A brain MRI with and without gadolinium contrast is the preferred method and can assist in securing the diagnosis.¹⁵⁴ In addition to the standard

diagnostic studies, CSF analysis in HIV/AIDS patients should include cytology, cryptococcal antigen/India ink staining, VDRL (for syphilis), and PCR for herpesviruses, JC virus, and *Mycobacterium tuberculosis*.¹⁵⁵ The clinical manifestations and management of several of the most common CNS infections in patients with HIV are briefly reviewed below.

Toxoplasmosis

An obligate intracellular protozoan, *Toxoplasma gondii* is the most common HIV-associated opportunistic infection of the CNS.¹⁵⁶ It is found in cat feces and undercooked pork, and infection rates in the United States are estimated to be between 15% and 25%.¹⁵⁷ In patients with CD4 counts lower than 100/ μ L, CNS reactivation of chronic toxoplasmosis infection most often presents as acute to subacute encephalitis.¹⁵⁸ Brain MRI with and without gadolinium contrast is more sensitive than CT,¹⁵⁹ but there are no pathognomonic findings.¹⁵⁴ MRI findings suggestive of toxoplasmic encephalitis include multiple nodular or ring-enhancing lesions, usually with extensive surrounding vasogenic edema, with a predilection for the basal ganglia and corticomedullary junction.¹⁶⁰ On noncontrast images, the appearance of lesions is highly variable; they may be iso- or hypointense on T1-weighted images and hypo-, iso-, or hyperintense on T2-weighted sequences. The “eccentric target sign” is an infrequent, but highly specific (95%), finding.¹⁶¹ Most patients with toxoplasmic encephalitis have positive serologies for toxoplasmosis, but their absence does not exclude the infection. PCR of the CSF for toxoplasmosis is highly specific but insensitive and is not universally available. Treatment consists of sulfadiazine, pyrimethamine, and leukovorin (given to prevent pyrimethamine-induced hematologic toxicity). Patients who are unable to take sulfadiazine can be given clindamycin. Maintenance therapy should be given to prevent further episodes of infectious reactivation. Corticosteroids should be reserved for patients with a significant mass effect. Surgical intervention is typically reserved for patients with signs of impending herniation or lack of radiographic response after 2 weeks of empiric therapy for toxoplasmosis, in which case a biopsy to exclude an alternative cause, such as CNS lymphoma, is indicated.

Cryptococcus

Cryptococcus neoformans, an encapsulated budding yeast, is commonly found in soil contaminated by bird feces. Cryptococcal meningitis is the second most common CNS infection in patients with HIV. Cryptococcus can cause meningitis or meningoencephalitis and typically presents as subacute (1–2 weeks) meningitis but can rarely present with fulminant disease progressing to death over several days. A high index of suspicion is warranted in patients with low CD4 counts (especially <100/ μ L). Neuroimaging findings are highly variable and may be normal. Some features that suggest cryptococcal meningoencephalitis include dilated Virchow-Robin spaces, pseudocystic and cystic masses, meningitis, or hydrocephalus.¹⁵⁴ Many patients present with evidence of elevated intracranial pressure (>20 cm H₂O) that is characterized by decreased consciousness, papilledema, and sixth nerve palsy. The CSF classically reveals a low nucleated cell count (<50/ μ L), with a mononuclear predominance, elevated protein, and low glucose levels but is normal in up to 30% of infected patients.^{162,163} The CSF should be tested for the presence of cryptococcal antigen.¹⁶⁴ Opening pressure should be checked in all patients undergoing lumbar puncture as elevated pressure is associated with an increased risk of mortality without treatment. Patients with elevated intracranial pressure should be treated with at least one therapeutic lumbar puncture.¹⁶⁵ Patients with moderately elevated intracranial pressure present with an opening pressure of less than 20 cm H₂O. When symptomatic patients have an extremely high pressure, the pressure target should generally be 50% of the initial value. Daily lumbar puncture may be necessary until normalization/stabilization of pressures, and some patients may require lumbar drains or ventriculoperitoneal shunting. Antifungal therapy includes an

induction phase with liposomal amphotericin B (amphotericin B deoxycholate is an alternative if the liposomal form is unavailable) and flucytosine for at least 2 weeks, followed by consolidation therapy with fluconazole.^{166,167}

Herpesviruses

Immunocompromised patients with herpetic infections of the CNS present a diagnostic challenge, and the index of suspicion should be high in order to avoid missing the diagnosis. Immunocompromised patients with herpes encephalitis are less likely to present with prodromal symptoms or focal neurologic deficits, have more extensive radiographic involvement (often distributed outside the temporal lobes), and have CSF pleocytosis.¹⁶⁸ Even with modern treatment and supportive care, mortality among the immunocompromised is significantly higher than among the immunocompetent, with reported mortalities of 35.7% and 6.7%, respectively. As in immunocompetent patients, acyclovir is the preferred agent.

Cytomegalovirus (CMV) is another herpesvirus that is latent in the majority of the population and may reactivate, most often in immunocompromised persons. CMV can cause encephalitis, retinitis, myelitis, polyradiculopathy, and peripheral neuropathy and is most likely to manifest when the CD4 count is less than 50/ μ L. Findings on MRI are neither sensitive nor specific. MRI may reveal diffuse or focal T2 hyperintense lesions predominantly involving the periventricular white matter and possibly evidence of ventriculoencephalitis, characterized by T2 hyperintense lesions along the ependymal lining of the lateral ventricles that may enhance with the administration of gadolinium.¹⁶⁹ Analysis of the CSF may reveal neutrophilic pleocytosis and elevated protein and low glucose levels, though these findings are variably present.¹⁶⁹ CMV PCR should be obtained from the CSF, and high levels of viral DNA in the proper clinical context confirm the diagnosis, although low levels may be difficult to interpret. There are several treatment regimens in use for neurologic infections with CMV. Most clinicians use a combination of ganciclovir and foscarnet for patients with CNS infection, but patients who are unable to tolerate combination therapy can be treated with either agent alone.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a life-threatening demyelinating disease of the CNS that results from reactivation of the polyoma JC virus.¹⁷⁰ Primary infection usually occurs in childhood, although one study found that 86% of adults have antibodies to the virus.¹⁷¹ In most patients, the virus remains latent in the kidneys and the lymphoid organs, but in an immunocompromised individual, the virus may reactivate and spread to the CNS where it causes a lytic infection of oligodendrocytes. PML usually manifests with subacute, progressive neurologic deficits including personality change, altered mental status, and focal neurologic deficits referable to the localization of the infection. Seizures may occur in up to 18% of patients and are likely related to cortical or juxtacortical involvement.¹⁷² Most patients with HIV who present with PML have CD4 counts of less than 100 μ L, but PML has been associated with immunosuppression that is related to a number of medications including mycophenolate mofetil,¹⁷³ rituximab,^{174,175} and natalizumab.^{176,177} PML classically affects the white matter, manifesting on MRI as symmetric or asymmetric T1-hypointense/T2-hyperintense lesions that may become confluent.¹⁵⁴ In patients with a profound immunocompromised status,¹⁷⁸ there may be minimal or no enhancement with gadolinium, but in the setting of PML-immune reconstitution inflammatory syndrome or with medications such as natalizumab, contrast enhancement is more common.¹⁷⁹ Viral PCR from the CSF should be obtained when PML is suspected and is highly specific. However, the sensitivity has decreased to 60% in the era of highly active antiretroviral therapy.¹⁸⁰ Consequently, in some cases, brain biopsy may be required to establish the diagnosis. There remains no specific treatment for PML; therefore, treatment is

aimed at restoring immune function. In patients with HIV, initiation or optimization of antiretroviral therapy is the best option and can prolong survival.^{181,182} As the serotonin receptor 5HT_{2a} can serve as a receptor for the virus, the addition of mirtazapine may be beneficial, but evidence is limited to case reports.¹⁸³⁻¹⁸⁵ In patients who develop PML while on natalizumab, the drug should be discontinued immediately and the patient should undergo emergent plasma exchange every other day for five treatments in order to remove natalizumab.¹⁸⁶ PML is associated with a bleak prognosis and is almost uniformly fatal in patients with AIDS.^{187,188}

Central Nervous System Lymphoma

Patients infected with HIV are predisposed to several malignancies including primary CNS lymphoma (PCL),¹⁸⁹ which are strongly linked to Epstein-Barr virus (EBV) infection.¹⁹⁰ PCL can mimic an opportunistic infection, and MRI may be helpful in differentiating the etiology of mass lesions in patients with AIDS. AIDS-related PCL is often associated with a high degree of contrast enhancement, which is typically irregular and inhomogeneous.^{191,192} Lesions that involve the corpus callosum and periventricular or periependymal areas are more likely to represent PCL, while PCL involves the posterior fossa in less than 10% of cases in this population.^{191,193} Among the conditions discussed here, PCL and toxoplasmosis are most likely to cause a mass effect.¹⁹⁴ As there is clinical and radiologic overlap with opportunistic infections, these should be thoroughly evaluated as outlined above with the inclusion of CSF testing for EBV PCR, cytology, and flow cytometry. In the absence of a pathologic diagnosis, empiric corticosteroids should be used with caution as these may decrease the diagnostic yield for CNS lymphoma.

PARADURAL ABSCESS

The epidural space is between the dura and the bony structures of the skull and vertebral column; the subdural space is between the subarachnoid membrane and the dura (see Fig. 124-2). Unlike the subarachnoid space, the paradural tissues are only potential spaces, with the arachnoid membrane and the dura limiting the spread of infection across their surfaces. Although subdural abscesses are more common within the cranium and epidural abscesses are more common within the vertebral column, the causes, pathophysiologies, and therapies are similar. These abscesses usually develop from a contiguous infection, surgery, or trauma.

Cranial Paradural Abscess

In the skull, the epidural tissues are dense and abscess formation is unusual. The subarachnoid membrane is less adherent to the dura, making the subdural space the more likely site of infection. Intracranial paradural abscesses tend to evolve rapidly, often producing irreversible damage to underlying neural structures. Antibiotics alone are inadequate, and neurosurgical drainage remains the mainstay of therapy. MRI has greatly aided in the rapid identification and management of intracranial paradural abscesses.

Cranial epidural abscesses most commonly occur adjacent to the frontal sinus, but if left untreated, infection can spread into the subdural space or even parenchyma. The abscess may be due to trauma but, most commonly, is a complication of sinusitis, which is reflected in the microbiology of cranial epidural abscesses.¹⁹⁵ Treatment requires emergent surgical drainage followed by antibiotics tailored against the bacteria cultured intraoperatively.

Cranial subdural empyema may be clinically indistinguishable from meningitis or a brain abscess, with the triad of fever, headache, and altered consciousness seen at presentation in approximately 50% of patients.¹⁹⁶ A subdural abscess is most commonly a complication of a prior neurosurgical procedure but can also occur following infection of the paranasal sinuses and, less commonly, the ears or mastoids.¹⁹⁷ Rarely, spontaneous development of a subdural abscess

following bacteremia has been reported. The microbiology of these infections reflects the pathophysiology. Infections following a neurosurgical procedure are typically due to skin flora such as *Staphylococcus* or *Enterobacteriaceae*. Infections that occur as a complication of upper respiratory tract infections are usually due to streptococci, pneumococci, *Haemophilus*, anaerobes, and staphylococci. Gram-negative enteric bacilli or *P. aeruginosa* may be associated with middle ear and mastoid infections. As with cranial epidural abscess, surgical drainage is crucial for treatment, followed by prolonged use of antibiotics.¹⁹⁵

Spinal Paradural Abscess

The incidence of spinal epidural abscess has increased in the past two decades, which is likely related to improved diagnostics with MRI and increases in comorbidities predisposing to infection. Risk factors for spinal epidural abscess include prior spinal surgery or trauma, injection drug use, diabetes, and end-stage renal dysfunction.¹⁹⁸ Patients typically present with localized spinal pain, with fever present in less than 50% of cases.^{199,200} In the absence of treatment, symptoms usually progress through four clinical phases: spinal ache, nerve root pain, radicular weakness, and paralysis. The triad of back pain, fever, and progressive neurologic deficits strongly suggests this syndrome; however, the presence of any of these signs or symptoms should raise concern for the diagnosis.

Diagnosis hinges on visualization of a collection in the epidural space (Fig. 124-4). The diagnostic study of choice is MRI, which defines cord compression and the presence and extent of abscess, identifies drainable paraspinal fluid collections, and detects concomitant vertebral osteomyelitis. Other procedures such as myelography and CT scanning may be used if MRI cannot be performed.

S. aureus accounts for more than two-thirds of cases of epidural abscess.^{199,201} Although most cases are community acquired, an increasing number are due to spinal instrumentation (surgery or nerve block), and nosocomial flora such as MRSA or *Pseudomonas* may be causative in this population. Other risk factors for spinal epidural abscess include IV drug use, diabetes mellitus, trauma, and comorbid conditions such as malignancy or alcohol use.¹⁹⁹ Empiric therapy is directed against the most likely organisms and typically includes vancomycin and an antipseudomonal agent such as cefepime. Therapy should be refined once cultures confirm a causative pathogen.

Emergency neurosurgical intervention is considered mandatory for a spinal paradural abscess if there is neurologic compromise. A recent retrospective study found that 41% of patients with a spinal epidural abscess failed medical therapy and that neurologic outcomes were improved for patients with immediate rather than delayed neurosurgical decompression.²⁰² Progressive weakness mandates the need for immediate MRI and neurosurgical consultation because decompression within 24 hours offers the best chance of neurologic recovery.²⁰¹

SEPSIS SYNDROME WITH CENTRAL NERVOUS SYSTEM INVOLVEMENT

In sepsis syndrome, an acutely ill patient develops CNS dysfunction late in the course of the illness, typically in the setting of multiorgan system failure. Altered mental status, attributable to hypotension and hypoperfusion, ranges from confusion to obtundation. Seizures may occur due to metabolic abnormalities, ischemia, or hemorrhage. In treating such patients, general supportive measures take precedence over CNS concerns. After a brief assessment, general life-support measures should correct hypotension, hypoxia, and anuria. Following blood culture, broad-spectrum antimicrobials should be administered. A careful history should be taken and physical examination performed. When findings suggest a focal infection of the CNS, directed evaluation through neuroimaging and lumbar puncture is warranted.

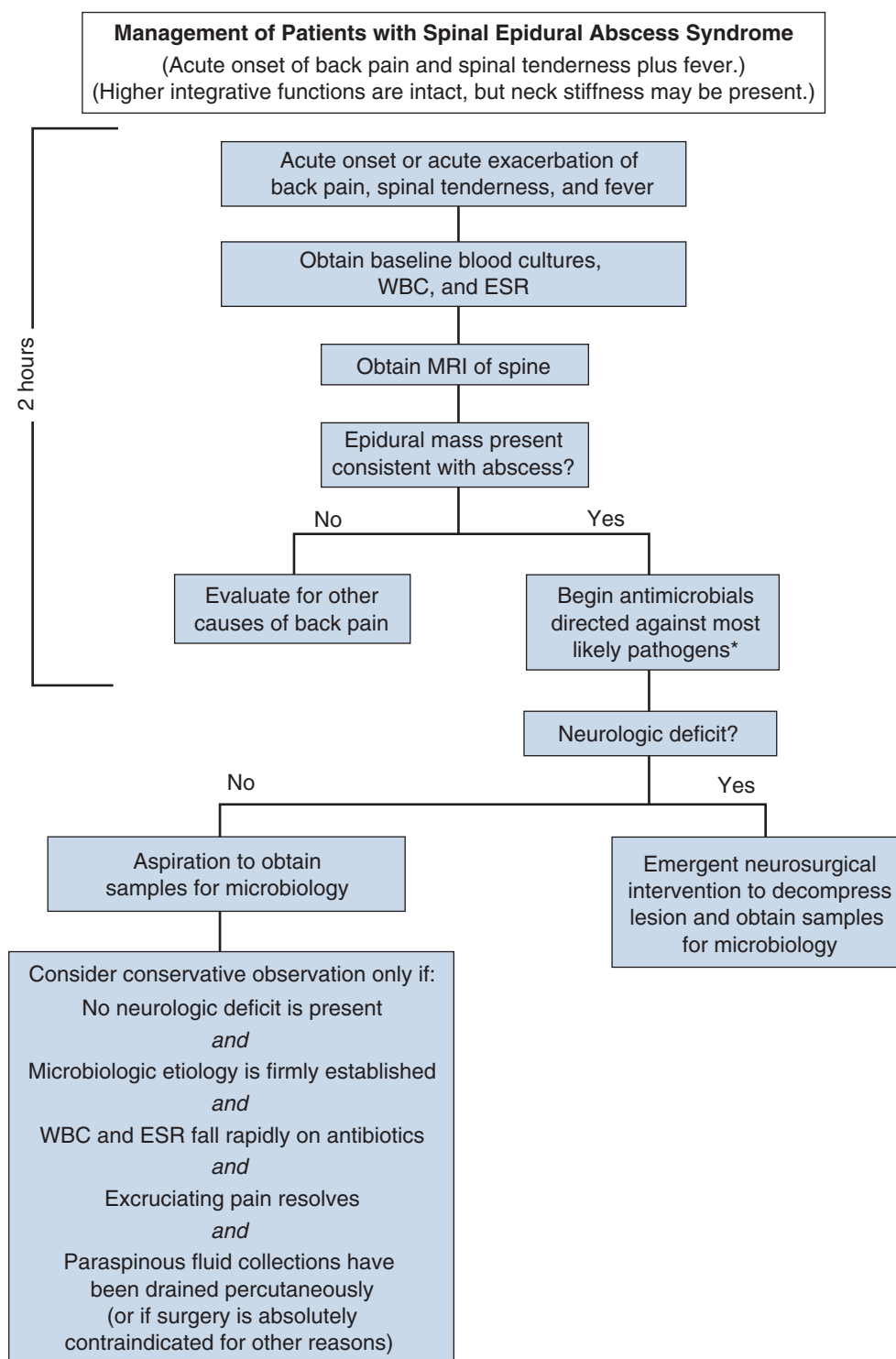


FIGURE 124-4 ■ Algorithm for the management of patients with the spinal epidural abscess syndrome. If magnetic resonance imaging (MRI) cannot be performed, myelography, high-contrast computed tomography (CT), or CT-myelography may be an acceptable alternative to localize an epidural abscess. *If abscess drainage can be performed promptly, antimicrobial drugs may be withheld until specimens for microbial analysis is obtained. ESR, erythrocyte sedimentation rate; WBC, white blood cell.

CONCLUSION

Acute infection of the CNS requires rapid therapeutic intervention. The four major syndromes of CNS infection (acute meningitis syndrome, subacute CNS infection syndrome that includes brain abscess, viral meningitis and encephalitis, spinal epidural abscess, and sepsis syndrome) differ in their signs and symptoms as well as in the approach

to definitive diagnosis and therapy. Moreover, diverse infectious and noninfectious causes may produce similar CNS syndromes. For therapy to be maximally effective, it must be instituted rapidly following the initial evaluation. Thus, in the practice of critical care medicine involving CNS disease, the goal remains the rapid institution of empiric therapy for treatable infectious syndromes while efficiently working to identify the specific disease process.

KEY POINTS

Bacterial Meningitis

1. Fever, headache, and meningismus are the classic presenting signs and symptoms of bacterial meningitis; however, absence of any one (or all) of these features may be seen.
2. A noncontrast head CT should precede lumbar puncture in the presence of papilledema, focal findings on neurologic examination, immunocompromise (human immunodeficiency virus [HIV] infection, malignancy, or transplant), and seizures in the week prior to presentation or coma.
3. Empiric antibiotic therapy should begin as soon as possible after appropriate cultures have been obtained; these can be modified later based on results of cerebrospinal fluid (CSF) Gram stain and culture.
4. Patients with negative cultures and limited clinical response after 48 hours of therapy should undergo repeat lumbar puncture and head CT or MRI scans.
5. Corticosteroid treatment in adults is controversial, but initial combination therapy with dexamethasone and antibiotics has been associated with improved outcomes in patients with pneumococcal meningitis.

Brain Abscess

1. MRI with contrast is superior to CT for imaging brain abscesses, especially in the early stages of infection.
2. Microbiology of brain abscesses is dependent on the route of infection; abscesses spreading from a contiguous focus are frequently polymicrobial.
3. Treatment of brain abscesses typically requires neurosurgical drainage and prolonged administration of antibiotics tailored to culture results.

Encephalitis

1. An infectious cause of encephalitis is found in less than 50% of cases.

2. Herpes simplex virus (HSV) must be included in the differential diagnosis of all cases of encephalitis, as this infection has a high morbidity and mortality unless treated with acyclovir. Herpes simplex encephalitis typically presents with temporal lobe lesions on MRI, and HSV polymerase chain reaction of CSF is more than 95% sensitive for diagnosis.
3. Autoimmune syndromes such as NMDAR encephalitis may mimic infectious etiologies but are treated with removal of the antigenic stimulus (i.e., surgical excision of a teratoma) and immunotherapy.

Central Nervous System Infection in HIV-Infected Patients

1. HIV-infected patients are at risk for a number of opportunistic infections. Because many of these cause mass lesions, CT or MRI should be performed before lumbar puncture.
2. Ring-enhancing lesions seen on neuroimaging are most frequently due to either toxoplasmosis or lymphoma. In patients with positive *Toxoplasma* serology, empiric therapy for 2 weeks is indicated; brain biopsy should be performed in patients with lack of radiographic improvement.
3. Cryptococcal meningitis can be rapidly diagnosed by the detection of cryptococcal antigen in either the serum or the CSF.

Epidural Abscess

1. Epidural infections typically present with back pain, fever, and progressive neurologic impairment. Diagnosis is confirmed by MRI.
2. In the presence of impaired neurologic function, surgical drainage is imperative; there is little chance of recovery if symptoms have been present for more than 24 hours before decompression. Empiric antibiotics to cover staphylococci and enteric gram-negative rods should be continued until culture results are available.

ANNOTATED REFERENCES

Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2015 Sep 12;9:CD004405. doi: 10.1002/14651858.CD004405.pub5. Review. PubMed PMID: 26362566.

This meta-analysis of 25 studies involving more than 4000 patients examined outcomes in patients with bacterial meningitis treated with corticosteroids in addition to antibiotics. There was no significant difference in mortality, hearing loss, or neurologic sequelae in patients treated with steroids. On subgroup analysis, adjuvant use of corticosteroids reduced mortality associated with S pneumoniae meningitis, and hearing loss in children with H. influenzae meningitis. When the study was stratified by site, co-administration of corticosteroids in high-income (developed) countries was associated with statistically significant reduction in hearing loss and neurologic morbidity. There was no beneficial effect of corticosteroids in patients with bacterial meningitis in low-income countries.

Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, Harrison LH, Farley MM, Reingold A, Bennett NM, Craig AS, Schaffner W, Thomas A, Lewis MM, Scallan E, Schuchat A;

Emerging Infections Programs Network. Bacterial meningitis in the United States, 1998-2007. *N Engl J Med*. 2011 May 26;364(21):2016-25. doi: 10.1056/NEJMoa1005384. PubMed PMID: 21612470.

This paper summarized the results of a large population-based laboratory surveillance program for bacterial meningitis performed in selected areas in the United States between 1998 and 2007. During this time period, there was a 31% overall decrease in the incidence of bacterial meningitis due to declining rates of pediatric meningitis from S. pneumoniae and H. influenzae due to vaccination. The median age of patients increased from 30.3 years to 41.9 years, with an aggregate case fatality rate of 14.8%. S. pneumoniae remained the leading cause of bacterial meningitis, accounting for 58% of cases.

Venkatesan A, Tunkel AR, Bloch KC, Learing AS, Sejvar J, Bitnun A, Stahl JB, Mailles A, Drebot M, Rupprecht CE, Yoder J, Cope JR, Wilson MR, Whitley RJ, Sullivan J, Granerod J, Jones C, Eastwood K, Ward KN, Durrheim DN, Solbrig MV, Guo-Dong L, Glaser CA; International Encephalitis Consortium. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. *Clin Infect Dis*. 2013 Oct;57(8):1114-28.

doi: 10.1093/cid/cit458. Epub 2013 Jul 15. PubMed PMID: 23861361; PubMed Central PMCID: PMC3783060.

The authors provide expert consensus recommendations on a working case definition for encephalitis and outline diagnostic algorithms for both pediatric and adult patients with encephalitis. These protocols were developed to include the most prevalent pathogens and to optimize empiric therapy of treatment etiologies. Clinicians are encouraged to pursue additional diagnostic testing based on local epidemiology, seasonality, specific exposures, or clinical characteristics.

Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, Cortese I, Dale RC, Gelfand JM, Geschwind M, Glaser CA, Honnorat J, Höftberger R, Iizuka T, Irani SR, Lancaster E, Leypoldt F, Prüss H, Rae-Grant A, Reindl M, Rosenfeld MR, Rostásy K, Saiz A, Venkatesan A, Vincent A, Wandering KP, Waters P, Dalmau J. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol*. 2016 Apr;15(4):391-404. doi: 10.1016/S1474-4422(15)00401-9. Epub 2016 Feb 20. Review. PubMed PMID: 26906964.

In the past decade autoimmune disorders have been increasingly recognized as leading causes of encephalitis. These inflammatory etiologies may mimic infectious causes, but the treatment involves immunosuppressive medications rather than antimicrobial agents. This consensus statement by experts in the field of neuroimmunology provides an evidence-based strategy to guide diagnostic testing and identify a subset of patients most likely to benefit from empiric immunotherapy.

Brouwer MC, Tunkel AR, McKhann GM 2nd, van de Beek D. Brain abscess. *N Engl J Med*. 2014 Jul 31;371(5):447-56. doi: 10.1056/NEJMra1301635. Review. PubMed PMID: 25075836.

This comprehensive review provides updated information regarding the pathogenesis, epidemiology, clinical presentation, microbiology, and optimal treatment of brain abscesses. The authors emphasize the role of surgical management and highlight the increasing use of stereotactic biopsy as a less invasive means of identifying the causative organism(s) and providing therapeutic drainage.

Kim SD, Melikian R, Ju KL, Zurakowski D, Wood KB, Bono CM, Harris MB. Independent predictors of failure of nonoperative management of spinal epidural abscesses. *Spine J*. 2014 Aug 1;14(8):1673-9. doi: 10.1016/j.spinee.2013.10.011. Epub 2013 Oct 30. PubMed PMID: 24373683.

This retrospective, case-control study compared outcomes among adult patients with nonsurgical spinal epidural abscess treated medically compared to those who underwent surgical decompression in addition to antibiotic therapy. Patients with neurologic compromise, age more than 65 years, diabetes mellitus, or infection due to methicillin-resistant Staphylococcus aureus had significantly higher rates of failure with solely medical management, and consideration of early surgical intervention in these populations is warranted.

■ References for this chapter can be found at expertconsult.com.

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Infections of the skin, soft tissue, and muscle include a broad range of diseases commonly encountered in intensive care units (ICUs) and are often potentially life-threatening. These infections include necrotizing soft-tissue infections (NSTIs), soft-tissue infections of the head and neck, and infectious complications of bites, burns, and pressure ulcers.

NECROTIZING SOFT-TISSUE INFECTIONS

NSTIs represent a spectrum of infectious processes that are extensive and rapidly progressive. Based on the depth of skin and soft-tissue involvement, NSTIs are divided into three categories: (1) necrotizing cellulitis, (2) necrotizing fasciitis, and (3) myonecrosis. Table 125-1 shows the classification of NSTIs. The sine qua non of these infections is the necrosis of subcutaneous tissue, fascia, and muscle, with the widespread undermining of the skin. The lack of anatomic boundaries and the fact that the infection is deep within the skin help account for the severity of the infection, as well as the frequent delay in its recognition. The trunk, extremities, and perineum are the most common sites of NSTIs, but any anatomic site may be involved. For example, intraabdominal abscess, bowel perforation, and pancreatitis can all present as a necrotizing infection of the abdominal wall or extend into the thigh. Similarly, cervical fasciitis due to dental or neck abscess can extend to the mediastinum.

Pathogenesis

Pathophysiologic factors involved in the development and progression of NSTIs are host resistance, the bacterial pathogens involved, and local barrier factors. Early development of systemic organ dysfunction and a lack of early resolution is associated with higher morbidity and mortality rates.¹

Host Resistance

As shown in Table 125-2, individuals who are immunocompromised or have chronic diseases are more likely to develop necrotizing skin and soft-tissue infections than those without such medical problems.

Bacterial Pathogens

Although necrotizing cellulitis and fasciitis may be caused by a single bacterial pathogen (e.g., group A *Streptococcus*, *Vibrio* spp., or zygomycetes), about 80% of necrotizing cellulitis or fasciitis results from polymicrobial infections with synergistic facultative aerobes and anaerobic gas-forming organisms. An average of 4.4 organisms are isolated from polymicrobial necrotizing infections.² The former include gram-positive and gram-negative aerobes, such as *Streptococcus pyogenes*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, or *Pseudomonas aeruginosa*, and the latter include *Clostridium perfringens*, *Bacteroides fragilis*, and *Peptostreptococcus*.³ Certain predisposing conditions can be correlated with specific bacteria; for example, trauma with *Clostridium* spp., diabetes mellitus with *Bacteroides* spp., *S. aureus*, and Enterobacteriaceae, as well as immunosuppression with *Pseudomonas* spp. and Enterobacteriaceae. Rare monomicrobial infections by *Haemophilus influenzae* have been described recently.

Traditionally, gas gangrene is synonymous with clostridial infection, and gas in the soft tissue is thought to be a grave finding. The majority of gas-producing infections do not involve *Clostridium* spp. but are instead necrotizing infections due to other bacterial pathogens. Many bacteria, especially facultative gram-negative bacilli (e.g., *E. coli*), produce insoluble gasses (e.g., hydrogen, nitrogen, and methane) whenever they are forced to use anaerobic metabolism. Thus, the presence of crepitus in a soft-tissue infection found during physical examination or radiographs imply anaerobic metabolism and the existence of an NSTI.

Local Barrier Failure

Most serious soft-tissue infections require some degree of tissue injury and a break in the skin to establish infection. The break in the skin may be due to a surgical incision or trauma, but in a significant percentage of cases, it is difficult to find evidence of a break in the skin or soft-tissue trauma.

Clinical Manifestations and Diagnosis

The critical aspect of diagnosing NSTIs is maintaining a high index of suspicion, which allows for early recognition of the necrotizing nature of the infection and the need for surgical intervention. Although necrotizing cellulitis and fasciitis may occur after an injury, up to 40% of NSTIs have no identifiable cause. NSTIs with identifiable barrier failure are more likely to be polymicrobial and are easier to diagnose than the more virulent infections caused by a single organism. In necrotizing cellulitis, gas is invariably found in the skin, but the fascia and deep muscle are spared. Early clinical findings are similar to those of common wound infections, including local edema (89%), erythema (30%), fever (71%), and local cutaneous anesthesia (27%) due to cutaneous nerve necrosis. These are followed by gangrenous skin changes with rapid extension beyond the borders of the original infection. Synergistic polymicrobial necrotizing fasciitis is characterized by "dishwater pus." Patients usually have a high fever, but no obvious source of clinical infection can be detected. Pain in the area of the infection is usually out of proportion with the physical findings. Diagnosis may be more difficult in patients with immunosuppression, resulting in delays in treatment and higher mortality rates.⁴ As the infection progresses, patients develop shock and multiple organ failure. Mortality rates are high, with necrotizing fasciitis being fatal in 23.5% of cases.⁵

Clostridial myonecrosis typically develops within 12 to 24 hours after a traumatic event or the closure of a deep, contaminated wound. Recurrent gas gangrene caused by *C. perfringens* has been described in individuals with nonpenetrating injuries at the sites of previous clostridial myonecrosis, where spores of *C. perfringens* remain quiescent in the tissue and then germinate when minor trauma provides conditions suitable for growth. Patients present with the triad of severe pain, tachycardia out of proportion to fever, and crepitus in the soft tissue. Once overt gangrene with edema and bronze, purplish, or brown discoloration with bullae and watery discharge occur, the disease is at an advanced stage. Gram staining of the exudate shows gram-positive rods occasionally accompanied by other flora. In contrast, streptococcal myonecrosis usually develops over 2 to 4 days after the trauma or closure of a wound. The onset is not as rapid, patients do not appear

TABLE 125-1 Classification of Necrotizing Skin, Soft-Tissue, and Muscle Infections

| DISEASE | BACTERIOLOGY | COMMENTS |
|--|--|--|
| NECROTIZING CELLULITIS | | |
| Clostridial cellulitis | <i>Clostridium perfringens</i> | Local trauma, recent surgery; facial/deep muscle spared |
| Nonclostridial cellulitis | Mixed: <i>Escherichia coli</i> , <i>Enterobacter</i> , <i>Peptostreptococcus</i> spp., <i>Bacteroides fragilis</i> | Diabetes mellitus predisposes; produces foul odor |
| Meleney's synergistic gangrene | <i>Staphylococcus aureus</i> , microaerophilic streptococci | Rare infection; postoperative; slowly expanding, indolent, ulceration in superficial fascia |
| Synergistic necrotizing cellulitis | Mixed aerobic and anaerobic, including <i>B. fragilis</i> , <i>Peptostreptococcus</i> spp. | Diabetes mellitus predisposes; variant of necrotizing fasciitis type I; involves skin, muscle, fat, and fascia |
| NECROTIZING FASCIITIS | | |
| Type I | Mixed aerobic and anaerobic; staphylococci, <i>B. fragilis</i> , <i>E. coli</i> , group A streptococci, <i>Peptostreptococcus</i> spp., <i>Prevotella</i> , <i>Porphyromonas</i> spp., <i>Clostridium</i> spp. | Usually requires a breach in the mucous membrane layer either through surgery, penetrating injuries, or from chronic medical conditions such as diabetes, peripheral vascular disease, malignancy, and anal fissures |
| Type II | Group A streptococci | Increasing in frequency and severity since 1985; very high mortality; often begins at the site of nonpenetrating minor trauma such as a bruise or muscle strain but there is often no identified precursor Predisposing factors: blunt/penetrating trauma, varicella (chickenpox), intravenous drug abuse, surgical procedures, childbirth, NSAID use |
| MYONECROSIS | | |
| Clostridial myonecrosis | <i>Clostridium</i> spp. | Predisposing factors: deep/penetrating injury, bowel and biliary tract surgery, improperly performed abortion and retained placenta, prolonged rupture of the membranes, and intrauterine fetal demise or missed abortion in postpartum patients. Recurrent gas gangrene occurs at sites of previous gas gangrene. |
| Streptococcal myonecrosis | Streptococci | |
| SPECIAL TYPE OF NECROTIZING SOFT-TISSUE INFECTION | | |
| Fournier's gangrene | Polymicrobial, with <i>E. coli</i> the predominant aerobe and <i>Bacteroides</i> the predominant anaerobe. Other microflora: <i>Proteus</i> , <i>Staphylococcus</i> , <i>Enterococcus</i> , aerobic and anaerobic <i>Streptococcus</i> , <i>Pseudomonas</i> , <i>Klebsiella</i> , and <i>Clostridium</i> | Necrosis of the scrotum or perineum that starts with scrotal pain and erythema and rapidly spreads onto the anterior abdominal wall and gluteal muscle. It is more often seen in diabetics and can be associated with trauma. |

TABLE 125-2 Factors Predisposing to Necrotizing Soft-Tissue Infections

Human, animal, or insect bites
 Contaminated or dirty surgical procedures
 Diabetes mellitus
 Long-term corticosteroid use
 Malignancy
 Trauma/burns
 Intravenous drug abuse
 Chronic alcoholism
 Malnutrition
 HIV infection/AIDS
 Cirrhosis
 Peripheral vascular diseases
 Chronic renal failure

as sick, pain is not as severe, and gas formation is not as obvious as in those with clostridial myonecrosis.

Management

The initial management of NSTIs involves aggressive fluid resuscitation, appropriate broad-spectrum parenteral antibiotics, and most important, expedient and radical surgical débridement. Other adjunctive therapies (e.g., hyperbaric oxygen, immunoglobulin, and immune-modulating peptide drugs) have been used, but the evidence for their efficacy at this time is not definitive.

Antibiotics

For type I necrotizing fasciitis (mixed aerobic and anaerobic), antibiotic treatment should be guided initially by the results of the Gram stain. Early empiric treatment should be initiated with extended-spectrum penicillins (e.g., ampicillin-sulbactam, piperacillin-tazobactam, and ticarcillin-clavulanic acid) or carbapenem antibiotics (e.g., imipenem-cilastatin) plus a drug that targets methicillin-resistant *S. aureus* (MRSA). If there is a suspicion that resistant coliforms might be participating (e.g., in patients who have been hospitalized or who have been treated with antibiotics recently or where there is suspicion of rectal or intestinal involvement), a third-generation cephalosporin, aminoglycoside, or aztreonam combined with either clindamycin or metronidazole may be used. For those patients with severe cases or in whom clostridia are suspected, clindamycin in addition to penicillin is useful for inhibiting toxin production. The incidence of community-acquired MRSA (CA-MRSA) in necrotizing soft tissue infections is increasing and mandates appropriate coverage.⁵ Linezolid is emerging as the preferred treatment; a meta-analysis demonstrated improved clinical and microbiological cure rates when compared to vancomycin.⁷

Although there are no data from clinical trials establishing the benefit of combined therapy in type II necrotizing fasciitis (group A streptococci), penicillin G combined with clindamycin is the antibiotic therapy of choice. Clindamycin is recommended not for its anti-anaerobic properties but because of its additional activity against gram-positive organisms, including the specific inhibition of toxin production.⁸ Cefotaxime and ceftriaxone are acceptable alternatives. For patients allergic to penicillin, vancomycin is the recommended treatment.

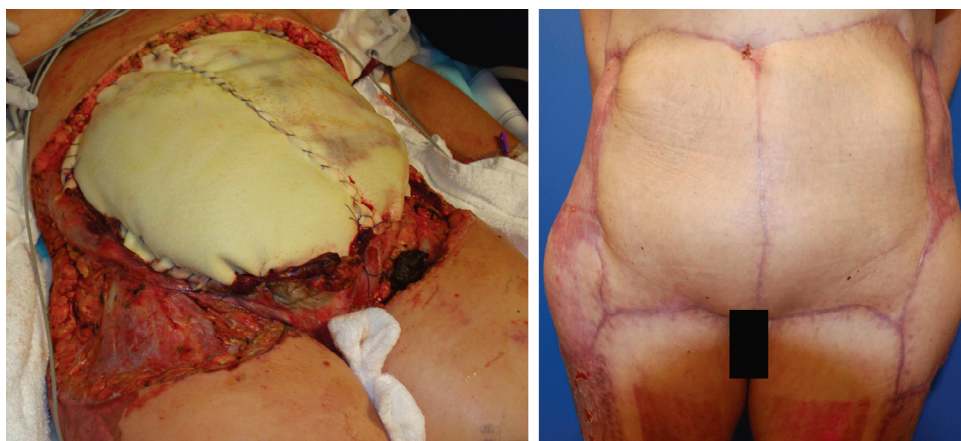


FIGURE 125-1 ■ Necrotizing fasciitis of the abdominal wall after extensive débridement and the application of a porcine dermal collagen implant for temporary abdominal closure (*left*) and after healing of the anterolateral thigh flaps to reconstruct the abdominal wall (*right*).

Surgical Intervention

Early surgical débridement is critical in the management of NSTIs.⁹ Aggressive surgical excision of all involved tissue with a margin of normal-appearing tissue is mandatory. All necrotic tissue should be excised back to healthy bleeding margins. The wound should frequently be reexamined for the viability of the tissue, and repeat operative débridement is frequently required. Aggressive fascial débridement of abdominal surgical wounds may necessitate the use of prosthetic material to replace an abdominal wall defect, as depicted in Figure 125-1. In Fournier's gangrene and perineal/perirectal NSTI, a colostomy or fecal management system may be necessary to keep the wound clean. The testes generally survive because their blood supply is usually spared, but they may need to be temporarily implanted in the soft tissue of the medial thighs if the scrotum must be débrided. On a rare occasion, NSTI of the extremities may require amputation.

Myonecrosis or gas gangrene requires radical débridement to viable muscle. When this process involves the extremities, control of the infection is more easily achieved, although as mentioned previously, amputation may be necessary. In contrast, clostridial myonecrosis involving the trunk may present some very difficult therapeutic decisions because the removal of nonviable tissue may leave the peritoneal or thoracic cavities open.

Adjunctive Therapy

Hyperbaric Oxygen. The use of hyperbaric oxygen (HBO) in NSTIs is controversial. Although there are no prospective randomized studies of HBO in these infections, *in vitro* data and reviews of clinical series show beneficial effects of HBO when combined with antibiotics and surgical débridement in the management of clostridial infection.¹⁰ A retrospective analysis of the University Health Consortium (UHC) database showed that complications and mortality were reduced in patients with a high severity of illness scores.¹¹ Hyperbaric oxygen is toxic to clostridia and inhibits bacterial growth, blocks the production of alpha-toxin, and preserves marginally perfused tissue. Debate also exists regarding the use of HBO for nonclostridial necrotizing skin and soft-tissue infection, with one report suggesting reduced mortality.¹⁰ Despite these results, HBO therapy is not widely utilized; only 7% of NSTI patients in academic medical centers with HBO capabilities actually received HBO.¹¹

Intravenous Immunoglobulin. Intravenous immunoglobulin (IVIG) has been administered to patients with streptococcal and staphylococcal toxic shock syndrome and may be efficacious in the treatment of

this toxin-mediated disorder. Some studies have demonstrated that IVIG has some beneficial effect for the treatment of NSTIs, theoretically owing to its neutralization of circulating clostridial toxins and streptococcal superantigens.¹² However, a large multicenter retrospective cohort study of children with streptococcal toxic shock syndrome showed no improvement in outcomes with the administration of IVIG.¹³ A recent Swedish prospective study did demonstrate improvement with the use of IVIG.¹⁴ There is no clear consensus at this time regarding the efficacy of IVIG.

CD28-Mimetic Peptide. An immune-modulating short peptide has been shown in phase II trials to reduce the rates of organ failure, ventilator days, ICU days, and the number of débridements required for severe NSTI.¹⁵ This agent acts by binding the CD28 receptor, blocking the activation of T-cell receptors and attenuating the response to streptococcal exotoxin A.¹⁶

IMPORTANT SOFT-TISSUE INFECTIONS OF THE HEAD AND NECK

Ludwig's Angina

Ludwig's angina is a potentially life-threatening, rapidly progressive, diffuse "woody" or brawny cellulitis of the submandibular and sublingual spaces that occurs most often in young adults with dental infections.

Pathogenesis

In adults, 50% to 80% of cases of Ludwig's angina are caused by dental caries, and the disease has a mortality rate of 5% to 10%. Submandibular and sublingual spaces freely communicate, and with the involvement of the deep cervical fascia, the infection may spread rapidly. Extension of the carotid sheath or the retropharyngeal space can cause mediastinitis; in a series of 130 patients, 28% had mediastinitis.¹⁷ Infection is commonly caused by oral cavity anaerobes such as *Fusobacterium*, anaerobic streptococci, *Bacteroides*, spirochetes, and hemolytic *Streptococcus* organisms, although the infection may be mixed with *Staphylococcus* and *Streptococcus*, *Klebsiella*, or a combination of aerobic or anaerobic organisms.¹⁸

Clinical Manifestations

The patient is febrile and complains of severe neck pain and swelling, odynophagia, dysphagia, drooling, and leaning forward to maximize

the airway diameter. Patients usually have a recent history of dental work, obviously poor dental hygiene, or deep neck abscess.

The examination may reveal a tender, symmetric, and indurated swelling, sometimes with palpable crepitus in the submandibular area. The tongue may be swollen or displaced upward and backward, and the mouth is held open because of the lingual swelling. The presence of stridor, dyspnea, or decreased air movement suggests airway compromise. The appearance of significant asymmetry of the submandibular area is an ominous sign because it may represent an extension of the inflammation to the parapharyngeal space.

Radiographic imaging may indicate the source of the infection, soft-tissue swelling around the airway, and possibly submandibular gas.

Management

Control of the Airway. Progression from the first findings of symptoms to asphyxia may occur rapidly over several minutes to a few hours. Therefore, airway protection is a critical component of initial management. In the past, the standard of care for Ludwig's angina was early emergency intubation or tracheostomy to protect the airway. However, this practice has gradually been abandoned. Recent data show that most cases can be managed initially by close observation in a critical care unit and intravenous antibiotics.¹⁹ If an artificial airway is required, flexible fiberoptic-guided nasotracheal intubation is the preferred method of airway control. Tracheostomy, under local anesthesia and performed through the cellulitis, remains the most widely recommended means of obtaining a surgical airway.

Antibiotics and Other Pharmacotherapy. Penicillin and clindamycin are the antibiotics of choice for treating Ludwig's angina. Ampicillin-sulbactam, metronidazole and penicillin, imipenem-cilastatin, piperacillin-tazobactam, as well as second and third-generation cephalosporins are other reasonable choices for treating obligate anaerobes that are most commonly encountered in this infection. Coverage for MRSA may be required based on patient and local factors.

Corticosteroids have been used empirically to treat airway edema. The value of corticosteroids in the setting of Ludwig's angina is unclear, and they are likely not indicated.²⁰

Surgical Intervention. Surgical débridement may only moderately improve the airway. Surgical incision and drainage were the therapies of choice in the preantibiotic era. Unless antibiotic therapy is significantly delayed, it is unlikely that pus will be identified, because purulent collections develop relatively late. With the exception of dental extraction, surgery is reserved for those patients who do not respond to medical therapy and those with crepitus and purulent collections.²¹ Any patient requiring surgical intervention should have an artificial airway in place before neck exploration. The location of abscesses should be identified using CT or magnetic resonance imaging (MRI). Infection localized above the carina is usually addressed by cervical incision, but infection below the carina requires the additional surgical drainage of the mediastinum.²²

Acute Epiglottitis

Acute epiglottitis is a rare, potentially life-threatening bacterial infection causing inflammation and edema of the epiglottis, aryepiglottic folds, and surrounding tissues. Before the era of *Haemophilus influenzae* vaccination, epiglottitis used to be a primarily pediatric infection. However, in recent years, the infection has become primarily an adult disease.

Pathogenesis

Invading bacteria cause inflammation and edema of the epiglottis, aryepiglottic fold, and the surrounding tissues. These structures may then protrude downward and over the glottic opening, causing an airway obstruction. In the past, most of the cases (50%-70%) were caused by *H. influenzae* B (HIB).²³ However, at present, other bacteria, including group A β -hemolytic *Streptococcus*, *S. aureus*, and *Streptococcus pneumoniae*, have become more common, and more patients present with an epiglottic abscess.

Clinical Manifestations and Management

Early signs of epiglottitis include hoarseness, dysphagia, odynophagia, and a sore throat (present in 94% of patients).²⁴ Some authors advocate direct or indirect laryngoscopy on adult patients without respiratory distress. The most common misdiagnosis is streptococcal pharyngitis. Patients who can maintain their airway and adequate oxygenation should be closely observed in an ICU. Corticosteroids, racemic epinephrine, and heliox can be considered for initial management, but their role is unresolved. Dyspnea and stridor indicate impending airway obstruction, and emergency airway control should be established. Flexible fiberoptic laryngoscopy is usually used during intubation.

The third-generation cephalosporins, cefotaxime, and ceftriaxone are the antibiotics of choice for acute epiglottitis. These antibiotics are usually effective against *H. influenzae*, streptococci, and staphylococci. A number of other antibiotics including cefuroxime, ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin-clavulanic acid, and levofloxacin are also effective in epiglottitis.

INFECTIONS OF BITE WOUNDS

Exposure to mouth flora occurs in bite wounds, clenched-fist injuries, and finger or thumb sucking. The incidence of infection after cat bites can be more than 50%, and infection after dog or human bite wounds can be 15% to 20%. Although the majority of patients with bite wounds do not seek medical attention, some bite wounds can lead to severe infections (i.e., NSTIs) and sepsis that results in loss of limb function or even requires amputation. Complications also include lymphangitis, septic arthritis, tenosynovitis, and osteomyelitis.

Pathogenesis

The microbiology of bite wounds is generally polymicrobial, reflecting the aerobic and anaerobic microbiology of the biter's oral flora and the skin of the victim.²⁵ Aerobes (*Eikenella corrodens*, *Staphylococcus*, *Streptococcus*, and *Corynebacterium* spp.) are the most common isolates from infected human bite wounds. *E. corrodens* is a slow-growing, gram-negative bacillus frequently associated with chronic infection and abscess formation in human bites. Commonly isolated anaerobes in human bites include *Bacteroides* and *Peptostreptococcus* spp., and *Pasteurella multocida* is the most prevalent organism found in 50% of dog bite wounds and 70% of cat bite wound infections.^{26,27} *S. aureus*, α -, β -, and δ -hemolytic streptococci, gram-negative organisms, and anaerobic microorganisms are frequently isolated from infected animal bites.

Management

Management goals for bite wounds are to prevent or appropriately treat infection and minimize soft-tissue deformities. For domestic animal bites, unless the animal is suspected of having rabies, rabies prophylaxis is not necessary. Many wild animals including, skunks, raccoons, foxes, and bats should be considered rabid unless proved otherwise, and a bite by such an animal should result in rabies prophylaxis. The tetanus immunization status must also be determined and the appropriate treatment administered.

Meticulous wound care is the cornerstone of human or animal bite wound management. Copious irrigation and careful débridement of the wound decrease the incidence of wound infection. Facial wounds may be closed primarily after débridement and irrigation without an increased risk of infection.²⁸ Immediate closure of bite wounds of the hand remains a controversial issue, but irrigation followed by delayed primary closure may be appropriate.²⁹

Cultures of clinically uninfected wounds are not indicated but should be performed in infected wounds that are not improving despite apparently adequate antibiotic treatment. In bite victims, prophylactic broad-spectrum antibiotics are recommended for patients

with high-risk bites but are only of proven benefit in human bites.³⁰ The risk factors for infection include human bites, wounds of the hand, foot, face, scalp, and perineum, puncture wounds, crush wounds, bites over vital structures (e.g., artery, nerve, or joint), a patient age older than 50 years, or immunosuppression. In most patients, amoxicillin-clavulanic acid is the preferred antibiotic. Alternatives include moxifloxacin, amoxicillin, doxycycline, and cefuroxime. In human bites, the amoxicillin-clavulanic acid will cover *E. corrodens* and most other oral flora. Other options include second- or third-generation cephalosporins, quinolones, or doxycycline. In patients who are allergic to penicillin, trimethoprim-sulfamethoxazole is an alternative for both dog and cat bites, whereas quinolones or erythromycin may be used for human bites.

Patients with complex wounds, sepsis, established infection, suspicion of musculoskeletal, neurologic, or vascular involvement, diabetes, or immunosuppression should be treated with parenteral antibiotics, irrigation, and débridement with cultures.³¹ Consultation with a hand surgeon should be considered for hand wounds, because of the higher risk of severe infection compared to other sites.

INFECTIOUS OF BURN WOUNDS

Burn wound infection/sepsis is one of the most common causes of death in burn patients. The highest risk of bacterial invasion from the skin flora into the eschar occurs 5 to 7 days after the burn. Mechanisms of burn wound infection include the breakdown of the natural cutaneous barrier, compromised host defenses, and exposure to pathogenic and opportunistic bacteria. The surface of a burn contains a large amount of necrotic tissue and protein-rich wound exudate, so it provides an excellent growth medium for surface bacteria, leading to bacterial colonization and invasion. Burns are also associated with an immunocompromised status. The percentage of total body surface area (TBSA) that is burned and the duration of hospitalization correlate well with the incidence of wound infections.³² The predisposing factors for the development of burn wound infection are listed in Table 125-3.

Pathogenesis

After a thermal injury, all burn wounds become contaminated with microorganisms, either from the patient's endogenous flora or resident microorganisms in the burn unit. This colonization occurs initially without clinical significance. However, surface-colonizing bacteria can penetrate the avascular eschar and proliferate beneath the eschar at the viable/nonviable tissue interface. When host defense mechanisms are compromised, bacteria can break this barrier and spread systemically, resulting in bacteremia and sepsis.

The most common organisms found in burn wound infections are bacteria, and 70% to 90% are endogenous to the patient. Bacterial organisms can also be acquired by cross-infection, principally from the hands of healthcare professionals. Before the era of penicillin, streptococci and staphylococci were the predominant pathogens. Since the 1950s, *P. aeruginosa* has become the most important species.³³

Other important bacterial species include *S. aureus*, group A *Streptococcus*, *Enterobacter cloacae*, *E. faecalis*, *Klebsiella* spp., and *Acinetobacter* spp.³⁴ Fungi, especially *Candida albicans* and *Aspergillus* spp., and viruses (herpesvirus) are also commonly isolated from infected burn wounds.³⁵

Clinical Manifestations and Diagnosis

Successful treatment of burn wound infections largely depends on the early detection of infection. Burn wound infection is difficult to diagnose on the basis of clinical signs and symptoms because burn-induced inflammatory responses (e.g., fever, leukocytosis) are indistinguishable from those of an infection. The local signs of infection may be absent, minimal, or late. Diagnosis is generally based on a combination of clinical signs that indicate sepsis (e.g., fever, leukocytosis, organ dysfunction, and hyperdynamic state) and the results of surveillance cultures. Any of the findings listed in Table 125-4 should raise suspicion of a burn wound infection.³⁶ The practice of culturing the burn wound surface does not accurately predict progressive bacterial colonization or incipient burn wound sepsis. Qualitative and quantitative correlations are poor between the flora on the surface of the burn wound, bacterial colonization, and the invasion of the deep layers of the eschar. It has been reported that a biopsy of the wound with quantitative cultures of greater than 10^5 CFU per gram of tissue is an accurate indicator of invasive burn wound infection.³⁷ When bacterial invasion to viable tissues is detected, excision of the infected wound is important, and systemic antibiotics are indicated.

Management

Prevention of Burn Wound Infections

Systemic antibiotic prophylaxis is not routinely administered to burn patients admitted to the hospital because the unexcised burn wound does not lead to significant bacteremia.³⁸ Frequent dressing changes with an evaluation of the burn wound and surrounding tissue allow for the early detection and therapy of cellulitis. Early excision and grafting of burn wounds have become the standard of care. *Early excision* is defined as the staged excision of all deep partial- and full-thickness burns by the third to seventh postburn day. The philosophy of early burn wound excision has resulted in improved survival in patients with TBSA burns greater than 30% to 40%, a shorter hospital length of stay, lower costs of hospital care, and fewer painful dressing changes. If for some reason (e.g., hemodynamic instability or severe respiratory failure) the patient cannot undergo grafting, temporary coverage with a porcine or cadaveric graft is performed. In lieu of this approach, surveillance wound cultures should be performed several times per week to diagnose a burn wound infection early. In addition, strict antiseptic measures such as hand washing, barrier isolation, and equipment and room cleaning decrease the incidence of wound infection.

Topical antimicrobials are commonly used in burn patients to prolong the sterility of the full-thickness burn wound, decreasing the conversion of partial-thickness to full-thickness wounds by local infection, and thereby reducing mortality. Aggressive removal of the necrotic tissue and closure of the wound with autografts is mandated. The commonly used topical agents are listed in Table 125-5.

TABLE 125-3

Predisposing Factors for Burn Wound Infections

- Burn wound greater than 30% total body surface area
- Full-thickness burn
- Extremes in patient age
- Preexisting diseases: immunosuppression, diabetes mellitus, vascular insufficiency
- Virulence and antibiotic resistance of colonizing pathogens
- Failure of skin graft
- Prolonged open burn wound
- Improper initial burn wound care

TABLE 125-4

Clinical Signs Suggestive of Burn Wound Infection

- Progression of second-degree to third-degree burn injury
- Increased pain, erythema, color changes
- Unexpected change in the appearance or depth of the wound
- Unexpected rapid eschar separation
- Metastatic septic lesion in the unburned tissue
- Systemic signs of sepsis

TABLE 125-5 Commonly Used Topical Agents in Burn Wounds

| AGENT | ADVANTAGE | DOSE | PRECAUTION |
|---|--|---|---|
| Silver sulfadiazine (SSD) | Useful for the prevention of infections from second- or third-degree burns. Bactericidal activity against many gram-positive and gram-negative bacteria; also effective against yeast. | Apply to open wounds twice or three times daily. | Does not penetrate eschar. Neutropenia. Caution in glucose-6-phosphate dehydrogenase deficiency. May increase the risk of burn wound infection. ⁴⁹ |
| Mafenide acetate cream and solution | Topical. Diffuses into the eschar and is highly effective against gram-negative organisms, including <i>Pseudomonas</i> spp. | Apply cream to open wounds twice or three times daily. Soaks with solution must be kept moist. | Pain/burning may occur. Metabolic acidosis due to inhibition of carbonic anhydrase (especially with cream). |
| Silver nitrate (0.5%) | Silver ion has broad-spectrum antibacterial activity but does not penetrate burn wound eschar; therefore, it is most effective when applied early. | Apply topically to the wound to a thickness of approximately 1.5 mm daily or twice daily as moistened dressings. | Not for internal use. Stains wound and everything else. Does not penetrate eschar. Hyponatremia. |
| Silver-impregnated silicone, gel, or mesh dressings (numerous brands) | Dressings impregnated with silver ions with broadest spectrum activity covering gram-negative organisms including <i>Pseudomonas</i> , gram-positive bacilli, methicillin-resistant <i>Staphylococcus aureus</i> , and vancomycin-resistant enterococcus. Good eschar penetration. | Apply to affected area, and monitor for adherence. If silver dressing is adherent, leave in place for 7-10 days. Some dressings should be kept moist. | Limited toxicity issues. Adherence is poor in wounds with significant exudates. |
| Mupirocin | Active against a wide variety of gram-positive bacteria, including MRSA. Also active against certain gram-negative bacteria. Exerts activity by binding to bacterial isoleucyl transfer RNA-synthetase. Good for the face. | Apply to affected areas three times a day and cover with a gauze dressing. | Prolonged use may result in the growth of resistant organisms; do not use on very large wounds where polyethylene glycol absorption is possible (especially in patients with moderate renal failure). |

Silver-impregnated silicone, gel, or mesh dressings are the preferred dressings for partial-thickness wounds.

Treatment of Burn Wound Infections

Antibiotics

Systemic antibiotics are not used prophylactically in patients with burn wounds but are reserved for use in cases of known or suspected invasive infection.³⁹ As long as bacterial culture results are available, antibiotics with the narrowest spectrum of activity should be used to minimize the development of resistant organisms. Recommendations for empiric therapy are based on the length of time since the burn was sustained, previous administration of antibiotics to the patient, and knowledge of likely pathogens and the local antibiogram. Inappropriate use of multiple antibiotics promotes the overgrowth of resistant pathogens including *Candida* spp., enterococci and does not decrease mortality.

Surgical Intervention

Invasive bacterial or fungal burn wound infections are treated with surgical excision to the level of viable tissue. Early burn wound excision significantly reduces bacterial colonization and reduces the risk of invasive burn wound infection. Patients who undergo topical treatment and delayed burn wound excision exhibit greater bacterial colonization and increased rates of infection.⁴⁰ Wounds that can be excised completely should be covered with an allograft or autograft. If complete débridement is not possible, topical antimicrobials should be applied, and the wound reexamined for possible repeat débridement.

INFECTIONS OF PRESSURE ULCERS

Pressure ulcers are caused by localized tissue necrosis and infection due to prolonged compression between a bony prominence and an external surface. Although infection of decubitus ulcers is high in the nursing home setting and spinal cord injury patients, it is an

uncommon cause of infection or sepsis in ICU patients.⁴¹ Pressure ulcers may pose a risk to other hospitalized patients by serving as a reservoir for drug-resistant organisms.

Pathogenesis and Classification

Risk factors for pressure ulcers in patients include limited physical activity, impaired sensory perception, poor nutritional status, chronic disorders (e.g., diabetes mellitus, cardiovascular disease, and cerebrovascular accidents), impaired circulation, low serum hemoglobin, and increased blood urea nitrogen and serum creatinine concentrations.⁴² Concomitant infections including cellulitis of surrounding tissue, contiguous osteomyelitis, and bacteremia are associated with infection of decubitus ulcers.⁴³

Infections of pressure ulcers are usually polymicrobial. Aerobes commonly recovered include staphylococci (including MRSA), enterococci, *Proteus mirabilis*, *E. coli*, and *Pseudomonas* spp. Anaerobic *Peptostreptococcus*, *Bacteroides fragilis*, and *Clostridium* spp. are also found in these infections. Pressure ulcers are a major reservoir of MRSA. Making an accurate microbiological diagnosis is usually impractical and difficult because all pressure ulcers are colonized with microorganisms, and a superficial culture will not distinguish between colonizing and infecting organisms. If it is necessary to determine the microbiology accurately, it is more appropriate to perform a deep-tissue biopsy or direct a needle through the intact skin and aspirate a specimen for bacterial culture from the margin of the ulcer.

Management

There are many different approaches for the treatment of pressure ulcers; however, none has demonstrated superiority.⁴⁴ Prevention of decubitus ulcers, including pressure relief with support surfaces and repositioning, appropriate nutrition, and skin moisturizers, is the best treatment.⁴⁵ Once the ulcer has been established, and an infection is present, débridement of necrotic and marginally viable tissue is

necessary to obtain healing. Topical agents such as povidone-iodine, hydrogen peroxide, and others have been widely used without significant impact. Proper use of occlusive dressings (e.g., balsam, Peru, trypsin, or castor oil preparations) increases patient comfort, enhances healing, decreases the possibility of infection, saves time, and reduces costs.⁴⁶ Topical antimicrobial agents have not been shown to be effective. Systemic antibiotic therapy should be reserved for infected ulcers. Skin grafting of clean wounds is effective if the underlying cause of the pressure ulcer has been removed. However, adequate treatment frequently requires more complex therapies, including tissue flaps and sometimes even amputation to facilitate wound closure.⁴⁷ Treatment of recalcitrant wounds can be difficult and costly. Several newer therapeutic strategies include vacuum-assisted closure, topical alginates, growth factor therapies (e.g., platelet-derived growth factor), and a variety of skin substitutes.⁴⁸

Broad-spectrum empiric antibiotic regimens are appropriate for patients with pressure ulcer-associated cellulitis, osteomyelitis, or bacteremia. Although malnutrition with protein deficiency is the most common cause of failure of these lesions to heal, osteomyelitis has to be ruled out by physical examination and imaging. If osteomyelitis is present, a more extended course of therapy is required.

KEY POINTS

1. Most serious soft-tissue infections require some degree of tissue injury and a break in the skin to establish an infection. The break in the skin may be due to a surgical incision or trauma.
2. Initial management of necrotizing soft-tissue infections (NSTIs) involves resuscitation, appropriate broad-spectrum parenteral antibiotics, as well as expedient and radical surgical débridement. Adjunctive therapies (e.g., hyperbaric oxygen and immunoglobulin) may be used, but their efficacy is not well established.
3. Topical antimicrobial agents are commonly used in burn patients, reducing local infection and mortality caused by burn wound infection. Systemic antibiotics are not used prophylactically in burn patients.

ANNOTATED REFERENCES

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■ References for this chapter can be found at expertconsult.com.

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Infections of the head and neck range in severity from minor to life threatening. The intensivist is called upon to manage such patients either when they are critically ill or when airway compromise has occurred or is imminent. Besides airway management and control of sepsis, the intensivist must also be aware of the local anatomy and relevant microbiology. This knowledge will help guide the choice of antimicrobial agents as well as allow the clinician to anticipate the potential for spread of infection to related anatomic spaces and subsequent complications.

NORMAL HEAD AND NECK FLORA

Huge numbers of bacteria reside in the oral cavity in health, with the bacterial load exceeding 10^{11} /mL in the gingival crevices of patients with teeth.¹ The main bacterial species are anaerobes including *Bacteroides*, *Fusobacterium*, *Prevotella*, and *Peptostreptococcus*. Other common oral inhabitants include *Streptococcus mutans*, *Staphylococcus aureus*, *Actinomyces* spp., and *Eikenella corrodens*. Pharyngeal colonization and subsequent infection with organisms such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Streptococcus pyogenes* may also occur.

In acute illness, an additional modifying factor is the decreased production of oral mucosal fibronectin. This is of relevance to the clinician because fibronectin in normal physiologic amounts will preferentially bind gram-positive bacteria (such as *S. mutans*); however, when the production of fibronectin is decreased, there is rapid colonization of the oral cavity with gram-negative organisms, including species such as *Pseudomonas aeruginosa*.² These gram-negative organisms may then participate in head and neck infections of oral or odontogenic origin, necessitating broad nosocomial-type gram-negative antibiotic coverage when the patient has been recently hospitalized or acquired the infection in the intensive care unit (ICU).

SITES OF DEEP HEAD AND NECK INFECTION

Serious infection of the head and neck can involve the following general anatomic areas:

- Sinus
- Pharynx
- Epiglottitis
- Retropharyngeal space
- Submandibular space (Ludwig's angina)
- Lateral pharyngeal space (anterior and posterior)
- Internal jugular vein (Lemierre syndrome)

Some of these anatomic areas are connected via actual or potential spaces. Thus infection beginning in one space may spread rapidly to involve others, with potential resultant damage or destruction of vital structures. Such connections are discussed in the following sections, and differentiating features are highlighted in Table 126-1.

Predisposing factors for the development of deep neck infection include uncontrolled dental infection, spread of infection from other local structures (tonsils, vertebrae), local IV catheter placement or injection drug use, diabetes, HIV infection, and local trauma (e.g., the use of laryngeal mask anesthesia).^{3,4} A poor level of education and living far from a tertiary care center have also been shown to increase the risk of development of severe deep neck space infection.⁵

CLINICAL SYNDROMES

Sinusitis

Acute bacterial sinusitis accounts for a high proportion of physician visits in the primary care setting.⁶ In the ICU, patients who are critically ill, with nasogastric, endotracheal, or nasotracheal tubes in place, may develop acute sinusitis caused by resistant nosocomial organisms (e.g., methicillin-resistant *S. aureus* [MRSA], *P. aeruginosa*) and anaerobes.⁷ Treatment involves the use of broad-spectrum antimicrobial agents (Table 126-2) and close collaboration with an otolaryngologist to determine if drainage is needed. In addition, application of topical vasoconstrictors and steroids to the nasal mucosa is often recommended to help the sinus secretions drain.

Complications of nosocomial sinusitis are related to the local anatomy. Spread via the diploic veins can result in meningitis, brain abscess, contiguous osteomyelitis, or cavernous sinus thrombosis. Spread from the ethmoid sinuses can result in frontal lobe brain abscesses, whereas sphenoid sinus infection can spread to involve the surrounding pituitary gland, optic chiasm, internal carotid artery, cavernous sinus, or temporal lobe of the brain.¹

In patients with diabetic ketoacidosis, high-dose steroid treatment, severe neutropenia, or history of desferrioxamine treatment, rhinocerebral mucormycosis or aspergillosis can develop. This infection can be rapidly fatal if the underlying problem cannot be corrected. The general teaching has been that high-dose antifungal therapy (see Table 126-2) plus extensive surgery is always required for any hope of survival. However, the need for major surgery in all cases has come into question recently.⁸ Close collaboration with appropriate surgeons and infectious disease colleagues is required in such cases.

Pharyngeal Infections

Life-threatening pharyngeal infections include acute anaerobic pharyngitis (Vincent's angina) caused by a combination of oral anaerobes and spirochetes. The clinical manifestations of this entity in the critically ill host include acute ulcerations and necrosis of the oral mucosa and gums. Secondary bacteremia with sepsis syndrome can complicate matters. Treatment involves adequate oral debridement and administration of antibiotics with both aerobic and anaerobic activity (see Table 126-2).¹

Quinsy (peritonsillar abscess) can complicate previous tonsillitis and is most common among young adults. Presenting symptoms include fever, pharyngeal pain, and unilateral pharyngeal swelling. If not adequately drained, the infection can spread into the lateral pharyngeal space, which was the most common cause of quinsy-related mortality in preantibiotic days. Infection with anaerobes can result in a higher rate of recurrence of quinsy.⁶ *Fusobacterium necrophorum* is currently the most commonly encountered organism in peritonsillar abscesses in Denmark.⁹

Recurrent bouts of tonsillitis (five or more) in patients aged under 30 years have been noted to be a risk factor for development of peritonsillar abscess.¹⁰

Diphtheria is now rare thanks to mass vaccination. It presents as a sharply demarcated adherent dark gray nasal or pharyngeal membrane. Clinical illness is caused by the release of a bacterial toxin that inhibits translocase (via inhibition of elongation factor 2). Myocardial

dysfunction and central nervous system toxin-mediated injury may occur late, but fulminant infections can be complicated by death from acute respiratory obstruction or circulatory failure (bull-neck diphtheria).¹ Culture of the organism (*Corynebacterium diphtheriae*) requires the use of a specific Loeffler medium.

Epiglottitis

Acute epiglottitis is primarily a disease of children who have not received the *Haemophilus influenzae* type b (Hib) vaccine and is thus rare at present.¹¹ Acute epiglottitis presents as an acute febrile illness

usually of less than 12 hours' duration, with the child characteristically sitting forward, drooling saliva, and taking shallow and apprehensive breaths (deeper breathing draws the epiglottis over the airway and produces obstruction). The diagnosis is made clinically, although lateral neck radiography (if the child is stable enough to go for x-ray) characteristically shows enlargement of the epiglottis 30% to 57% of the time. Attempts to visualize the classically described edematous cherry-red epiglottis directly may precipitate acute airway obstruction and should not be attempted unless the ability to secure an airway immediately is certain. Blood and epiglottis cultures usually grow *H. influenzae* type b. However, since the introduction of mass vaccination against *H. influenzae* type b, the incidence of infection with non-type b strains is increasing.¹¹

Antibiotic options for epiglottitis are outlined in Table 126-2. There is no clear consensus on the role of exogenous corticosteroids to decrease epiglottic edema. Rifampin prophylaxis should be administered for 4 days to close household and hospital contacts of patients (especially those younger than 4 years) with invasive *H. influenzae* type b disease.

Retropharyngeal Infections

The area situated between the pharynx anteriorly and the vertebrae posteriorly constitutes the retropharyngeal space, which begins behind the pharynx and ends at the junction of the cervical and thoracic vertebrae (see Table 126-1). The space is subdivided into several distinct anatomic spaces (retropharyngeal, prevertebral, "danger space"), some of which may provide the means of spread of infection from the initial retropharyngeal area to distant sites.¹²

Located between the prevertebral space posteriorly and the retropharyngeal space anteriorly is a potential space called the "danger space," which connects the base of the skull with the posterior mediastinum and diaphragm. Infection may spread unimpeded within this space. In addition, infection occurring between the vertebrae and the prevertebral fascia may spread along the length of the vertebral column.

Infections of the retropharynx occur either as:

- Primary infections
- Secondary to extension posteriorly from the pharynx or anteriorly from infected cervical vertebrae
- Via hematogenous spread

TABLE 126-1 Differentiating Features of Deep Neck Infections

| SPACE | CLINICAL FEATURES* |
|--|---|
| Submandibular space (Ludwig's angina) | Woody submental induration, protruding swollen/necrotic tongue, no trismus, rotted lower molars commonly present |
| Lateral pharyngeal space (anterior) | Fever, toxicity, trismus, neck swelling |
| Lateral pharyngeal space (posterior) | No trismus, no swelling (unless ipsilateral parotid is involved), cranial nerve IX-XII palsies, Horner's syndrome, carotid artery erosion |
| Retropharyngeal space (retropharynx) | Neck stiffness, decreased neck range of motion, soft-tissue bulging of posterior pharyngeal wall, sore throat, dysphagia, dyspnea |
| Retropharyngeal space ("danger space") | Mediastinal or pleural involvement |
| Retropharyngeal space (prevertebral) | Neck stiffness, decreased neck range of motion, cervical instability, possible spread along length of vertebral column |
| Jugular vein septic thrombophlebitis (Lemierre syndrome) | Sore throat, swollen tender neck, dyspnea, chest pain, septic arthritis |

*Fever and signs of systemic toxicity are common to all.

TABLE 126-2 Therapeutic Options for Sinusitis, Pharyngitis, Epiglottitis

| SYNDROME | LIKELY FLORA | ANTIBIOTIC OPTIONS* |
|--------------------------------|--|---|
| Sinusitis (community acquired) | <i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i> | Ampicillin-sulbactam (3 g IV q 6 h) Levofloxacin (500 mg IV q 24 h) or moxifloxacin (400 mg IV q 24 h) Levofloxacin (500 mg IV q 24 h) plus clindamycin (300-900 mg IV q 8 h) or moxifloxacin (400 mg IV q 24 h) |
| Sinusitis (ICU acquired) | <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> and related coliforms, methicillin-resistant <i>S. aureus</i> (MRSA) | Ceftazidime (2 g IV q 8 h) or piperacillin-tazobactam (3.375 g IV q 4 h) plus an aminoglycoside, plus vancomycin (1 g IV q 12 h) |
| Sinusitis (fungal) | <i>Aspergillus</i> spp. <i>Mucorales</i> spp. | Amphotericin B (1-1.5 mg/kg/d IV) Liposomal amphotericin B (5-10 mg/kg/d IV) Voriconazole (6 mg/kg q 12 h × 2 doses, then 4 mg/kg q 12 h) Caspofungin (70 mg IV day 1, then 50 mg/d IV) Itraconazole (200 mg IV q 12 h × 4 doses, then 200 mg/d IV) |
| Pharyngitis | <i>Corynebacterium diphtheriae</i> Epstein-Barr virus (with airway compromise) | IV penicillin or erythromycin plus diphtheria antitoxin No antiviral therapy effective IV steroids |
| Epiglottitis | <i>H. influenzae</i> type b <i>Streptococcus pyogenes</i> (group A strep) | Ceftriaxone (1-2 g IV q 24 h) Ampicillin-sulbactam (3 g IV q 6 h) Rifampin prophylaxis (600 mg orally q 24 h) for close contacts for 4 days |

*Antibiotic choices listed are examples, since for most infections, multiple different antibiotics are effective; individual choice will be influenced by patient factors (e.g., allergies), local hospital bacterial resistance rates, and microbiological culture results.

Clinically, retropharyngeal infections present with acute fever, systemic toxicity, sore throat, neck stiffness, dysphagia, and dyspnea. Airway obstruction may occur as a consequence of anterior bulging of the pharyngeal wall with supraglottic compression.

Prevertebral infections usually involve the cervical vertebrae and present with neck pain and stiffness and prevertebral soft-tissue swelling. Rarely, instability or destruction of the cervical vertebrae may develop, with death due to acute spinal cord compression.

Danger-space infection is suspected when pleural or mediastinal infection or pain complicates a retropharyngeal infection.¹² Mediastinitis secondary to danger-space infection is generally fulminant, with pleural extension and a high mortality rate. Rarely, mediastinal infections, such as may occur after coronary artery bypass graft surgery, may spread upward through the danger space and present in the retropharynx.

The bacteriology of retropharyngeal infections is that of mixed aerobic/anaerobic oral bacteria. In the critically ill host with nosocomial infection, colonization of the oropharynx with resistant pathogens will necessitate modification of antimicrobial coverage. The imaging techniques needed include plain lateral neck x-rays that will show loss of normal cervical lordosis as well as thickening of the retrotracheal area (usually <22 mm) or of the prevertebral fascia (usually <7 mm). Bedside ultrasonography may provide information regarding the presence or absence of drainable collections, but if the patient is stable enough to go to the radiology suite, computed tomography (CT) or magnetic resonance imaging (MRI) scans provide the best definition studies.¹³ The presence of a hypodense mass with rim irregularity on a contrast-enhanced CT scan is highly suggestive. Close collaboration with appropriate surgical colleagues is necessary for successful management.¹² Therapy is outlined in Table 126-3. On occasion, non-bacterial processes such as Kawasaki disease can mimic retropharyngeal abscesses.¹⁴

Submandibular Space Infection (Ludwig's Angina)

The submandibular space is contained between the mucous membranes of the floor of the mouth superiorly and the muscle and fascia attachments of the hyoid bone inferiorly. The most common route of infection into this space is via infected lower molar teeth, and infection is more common in persons with underlying diabetes, neutropenia, or systemic lupus erythematosus.

Clinical presentation of submandibular space infection is that of an acutely ill patient with mouth pain, dysphagia, drooling of saliva, stiff neck, and fever. The submandibular tissues are "woody," not fluctuant, and true drainable collections are uncommon. The tongue may be swollen and displaced upward against the palate and also protrude out of the mouth. Trismus is not present; however, if the infection spreads to the lateral pharyngeal space, trismus may occur. Unrecognized lateral pharyngeal space involvement may be complicated by subsequent spread to the retropharyngeal space. Late complications of Ludwig's angina include death from airway obstruction, aspiration pneumonia, carotid artery erosion, and tongue necrosis.¹⁶

Lateral neck x-rays will demonstrate edema of the submandibular soft tissues. Pockets of gas may be seen if gas-forming organisms are involved. CT scanning is most helpful diagnostically. However, attention must be paid to having qualified staff accompany the patient to the CT scanner in case acute airway obstruction develops. Should airway protection be needed, tracheotomy or cricothyroidotomy is advocated because of the risk of inducing acute airway obstruction with routine "blind" nasal or oral intubation. The infection is commonly polymicrobial, and appropriate antibiotic therapy options are described in Table 126-3. In approximately 50% of cases, surgical drainage is required. In addition, causative rotted molar teeth (if present) should be removed.¹⁶

Lateral Pharyngeal Space Infections

Infection of the lateral pharyngeal space is one of the most common deep neck infections encountered. In a review of 110 deep neck infections in adults seen at an academic medical center over a 10-year period, infections of the lateral pharyngeal space accounted for 55%.¹⁶ In contrast, such infections are rare in children, with peritonsillar infection (quinsy) being the most common deep neck infection.

The lateral pharyngeal space is cone shaped, extending from the sphenoid bone down to the hyoid bone. Posteriorly, it is bound by the prevertebral fascia (that separates it from the retropharyngeal space) and anteriorly by the buccinator and superior constrictor muscles. The parotid gland communicates with this space. The styloid process divides the space into an anterior compartment (containing fat, lymph nodes, and muscle) and a posterior compartment (containing the carotid artery, cranial nerves IX–XII, and the cervical sympathetic trunk).

TABLE 126-3 Therapeutic Options for Deep Neck Infections

| SYNDROME | LIKELY FLORA | THERAPEUTIC OPTIONS* |
|--|---|---|
| Submandibular space infection (community acquired) | Anaerobes, streptococci, <i>Staphylococcus aureus</i> | Ampicillin-sulbactam (3 g IV q 6 h) Ceftriaxone (1–2 g IV q 24 h) <i>plus</i> clindamycin (300–900 mg IV q 8 h) <i>or</i> metronidazole (500 mg IV q 6 h) Ertapenem (1 g IV q day) |
| Submandibular space infection (hospital/ICU acquired) | <i>Pseudomonas aeruginosa</i> , methicillin-resistant <i>S. aureus</i> (MRSA), anaerobes | Imipenem (500 mg IV q 6 h) <i>or</i> piperacillin-tazobactam (3.375 g IV q 8 h by continuous infusion) <i>plus</i> vancomycin (1 g IV q 12 h) ¹⁵ |
| Retropharyngeal space infection | Anaerobes, streptococci, <i>S. aureus</i> | Ampicillin-sulbactam (3 g IV q 6 h) Ceftriaxone (1–2 g IV q 24 h) <i>plus</i> clindamycin (300–900 mg IV q 8 h) <i>or</i> metronidazole (500 mg IV q 6 h) Ertapenem (1 g IV q day) |
| Lateral pharyngeal space infection | Anaerobes, streptococci, <i>S. aureus</i> | Ampicillin-sulbactam (3 g IV q 6 h) Ceftriaxone (1–2 g IV q 24 h) <i>plus</i> clindamycin (300–900 mg IV q 8 h) <i>or</i> metronidazole (500 mg IV q 6 h) Ertapenem (1 g IV q day) |
| Internal jugular vein septic thrombophlebitis | <i>Fusobacterium necrophorum</i> | Metronidazole (500 mg IV q 6 h) Clindamycin (300–900 mg IV q 8 h) Ampicillin-sulbactam (3 g IV q 6 h) |

*Antibiotic choices listed are examples, since for most infections, multiple different antibiotics are effective; individual choice will be influenced by patient factors (e.g., allergies, concurrent medications), local hospital bacterial resistance rates, and microbiological culture results.

Common precipitating causes of lateral pharyngeal space infection include dental disease (33%), injection drug use (inserting needles directly into the space) (20%), local trauma (9%), and tonsillitis (4%). Patients frequently have underlying diabetes or human immunodeficiency virus (HIV) infection.

Clinically, anterior lateral pharyngeal space infections present with fever, pain, trismus, and systemic toxicity. Turning the head to the opposite side causes increased pain due to stretching of the ipsilateral sternocleidomastoid muscle.

Infection of the posterior lateral pharyngeal space presents differently from infections involving the anterior pharyngeal space. Common symptoms include fever, systemic toxicity, and parotid swelling. Trismus and external swelling do not occur. Involvement of local vital structures can occur, including carotid artery erosion or clot, septic thrombophlebitis of the internal jugular vein, cranial nerve IX–XII palsies, or Horner's syndrome.

Therapy involves urgent surgical intervention to drain purulent material and prevent spread of infection to the retropharyngeal space or erosion of the carotid artery. The choice of antibiotics for this frequently polymicrobial infection is shown in Table 126-3.

Descending Necrotizing Mediastinitis

Rapid downward spread of deep neck infections can result in the development of necrotizing soft-tissue infections of the chest wall and mediastinum. A recent study of 45 such cases collected over a 12-year period demonstrated that they tended to develop as a complication of dental or deep neck polymicrobial infections, affecting persons aged 40 to 60 years most commonly. Mixed aerobic/anaerobic flora was the rule, and risk factors included alcoholism and diabetes mellitus. Mortality was around 15% to 20%.¹² Death may be sudden due to medical complications of the infectious process.¹⁷

Internal Jugular Vein Septic Thrombophlebitis (Lemierre Syndrome)

Septic thrombophlebitis of the internal jugular vein is known as *Lemierre syndrome*. This relatively rare entity is usually caused by infection with the anaerobe *Fusobacterium necrophorum*, a normal inhabitant of the human gingival crevice. Latest theories on the pathogenesis of this infection indicate that the first stage of infection is pharyngitis in approximately 87% of cases. Recent data suggest that *F. necrophorum* causes pharyngitis in young adults aged 15 to 24 years as frequently as *Streptococcus pyogenes*.⁹ This infection is then followed by invasion of the lateral pharyngeal space, with development of septic thrombophlebitis of the internal jugular vein.¹⁸ Subsequently, bloodstream infection develops, with the classic findings of septic pulmonary emboli or cavitating pneumonia and septic arthritis. Other precipitating factors

include mastoiditis, lateral pharyngeal space infection, and trauma to the internal jugular vein.

Clinically, Lemierre syndrome begins with fever and sore throat. When internal jugular vein involvement develops, patients complain of a swollen and/or tender neck, which is thus a warning sign of danger in a patient with recent pharyngitis. Dyspnea and pleuritic chest pain indicate pulmonary involvement.

Early diagnosis is critical to minimize the risk of infectious metastatic complications requiring surgical intervention or drainage. Blood cultures should be promptly obtained and empirical antianaerobic bacterial coverage begun. Radiologic diagnosis is made most reliably by CT scanning, although bedside ultrasound examination of the internal jugular vein can be useful in the critically ill patient who cannot leave the ICU. If the infection occurs secondary to mastoiditis, it is necessary to rule out intracerebral vein thrombosis by MRI scanning. The patient may also develop secondary complications such as carotid artery thrombosis or parotid gland infection with abscess formation.¹⁹

Antibiotic choices are outlined in Table 126-3. There are no firm data to support or refute the use of anticoagulants in Lemierre syndrome.²⁰ In addition, surgical ligation or excision of the internal jugular vein for uncontrollable sepsis was necessary in approximately 8% of cases in a recently published series of cases.²⁰ MRSA has recently been shown to cause Lemierre syndrome, especially in injection drug users or patients with the infection developing as a complication of venous cannulation.²¹

CONCLUSION

The intensivist will frequently be asked to assist in the care of patients with serious deep neck infections. Critical issues encountered include protection of the airway, sepsis management, and the potential for erosion of the infection into surrounding vital structures in the neck. Such infections are frequently polymicrobial in nature; thus, broad-spectrum antibiotics with both aerobic and anaerobic coverage should be chosen.

Common issues to be decided for each patient individually include the following:

- The safety of performing an intraoral examination given the risk of precipitating acute airway obstruction.
- The safety of sending a patient out of the ICU for studies such as CT scanning. Although patients may appear stable initially, they are at risk for sudden development of acute airway obstruction and thus should always be accompanied by a team capable of securing an airway when they travel out of the ICU for tests or procedures.
- The need for and timing of possible surgical intervention. Early close collaboration with otolaryngologists, head and neck surgeons, neurosurgeons, or vascular surgeons is critical for successful management of these complex and frequently critically ill patients.

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Many immunocompromised patients are managed in intensive care units (ICUs) every year, with infection being a leading cause of ICU admission. Common examples of such infections include community-acquired pneumonia, bacteremia, and central nervous system (CNS) infections. The incidence of infections acquired by immunocompromised patients during ICU admissions is also significant.¹ Mortality from certain infections in immunocompromised patients exceeds 50%.² Early diagnosis, initiation of appropriate antimicrobial and supportive therapy, and reduction in immunosuppression where possible can improve outcomes significantly.

COMMONLY ENCOUNTERED IMMUNOCOMPROMISING CONDITIONS

Immunocompromise can be broadly defined as a state in which the response of the host to a foreign antigen is subnormal. It can be congenital (primary) or acquired. Congenital immunodeficiencies are now much less common than acquired immunodeficiencies. In general, congenital immunodeficiency is observed more frequently in patients in pediatric ICUs than in those in adult ICUs. Patients with congenital immunodeficiencies usually have repeated infections, especially infections affecting the sinuses and lower respiratory tract. Congenital immunodeficiencies are usually “pure,” in that the defects in the host response to foreign antigens are usually specific and well defined. For example, Bruton’s X-linked agammaglobulinemia is associated with a defect in the normal maturation process of immunoglobulin-producing B cells. As a result, mature circulating B cells, plasma cells, and serum immunoglobulin are absent. The patient is susceptible to organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, normally dealt with by immunoglobulins. Other congenital immunodeficiency syndromes are listed in Table 127-1.

Most immunocompromised patients managed in adult ICUs have acquired immunocompromise. Although the response of host defenses in the elderly, diabetics, and alcoholics is compromised, this chapter deals primarily with four categories of immunocompromised patients: (1) patients receiving chemotherapy for hematologic malignancies and solid tumors; (2) patients receiving immunosuppressive therapy in the context of solid organ transplantation; (3) patients receiving corticosteroids, methotrexate, monoclonal antibodies to tumor necrosis factor, and other disease-modifying agents for rheumatoid arthritis, Crohn’s disease, and autoimmune disorders; and (4) patients with human immunodeficiency virus (HIV) infection.

Hematologic Malignancies and Solid Tumors

Prolonged neutropenia from chemotherapy carries a significant risk of bacterial and fungal infection. Classically, gram-negative organisms such as *Pseudomonas aeruginosa* and fungal organisms such as *Aspergillus* species have been associated with severe neutropenia. It has long been known that the severity and duration of neutropenia influence the risk of infection.³ It has also been well established that aggressive chemotherapy and radiotherapy for Hodgkin’s disease coupled with splenectomy significantly impair humoral defense against encapsulated organisms such as *S. pneumoniae*, *H. influenzae*, and *Neisseria meningitidis*.⁴ Stem cell transplantation (particularly allograft transplantation) is associated with a substantial risk of graft-versus-host disease (GVHD). Prophylaxis and treatment for GVHD may involve use of

drugs such as cyclosporine or tacrolimus plus corticosteroids. Cyclosporine and tacrolimus inhibit calcineurin, an enzyme important in the lymphocyte activation cascade. Corticosteroids also affect lymphocyte function and depress functions of activated macrophages. As a result, patients receiving therapy for GVHD may be prone to fungal, viral, and mycobacterial infections, in addition to bacterial infections associated with prolonged neutropenia.

Solid Organ Transplantation

Solid organ transplant recipients are uniquely susceptible to infection.⁵ They undergo significant surgery, breaching the defenses provided by the skin. Furthermore, they remain in ICUs for prolonged periods of time, requiring intravenous access and mechanical ventilation—here, cutaneous and pulmonary barriers to infection are breached. Finally, solid organ transplant recipients receive immunosuppressive therapy to prevent graft rejection. The commonly used immunosuppressive medications are listed in Table 127-2. Immunosuppressive regimens are in a constant state of flux—more recent trends have been toward aggressive “pretreatment” immediately before transplantation, coupled with decreased immunosuppression in the posttransplant period.⁶

In the early posttransplant period, transplant recipients are susceptible to nosocomially acquired bacterial infections such as pneumonia, catheter-related bloodstream infection associated with general ICU care, and wound and intraabdominal infections associated with surgical procedures. Opportunistic infections may be acquired from the organ graft; cytomegalovirus (CMV) is the most pertinent example,⁷ but a wide variety of infections (e.g., rabies, histoplasmosis, tuberculosis, and West Nile virus) have also been acquired from grafts. Solid organ transplant recipients, by virtue of their iatrogenic immunosuppression, are also susceptible to reactivation of latent infection (e.g., CMV infection, tuberculosis, or histoplasmosis) or to infections acquired through the hospital environment (e.g., aspergillosis, legionellosis, or tuberculosis).

Rheumatoid Arthritis and Autoimmune Disorders

Therapy for rheumatoid arthritis and other autoimmune disorders may be with simple analgesics or nonsteroidal antiinflammatory drugs. Drugs with the potential to cause significant immunocompromise are also frequently used. Classically, therapy has been with corticosteroids or disease-modifying antirheumatic drugs such as azathioprine, cyclosporine, penicillamine, gold salts, hydroxychloroquine, leflunomide, methotrexate, or sulfasalazine. The effects of corticosteroids, azathioprine, and cyclosporine on host defenses have been noted previously (see Table 127-2). Methotrexate reversibly inhibits dihydrofolate reductase and interferes with DNA synthesis and repair and cellular replication. In addition to its use in rheumatoid arthritis, it can be used as an antineoplastic agent. Methotrexate, however, can cause significant neutropenia, and low-dose methotrexate is generally less likely to increase the infection risk in patients with rheumatoid arthritis.^{8,9}

A variety of “biologic” agents have become available for rheumatoid arthritis (Table 127-3). The biologics may also be used in treatment of Behçet’s disease, Crohn’s disease, GVHD, hairy cell leukemia, psoriasis, pyoderma gangrenosum, sarcoidosis, and ulcerative colitis. Considerable attention has been paid to the possibility of tuberculosis

TABLE 127-1 Congenital (Primary) Causes of Immunodeficiency

| CONDITION (IMMUNODEFICIENCY) | ORGANISMS WITH INCREASED TENDENCY TO CAUSE INFECTION IN THIS CONDITION |
|--|--|
| T-LYMPHOCYTE DEFICIENCIES | |
| DiGeorge syndrome (thymic aplasia with reduced CD4 and CD3 cells) | Viruses (especially HSV and measles), sometimes <i>Pneumocystis jirovecii</i> , fungi, or gram-negative bacteria |
| Purine nucleoside phosphorylase deficiency (marked T-cell depletion) | <i>P. jirovecii</i> and viruses |
| B-LYMPHOCYTE DEFICIENCIES | |
| Bruton's X-linked agammaglobulinemia (absence of B cells, plasma cells, and antibody) | <i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>P. jirovecii</i> (after the first 4-6 months of life when maternal antibody has been consumed) |
| Selective IgG subclass deficiencies | Variable |
| Selective IgA deficiency | <i>S. pneumoniae</i> , <i>H. influenzae</i> |
| Hyper-IgM immunodeficiency (elevated IgM but reduced IgG and IgA) | <i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>P. jirovecii</i> (rarely) |
| MIXED T- AND B-LYMPHOCYTE DEFICIENCIES | |
| Common variable immunodeficiency (leads to various B-cell activation or differentiation defects and gradual deterioration of T-cell number and function) | <i>S. pneumoniae</i> , <i>H. influenzae</i> , CMV, VZV, <i>P. jirovecii</i> |
| Severe combined immunodeficiency (severe reduction in IgG and absence of T cells) | <i>P. jirovecii</i> , viruses, <i>Legionella</i> |
| Wiskott-Aldrich syndrome (decreased T-cell number and function, low IgM, occasionally low IgG) | <i>S. pneumoniae</i> , <i>H. influenzae</i> , HSV, <i>P. jirovecii</i> |
| Ataxia-telangiectasia (decreased T-cell number and function; IgA, IgE, IgG ₂ , and IgG ₄ deficiency) | <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>H. influenzae</i> |
| DISORDERS OF COMPLEMENT | |
| C3 deficiency (congenital absence of C3 or consumption of C3 due to deficiency of C3b inactivator) | <i>S. pneumoniae</i> , <i>H. influenzae</i> , enteric gram-negative bacilli |
| PHAGOCYTE DEFECTS | |
| Chronic granulomatous disease (defect in NADPH oxidase in phagocytic cells) | <i>S. aureus</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Enterobacter cloacae</i> , <i>S. marcescens</i> , <i>P. aeruginosa</i> , <i>Aspergillus</i> |
| Chédiak-Higashi syndrome (impaired microbicidal activity of phagocytes) | <i>S. aureus</i> , <i>H. influenzae</i> , <i>Aspergillus</i> |
| Kostmann syndrome, Shwachman-Diamond syndrome, cyclic neutropenia (low neutrophil count) | <i>S. aureus</i> , enteric gram-negative bacilli, <i>P. aeruginosa</i> |

CMV, cytomegalovirus; HSV, herpes simplex virus; Ig, immunoglobulin; NADPH, nicotinamide adenine dinucleotide phosphate; VZV, varicella-zoster virus.

TABLE 127-2 Immunosuppressive Drugs Used in Solid Organ Transplantation and Their Mechanisms of Activity

| IMMUNOSUPPRESSIVE | MODE OF ACTION |
|---------------------------|--|
| Corticosteroids | Negative regulation of cytokine gene expression |
| Azathioprine | Inhibits DNA and RNA synthesis; inhibits T- and B-cell function |
| Cyclosporine | Calcineurin inhibitor; inhibits cytokine expression |
| Tacrolimus | Calcineurin inhibitor; inhibits cytokine expression |
| Sirolimus (rapamycin) | Prevents translation of mRNAs encoding cell cycle regulators |
| Mycophenolate mofetil | Blocks purine biosynthesis; inhibits T- and B-cell proliferation |
| Polyclonal antilymphocyte | Lymphocyte depletion antibodies (e.g., Atgam, Thymoglobulin) |
| Muromonab-CD3 (OKT3) | Anti-CD3 monoclonal antibody |
| Alemtuzumab (Campath) | Anti-CD52 monoclonal antibody |
| Daclizumab, basiliximab | Anti-CD25 monoclonal antibody |

TABLE 127-3 Commonly Used Anticytokines for Management of Rheumatoid Arthritis

| DRUG | MECHANISM OF ACTION | FDA-APPROVED INDICATIONS |
|-----------------------|---|--|
| Adalimumab (Humira) | Recombinant, fully human anti-TNF monoclonal antibody | Ankylosing spondylitis Crohn's disease Psoriatic arthritis Rheumatoid arthritis |
| Anakinra (Kineret) | Recombinant human interleukin-1 receptor antagonist | Rheumatoid arthritis |
| Etanercept (Enbrel) | TNF receptor p75 Fc fusion protein | Ankylosing spondylitis Juvenile rheumatoid arthritis Plaque psoriasis Psoriatic arthritis Rheumatoid arthritis |
| Infliximab (Remicade) | Chimeric monoclonal antibody to TNF | Ankylosing spondylitis Crohn's disease Psoriatic arthritis Plaque psoriasis Rheumatoid arthritis Ulcerative colitis |
| Tocilizumab (Actemra) | IL-6 receptor-inhibiting monoclonal antibody | Rheumatoid arthritis |

FDA, U.S. Food and Drug Administration; IL-6, interleukin 6; TNF, tumor necrosis factor.

developing after treatment with such agents.¹⁰ The risk is sufficiently high that it is recommended that tuberculin skin testing or interferon gamma (IFN- γ) release assays be performed to detect latent tuberculosis before the initiation of anticytokine agents. Invasive infections with *Histoplasma*, *Candida*, *Pneumocystis jirovecii*, *Aspergillus*, *Cryptococcus*, *Nocardia*, *Salmonella*, *Listeria*, *Brucella*, *Bartonella*, nontuberculous mycobacteria, *Leishmania*, and *Toxoplasma* have also been reported to be associated with the use of these medications.^{11–14} As is the case with transplant-associated immunocompromise, these infections may represent reactivation of latent infection or new acquisition of organisms through environmental exposure.

Human Immunodeficiency Virus Infection

HIV infection remains a relatively common infection, but acquired immunodeficiency syndrome (AIDS) has become less frequently encountered in ICUs since the advent of highly active antiretroviral therapy. A decline in CD4 counts creates a predisposition to *P. jirovecii* pneumonia, mycobacterial infection, fungal infection (e.g., cryptococcal meningitis), and viral infection (e.g., CMV infection). Many patients with HIV infection are co-infected with hepatitis C virus, and as a result, liver failure is now a relatively common reason for ICU admission in HIV-infected patients. In some centers, liver transplantation is performed in HIV-infected patients with hepatitis virus–induced liver diseases.^{15,16}

GENERAL DIAGNOSTIC APPROACH TO IMMUNOCOMPROMISED PATIENTS WITH SEVERE INFECTIONS

Immunocompromised patients are a heterogeneous group. The infections commonly encountered by a patient with neutropenia as a consequence of chemotherapy may be different from infections observed in a patient with rheumatoid arthritis who is receiving infliximab. Even within a particular category, different renal transplantation recipients, for example, may have a different degree of immunocompromise and a different susceptibility to infection. In solid organ transplant recipients, the “net state of immunosuppression” (i.e., the cumulative burden of immunosuppression with a special weighting toward recent T-cell ablative therapy) influences the risk of infection. A renal transplant recipient who is receiving tacrolimus monotherapy twice per week would be less susceptible to opportunistic infection than a patient with recent acute cellular rejection who is receiving OKT3 or alemtuzumab. There have been more recent attempts to quantify immune function in solid organ transplant recipients,¹⁷ although it has not yet been definitively proved that such tests predict infection risk. In contrast, with HIV infection, CD4 lymphocyte count and HIV RNA quantification (“viral load”) predict risk of infection.¹⁸ Patients with CD4 counts greater than 500 are unlikely to be infected with an opportunistic pathogen, whereas those with CD4 counts of 200 to 500 may be infected with organisms such as *Mycobacterium tuberculosis*, but they are unlikely to be infected with opportunistic pathogens such as CMV or *M. avium* complex. Patients with CD4 counts less than 200 have an increased risk of a wide variety of opportunistic infections.

Specific environmental exposures may be potentially important for immunocompromised patients. A travel history to the deserts of the southwestern United States and northern Mexico, for example, may increase the likelihood that an immunocompromised patient has coccidioidomycosis¹⁹; histoplasmosis is endemic in the Ohio River valley.²⁰ Alternatively, there may be environmental risks within the ICU. Outbreaks of invasive pulmonary aspergillosis have been linked to construction activity within the hospital. Outbreaks of legionellosis may be waterborne via air conditioning cooling units, drinking water, or aerosolization from showers.²¹ Furthermore, it is possible that many fungal and bacterial infections are waterborne.^{22,23} Tuberculosis transmission has been well described in ICUs caring for transplant recipients or HIV-infected patients.²⁴ In summary, the net state of immunosup-

pression must be considered in the context of recent environmental exposures.

Although elements of history taking and physical examination may narrow the differential diagnosis of the causative agent of infection in immunocompromised patients, some of the “rules” applied to diagnosis in immunocompetent patients do not apply. Caution must be exercised in use of the diagnostic principle that follows Occam’s razor: “entities are not to be multiplied without necessity.” In an immunocompetent patient, given all the patient’s symptoms, signs, and noninvasive laboratory test results, one unifying diagnosis usually explains all. In contrast, immunocompromised patients may have more than one infection at any given time. A neutropenic patient may have bacterial pneumonia and invasive pulmonary aspergillosis simultaneously, whereas an immunocompromised patient with HIV infection may have *P. jirovecii* pneumonia and pulmonary infiltrates due to human herpesvirus (HHV)-8 infection (Kaposi sarcoma).

The potential for multiple diagnoses underscores the need for early invasive testing in immunocompromised patients with severe infection. Patients with unexplained severe community-acquired pneumonia may be best managed by early bronchoalveolar lavage performed before antimicrobial therapy has commenced. Bronchoalveolar lavage could be sent for Gram stain, Ziehl-Neelsen stain, modified acid-fast stain, calcofluor stain, direct fluorescent antibody tests, polymerase chain reaction (PCR), and cytologic analysis to enable rapid diagnosis of infection with bacteria, mycobacteria, *Nocardia*, fungi, *Legionella*, CMV, community-acquired respiratory viruses, and *P. jirovecii*. The bronchoalveolar lavage should be inoculated onto solid media, and molecular diagnostic testing should be used as appropriate. An outline of the diagnostic approach in immunocompromised patients is given in [Box 127-1](#).

MAJOR MANIFESTATIONS OF INFECTION IN IMMUNOCOMPROMISED PATIENTS

The organism causing infection in an immunocompromised patient sometimes can be inferred by the specific host defect in the immunologic defense or the specific clinical manifestation. In most circumstances, the differential diagnosis is too broad, however, for making a definitive clinical diagnosis.

Pulmonary Infection

Pneumonia is a significant cause of morbidity and mortality in immunocompromised patients. In contrast to a normal host, the impaired responsiveness of the immune system means that the disease presents in unusual ways, which may lead to challenges in establishing a diagnosis.

Infectious microorganisms usually gain access to the respiratory tract through inhalation, although hematogenous spread sometimes may occur. Mechanical defenses remove the bulk of potentially harmful agents from the lungs ([Table 127-4](#)); inhaled particles greater than 10 μm in diameter usually become trapped in the upper airways or are removed by coughing or mucociliary clearance. Most bacteria range from 0.5 to 2 μm in size and are able to reach the terminal airways/alveoli and potentially cause infection. In the alveoli, the alveolar macrophages are the first line of defense. Subsequently, an inflammatory response consisting of polymorphonuclear neutrophils is important. Finally, specific T-cell and B-cell immune responses are essential for successful defense against many pathogens.

As noted earlier, although it may be possible to pinpoint a major immunologic deficiency, most immunocompromised individuals have an assortment of deficiencies in host defenses working together. An organ transplant recipient may be intubated, have multiple intravenous lines, be diabetic, and be on corticosteroids and tacrolimus. All these factors contribute to the overall degree of immunity, each paving the way for its own peculiar array of susceptibilities to pulmonary

BOX 127-1

Diagnostic Approach for Severe Infections in Immunocompromised Patients

HISTORY TAKING AND REVIEW OF PRIOR RECORDS

Likely degree of immunocompromise

Recent CD4 lymphocyte count and HIV viral load

Time since transplantation

Recent acute cellular rejection or GVHD and treatment thereof

Current or recent receipt of immunosuppressive medications

Current or recent receipt of antiretroviral medications

Prophylaxis against opportunistic infections

Receipt of antimicrobial prophylaxis against *Pneumocystis jirovecii*, HSV, or CMV

Vaccination status (pneumococcus, influenza, *Neisseria meningitidis*)

Family history

Personal or family history of tuberculosis or chickenpox

Potential environmental exposures

Travel history to southwestern United States

Exposure to hospital construction activity (aspergillosis)

Exposure to hospital water supply (legionellosis, aspergillosis)

Exposure to patients with tuberculosis or chickenpox

Donor and recipient serostatus for CMV or *Toxoplasma gondii*

PHYSICAL EXAMINATION

Skin

Presence of cutaneous nodules consistent with cryptococcosis or nocardiosis

Presence of cutaneous manifestations of GVHD

Kaposi sarcoma

Line insertion site erythema or pus

Peripheral embolic phenomena

Scars consistent with prior surgery

Mouth and other mucous membranes

Presence of candidiasis

Respiratory system

Presence of signs of focal versus multilobar pneumonia

Cardiovascular system

Murmurs, prosthetic heart sounds

Abdominal examination

Signs of peritonitis

Hepatomegaly or splenomegaly

Tenderness of renal allograft

Neurologic examination

Nuchal rigidity

Cranial nerve signs

NONINVASIVE LABORATORY TESTS

White blood cell count and differential

Blood and urine cultures

Serum cryptococcal antigen

Serum galactomannan antigen (aspergillosis)

Serum and urine *Histoplasma* antigen

Urinary *Legionella* antigen

INVASIVE LABORATORY TESTS

Bronchoalveolar lavage

Pleural fluid aspiration

Upper gastrointestinal endoscopy

Colonoscopy

Biopsy of liver, kidney, bone marrow

CMV, cytomegalovirus; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; HSV, herpes simplex virus.

infection. In solid organ transplant recipients, specific causes of pulmonary infection are most frequent at certain times post transplantation (Table 127-5). In a similar manner, specific causes of pulmonary infection are more frequent at different CD4 lymphocyte counts for patients with HIV infection (Table 127-6).

A normal chest radiograph does not rule out pulmonary infection in immunocompromised patients. Additionally, although some diseases have suggestive radiologic findings (e.g., apical cavitations in tuberculosis), most radiographic findings have to be interpreted in light of all other data available. Frequently, computed tomography

TABLE 127-4

Host Defenses Against Respiratory Infections and How They Are Affected in Immunocompromised Patients

| LOCATION | HOST DEFENSE | DEFECT |
|----------------------------|--|--|
| Upper airway | Filtration Mucociliary apparatus Cough | Endotracheal intubation CF, cigarette smoking Impaired consciousness |
| Lower airway (nonspecific) | Alveolar macrophages Polymorphonuclear leukocytes | Immunosuppressive medication, corticosteroids Corticosteroids, malnutrition, chemotherapy, malignancies |
| Lower airway (specific) | B lymphocytes T lymphocytes | Hypogammaglobulinemia, CLL, MM AIDS, malignancies, immunosuppressants |

AIDS, acquired immunodeficiency syndrome; CF, cystic fibrosis; CLL, chronic lymphocytic leukemia; MM, multiple myeloma.

TABLE 127-5

Occurrence of Pulmonary Infection After Solid Organ Transplantation Stratified by Time from Transplantation

| TIME AFTER TRANSPLANT (MO) | ORGANISM |
|----------------------------|--|
| <1 | Nosocomial bacteria (e.g., MRSA, ESBL-producing Enterobacteriaceae, <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter baumannii</i>) <i>Legionella</i> spp. Respiratory viruses (e.g., influenza virus, parainfluenza virus, RSV, adenovirus, rhinovirus, human metapneumovirus) <i>Aspergillus</i> spp. |
| 1-6 | Nosocomial bacteria (if still mechanically ventilated) <i>Legionella</i> spp. <i>Nocardia</i> spp. [†] <i>Mycobacterium tuberculosis</i> Herpesviruses (e.g., HSV, VZV, CMV) [‡] Respiratory viruses (e.g., influenza virus, parainfluenza virus, RSV, adenovirus, rhinovirus, human metapneumovirus) <i>Pneumocystis jirovecii</i> [†] <i>Cryptococcus neoformans</i> <i>Aspergillus</i> spp. <i>Coccidioides</i> spp. <i>Histoplasma</i> spp. |
| >6 | Bacteria associated with community-acquired pneumonia (e.g., <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Legionella</i> spp., <i>Mycoplasma pneumoniae</i>) <i>Nocardia</i> spp. [†] <i>Rhodococcus equi</i> [*] <i>Mycobacterium tuberculosis</i> Atypical mycobacterium <i>Aspergillus</i> spp. [*] <i>Zygomycetes</i> [*] <i>Cryptococcus neoformans</i> [*] |

*These organisms should be considered when immune-suppression is still substantial.

†These organisms are less likely in patients on prophylactic cotrimoxazole.

‡These viruses are less likely in patients on prophylactic ganciclovir or valganciclovir.

CMV, cytomegalovirus; ESBL, extended-spectrum β -lactamase; HSV, herpes simplex virus; MRSA, methicillin-resistant *Staphylococcus aureus*; RSV, respiratory syncytial virus; VZV, varicella-zoster virus.

TABLE 127-6

Etiology of Pulmonary Infections in Patients Infected with Human Immunodeficiency Virus, Stratified by CD4 Lymphocyte Count

| ORGANISM | CD4 COUNT (CELLS/mm ³) | | | |
|---------------------------------|------------------------------------|------------------------|-----------------------------------|----------------------------------|
| | >500 | 200-500 | 50-200 | <50 |
| <i>Streptococcus pneumoniae</i> | | <i>S. pneumoniae</i> | <i>Pneumocystis jirovecii</i> | <i>P. jirovecii</i> |
| <i>Haemophilus influenzae</i> | | <i>H. influenzae</i> | <i>Mycobacterium tuberculosis</i> | <i>Cryptococcus</i> |
| | | <i>M. tuberculosis</i> | <i>Cryptococcus</i> | CMV MAC <i>Aspergillus</i> |

CMV, cytomegalovirus; MAC, *Mycobacterium avium* complex.

(CT) is required (e.g., evaluation of pulmonary nodules). Pulmonary nodules have a broad differential diagnosis in immunocompromised patients, including infections due to fungi (especially *Cryptococcus neoformans*, *Coccidioides immitis*, and *Aspergillus fumigatus*), *Nocardia*, mycobacteria, *Rhodococcus equi*, and *Bartonella*. Additionally, carcinomas and posttransplant lymphoproliferative disorders may present with pulmonary nodules. The differential diagnosis of cavitary lesions includes mycobacteria, invasive pulmonary aspergillosis, legionellosis, and infection with *R. equi*. As noted earlier, the broad differential diagnosis of pulmonary infection in immunocompromised patients mandates early and aggressive diagnostic strategies such as bronchoscopy with the bronchoalveolar lavage sent for a comprehensive battery of microbiological investigations.

Central Nervous System Infections

Most infectious agents reach the CNS via hematogenous dissemination from an extraneural site. Exceptions include retrograde propagation of infected thrombi within emissary veins, spread along olfactory nerves, and spread from a contiguous focus of infection. The blood-brain barrier presents a natural and an efficient barrier to hematogenous infection. The function of the blood-brain barrier in immunocompromised patients has not been well studied. It is well known, however, that when a CNS infection is established, immune defenses (even in immunologically competent hosts) are inadequate to control the infection. Local opsonization is deficient within the brain. In animal models of bacterial brain abscess, corticosteroid administration led to a reduction in macrophage and glial response, with an increased number of viable bacteria in the abscess.²⁵

Bacterial meningitis due to *N. meningitidis* is relatively uncommon in immunocompromised patients, except if they have undergone splenectomy. In contrast, pneumococcal meningitis seems to occur with increased frequency in patients who have undergone stem cell transplantation²⁶⁻²⁸ and in those with HIV infection.^{29,30} Meningitis due to *Listeria monocytogenes* is classically associated with immunocompromise, reflecting the need for adequate T-cell function and IFN- γ production to kill this intercellular pathogen.³¹ In addition to meningitis, *Listeria* infection may be associated with a brain abscess, particularly that occurring in the brainstem.^{32,33} Enteric bacteria (e.g., *Escherichia coli*) are rare causes of bacterial meningitis in immunocompromised patients. A classic association exists, however, between meningitis with such organisms and disseminated infection with *Strongyloides stercoralis*.^{34,35} In the presence of immunosuppression (e.g., large doses of corticosteroids), *Strongyloides* can migrate from the gastrointestinal (GI) tract to the CNS, carrying enteric bacterial flora into the CNS. Mortality is high without prompt recognition and treatment. *Nocardia* and mycobacteria must also be considered in the differential diagnosis of CNS infections in immunocompromised patients;

TABLE 127-7

Central Nervous System Infections in the Immunocompromised Host

| ETIOLOGIC AGENT | SPECIAL CONSIDERATIONS |
|-----------------------------------|---|
| MENINGITIS | |
| <i>Streptococcus pneumoniae</i> | Especially in HIV-infected individuals |
| <i>Listeria monocytogenes</i> | Predilection for brainstem |
| Enteric bacteria | Associated with disseminated <i>Strongyloides</i> infection |
| <i>Cryptococcus neoformans</i> | Rapid diagnosis by cryptococcal antigen or India ink stain |
| <i>Mycobacterium tuberculosis</i> | Consider PCR for rapid diagnosis |
| MENINGOENCEPHALITIS | |
| HSV | Rare in immunocompromised patients |
| HHV-6 | May be associated with lack of CSF pleocytosis |
| VZV | Skin lesions yield diagnosis |
| West Nile virus | Transmitted via transplanted organ or blood |
| SPACE-OCCUPYING LESIONS | |
| <i>Nocardia</i> | Pulmonary lesions usually also present |
| <i>Toxoplasma gondii</i> | Especially in HIV-infected individuals |
| Fungi | Pulmonary lesions usually also present |

CSF, cerebrospinal fluid; HHV-6, human herpesvirus-6; HIV, human immunodeficiency virus; HSV, herpes simplex virus; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

diagnostic samples should be sent for inoculation onto appropriate media for isolation of these organisms.³⁶⁻³⁸

Fungal infection of the CNS may cause meningitis or space-occupying lesions. Cryptococcal meningitis is associated with advanced HIV infection (CD4 lymphocyte count <100/mm³) but can also occur in transplanted patients.³⁹ The presentation is usually subacute, although dangerous elevations in intracranial pressure are sometimes observed. Space-occupying lesions in the brain may occur with disseminated mold infections; these infections usually arise in the lung, but dissemination to the brain is part of multiorgan spread. Mortality is extremely high in these cases. Any of the pathogenic molds^{40,41} such as *Aspergillus*,² zygomycetes,^{42,43} *Scedosporium*,⁴⁴ or *Fusarium*⁴⁵ can undergo dissemination to the brain. The dimorphic fungi (e.g., *Histoplasma*, *Coccidioides*) may also disseminate from the lung, causing infection of the CNS. Zygomycetes may also be associated with frequently fatal infection arising within the nose or sinuses (rhinocerebral mucormycosis).^{42,43}

The most common protozoal pathogen to affect the CNS is *Toxoplasma gondii*. The classic association is between *T. gondii* infection and advanced HIV infection, although cases have shown associations with other forms of immunocompromise.⁴⁶⁻⁴⁸ Amebic encephalitis has been reported occasionally in conjunction with advanced HIV infection or organ transplantation.⁴⁹

Additionally, a variety of viruses can cause CNS infections in immunocompromised patients. Perhaps as a result of the widespread use of antihherpesvirus prophylaxis in many immunocompromised populations, herpes simplex virus (HSV) encephalitis is rare.⁵⁰ Some of the newer herpesviruses, such as HHV-6, have been associated with neurologic infection in transplant recipients.⁵¹⁻⁵³ Lack of diagnostic capabilities for these viruses may partially explain their apparent infrequency. CMV meningoencephalitis is well described in patients with advanced HIV infection⁵⁴ and occasionally has been reported in transplant recipients.⁵⁵ Further, disseminated infections with varicella-zoster virus (VZV) in immunocompromised patients may result in CNS infection; West Nile virus may also be acquired from transplanted organs or blood transfusions and is associated with a significant meningoencephalitis in transplant recipients.^{56,57} Table 127-7 summarizes the agents capable of causing CNS infections in an immunocompromised host.

The wide variety of organisms that could be responsible for CNS infection presents a need for a broadly based diagnostic workup before empiric therapy is begun. If the cerebrospinal fluid (CSF) is collected, it should be sent for Gram stain and Ziehl-Neelsen stain for rapid diagnosis of bacterial and mycobacterial infections. PCR can be performed for the diagnosis of most viral infections such as HSV, CMV, and VZV. Cryptococcal antigens can be detected rapidly in the CSF, enabling a rapid diagnosis of this form of meningitis, but for patients with space-occupying lesions of the brain, collection of the CSF may not be possible. Aspiration may be performed in some circumstances. Before invasive diagnostic testing of the brain is performed, however, the patient's skin is examined for lesions (such as that which may occur with cryptococcosis or nocardiosis), and the lungs are carefully reviewed by CT. Because most CNS lesions arise from infection in other parts of the body, a diagnosis may often be made more easily by microbiological sampling of these body sites.

Gastrointestinal Infections

Severe GI infections in immunocompromised patients may occasionally warrant ICU admission because of dehydration or visceral perforation. As with respiratory and CNS infections, the differential diagnosis is usually broad, and a precise diagnosis rarely can be made based on clinical suspicion alone. Immunocompromised patients have an increased predisposition to GI infections, depending on the type and degree of immunocompromise and exposure to certain pathogens.

The most commonly involved organisms in the etiology of infective esophagitis or gastritis are *Candida*, CMV, and HSV, although a variety of other organisms (e.g., mycobacteria and zygomycetes) occasionally are implicated. Candidal esophagitis is a common opportunistic infection in patients with AIDS. Approximately 13.3 events of candidal esophagitis per 100 person-years occur in HIV-infected patients with CD4 counts less than 300/mm³.⁵⁸ A study of renal transplant patients in the United States showed that esophageal candidiasis is the most common fungal infection in these patients, making up 22% of all fungal infections.⁵⁹ Other predisposing factors for severe esophageal candidiasis include broad-spectrum antibiotic therapy, steroid therapy, cancer chemotherapy, diabetes mellitus, cutaneous burns, radiotherapy, and hematologic stem cell transplant. Although *C. albicans* is the most frequently diagnosed organism, there is an increase of other species, including *C. krusei* and *C. glabrata*—this is notable because of the increase in resistance to fluconazole in these species. Finally, as noted previously, immunocompromised patients may have a combination of pathogens causing infection at any one time. Upper GI endoscopy with biopsy is the gold standard for making the diagnosis.

Diarrhea is a common problem in immunocompromised patients with multifactorial etiologies. It may lead to the diagnosis of immunosuppression in a previously undiagnosed patient when an opportunistic pathogen is found and appropriately investigated. Severe complications such as malabsorption leading to malnutrition, dehydration, and wasting can occur. Occasionally, intestinal perforation may result from a GI infection. In an immunosuppressed patient, it is important to differentiate diarrhea due to opportunistic infections from diarrhea due to neoplasms, GVHD, drugs, and other therapeutic agents. GVHD accounts for more diarrhea in blood and bone marrow transplant patients than infective organisms.⁶⁰ In these patients, organisms that cause mild self-limiting disease in the normal host may cause severe and life-threatening infections.⁶⁰

Prolonged use of multiple antibiotics in high doses predisposes patients to colonization with *Clostridium difficile* and development of pseudomembranous colitis. Antibiotic prophylaxis to prevent *P. jirovecii* pneumonia or spontaneous bacterial peritonitis has been associated with *C. difficile*. In addition to the classic antibiotic risk factors of clindamycin or cephalosporin use, fluoroquinolones may predispose to epidemic strains of *C. difficile* (BI/NAP1/027 strain).⁶¹ Enteric bacterial pathogens such as *Salmonella* occur at increased frequency in immunocompromised patients, especially HIV-infected individuals. In

some regions of Africa, nontyphoidal *Salmonella* infections are among the most common causes of bacteremia.⁶² Severe *Salmonella* infections may be associated with intestinal perforation. *Shigella*, *Campylobacter jejuni*, *E. coli* (enterotoxigenic, enteroadherent, and enteroaggregative), and *Yersinia* species are other bacterial causes of diarrhea, although they are less commonly associated with bacteremia.

Protozoal infections are seen more commonly in HIV-infected patients than other immunocompromised groups. At CD4 counts less than 200 cells/mm³, patients with HIV infection may present with unusual protozoa (e.g., *Cryptosporidium* and *Microsporidium*). Occasionally, these pathogens are also seen in transplant recipients.^{63,64} Such pathogens are not detected on routine microscopic examination for ova, cysts, and parasites. Special stains and microbiological techniques are needed. A routine examination usually detects *Giardia lamblia*, *Entamoeba histolytica*, and other more common pathogenic protozoa.

CMV can cause significant colitis in all immunocompromised populations. CMV colitis may occur in the absence of systemic evidence of infection (i.e., PCR finding on peripheral blood may be negative^{65,66}). An intestinal biopsy may be required to make the diagnosis. A CMV intestinal infection may present with diarrhea but may have more profound presentations such as intestinal perforation.^{67,68}

Finally, mycobacterial infections such as tuberculosis occasionally can be associated with colitis.⁶⁹ *M. avium* complex can be grown readily from the feces of patients with HIV infection and CD4 counts less than 50/mm³, but it is not always the cause of diarrhea in such patients.

THERAPEUTIC DIFFICULTIES IN IMMUNOCOMPROMISED PATIENTS

Empiric Therapy

The choice of empiric antimicrobial therapy is often difficult in immunocompromised patients because of the broad differential diagnosis involved and the substantial risk of antimicrobial resistance (stemming from prolonged hospitalization and frequent prior use of antibiotics). As emphasized earlier, management of infection in an immunocompromised patient can be simplified by narrowing the differential diagnosis by thorough history taking, review of prior medical records, and careful physical examination. Aggressive early diagnostic maneuvers before beginning empiric antimicrobial therapy can enable a definitive diagnosis to be made. Failure to collect specimens before beginning empiric therapy can lead to prolonged, expensive, and unnecessary therapy.

Empiric antibiotic therapy in suspected bacterial infections should be tailored to the individual to maximize the chance that the therapy is microbiologically adequate. There is a clear link between microbiologically adequate empiric therapy and successful outcomes from infections in the ICU.⁷⁰ In settings such as severe pneumonia in an immunocompromised patient, empiric regimens comprising vancomycin, ciprofloxacin, meropenem, amphotericin (or voriconazole), ganciclovir, and trimethoprim/sulfamethoxazole may be necessary to cover potentially lethal infections with methicillin-resistant *Staphylococcus aureus*, *P. aeruginosa*, *Legionella*, fungi, CMV, and *P. jirovecii*. However, increasing resistance to carbapenems may necessitate consideration of newer antibiotics such as ceftazidime-avibactam and ceftolozane-tazobactam. Nephrotoxic antibiotics such as colistin, polymyxin B, or amikacin may be problematic in immunocompromised patients with baseline renal impairment, despite the activity of these antibiotics against many carbapenem-resistant organisms.

There is no established role of combination empiric therapy with antifungal agents. The decision to start empiric mycobacterial therapy is never an easy one. In general, it is only advised when there is a substantial risk of tuberculosis. Empiric therapy for disseminated *Strongyloides* infection may have a role in immunocompromised patients coming from an endemic area and with the classic presentation of disseminated infection.

Immunocompromised patients presenting with acute meningitis should receive treatment that covers *S. pneumoniae* and *L. monocytogenes*. The combination of vancomycin, ampicillin, and ceftriaxone may be necessary (vancomycin and ceftriaxone for multidrug-resistant *S. pneumoniae* and ampicillin for *Listeria*). The combination of amphotericin and 5-flucytosine is recommended empirically for meningitis in which antigen testing or India ink stain of the CSF reveals encapsulated fungi consistent with *C. neoformans*. Immunocompromised patients with space-occupying lesions of the brain can be treated empirically with an antifungal drug (amphotericin or voriconazole) if the suspicion of disseminated fungal infection is high, although nocardiosis, toxoplasmosis, or mycobacterial infection would not be covered without specific therapy.

For immunocompromised patients with severe diarrhea requiring ICU admission, empiric therapy with metronidazole or oral vancomycin (for *C. difficile*) and ganciclovir (for CMV) may be given after fecal samples have been collected. Colonic biopsy may be necessary if it can be safely performed. For immunocompromised patients with intestinal perforation, antibiotic coverage against gut flora (i.e., treatment of peritonitis) plus treatment of the most likely causes of perforation (e.g., ganciclovir for CMV) may be chosen.

Pathogen-Directed Therapy

The importance of appropriate specimen collection is that empiric therapy can be streamlined (de-escalated) if cultures or other diagnostic tests reveal positive findings. With immunocompromised patients, antimicrobial therapy is often complicated by drug interactions or adverse reactions. Transplant recipients taking calcineurin inhibitors (e.g., cyclosporine or tacrolimus) or HIV-infected patients taking protease inhibitors are most at risk because these drugs may be metabolized by the cytochrome P450 system.^{71,72} Significant interactions may occur between rifampin, macrolide antibiotics, azole antifungal drugs, and calcineurin inhibitors.⁷² Aggressive treatment of infections in immunocompromised hosts (e.g., with amphotericin, pentamidine, or foscarnet) may be associated with renal dysfunction, compounding the nephrotoxic effects of calcineurin inhibitors. Antimicrobial agents such as linezolid or ganciclovir frequently cause neutropenia, potentially adding further host defense defects.

CONCLUSION

Infection is likely to be one of the most significant problems an immunocompromised patient faces. These patients may present with severe infection or acquire infection while critically ill due to other causes. Prevention of infection in the ICU is of primary importance. Pneumonia can be readily prevented by many strategies. Ventilator-associated pneumonia may be prevented by a bundle of interventions.⁷³ Aspiration of subglottic secretions and selective digestive tract decontamination, while supported by some trials, are still controversial. Opportunistic pneumonia with *P. jirovecii* can be prevented by use of prophylaxis with trimethoprim/sulfamethoxazole, dapsone, or nebulized pentamidine. Environmental exposure to *Legionella* and *Aspergillus* spp. can be prevented by ensuring water purification techniques (e.g., copper-silver ionization) and by preventing exposure of patients

to construction activity. Infections due to pathogens transmitted human to human, such as *M. tuberculosis*, can be prevented by isolation precautions.

Many extrapulmonary infections can also be prevented. CMV infection can be prevented by universal prophylaxis with ganciclovir, valganciclovir, valacyclovir, or a preemptive approach using serial PCR of peripheral blood.^{74,75} A similar preemptive approach may be useful in preventing aspergillosis by monitoring peripheral blood for the galactomannan antigen, although this remains controversial.^{76,77} *C. difficile* infection is difficult to prevent because there is a clear need for antibiotic therapy for immunocompromised patients with infection. The increasing incidence, severity, and high rate of recurrence of *C. difficile* infection have become significant problems.⁷⁸ A recent randomized controlled study demonstrated that the addition of monoclonal antibodies against *C. difficile* toxins to antibiotic agents significantly reduced the recurrence of *C. difficile* infection, even among patients with the epidemic BI/NAP1/027 strain.⁷⁹ Finally, attention to classic infection control practices such as appropriate immunizations,⁸⁰⁻⁸² hand hygiene, and contact isolation is paramount in immunocompromised patients.

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KEY POINTS

1. The degree of immunocompromise in a patient is a guide to the likelihood of particular opportunistic infections and may be indicated by the type and timing of immunosuppressive therapy and, in human immunodeficiency virus-infected patients, by the CD4 lymphocyte count and viral load.
2. Environmental exposures can be important predictors of infection type. Travel history and exposure to *Mycobacterium tuberculosis*, *Aspergillus*, or *Legionella* are important considerations.
3. The differential diagnosis of opportunistic lung infection in immunocompromised hosts is so broad that bronchoscopy with bronchoalveolar lavage, before antimicrobial therapy, is highly desirable.
4. Central nervous system lesions in immunocompromised hosts are often the result of disseminated infection. Careful examination of the skin, with biopsy of suspicious lesions, and computed tomography of the lungs may obviate the need for brain biopsy.
5. Antimicrobial therapy in immunocompromised hosts is beset by difficulties with antimicrobial resistance (especially carbapenem resistance), drug interactions, and adverse effects. Increased frequency of monitoring of immunosuppressive drug levels is essential.

ANNOTATED REFERENCES

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Antiretroviral therapy has changed the long-term prognosis and clinical spectrum of diseases in patients with HIV infection who are admitted to the ICU.

Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor- α neutralizing agent. *N Engl J Med* 2001;345:1098–1104.

Although patients with rheumatoid arthritis may become immunocompromised by way of therapy with corticosteroids or methotrexate, the development of anticytokine agents for this condition has

opened the way for a new range of opportunistic infections in this patient population. This study showed that tuberculosis occurs with increased frequency in patients receiving infliximab.

Kotton CN, Kumar D, Caliendo AM, et al. International consensus guidelines on the management of CMV in solid organ transplantation. *Transplantation* 2010;89:779–795.

CMV is one of the most common infections after solid organ transplantation, resulting in significant morbidity and mortality. However, management of CMV varies considerably among transplant centers. This evidence and expert opinion-based guidelines include topics on diagnostics, immunology, prevention, treatment, resistance, and pediatrics.

Kowalski R, Post D, Schneider MC, et al. Immune cell function testing: an adjunct to therapeutic drug monitoring in transplant patient management. *Clin Transplant* 2003;17:77–88.

The degree of immunocompromise and the subsequent risk of infection in transplant recipients have been difficult to quantify. This study examined the utility of an in vitro immune cell function assay as a means of quantifying global immune response in transplant recipients.

References for this chapter can be found at expertconsult.com.

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Infectious endocarditis (IE) is a rare disease with an incidence of 3 to 10 episodes per 100,000 person-years, varying among countries and increasing dramatically with age. It is presently classified by the mode of acquisition (e.g., healthcare-associated IE, community acquired, and IE in intravenous drug users [IVDU]), by localization as left- or right-sided prosthetic or native valve IE, or as cardiac implantable electronic device (CIED) related (e.g., pacemaker or cardioverter defibrillator). The new classification of *healthcare-associated infectious endocarditis* (HAIE) includes patients hospitalized for more than 48 hours before the symptoms of IE develop (previously called *nosocomial IE* [NIE]) or patients with symptoms less than 48 hours after admission but with extensive healthcare contact defined as (1) home-based nursing or IV therapy, hemodialysis, or IV chemotherapy fewer than 30 days before onset of IE symptoms; (2) hospitalization fewer than 90 days before onset of IE; or (3) residency in a nursing home or a long-term care facility. The definition of HAIE applies both to native (NVE) and prosthetic valve endocarditis (PVE). Early prosthetic valve endocarditis (now defined as presenting <1 year post surgery) has a portion included in the HAIE definition.^{1,2}

HAIE was estimated to have occurred in 0.8 of 10,000 hospital admissions and is often diagnosed late during hospitalization (39 ± 25 days).³ It is associated with considerable morbidity and mortality. The current in-hospital mortality rate for patients with IE is 15% to 20%, with a 1-year mortality approaching 40%.⁴

HEALTHCARE-ASSOCIATED NATIVE VALVE ENDOCARDITIS

The current understanding of HAIE has been based primarily on retrospective studies with a small sample size. New data emerged from the International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) from 61 medical centers in 28 countries.⁵ From this database, as defined by the modified Duke criteria, native valve IE in patients without IV drug abuse was recognized in 1622 patients. Of these patients, 1065 had a community-acquired infection, and 557 (34%) had healthcare-associated native valve endocarditis (HANVE), consistent with the contemporary high incidence of healthcare-associated infection.⁶ Almost half of these infections were acquired outside of the hospital, a result consistent with previous reports of healthcare-associated bacteremia. Compared with patients with community-acquired IE, patients with HANVE more often have comorbid conditions (e.g., diabetes mellitus, cancer, or long-term immunosuppressive therapy). Fever is the most common presenting feature, but physical signs of IE present more rarely in HANVE, suggesting a more acute course. Nonnosocomial acquisition of HANVE is most often dependent on hemodialysis or an intravascular catheter (54%), while patients with nosocomial acquisition more often have a preexisting valvular disease or undergo a nondental invasive medical procedure. The mitral valve is most frequently involved, followed by the tricuspid and aortic valve.⁵ Staphylococci (both *Staphylococcus aureus* and coagulase-negative strains) represent the major pathogens in HAIE. *S. aureus* is responsible for 52% to 57% of HAIE episodes, 91% of which have an intravascular device as the most probable source of bacteremia.³ In the ICE-PCS study, *S. aureus* was the most common pathogen in HANVE, among which 47% was methicillin-resistant *S. aureus* (MRSA).⁵ The second most common bacteria was enterococci (15%), followed by coagulase-negative strains of staphylococci (13%).

MRSA is more prevalent in hospital-acquired infections (57% vs. 41% of HANVE acquired outside the hospital).⁵ Among coagulase-negative strains of staphylococci, *Staphylococcus lugdunensis* deserves attention because it behaves like *S. aureus* with high virulence, has a 50% probability of complicated infection when isolated in blood, and an aggressive course when it is the cause of IE.⁷

Gram-negative bacilli are rare causes of HANVE despite the fact that they cause lethal bacteremias in hospitals, probably as a result of their decreased ability to adhere to heart valves and susceptibility to bactericidal action of serum.^{3,8} Recently, cases of IE due to MDR and XDR gram-negatives (e.g., *Pseudomonas*, *Acinetobacter*, and *B. cepacia*) have been published with poor outcomes despite aggressive management because of a lack of effective treatment options.

Fungal infectious endocarditis is a rare infection, comprising in total less than 2% of IE cases, with a mortality rate exceeding 30%. However, an increased frequency of fungal endocarditis has been observed in recent years, attributed to the increasing use of vascular lines, as well as to noncardiac surgery and increased numbers of immunocompromised patients.^{9,10} The fungi most commonly associated with endocarditis are *Candida* (*albicans* and non-*albicans*, 50%-80%) and *Aspergillus* spp. (20%-25%). In contradistinction to *Candida* spp., in which blood cultures in cases of IE are positive in 83% to 95% of cases, blood cultures are positive in only 11% or less of patients with *Aspergillus* spp. In cases of fungal endocarditis, prolonged symptoms before hospitalization and the embolization of major arteries are classic findings. However, the diagnosis is delayed or missed in 82% of patients. For fungal endocarditis to be diagnosed early, it should be considered in the differential diagnosis and echocardiography performed, which then demonstrates large, bulky vegetations. Peripheral blood cultures should be obtained and accessible embolic specimens subjected to histologic examination.^{9,10} HANVE has higher mortality compared to community-acquired NVIE (25% versus 13%). In HANVE, factors recognized to be independently associated with increased risk of death are increased age (>60), diabetes, *S. aureus* infection, paravalvular abscess, stroke, heart failure, and new conduction abnormality. Cardiac surgery during the IE episode is found to be associated with a lower mortality,⁵ and therefore, early surgical intervention is often mandatory. In fungal endocarditis, the removal of the infected valve is indicated, and postsurgery suppressive therapy for 2 or more years along with close follow-up is required to detect relapses.^{9,10} Special consideration should be given to chronic hemodialysis (HD) patients, in whom IE is significantly more common (16-18 times) and causes greater morbidity and mortality. In this group of patients, IE is the second leading cause of death after cardiovascular disease, and it has been proposed to be added as a fifth category in classification by acquisition.^{11,12} In the ICE-PCS study, 63% of HANVE were HD patients.⁵ *S. aureus* was the pathogen in 75% to 80% of cases, half of which were MRSA. Fever may not be present, and blood cultures may less often be positive, complicating a diagnosis by the Duke criteria. Mortality remains high: 30% during the first month, about 65% during the first year, and reaching more than 70% if cardiac surgery is indicated. An age older than 65, diabetes as the cause of renal failure, mitral involvement, large vegetations, septic emboli, and infections due to MRSA or VRE have been identified as risk factors for mortality.¹¹

For methicillin-sensitive *S. aureus* (MSSA), antistaphylococcal penicillins should be the treatment of choice whereas, in cases of

MRSA with minimum inhibitory concentration (MIC) over 1 mg/L to vancomycin, antimicrobial choices include daptomycin and linezolid.¹ If vancomycin is indicated, drug levels should be followed, with trough levels of 25 to 30 mg/L required for efficacy.¹³

HEALTHCARE-ASSOCIATED PROSTHETIC VALVE ENDOCARDITIS

PVE accounts for 9.5% to 20% of all cases of IE, with mortality rates ranging between 25% and 60%.¹⁴ It occurs in 3% to 4% of patients within 5 years after surgery.

More than one-third is health-care acquired. Contamination of prosthetic valves during this early period occurs either directly at the time of implantation by a break in sterile surgical techniques or via transient episodes of bacteremia, emanating mostly from infected intravascular catheters and wound or skin infections while the patient is still hospitalized, therefore representing a real nosocomial infection.¹⁴ Early PVE (<1 year) presents mostly during the first 2 to 3 months after surgery.

PVE may manifest as an indolent illness with low-grade fever and immune-mediated manifestations or as a fulminant acute febrile disease with hypotension. When early PVE is caused by *S. aureus*, the clinical picture is accompanied in more than 40% of cases by the central nervous system (CNS) and intracardiac complications, with a subsequent mortality ranging from 42% to 85%. The microbiology of PVE is shown in Table 128-1. In the ICE-PCS study, 556 definite cases of PVE were found among 2670 cases of IE (20%), with 36.5% being healthcare-associated prosthetic valve endocarditis (HAPVE) and 70% acquired in the hospital.¹⁴ Of the cases of PVE, 71% were diagnosed during the first year post surgery and the majority on day 60 (median on day 84). In 43% of HAPVE, an intravascular device was in place. *S. aureus* was the most common pathogen E, with a higher incidence in cases with HAPVE (34% and 13.3% MRSA), followed by coagulase-negative staphylococci.¹⁴

Recent progress in transesophageal echocardiography (TEE), applying a high-resolution biplane or multiplane transducer, has enhanced the diagnostic approach to PVE. Sensitivity and specificity of TEE in the diagnosis of PVE exceeds 90% versus a sensitivity of 40% to 70% with transthoracic echocardiography (TTE).¹⁵ New diagnostic modalities are currently used and recommended for the diagnosis of PVE, including multislice cardiac CT, 18F-FDG PET/CT and radiolabeled leukocyte SPECT/CT, when suspicion for the presence of PVE is high and the TEE is not diagnostic. These new methods have been incorporated in the modified Duke criteria (Table 128-2) in the last

update of guidelines of IE, which are effectively used to confirm the diagnosis of PVE.^{15,16} Mortality in PVE is still substantial, being higher in early PVE (77%) than in late-onset infection (42%). The leading causes of death in early PVE are septic shock (36%), congestive heart failure (29%), and renal failure (21%).^{3,17,18} In the ICE-PCS study, overall mortality for PVE was 22.8%, with the mortality from HAPVE being higher at 30.5%. Other factors related to an increased risk of death were older age, *S. aureus* as the pathogen, and complications such as heart failure, stroke, intracardiac abscess, and persistent bacteremia.¹⁶ The survival rate with medical therapy alone in cases of moderate to severe chronic cardiac failure due to prosthesis dysfunction is almost nil. However, valve replacement in this group plus antimicrobial therapy will achieve a survival rate of 44% to 64%.¹⁹ It is noteworthy that PVE recurs in only 6% to 15% of patients who are operated on with active bacterial invasive infection. After surgery for the removal of the infected prosthetic valve, antibiotics should be continued for at least 6 weeks.¹⁴

INFECTIVE ENDOCARDITIS IN THE ICU

Five studies have focused on patients with IE admitted to the ICU in the past decade.²⁰⁻²⁴ Patients with IE are admitted because of complications (e.g., severe sepsis or septic shock, heart failure with hemodynamic instability, embolic phenomena especially from the CNS, multiorgan failure, or after acute surgery for IE). They usually need prolonged hospitalization, and more than 50% undergo cardiac surgery, which is a protective factor for mortality. A total of 15% to 20% of IE patients admitted to the ICU are healthcare associated, 15% to 36% involve a prosthetic valve, and one-third are accompanied by embolic phenomena most commonly from the CNS. Pathogens recorded are usually *Staphylococcus aureus* and streptococci. Mortality rates are 30% to 45%, among studies, for the first 30 days, with risk factors for mortality in recent years being high values of severity scores at admission (SAPS II, SOFA) and multiorgan failure. Long-term mortality has been recently studied by Mirabel et al.,²⁴ and it was found to be 69% for the subsequent 5 years, with risk factors for mortality being a high SOFA score at admission, the presence of a prosthetic valve, and the size of the vegetation (>15 mm). IE may also be acquired in the ICU, usually as a result of bacteremia related to a medical procedure, and *S. aureus* is the most common pathogen.²⁵ The expected classic clinical features of IE are often not present in ICU patients. For instance, central nervous system (CNS) signs due to sedation may be blunted, and manifestations of renal failure are usually attributed to septic multiple organ dysfunction syndrome.

TABLE 128-1 Etiology of Prosthetic Valve Endocarditis Versus Nosocomial Native Valve Endocarditis

| | NATIVE VALVE ENDOCARDITIS | | PROSTHETIC VALVE ENDOCARDITIS | |
|--|---------------------------|--------------------|-------------------------------|---------------|
| | HEALTHCARE ASSOCIATED | COMMUNITY ACQUIRED | EARLY (<12 mo) | LATE (>12 mo) |
| <i>Streptococcus</i> species | 8% | 28% | 3.8% | 20% |
| <i>Enterococcus</i> species | 15% | 9% | 7.5% | 12.7% |
| <i>Staphylococcus aureus</i> | 45% | 20% | 36% | 18% |
| MRSA | 47% | 12% | 19% | 3.3% |
| Coagulase-negative <i>Staphylococcus</i> | 13% | 6% | 17% | 19.9% |
| Gram-negative bacilli* | | | 3% | 1.2% |
| HACEK* | | | 0% | 2.1% |
| Fungi* | | | 9.4% | 3.3% |
| Culture negative | 5% | 11% | 11.2% | 12.4% |

Modified from Benito N, Miró JM, de Lazzari E, et al. Health care-associated native valve endocarditis: importance of non-nosocomial acquisition. *Ann Intern Med* 2009;150:586-94; and from Wolff M, Witzsch S, Chastang C, et al. Prosthetic valve endocarditis in the ICU: prognostic factors of overall survival in a series of 122 cases and consequences for treatment decision. *Chest* 1995;108:688-94.

*Rare; approximately 2% among all cases of native valve endocarditis.

HACEK, *Haemophilus* spp. (*H. parainfluenzae*, *H. aphrophilus*, *H. paraphrophilus*), *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* spp.; MRSA, methicillin-resistant *Staphylococcus aureus*.

TABLE 128-2 Modified Duke Criteria for the Clinical Diagnosis of Infectious Endocarditis**MAJOR CRITERIA****1. BLOOD CULTURES POSITIVE FOR IE**

- a. Typical microorganisms consistent with IE from two separate blood cultures:
 - *Viridans* streptococci, *Streptococcus gallolyticus* (*Streptococcus bovis*), HACEK group, *Staphylococcus aureus*; or
 - Community-acquired enterococci, in the absence of a primary focus; or
- b. Microorganisms consistent with IE from persistently positive blood cultures:
 - ≥ 2 positive blood cultures of blood samples drawn >12 h apart; or
 - All of 3 or a majority of ≥ 4 separate cultures of blood (with and last samples drawn ≥ 1 h apart); or
- c. Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer $>1:800$

2. IMAGING POSITIVE FOR IE

- a. Echocardiogram positive for IE:
 - Vegetation;
 - Abscess, pseudoaneurysm, intracardiac;
 - Valvular perforation or aneurysm;
 - New partial dehiscence of prosthetic valve.
- b. Abnormal activity around the site of prosthetic valve implantation detected by 18F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabeled leukocytes SPECT/CT.
- c. Definite paravalvular lesions by cardiac CT.

MINOR CRITERIA

1. Predisposition such as predisposing heart condition or injection drug use.
2. Fever as temperature $>38^{\circ}\text{C}$.
3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions.
4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with an organism consistent with IE.

DEFINITE IE

- Two major criteria; or
- One major criterion and three minor criteria; or
- Five minor criteria

POSSIBLE IE

- One major criterion and one minor criterion; or
- Three minor criteria

REJECTED IE

- Firm alternate diagnosis; or
- Resolution of symptoms suggesting IE with antibiotic therapy for ≤ 4 days; or
- No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for ≤ 4 days; or
- Does not meet criteria for possible IE, as above

From Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC): 2015 ESC Guidelines for the management of infective endocarditis. Eur Heart J 2015;36(44):3075-128.

Since the risk of HAIE is proportionally increased with the duration of hospitalization, the diagnosis of IE should always be suspected in the presence of a fever of unknown origin with positive blood cultures after a prolonged stay in the ICU. The latter suspicion is strengthened in patients with prosthetic valves or cardiac implantable electronic devices (CIED), in those undergoing procedures that may damage the right side of the heart, and whenever bacteremia lasts for more than 72 hours after catheter removal and/or positive blood cultures that persist 3 days after starting appropriate antimicrobials, especially if the microorganism isolated in blood is *S. aureus*.²⁶

The diagnostic value of echocardiography in the diagnosis of IE and particularly of the transesophageal view has been established. In a patient with *S. aureus* bacteremia, a TTE should always be performed. If bacteremia persists beyond 48 to 72 hours and/or the patient has an implantable cardiac device or a prosthetic valve, then a TEE should also be performed because the risk of IE is high.^{27,28} In the case of a negative TEE, if clinical suspicion continues to be high, a second examination should be advocated (a multislice CT for native valves and 18F-FDG PET/CT, as well as radiolabeled leukocyte SPECT/CT for prosthetic valves or CIED).¹ HAIE in the ICU requires the prompt initiation of antimicrobial therapy and cardiosurgical evaluation, keeping in mind that mortality increases sharply with *S. aureus* as a pathogen, with age, and with the origin of the infection (i.e., ICU-acquired vs. community-acquired). Of note, the treatment duration of catheter-related staphylococcal (*S. aureus*) bacteremia aiming to treat successfully any seeded valve (as occurs in 23% of the cases) should never be shorter than 2 weeks, and echocardiography should be performed before treatment discontinuation. Otherwise, a treatment duration of 4 weeks is recommended.²⁹

Prophylaxis of HAIE, especially in ICU patients, mandates (1) IV access and intravascular procedures to be performed with aseptic care; (2) IV and intraarterial catheters to remain in place for as brief a duration as possible; and (3) tunnelization, although a controversial issue, to be considered either as an immediate approach for temporary dialysis catheters or as a systemic procedure if the catheter has been or will be in place for more than 4 days.³⁰ Antimicrobial prophylaxis is not justified before performing TEE.¹

KEY POINTS

1. ICU infectious endocarditis (ICU-IE) shares overlapping characteristics with healthcare-associated infectious endocarditis (HAIE) and is either acquired in the ICU or is an emergency necessitating critical care, involving native or prosthetic valves.
2. Major pathogens (90%) include staphylococci (*S. aureus*, with increasing rates of MRSA) and *Enterococcus* spp.
3. Mortality of HAIE is higher in the elderly, in patients with *S. aureus* and fungal endocarditis, and in patients with complications (e.g., heart failure, stroke, intracardiac abscess, persistent bacteremia). Early surgical intervention is mandatory and may improve the in-hospital outcome.
4. Fungal endocarditis is rare, presenting as a complication of intravascular instrumentation or surgery or in the context of an immunocompromised state. *Candida* is the most common fungal causative agent. Delayed diagnosis, major embolic phenomena, and large vegetations are the rule. Combined surgical and medical treatment of long duration is needed to ameliorate the high ($>50\%$) mortality rate.
5. Transesophageal echocardiography (TEE) has enhanced our diagnostic approach in HAIE (NVE or PVE), especially when the Duke diagnostic clinical criteria are effectively used, and it must always be performed in patients with persisting *S. aureus* bacteremia and prosthetic valves or CIED.

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■ References for this chapter can be found at expertconsult.com

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Medical advances continue to improve the prognosis of patients with cancer and other immunodeficiencies. In the past 50 years, the field of transplantation has greatly impacted the management of patients with cancer and renal, cardiac, and liver diseases. Moreover, advances in neonatology continue to increase the survival of premature infants. These advances have benefited society greatly, but they have also fueled the emergence of invasive fungal infections. *Candida* species first appeared as significant nosocomial pathogens approximately 30 years ago.¹ For two decades, infections caused by these pathogens increased dramatically.

Fungal infections among critically ill patients are primarily due to *Candida* spp. However, infections caused by other opportunistic fungal pathogens including *Aspergillus*, *Fusarium*, Mucorales, and *Cryptococcus neoformans* also occur in critically ill populations (e.g., solid-organ transplant [SOT] and hematopoietic stem cell transplant [HSCT] recipients and patients with acquired immunodeficiency syndrome [AIDS]). Moreover, primary or endemic mycosis caused by *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Histoplasma capsulatum* can cause severe disseminated infection in immunocompetent or compromised hosts.

Fungal infections are generally more prevalent in intensive care units (ICUs) than on the general medical wards.² The importance of effective preventive measures against invasive fungal infection is widely appreciated in patients with leukemia or in HSCT recipients. As our understanding of these infections continues to improve, so too does the ability to institute appropriate preventive measures. In the past decade, the development of agents possessing either different modes or a broader spectrum of activity, less toxicity, or a reduced propensity to interact with other drugs has increased the number of systematically active antifungal agents available. Consequently, clinicians can now tailor antifungal therapy to specific patients. Moreover, our understanding of antifungal pharmacodynamics is developing, and methods to measure susceptibility to antifungal agents are improving.

FUNGAL INFECTIONS IN THE CRITICALLY ILL

Candida Infections in the ICU

Epidemiology

Candida albicans remains the fourth most common pathogen in healthcare-associated infections; only coagulase-negative staphylococci, *Staphylococcus aureus*, and enterococci are more common.³ *Candida* spp. have consistently caused a substantial disease burden for at least the past decade.⁴⁻⁶ ICUs have a higher incidence of *Candida* bloodstream infections (BSIs) than medical and surgical wards.^{2,7} Although prior data had suggested the frequency of *Candida* BSIs among ICU patients had declined, estimates from national secondary databases and population-based studies suggest the disease burden may be shifting from the ICU to the general hospital population.¹

C. albicans remains the most common invasive *Candida* spp. worldwide.⁸ However, decreasing trends in the isolation of these species over time have been observed in the ICU and non-ICU setting.^{8,9} An increased prevalence of *C. albicans* and *C. parapsilosis* among neonatal ICU patients and an increasing prevalence of *C. glabrata* infections

among adults has been widely appreciated.^{1,8-11} *C. albicans* is responsible for approximately 45% of episodes of candidemia.¹² The incidence of infection due to a particular *Candida* sp. varies considerably by the clinical service on which the patient is hospitalized. However, in general, *C. albicans* is the primary fungal pathogen in the ICU setting, followed by *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, *C. guilliermondii*, and *C. lusitaniae*.¹² This rank order varies little across infection site, but it may vary with age, underlying disease, or local epidemiology.^{1,8,9,12} Surveillance data have noted that candidemia in neonatal ICUs is predominantly due to *C. albicans* and *C. parapsilosis* and rarely to *C. glabrata* or other *Candida* spp.^{1,8,9,12} Surveillance studies have demonstrated that BSI due to *C. albicans* occurs less frequently with increasing age.^{1,8,9,12} In contrast, *C. glabrata* is rarely isolated among infants and children but is more frequently found with increasing patient age.^{1,8,9,12}

C. albicans is part of the normal flora of the gastrointestinal tract. Infections including BSIs caused by most *Candida* spp., particularly *C. albicans*, arise endogenously from the gastrointestinal mucosa, skin, and urinary tract.¹³ Invasive *Candida* infections occur when alteration of endogenous flora leads to overgrowth of yeast which, in the presence of compromised skin or gastrointestinal mucosa integrity, translocates from its commensal environment to the bloodstream.¹³ However, *Candida* spp., including *C. albicans*, may be transmitted exogenously in ICU settings.^{14,15} Exogenous transmission of non-*albicans* *Candida* spp. through indirect contact with the ICU environment occurs commonly.¹⁴ For example, *C. parapsilosis* is an exogenous pathogen known for its ability to form biofilms on catheters and inert devices. *C. parapsilosis* persists in the nosocomial environment.¹⁶ Moreover, it is spread throughout the hospital through hand carriage by healthcare workers.¹⁶ Therefore, colonization with this pathogen is not a prerequisite for infection.¹⁶

Mortality

Candida BSIs are often difficult to detect. Symptomatically, BSIs due to *Candida* spp. are indistinguishable from BSIs of bacterial etiology. *Candida* spp. are cleared from the blood very efficiently by several organs, particularly the liver, and blood cultures yield positive results in only 50% of patients with hematogenously disseminated candidiasis.^{17,18} However, the ability of automated blood culture systems to recover *Candida* spp. has continued to improve. For example, in a simulated candidemia study, *Candida* spp. were isolated in 74% (479/648) of blood culture bottles.¹⁹ However, isolation rates were highest in aerobic blood and mycology culture bottles (98% [211/216] and 97% [210/216], respectively) but lowest in anaerobic culture bottles (27% [58/216]).¹⁹ The ability to detect growth improved as inoculum size increased.¹⁹ Although the time to detect growth varied with *Candida* spp., most species were detected within 24 to 48 hours. Growth was detected faster in aerobic and mycology culture bottles than in anaerobic bottles. These data and other studies demonstrated the improved ability of current technology to detect simulated or clinical candidemia due to most common and uncommon *Candida* pathogens in aerobic cultures.^{19,20} New nanomolecular diagnostic approaches with T2 magnetic resonance were developed to enable timely diagnosis, and these show promising results.²¹

Even with improved ability to recover *Candida* spp. from the blood, *Candida* BSIs carry a relatively poor prognosis. *Candida* spp. isolated

from the blood have consistently been identified as an independent predictor of mortality.²²⁻²⁴ The overall attributable mortality of nosocomial BSIs among critically ill patients is 35%.²⁵ This mortality rate for nosocomial BSIs in the ICU setting is comparable to the mortality rate associated with BSIs due to *Candida* spp. Historically, the estimated crude mortality rate associated with *Candida* BSIs hospital-wide and in the ICU setting has ranged from 35% to 69%, while the estimated attributable mortality has been 38%.^{24,26,27}

Recent estimates suggest that the mortality attributable to candidemia and other forms of invasive candidiasis ranges from 10% to approximately 50%.¹ Moreover, data demonstrate that despite the advent of potent and safer antifungal therapy, the mortality risk associated with candidemia has essentially remained unchanged for at least two decades.^{28,29} Inadequate treatment may be a reason why mortality has not improved despite the availability of potent and safe antifungal therapy. Delays in administration, treatment with an agent to which the organism is resistant, inadequate dosing or treatment duration, or failure to recognize and treat candidemia all contribute to the mortality associated with *Candida* BSI.³⁰⁻³⁶ Delaying initiation of adequate antifungal therapy even 12 to 48 hours is independently associated with mortality in patients with candidemia.^{31,32,34,37-39}

Candidemia produces significant morbidity and increases the length of hospital stay.^{1,13} Given the severity of illness associated with this infection, the added length of stay utilizes significant healthcare resources.⁴⁻⁶

Risk Factors

Among critically ill patients, risk factors for *Candida* infections are well described.^{7,40-44} Broad-spectrum antimicrobial use, colonization, indwelling vascular catheters, extremes of age, and hemodialysis have been consistently identified as independent risk factors for *Candida* BSIs.^{7,24} In most ICU settings, many of these risk factors are commonly present and unavoidable. The ICU itself provides an ideal environment for transmission of *Candida* spp. among patients; thus it is not surprising that prolonged ICU stay has been identified as an independent risk factor.⁴⁵ A study using validated risk factors in a simulated ICU population demonstrated that in the presence of multiple risk factors, the probability of infection increases exponentially.⁴⁵ For example, in a hypothetical critical care unit, if a patient had prior exposure to four antibiotic classes, the calculated risk of candidemia for that patient would range from 5% to 35%, depending on the overall baseline candidemia rate in the ICU, usually between 1% and 5%. However, if that same hypothetical patient subsequently had *Candida* spp. cultured from another (nonbloodstream) anatomic site, the calculated risk would increase substantially to 40% to 80%.⁴⁵ Given how common many of the risk factors (such as indwelling catheters, antibiotics, immunosuppressants, and total parenteral nutrition) are in the ICU, these data illustrate the need to accurately predict or identify patients who truly are at risk so that therapy can be instituted as early as possible.

The risk factors for BSIs with any *Candida* spp. are similar, and the specific type of infection cannot be differentiated based on clinical characteristics alone.^{40,41} Several studies have developed prediction rules to stratify patients at increased risk for developing invasive infections with either *C. albicans* or other *Candida* spp. in hopes of providing guidance for clinical decision making to prevent candidemia in the ICU. These prediction rules are based upon retrospective studies and assess the combination of ICU length of stay, prior *Candida* colonization, and other host risks.⁴⁶⁻⁴⁸ While these systems demonstrate risk stratification is possible, they are somewhat complicated to apply, and some have questioned the practicality of certain components of individual prediction rules.^{41,49} Using the database from a large prospective multicenter Spanish study in which fungal colonization was assessed weekly along with other potential risk factors, León and colleagues developed the “*Candida* score” based upon four independent risk factors: multifocal *Candida* spp. colonization, surgery upon ICU admission, severe sepsis, and total parenteral nutrition. The score, obtained by adding the statistical weight of each risk factor, has a cutoff

value of 2.5, providing a sensitivity of 81% and specificity of 74% for identifying patients with current or future *Candida* infection. Patients with a score greater than 2.5 were more than 7 times as likely to have proven infection as patients with a *Candida* score ≤ 2.5 .⁴⁷ A prospective multicenter observational study demonstrated that a *Candida* score ≥ 3 discriminated between colonization and invasive candidiasis in nonneutropenic ICU patients colonized with *Candida* spp., with a minimum length of ICU stay of 7 days.⁴⁹ These data lend credence to the idea of using the *Candida* score for guiding the start of empiric antifungal therapy in the ICU. However, even though the *Candida* score is promising, the clinical utility of such prediction rules in establishing the benefit of targeted antifungal prophylaxis remains to be established in prospective studies.⁵⁰⁻⁵²

Opportunistic Fungal Infections in Immunocompromised Critically Ill Patients

Invasive Aspergillosis in Critically Ill Patients with Hematologic Malignancies

In contrast to *Candida* spp., the burden of infection due to *Aspergillus* spp. is small.^{1,13} *Aspergillus* spp. cause infection in critically ill populations immunocompromised by burns, cytotoxic chemotherapy, prolonged corticosteroid therapy, malignancy, leukemia, SOT or HSCT, and other congenital or acquired immunodeficiencies. *Aspergillus* spp. are ubiquitous environmental molds. While several hundred species of *Aspergillus* have been described, relatively few are known to cause disease in humans. Most *Aspergillus* infections are acquired exogenously via inhalation. In the absence of an effective immune response, airborne conidia invade sinus or lung vasculature. Although the lung is the most common site of invasive aspergillosis, *Aspergillus* spp. also demonstrate tropism for cutaneous, central nervous system (CNS), bone, and cardiac vasculature.⁵³

The incidence of invasive aspergillosis in immunocompromised patients varies among specific populations. Among patients with hematologic malignancies, those with acute myelogenous leukemia have the highest incidence of invasive aspergillosis.⁵⁴⁻⁵⁶ Patients in ICUs are at increased risk and susceptibility in general, depending on the use of immunosuppressants, structural lung damage and genetic predisposition.⁵⁷⁻⁶³ Like patients with leukemia, patients undergoing HSCT are at high risk for invasive aspergillosis. The incidence of invasive aspergillosis varies depending on transplant type but not the type of conditioning regimen (myeloablative vs. nonmyeloablative). The incidence is higher among allogeneic HSCT recipients than among recipients of autologous stem cells. In the HSCT population, whether the incidence of invasive aspergillosis is truly increasing or decreasing is difficult to ascertain, because the rate of autopsies continues to decline. The incidence of invasive aspergillosis among SOT is highest after lung transplant and lowest after renal transplant. Patients receiving HSCT or SOT can develop invasive aspergillosis shortly (within 40 days) after transplantation, but typically it occurs late post-HSCT (>40-100 days) or SOT (>90 days).⁶⁴⁻⁶⁹

In patients with acute leukemia or in HSCT recipients, prolonged neutropenia after cytotoxic chemotherapy or HSCT is the primary risk for early invasive aspergillosis. Risk factors associated with invasive aspergillosis in HSCT and SOT recipients vary with time after the transplant. However, in general, risks early in the transplant process are related to transplant-related factors (underlying disease, neutropenia, type of transplant), biological factors (hyperglycemia, iron overload), and extrinsic factors (spores from the environment, air filtration). In contrast, risks for invasive aspergillosis occurring later in the transplant process include transplant complications such as acute GVHD (grade ≥ 3) and high-dose corticosteroid therapy.⁶⁸

Lesions associated with invasive pulmonary aspergillosis evolve over a period of weeks. CT findings, especially nodular infiltrates with a “halo sign,” are strongly suggestive of invasive aspergillosis or infection from other angioinvasive fungi in immunocompromised patients. Moreover, this finding is associated with significantly improved

response and survival if antifungal therapy is initiated shortly upon detection of this sign of infection.⁷⁰

Recent diagnostic efforts have focused on detecting non-culture-based serum markers (e.g., galactomannan test, 1,3- β -D-glucan, polymerase chain reaction). Galactomannan is a cell wall constituent of *Aspergillus* spp. that can be detected in the serum during invasive infection. The test is specific for invasive aspergillosis and is commercially available as a sandwich enzyme immunoassay that detects circulating galactomannan. The values from this test have been shown to correlate strongly with the clinical outcome of patients with invasive aspergillosis.⁷¹⁻⁷³ Because 1,3- β -D-glucan is a cell-wall component of many fungal pathogens, it can be detected by colorimetric detection assays. Although the test is highly sensitive, the presence of 1,3- β -D-glucan in the serum is not specific for any fungi. Using both of these non-culture-based serum markers may improve the ability to diagnose invasive aspergillosis in high-risk populations and could lead to earlier diagnosis or improved monitoring of the success of antifungal therapy.^{74,75} CT-guided biopsy has a high diagnostic yield, and samples should undergo both histopathologic and cultural evaluation.⁷⁶ The combination of radiologic, serologic, cultural, histopathologic, and clinical data may ultimately improve the diagnosis of invasive aspergillosis and speed up initiation of appropriate antifungal therapy.

Miscellaneous Pathogens in Critically Ill Patients with Hematologic Malignancies

Candida and *Aspergillus* spp. are the primary fungal pathogens in critically ill patients with hematologic malignancies. However, other pathogens such as *Fusarium* spp., *Pseudallescheria* spp./*Scedosporium apiospermum*, and the members of the Mucorales order are increasing in frequency.¹³ Each of these less common organisms has particular clinical characteristics or tissue tropism. In addition, they are often less susceptible than *Aspergillus* spp. to systemic antifungal agents. Consequently, infections due to these pathogens are associated with high mortality. Of these, the Mucorales are the most common among critically ill patients. These angioinvasive pathogens are acquired through inhalation and produce a necrotic infection with the highest morbidity and mortality.⁷⁷ Rhinocerebral, paranasal, pulmonary, cutaneous and gastrointestinal infections are common manifestations of mucormycosis. Common risks are diabetic ketoacidosis, immunosuppression, organ transplantation, (traumatic) skin damage, and a prolonged ICU stay.^{77,78} Pulmonary and disseminated infections mostly affect patients with hematologic malignancy, while rhinocerebral and paranasal mucormycosis is predominant in patients with uncontrolled diabetes.^{79,80} The “reversed halo” sign on CT is indicative of pulmonary mucormycosis, although the diagnosis should be confirmed by cultural and histopathologic evaluation of biopsy specimens.⁸¹⁻⁸³ Management of mucormycosis, including the important role of surgical débridement, is detailed in a current guideline of the European Confederation of Medical Mycology.⁸⁴

Cryptococcosis, Histoplasmosis, Blastomycosis, and Coccidioidomycosis in Critically Ill Patients

Cryptococcus neoformans, *C. deneoformans*, *Histoplasma capsulatum* var. *capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis* are not common pathogens in the ICU setting. These organisms can cause infection in patients with intact immune function. However, with the exception of *B. dermatitidis*, severe infections due to these pathogens are more common among critically ill immunocompromised populations, particularly those with AIDS and recipients of SOT. Cryptococcosis is the third most common invasive fungal infection among SOT recipients.^{13,85}

C. neoformans is a ubiquitous encapsulated yeast isolated from diverse environmental sources (e.g., soil, trees and plant material, and pigeon droppings). This pathogen is primarily acquired by inhalation.⁸⁶ In the lung, the organism elicits a cell-mediated response involving neutrophils, monocytes, and macrophages. The cryptococcal

polysaccharide capsule, an important virulence factor, facilitates laboratory identification and recognition by host cell-mediated immune response, and it possesses immunosuppressive properties. The advent of AIDS significantly altered the incidence of cryptococcosis. Before the AIDS epidemic, cryptococcosis was an uncommon disease in the United States, but since then, the majority of cases have been associated with HIV infection.^{87,88} The prevalence of cryptococcosis in HIV in the United States has declined with the widespread use of fluconazole and highly active antiretroviral therapy to treat HIV infection. Cryptococcosis still produces significant acute mortality, but overall long-term outcomes have improved dramatically in the past two decades.⁸⁹ Mortality among HIV-infected patients and SOT recipients is similar and is estimated to be approximately 15% to 20%.⁸⁹⁻⁹¹

Among critically ill immunosuppressed populations, cryptococcal infections typically involve the CNS.⁸⁵ However, HIV-negative patients may have only extra-CNS (i.e., skin, soft tissue, or osteoarticular) manifestations. The onset of this infection may be acute or gradual, and patients often present with nonspecific complaints.⁹² When the disease manifests as subacute meningitis or meningoencephalitis, classic meningeal findings such as photophobia or nuchal rigidity may be absent.

In cases of cryptococcal meningitis, characteristic cerebrospinal fluid (CSF) findings may be present; however, CSF leukocyte count can be low, and CSF protein and glucose values may be normal. Therefore, CSF analysis for cryptococcal antigen and culture of the organism are required to diagnose cryptococcal meningitis. Detection of the organism by India ink stain is highly specific but has low sensitivity. Determination of serum cryptococcal antigen using latex agglutination is a highly sensitive and specific test and is therefore an important component of the diagnosis of cryptococcal disease. In patients with cryptococcal meningitis, particularly those with AIDS, the serum cryptococcal antigen is usually positive, and titers are commonly very high. Detection of antigen in the CSF strongly suggests infection, but in HIV-infected patients, false-negative results can occur in up to 10%, even in the presence of positive cultures. The definitive diagnosis of cryptococcal infection requires a positive culture for *C. neoformans*.

Histoplasmosis (caused by *H. capsulatum* var. *capsulatum*), blastomycosis (*B. dermatitidis*), and coccidioidomycosis (*C. immitis*) are the major endemic mycoses found in North America. Infections by these pathogens occur primarily in distinct geographic areas, but owing to population mobility, they can be reported throughout the United States. Diagnosis is established via antigen and antibody detection from urine or serum, respectively.^{93,94} *H. capsulatum* is endemically distributed primarily in the Mississippi and Ohio River valleys. *B. dermatitidis* is found chiefly in the south central United States, the Mississippi and Ohio River valleys, and in certain regions of Illinois and Wisconsin. *C. immitis* is found mainly in the arid southwest regions of the United States. Infection with all these pathogens is acquired via inhalation. Overall, hospitalization is required in an estimated 4.6 and 28.7 cases per million children and adults, respectively.⁹⁵ Nationwide, endemic mycoses require substantial healthcare resources to manage, and they produce significant crude mortality rates in children and adults (5% and 7%, respectively).⁹⁵ The severity of histoplasmosis depends on host immune function and the extent of exposure, particularly in the immunocompetent host. Hematogenous dissemination from the lungs occurs in all infected patients, but in immunocompetent hosts, it is controlled by the reticular endothelial system. However, among elderly hosts or those with cell-mediated immune disorders (e.g., HIV infection), progressive dissemination of the infection readily occurs. After inhalation, *B. dermatitidis* can disseminate from the lungs to other organs as the yeast form. The primary pneumonia is often undetected and resolves without sequelae. Endogenous reactivation in the lungs, skin, or bones is often the first sign of infection.

C. immitis requires the inhalation of only a few arthroconidia to produce primary coccidioidomycosis. Like the other endemic mycoses, in the majority of patients, it typically manifests as an asymptomatic pulmonary disease.⁹⁶ However, it can also manifest

as an acute respiratory illness, chronic progressive pneumonia, pulmonary nodules and cavities, extrapulmonary nonmeningeal disease, and meningitis.^{97,98}

Among critically ill patients, histoplasmosis manifests as either chronic pulmonary histoplasmosis or progressive disseminated (extrapulmonary) histoplasmosis. Chronic or cavitary pulmonary histoplasmosis occurs in middle-aged and elderly patients with underlying lung disease that compromises the ability of nonspecific host defenses to effectively clear the organism.

Progressive disseminated histoplasmosis occurs in healthy or critically ill immunocompromised hosts, but it is more common and severe in the latter population (e.g., patients with malignancies or HIV infection). The infection can disseminate to a variety of organs including the reticuloendothelial system, oropharyngeal and gastrointestinal mucosa, skin, adrenal glands, and kidneys.⁹⁶

Clinical manifestations of blastomycosis can mimic many other diseases, such as tuberculosis and cancer, but it typically occurs as an asymptomatic infection, acute or chronic pneumonia, or disseminated (extrapulmonary) disease.⁹⁹ Extrapulmonary blastomycosis typically afflicts the skin, bones, and genitourinary system.⁹⁹ Cutaneous lesions are the most common skin manifestations of this disease.⁹⁹ Extrapulmonary (disseminated) coccidioidomycosis afflicts 1% to 5% of all patients infected with *C. immitis* and is deadly if not treated properly. Even with appropriate treatment chronic infection is common.⁹⁷

■ SYSTEMIC ANTIFUNGAL AGENTS

Amphotericin B Formulations

Amphotericin B Deoxycholate

Amphotericin B deoxycholate (AmB-d), a polyene antifungal agent, disrupts biological membranes, thereby increasing their permeability. AmB-d also stimulates the release of cytokines that cause arteriolar vasoconstriction in the renal vasculature.¹⁰⁰

Pharmacology and Pharmacokinetics. The majority (70%) of an administered AmB-d dose is recovered from the urine and feces over a 7-day period; approximately 30% of the administered dose remains in the body a week after dosing.¹⁰¹

Overview of Toxicity. AmB-d infusion-related reactions, including hypotension, fever, rigors, and chills, occur in approximately 70% of patients.¹⁰²⁻¹⁰⁶ These reactions occur early in therapy and often subside with time. Pretreatment regimens consisting of diphenhydramine, acetaminophen, meperidine, and hydrocortisone may be used to prevent infusion-related reactions. The efficacy of these regimens is unclear, so their routine use is discouraged until the reactions occur, after which pretreatment regimens should be employed with subsequent dosing.¹⁰² Although common and noxious, infusion-related reactions rarely cause early termination of AmB-d therapy or interfere with the use of other medications.

AmB-d also produces dose-related toxicities, including nephrotoxicity, azotemia, renal tubular acidosis, electrolyte imbalance, cardiac arrhythmias, and anemia,^{100,103} of which AmB-d-induced nephrotoxicity is the most common.¹⁰⁷ In the ICU, this toxicity often limits the use of AmB-d or interferes with the ability to use other medicines. Saline hydration before dosing can reduce the incidence of AmB-d-induced nephrotoxicity, but in the ICU setting, the utility of saline hydration may be limited by fluid restriction necessary to manage the fluid status of critically ill patients. Use of the deoxycholate formulation of amphotericin B is discouraged in most, if not all, indications.¹⁰⁸

Lipid Amphotericin B Formulations

Amphotericin B lipid complex (ABLC) and liposomal amphotericin B (LAmB) are lipid amphotericin B formulations that in many centers have supplanted the use of AmB-d. They retain the activity of AmB-d but have significantly less associated nephrotoxicity than the parent drug.^{107,109}

Pharmacokinetic Comparisons of Lipid Amphotericin B Formulations. The lipid amphotericin B formulations differ in physicochemical properties and composition. These differences produce subtle differences in their pharmacokinetic behavior that may ultimately prove to be clinically significant. The disposition and activity of these formulations in human tissue is poorly characterized. However, animal data indicate that high serum concentrations may influence the delivery of lipid AmB formulations to certain infection sites such as the CNS and lungs.¹¹⁰

Toxicity Comparisons of Lipid Amphotericin B Formulations. Compared with AmB-d, the lipid formulations have significantly less associated nephrotoxicity.¹⁰⁷ The formulations differ in the incidence of infusion-related reactions and other adverse events associated with AmB-d infusion.^{105,111} These reactions typically do not result in early termination of therapy.^{111,112} Observational safety comparisons between ABLC and LAmB suggest the two formulations have a similar nephrotoxicity profile, but prospective comparative data suggest LAmB is less nephrotoxic than ABLC.^{107,113,114} There are few data comparing the safety of lipid AmB formulations to the azole antifungal agents in critically ill patients.

Azole Antifungal Agents

Fluconazole, Itraconazole, Isavuconazole, Posaconazole, and Voriconazole

The systemic azoles exert a fungistatic effect by dose-dependent inhibition of cytochrome P450 (CYP)-dependent 14 α -demethylase. This enzyme is necessary for the conversion of lanosterol to ergosterol, leading to the depletion of ergosterol, the essential sterol of the fungal cell wall, an event that ultimately compromises cell wall integrity. The degree of inhibition varies among the different azole agents, which accounts for differences in the spectrum of activity.

Pharmacology and Pharmacokinetics. The azoles differ in chemical properties, forming the basis of the pharmacokinetic differences between the agents and the propensity of this class to interact with other medications.

Several studies have examined fluconazole pharmacokinetics in critically ill patients.¹¹⁵⁻¹¹⁷ In surgical ICU patients, fluconazole clearance correlates with creatinine clearance (CrCl), and its volume of distribution correlates with body weight.¹¹⁶ In addition, fluconazole's volume of distribution is greater in this population than in healthy volunteers.¹¹⁶ The fluconazole half-life is markedly prolonged in surgical ICU patients.¹¹⁶ In patients with severe renal dysfunction (CrCl < 30 mL/min), some authors recommend dosage reductions of 50%,¹¹⁶ but such reductions should be made cautiously and take into account the infecting pathogen in patients receiving fluconazole via enteral feeding tubes.¹¹⁶ Data suggest that the systemic availability of fluconazole is relatively unaffected by administration by feeding tube. However, serum concentrations obtained with standard doses administered in this way may not be adequate to treat certain infections such as those caused by *C. glabrata*.¹¹⁷ Moreover, in critically ill patients with abdominal trauma with and without abdominal wall closure, intravenous (IV) fluconazole may be warranted because the bioavailability of enterally dosed fluconazole in these patients is highly variable.¹¹⁵

Itraconazole is a highly lipophilic weak base and practically insoluble in water. It is available as a capsule and as an oral solution formulated in hydroxypropyl- β -cyclodextrin (HP- β CD). The IV solution was removed from the U.S. market in 2008; however, this dosage form may be available in other countries. Slow and erratic absorption of the capsule formulation precludes its use in critically ill ICU patients. HP- β CD enhances itraconazole solubility and improves its oral systemic availability. HP- β CD itself is poorly absorbed from the gastrointestinal tract, stimulates gastrointestinal secretion and propulsion, and causes diarrhea.

Under fasting conditions in healthy adults, itraconazole is rapidly absorbed when given as an oral solution, and compared with the capsule form, there is less interpatient and inpatient variability in serum concentrations.¹¹⁸ After IV administration, renal elimination of

itraconazole is negligible, but HP- β CD is renally eliminated (80%-90%). IV itraconazole is therefore contraindicated in cases of significant renal impairment ($\text{CrCl} \leq 30 \text{ mL/min}$) because of concerns over accumulation of HP- β CD. Rare cases of congestive heart failure are documented in the literature.¹¹⁹

Isavuconazole is available as an IV formulation and capsules since March 2015.¹²⁰ It has a prolonged half-life of 100-130 hours, with persisting tissue levels enabling once daily dosing after a 1-day loading dose. Oral absorption is independent of food intake.¹²¹⁻¹²³ Isavuconazole clearance is dependent on hepatic CYP3A4 metabolism. Based on data from animal studies, it is hypothesized that it is excreted in the feces.¹²⁴

Posaconazole is available in oral suspension, delayed-release tablet, and IV formulations. It exhibits linear pharmacokinetics with doses between 50 and 800 mg/d. However, absorption of the oral suspension is saturated at doses exceeding 800 mg/d. Posaconazole oral suspension absorption is influenced by gastric pH and is optimal under acidic conditions. Both absorption and exposure are maximized by dividing the total daily dose and giving it 4 times daily rather than administering it as a single dose.^{125,126} Posaconazole absorption and exposure are also enhanced by administration with or shortly after a meal, although in the ICU, it is often impractical to give it that way. However, absorption and exposure are also enhanced by administering the drug with a liquid nutritional supplement. With the introduction of the posaconazole tablet formulation, the issue of pH- and meal-dependent absorption is overcome.¹²⁷ In critically ill patients—for example, those with severe mucositis or on mechanical ventilation—IV administration is preferred.¹²⁸ Although posaconazole binds extensively (>95%) to plasma proteins, its large estimated volume of distribution suggests that it distributes widely throughout the body. There are, however, few data describing its penetration into the CSF. Posaconazole is primarily eliminated in feces and urine as unchanged drug.

Voriconazole is a derivative of fluconazole with limited aqueous solubility and improved antifungal activity. It is available in IV and oral formulations. IV voriconazole contains sulfobutyl ether β -cyclodextrin (SBECD) as a solubilizing agent. There are few data on how critically ill patients handle voriconazole. In healthy volunteers, voriconazole exhibits good oral availability and wide tissue distribution, with hepatic metabolism and renal excretion of metabolites.¹²⁹ In patients with moderate to severe renal impairment, SBECD accumulates, and it is recommended that oral dosing be used in patients with a CrCl less than 50 mL/min.¹³⁰ Oral dosing in critically ill patients is often not possible, however. Therefore the question of how SBECD is handled in critically ill patients on dialysis has been examined. A small study observed accumulation of SBECD in three patients during hemodialysis. No toxicity due to this accumulation was observed, and the accumulated dose values were lower but comparable with those used in previous toxicity studies with animals.¹³⁰ Nonetheless, if possible, use of IV voriconazole in patients on hemodialysis should be avoided. Data demonstrate that voriconazole achieves adequate CSF concentrations.^{129,131}

For all azoles, therapeutic drug monitoring is generally indicated as pharmacokinetic variability is extensive and levels may be unpredictable.¹³²

Overview of Toxicity. The azoles are a relatively safe class of drugs and are associated with few serious adverse effects. The advent of fluconazole and subsequent agents greatly improved the safety of this class. All the azoles are associated with gastrointestinal intolerance, transient transaminitis, hepatic toxicity, rashes, and dizziness. Nausea, vomiting, and diarrhea commonly occur with all agents in this class, particularly with oral itraconazole solution. These effects are usually observed with high doses of the azoles, but rarely are they severe enough to warrant discontinuation of therapy. All azoles may produce significant elevations in transaminases. Patients experiencing azole-associated transaminase abnormalities are asymptomatic, but these increases can on rare occasions evolve into fatal drug-induced hepatitis. The azoles can also produce allergic skin rashes that are generally mild and subside with discontinuation of the drug.

Fluconazole is perhaps the safest azole, and doses four to five times the recommended daily dose have been well tolerated. Reported adverse effects of isavuconazole are gastrointestinal disturbances, transaminase abnormalities, and hypersensitivity reactions.¹²³ Whether isavuconazole leads to QTc prolongation or shortening is not yet understood.^{123,133,134} The common adverse effects associated with posaconazole have been similar to those observed with the other agents in the class (i.e., gastrointestinal, transient transaminase abnormalities), but it appears to be more tolerable than earlier azoles.¹³⁵ During phase II and III clinical trials, QTc prolongation was described in 4% of patients.¹³⁶ In addition to the adverse effects seen with other azoles, voriconazole produces transient visual disturbances in approximately 30% of patients, which rarely lead to discontinuation of therapy. These disturbances are acute and include changes in color discrimination, blurred vision, photophobia, and the appearance of bright spots.

Azole Drug Interactions. Drug interactions occur primarily in the intestine, liver, and kidneys by a variety of mechanisms. In the intestine, they can occur as a result of changes in pH, complex formation with ions, or interference with transport and enzymatic processes involved in gut wall (i.e., presystemic) drug metabolism. In the liver, drug interactions can occur because of interference with drug-metabolizing enzymes. Drug interactions in the kidney can occur through interference with glomerular filtration, active tubular excretion, or by other mechanisms. The azoles are one of the few drug classes that can cause or be involved in drug interactions at all of these anatomic sites by one or more of the above mechanisms. Drug interactions involving the azoles have been extensively reviewed.¹³⁷ Several of the drug-drug interactions involving the azoles occur class-wide. Therefore, when using the azoles, the clinician must be aware of the many drug-drug interactions, both real and potential, associated with this class.

Interactions involving the azoles result because of their physicochemical properties. All azoles are somewhat lipophilic and thus undergo CYP-mediated metabolism.¹³⁸ The azoles all inhibit one or more CYP enzymes. Of the five azoles reviewed here, itraconazole and isavuconazole interact significantly with P-glycoprotein (P-gp), which is a transport protein involved in drug distribution.^{124,137} Fluconazole is not affected by agents that increase gastric pH, but its potential to cause CYP-mediated interactions is more than that suggested by in vitro studies. CYP-mediated interactions involving fluconazole are often dose dependent and can involve drugs metabolized by CYP3A4 (e.g., midazolam, rifampin, phenytoin) and CYP2C9 (e.g., warfarin).¹³⁷ Because of its linear and predictable pharmacokinetic properties, these interactions may sometimes be avoided or managed by using the lowest effective fluconazole dose. In patients with SOT or bone marrow transplantation, cyclophosphamide, tacrolimus, and sirolimus levels are increased if fluconazole is concomitantly administered.¹³⁹⁻¹⁴²

Itraconazole is subject to pH-based interactions and interactions involving CYP3A4 and P-gp. Drugs that can interact with itraconazole include agents that increase gastric pH (e.g., protonics) and lipophilic CYP3A4 (e.g., HMG-CoA reductase inhibitors, benzodiazepines, immunosuppressive agents), and/or P-gp substrates (e.g., digoxin) with poor oral availability.¹³⁷ Voriconazole is not affected by agents that increase gastric pH. However, CYP-mediated interactions involving voriconazole can involve drugs metabolized by CYP3A4 (e.g., midazolam, rifampin, phenytoin), CYP2C9 (e.g., warfarin), or CYP2C19 (e.g., omeprazole), and plasma levels of immunosuppressants are increased.^{137,143} Approximately 17% of a posaconazole dose undergoes biotransformation.¹⁴⁴ Unlike other azoles, posaconazole is only minimally (2%) metabolized by CYP; instead its metabolites are glucuronide conjugates formed via uridine diphosphate glucuronosyltransferase pathways.^{144,145} Although posaconazole is minimally metabolized by CYP, it inhibits hepatic CYP3A4.¹⁴⁶ Like the other azoles, the most clinically significant interactions associated with posaconazole involve benzodiazepines (oral midazolam), calcineurin inhibitors (cyclosporine, tacrolimus), other immunosuppressive agents (sirolimus), and phenytoin.¹³⁷ With more widespread use of posaconazole, the list of medications it interacts with will likely grow.

Isavuconazole acts as a moderate CYP3A4 inhibitor, and its clearance is highly dependent on CYP3A4 metabolism.¹²⁴

Drug interactions involving the azoles that are relevant to the ICU setting are summarized in Table 129-1.

Emergence of Resistance and the Selective Pressure of Azoles. Azole resistance in *Candida* spp. has been widely observed and studied—for example, fluconazole resistance in *C. albicans*. Resistant isolates of *Aspergillus fumigatus* were detected with a substitution of leucine for histidine in the cyp51A gene in combination with a 34-base pair tandem sequence in the promotor gene (TR/L98H) in patients and environmental isolates.¹⁴⁷⁻¹⁴⁹ The emergence of resistant *Candida* and *Aspergillus* raises concerns about the clinical relevance for patients at high risk of invasive fungal infection.

Echinocandin Antifungal Agents

Caspofungin, Micafungin, Anidulafungin

Pharmacology and Pharmacokinetics. The echinocandins are generally fungicidal and disrupt cell wall synthesis by inhibiting 1,3- β -D-glucan synthase. The echinocandins are active against *Aspergillus* and *Candida* spp. In addition, their spectrum of activity extends to *Pneumocystis jirovecii*. These agents have little or no activity against *H. capsulatum*, *B. dermatitidis*, or *C. neoformans*. The echinocandins are large lipopeptide compounds with poor enteral absorption and thus are not formulated for oral dosing. The individual echinocandins all demonstrate linear pharmacokinetic behavior. Each agent differs slightly in how it distributes throughout the body and how it is metabolized or degraded, although these differences are not clinically significant. The echinocandins are not appreciably metabolized by the cytochrome P450 enzyme system, but their interactions with drug transport proteins remain to be elucidated.

Caspofungin binds extensively to plasma proteins (primarily albumin). Caspofungin distribution is multiphasic; initially it distributes to plasma and extracellular fluid before being actively transported at a slow rate into the liver and other tissues via organic anion transport proteins.¹³⁷ The prolonged elimination half-life (8-13 hours) of caspofungin is due in part to this slow multiphasic distribution.¹³⁷ Caspofungin is slowly metabolized in the liver via *N*-acetylation and peptide hydrolysis to inactive metabolites, which are then excreted in bile and feces.¹⁵⁰ Average serum concentrations of caspofungin in surgical ICU patients 24 hours after administration vary greatly and are elevated above those seen in healthy subjects.¹⁵¹ Body weight and hypoalbuminemia were found to be prognostic factors responsible for these increased caspofungin concentrations.¹⁵¹ The clinical significance of such findings is unclear. Dosage adjustment is not required in patients with impaired renal function, but the dose should be reduced by 50% in patients with significant hepatic impairment.^{152,153} Micafungin distribution and metabolism are not fully understood. Following IV administration, micafungin binds extensively to albumin, but the significance of this interaction on drug activity is unclear.¹⁵⁴ Micafungin is hepatically metabolized to several metabolites, which along with parent drug, are eliminated in the feces. The pharmacokinetics are unaltered in renal dysfunction.^{154,155} Micafungin is a weak CYP3A4 inhibitor.¹⁵⁶

Anidulafungin distribution and metabolism are not fully understood. Of all the echinocandins, anidulafungin binds least to plasma proteins. It has a larger volume of distribution and achieves lower peak serum concentrations.^{157,158} Anidulafungin is not hepatically metabolized. Rather it undergoes slow nonenzymatic chemical degradation in the plasma to an inactive peptide breakdown product, which likely undergoes further enzymatic degradation and is excreted in feces and bile.¹⁵⁷ The majority of an anidulafungin dose is excreted in feces or urine as unchanged drug.¹⁵⁷

Toxicity and Drug Interactions. In general, echinocandins are well tolerated but are associated with nonspecific adverse effects (e.g., fever, headache, nausea, phlebitis, rash, elevated hepatic enzymes), which are generally mild and rarely cause early discontinuation of

therapy. Similarly, echinocandins have low potential to interact with other drugs, although interactions with cyclosporine and tacrolimus have been reported.¹³⁷

Pyrimidine Antifungal Agents

5-Fluorocytosine

Pharmacokinetics and Toxicity. 5-Fluorocytosine (5-FC, also called *flucytosine*) is a fluorinated pyrimidine related to 5-fluorouracil. It is the only agent in this therapeutic class. This antimycotic possesses a narrow spectrum of activity and is often associated with significant toxicity. Moreover, when used as monotherapy, resistance develops rapidly. Orally, 5-FC is nearly completely absorbed and distributes to total body water. Hepatic metabolism and protein binding are negligible. Nearly all is renally excreted as unchanged drug, and renal clearance is highly correlated with CrCl. Reductions in CrCl prolong the half-life of 5-FC.

Myelosuppression is the primary toxicity associated with 5-FC. In addition, it can cause significant rash, nausea, vomiting, diarrhea, and liver dysfunction. Flucytosine toxicity is associated with elevated drug concentrations and often occurs in the presence of renal dysfunction. Because 5-FC is primarily used in combination with amphotericin B, the effects of renal dysfunction on 5-FC pharmacokinetics and the subsequent risk of toxicity cannot be ignored.

Dosing and Therapeutic Drug Monitoring. Therapeutic drug monitoring for 5-FC is beneficial. Ideally, serum concentrations should be maintained between 25 and 100 μ g/mL to minimize toxicity and avoid the emergence of resistance. There are several nomograms for dosing 5-FC based on CrCl in patients with renal dysfunction. However, as they are based on serum creatinine measurements, they should only be used for patients with chronic renal dysfunction where the creatinine is not fluctuating rapidly. In addition, the nomograms should be used cautiously in elderly patients. During therapy, any necessary dosage adjustments should be made on the basis of plasma concentrations. Use of lower 5-FC doses (75-100 mg/kg/d) to minimize toxicity has been advocated. In vitro data suggest antifungal efficacy would not be compromised by such dosing.

IN VITRO SUSCEPTIBILITY TESTING OF SYSTEMIC ANTIFUNGAL AGENTS

In vitro susceptibility testing of *Candida* spp. is widely accepted. Standardized broth microdilution and disk diffusion methods developed by the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) for in vitro susceptibility testing of *Candida* spp. are reproducible and accurate. Interpretative breakpoints for *Candida* spp. exist for fluconazole, itraconazole, voriconazole, 5-FC, the echinocandins, and posaconazole. For antifungal breakpoints, either CLSI or EUCAST provide data categorizing isolates into susceptible, resistant, and intermediate isolates.¹⁵⁹⁻¹⁶⁶ In contrast to *Candida* spp., in vitro susceptibility testing of *C. neoformans* is not routinely performed, because primary resistance to first-line antifungal drugs (5-FC, amphotericin B, fluconazole) is not currently a significant clinical problem. In addition, the susceptibility testing methods and interpretive breakpoints for *Cryptococcus* spp. with regard to any antifungal are not validated.¹⁶⁷ Validated broth microdilution methods for in vitro susceptibility testing methods of *Aspergillus* spp. for the azoles and amphotericin B have been developed, but interpretive breakpoints for these agents have not been established.¹⁶⁸ Validated agar-based disk diffusion methods and commercial kits (Etest) are available and may be reliable methods for determining susceptibilities of *Aspergillus* spp.¹⁶⁸ Although broth microdilution methods for susceptibility testing of *Aspergillus* spp. for the echinocandins exist, the minimum inhibitory concentration is not the ideal measure of drug activity for this class of agents.¹⁶⁸ The EUCAST Subcommittee on Antifungal Susceptibility Testing determined breakpoints based on pharmacokinetic and

TABLE 129-1 Drug Interactions Involving Azoles in the ICU Setting

| | FLUCONAZOLE | ITRACONAZOLE | VORICONAZOLE | POSACONAZOLE | ISAVUCONAZOLE | COMMENTS |
|--|-------------|--------------|--------------|--------------|---------------|--|
| CYP INDUCERS | | | | | | |
| Carbamazepine | X | + | X | X | X | Avoid combination; significantly ↓s azole concentration |
| Phenobarbital | X | + | X | X | X | Avoid combination; significantly ↓s azole concentration |
| Phenytoin | + | + | + | + | X | Avoid combination; significantly ↓s azole concentration |
| Rifampin | + | + | + | + | X | Avoid combination; significantly ↓s azole concentration |
| CYP INHIBITORS | | | | | | |
| Amiodarone | X | X | X | X | X | Decreases the metabolism of CYP3A4 substrates |
| Aprepitant | X | X | X | X | X | Avoid combination |
| Clarithromycin | X | X | X | X | X | Avoid combination; may ↑ azole concentration |
| Diltiazem | X | X | X | X | X | Monitor therapy |
| Dronedarone | X | X | X | X | X | Monitor therapy |
| HAART | X | X | X | X | X | Avoid combination; may ↑ azole concentration |
| Idelalisib | X | X | X | X | X | Avoid combination; may ↑ azole concentration |
| Nilotinib | X | X | X | X | X | Monitor therapy |
| Verapamil | X | X | X | X | X | Monitor therapy |
| BENZODIAZEPINES AND ANXIOLYTICS | | | | | | |
| Diazepam | + | + | + | X | X | Effect of midazolam ↑d by azoles |
| Midazolam | + | + | + | + | X | Effect of midazolam ↑d by azoles |
| Triazolam | + | + | X | X | X | Effect of midazolam ↑d by azoles |
| IMMUNOSUPPRESSANTS | | | | | | |
| Cyclosporine | + | + | + | + | X | Azoles ↑ calcineurin exposure, troughs |
| Sirolimus | + | + | + | + | X | Azoles ↑ calcineurin exposure, troughs |
| Tacrolimus | + | + | + | + | + | Azoles ↑ calcineurin exposure, troughs |
| GASTRIC PH MODIFIERS | | | | | | |
| Antacids | X | + | X | — | X | Significantly ↓s itraconazole concentration |
| H ₂ Antagonists | — | + | X | X | X | Significantly ↓s itraconazole concentration |
| PPIs | X | + | X | + | X | Significantly ↓s itraconazole and posaconazole concentration |

KEY: (+) = interaction documented by clinical study or case series; (—) = no interaction as documented by clinical study; X = no published data. HAART, highly active antiretroviral therapy; PPI, proton pump inhibitor.

PPI, proton pump inhibitor data updated from <http://www.uptodate.com/crslql/interact/frameset.jsp> on March 13, 2016.

pharmacodynamic data, epidemiologic cutoff values, and clinical experience.¹⁶⁰

TREATMENT OF FUNGAL INFECTIONS IN THE CRITICALLY ILL

Candidiasis in the ICU

There are many options for empiric therapy of fungal infections in the ICU. For many years, the poor prognosis associated with invasive candidiasis fueled widespread use of antifungal agents, particularly fluconazole, in ICU patients with or without an established source of fungal infection.

The paradigms of preventive antimycotic therapy are prophylaxis and empiric or preemptive therapy. Prophylaxis is generally regarded as the initiation of treatment for all patients in a population in anticipation of certain risk factors, regardless of whether they ever manifest. There are few data to justify the use of this paradigm in the ICU setting,^{169,170} where concerns regarding selection of resistant fungal pathogens with indiscriminate antifungal use persist.¹⁷¹ Moreover, the risk for invasive candidiasis is not the same for all ICU patients, and some risk factors evolve during an ICU stay. Therefore, universal institution of antifungal prophylaxis in the general ICU population is generally discouraged in favor of a more targeted approach selectively directed toward those patients at the highest risk.^{169,171} *Empiric treatment* or a fever-driven approach describes the situation of a patient at risk for invasive candidiasis who has a persistent fever but no other symptoms or microbiological evidence of a specific infection.

Preemptive therapy is the administration of antifungal treatment before the occurrence of a septic syndrome in patients with several known risk factors for infection and evidence of significant *Candida* colonization.¹⁷¹ Historically, AmB-d was the sole option for prevention or treatment of candidiasis in the ICU setting. However, the risk of nephrotoxicity and the advent of safe and effective alternatives such as the echinocandins have diminished its use in the ICU.

Prophylaxis

Most studies of prophylactic antifungal use in the ICU setting have evaluated fluconazole. A placebo-controlled study for the prevention of intraabdominal *Candida* infections in a selected group of high-risk abdominal surgical patients showed that daily fluconazole (400 mg) significantly reduced the incidence of invasive candidiasis.¹⁷² This study included patients who had recurrent gastrointestinal perforations or anastomotic leaks; therefore, they were at very high risk of developing intraabdominal candidiasis. The patients in this study had moderate acuity (APACHE II score 13), but prophylactic fluconazole prevented *Candida* colonization and dissemination of *Candida* spp. Similar to experiences with HSCT recipients, this study illustrates that when the prophylactic paradigm is selectively applied, it may benefit specific patient populations. This has also been shown in patients with HSCT.^{172,173} Similar results were obtained in critically ill surgical patients staying in the ICU longer than 3 days.^{117,174} However, these results should be interpreted cautiously. This was a single-center study, and true to the paradigm, patient selection was somewhat subjective and based on an anticipated ICU stay of 3 or more days and the clinician's experience. Therefore, the results may not be widely generalizable. Others have also prospectively studied prophylactic fluconazole and shown an advantage for low-dose IV fluconazole (100 mg/d) in reducing *Candida* colonization and candidemia, but with no effect on either invasive candidiasis or overall mortality.¹⁷⁵ In this double-blind randomized placebo-controlled study, all patients received selective digestive decontamination. The incidence of *Candida* infections, particularly candidemia, was significantly less in the fluconazole-treated patients.

Using these three studies and others that included ketoconazole or nonabsorbable antifungal agents, three meta-analyses have attempted

to provide further insight into the role of antifungal prophylaxis in critically ill patients but with disparate results. One analysis concluded that prophylactic fluconazole administration to prevent mycoses in surgical ICU patients successfully decreased the rate of fungal infections, but it did not improve survival.¹⁷⁶ Conversely, a second analysis demonstrated that antifungal prophylaxis indeed reduced the risk of candidemia and resulted in a reduction of overall mortality and attributable mortality (31% and 79%, respectively).¹⁷⁷ The third and perhaps most rigorous meta-analysis demonstrated that antifungal prophylaxis in nonneutropenic critically ill patients reduces proven invasive fungal infections by approximately half and total mortality by approximately one-quarter.¹⁶⁹ Although the analyses had slightly differing results, all concluded that if antifungal prophylaxis is employed, it should be done so selectively and targeted toward those patients at high risk of developing infection.^{169,176,177} Thus, what the prophylactic studies have highlighted is the need to identify high-risk patients for empiric or preemptive therapy.

Empiric Therapy

Empiric therapy is defined as a fever-driven approach in a persistently febrile patient at risk for invasive candidiasis but without microbiological proof of infection. Early treatment of presumed candidemia is favored as it is associated with higher survival rates. However, current clinical trials have not shown statistically significant prevention of invasive candidiasis.^{18,51,52} The optimal time to start empiric antifungal therapy remains unclear. The choice of the antifungal administered should be based on local epidemiology and currently administered drugs (interactions).

Preemptive Therapy

There are few randomized prospective data addressing preemptive therapy, a diagnosis-driven approach. In the absence of mechanisms to identify patients who would most benefit by preemptive antifungal therapies, this strategy shares similar drawbacks to the prophylactic strategy. However, a growing body of data clearly demonstrates the importance of early institution of antifungal therapy in the adult ICU.^{31,33,34,37,38,178} There are a number of predictive rules of varying complexity described in the literature. All of the studies have produced different predictive algorithms; few have been prospectively validated.⁴⁹ While the methods are improving, published methods have yet to be widely applied in ICU patients as part of routine practice. Moreover, there are few data describing the outcomes associated with preemptive therapy instituted based upon a predictive rule. One small study assessed the use of a scoring system to identify high-risk patients and demonstrated that fluconazole significantly decreased the incidence of invasive candidiasis in patients with a corrected colonization index (CCI) of ≥ 0.5 .¹⁷⁹ Another prospective study to assess whether preemptive antifungal therapy would reduce invasive candidiasis in high-risk ICU patients (CCI ≥ 0.4) demonstrated a significant decrease in the incidence of surgical ICU-acquired invasive candidiasis with preemptive therapy compared to historic controls.¹⁸⁰ However, to generate the CCI, required weekly surveillance cultures at multiple anatomic sites in all ICU patients is necessary. This method is not practical for most ICUs, and it is doubtful that the CCI could be used with similar success without routine surveillance cultures.⁴¹ The serologic detection of 1,3- β -D-glucan, which is not specific for *Candida* spp., is a useful tool for ruling out invasive fungal infection.¹⁷

With the exception of fluconazole, there are few prospective data assessing the efficacy of other antifungal agents as preemptive therapy in the ICU. Administering itraconazole capsules through feeding and nasogastric tubes, which are often placed in ICU patients, is difficult. Although the oral solution solves this problem, there are few data assessing its effectiveness in preventing or treating invasive candidiasis. Furthermore, the use of itraconazole in critically ill patients is also limited by a significant drug-drug interaction profile with agents commonly used in the ICU.

The recommended antifungal therapy for candidiasis in the ICU setting is summarized in Table 129-2.

TABLE 129-2 Summary of Recommended Antifungal Therapy for Aspergillosis, Candidiasis, and Mucormycosis in the ICU Setting

| Infection | Recommended Treatment | Alternative Treatment |
|--|---|--|
| INVASIVE ASPERGILLOSIS | | |
| Targeted Therapy | VCZ, 6 mg/kg IV q 12 h for 1 day, followed by 4 mg/kg q 12 h; oral dose is 200 mg q 12 h <i>or</i> ISA, 200 mg TID IV for 2 days, followed by 200 mg/d IV thereafter | Consider, if prior azole exposure, LAmB, 3 mg/kg/d IV Caspofungin, 70 mg IV on day 1 and 50 mg/d IV thereafter |
| Empirical therapy (fever-driven approach) | Caspofungin, 70 mg IV on day 1 and 50 mg/d IV thereafter | |
| Prophylaxis against invasive aspergillosis | PCZ tablet, 300 mg BID PO on day 1 and 300 mg/d PO thereafter PCZ, 300 mg BID IV on day 1 and 300 mg/d IV thereafter in patients unable to swallow | |
| INVASIVE CANDIDIASIS (CANDIDEMIA) | | |
| Treatment (non-neutropenic patients) | Echinocandin-Anidulafungin, 200 mg IV on day 1 and 100 mg/d IV thereafter, <i>or</i> caspofungin, 70 mg IV on day 1 and 50 mg/d IV thereafter, <i>or</i> micafungin, 100 mg/d IV. Consider local epidemiology (<i>C. parapsilosis</i> , <i>C. krusei</i>) and susceptibility testing: if <i>C. parapsilosis</i> switch to FCZ, 400 mg/d IV. | LAmB, 3 mg/kg/d, <i>or</i> VCZ, 6 mg/kg IV q 12 h for 1 day, followed by 4 mg/kg q 12 h; oral dose is 200 mg q 12 h |
| Alphabetical order | | |
| Treatment (neutropenic patients) | Caspofungin, 70 mg IV on day 1 and 50 mg/d IV thereafter, <i>or</i> micafungin, 100 mg/d IV | Anidulafungin, 200 mg IV on day 1 and 100 mg/d IV thereafter, <i>or</i> LAmB, 3 mg/kg/d. FCZ, 400 mg/d IV, should be used as step-down only. |
| Suspected candidiasis treated with empirical antifungal therapy (non-neutropenic patients) | Early treatment for suspected candidiasis is associated with higher survival. However, due to lack of data no specific drug can be recommended. Choose according to local epidemiology, administered drugs (interactions) from antifungals recommended for candidemia. | |
| Suspected candidiasis treated with empiric antifungal therapy (neutropenic patients) | LAmB, 3 mg/kg/d, <i>or</i> caspofungin, 70 mg IV on day 1 and 50 mg/d IV thereafter | Micafungin, 100 mg/d IV, <i>or</i> VCZ, 6 mg/kg IV q 12 h for 1 day, followed by 4 mg/kg q 12 h; oral dose is 200 mg q 12 h |
| Prophylaxis | FCZ, 400 mg/d, while patients are at high risk | Micafungin, 50 mg/d IV; caspofungin, 70 mg IV on day 1 and 50 mg/d IV thereafter |
| MUCORMYCOSIS | | |
| Targeted therapy | LAmB, (5-) 10 mg/kg/d* IV | ISA, 200 mg TID IV for 2 days, followed by 200 mg/d IV thereafter PCZ, 300 mg BID IV on day 1 and 300 mg/d IV thereafter |
| Prophylaxis | PCZ tablet, 300 mg BID PO on day 1 and 300 mg/d PO thereafter | |

*Consider increasing dosages for extensive disease if renal function is adequate.

BID, twice daily; FCZ, fluconazole; ISA, isavuconazole; ITZ, itraconazole; IV, intravenous; LAmB, liposomal amphotericin B; PCZ, posaconazole; PO, per os; TID, 3 times a day; VCZ, voriconazole.

Adapted from Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med*. 2002;347:2020-2029; Pappas PG, Kaufman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48:503-535; Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;46:327-360; Cornely OA, Arian-Akdag S, Dannaoui E, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. *Clin Microbiol Infect*. 2014;20(Suppl. 3):5-26; Cornely OA, Bassetti M, Calandra T, et al. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect*. 2012;18(Suppl. 7):19-37; Ullmann AJ, Akova M, Herbrecht R, et al. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). *Clin Microbiol Infect*. 2012;18(Suppl. 7):53-67; and Koehler P, Cornely OA. Contemporary strategies in the prevention and management of fungal infections. *Inf Dis Clin North Am*. 2016;30(1):265-275.

Invasive Aspergillosis, Mucormycosis, and Other Opportunistic Mycoses in Bone Marrow Transplantation

Fever and neutropenia are common among critically ill immunocompromised individuals with hematologic malignancies. Although fever can be due to many causes, these patients, particularly those with leukemia or HSCT recipients, are at risk of developing invasive fungal infections due to *Candida*, *Aspergillus* spp., or Mucorales. Owing to the difficulty in diagnosing infections due to these pathogens, antifungal prophylaxis is standard in HSCT patients. Fluconazole has been shown to decrease the incidence of invasive infections with *Candida* spp. and is widely used in the prophylactic paradigm.¹⁷² As stated previously, invasive aspergillosis occurs relatively late after transplantation. Therefore, persistently febrile HSCT recipients should be treated empirically with antifungal agents with activity against molds, particularly *Aspergillus* spp.

For many years, high-dose AmB-d was employed as standard empiric therapy of invasive aspergillosis, but within the past decade, based upon data from a randomized trial that compared voriconazole to AmB and suggested superiority with the azole, voriconazole has been considered the gold standard therapy for documented and suspected aspergillosis.¹⁸¹ Although voriconazole is considered an initial option for prophylaxis, the choice of therapy may vary depending on the individual's organ function. Voriconazole may not be ideal in cases where liver disease is present or if the patient is being treated concomitantly with medicines that interact with this azole. Similarly, the presence of reduced renal function may preclude the use of lipid amphotericin B formulations. Fluconazole lacks activity against molds. Itraconazole has activity against *Aspergillus* spp., but as discussed previously, the capsule dosage form is not suitable for many critically ill patients and produces erratic blood levels. The oral solution of itraconazole is not well tolerated and is commonly associated with diarrhea. Even if available, IV itraconazole suffers the same

drawback as lipid amphotericin B formulations in patients with diminished renal function. With the new tablet and IV formulations, posaconazole can be administered to critically ill patients independent of food intake.

The latest clinical data on isavuconazole shows noninferiority and better tolerability in comparison with voriconazole for the treatment of invasive aspergillosis.¹³³ With their lack of toxicity and low propensity for drug-drug interactions, the echinocandins are also promising agents for empiric therapy of invasive aspergillosis in critically ill patients.

Patients with profound immunosuppression are at risk for mucormycosis, and targeted treatment differs considerably from therapy of invasive aspergillosis. While surgery is an integral part of therapy, as it decreases mortality, initiation of high-dosage liposomal amphotericin B or isavuconazole appears warranted.^{82,84,133,134,182} The combination of isavuconazole or posaconazole with high-dose LAmB may be needed in patients with extensive disease.^{82,84}

Recommended antifungal therapy for the treatment of invasive aspergillosis and mucormycosis in the ICU setting is summarized in Table 129-2.

Cryptococcosis, Histoplasmosis, and Blastomycosis

Although cryptococcosis, histoplasmosis, blastomycosis, and coccidioidomycosis are not considered nosocomial mycoses, patients with severe infections with these organisms may require intensive care. Recommended antifungal therapy for treatment of these three organisms in the ICU setting is summarized in Table 129-3. The treatment of cryptococcosis, particularly in the CNS, evolved from a series of classic clinical trials. Current guidelines base their recommendations on the best data available to address unresolved questions surrounding treatment of this infection.

Management of Increased Intracranial Pressure in CNS Cryptococcosis

Elevations in intracranial pressure (ICP) occur in more than half of patients with cryptococcal meningitis and contribute significantly to the morbidity and mortality associated with this infection.¹⁵⁷ Most data on the management of acutely elevated ICP have been derived from studies of patients with AIDS. Therefore, ICP management may be

TABLE 129-3

Summary of Recommended Antifungal Therapy for Cryptococcosis and Endemic Mycoses in the ICU Setting

| INFECTION | RECOMMENDED TREATMENT(S) | ALTERNATIVE TREATMENT |
|--|--|---|
| CRYPTOCOCCOSIS | | |
| CNS infection (HIV infected): antiretroviral therapy should be delayed to avoid immune reconstitution syndrome | Induction: AmB-d, 0.7-1 mg/kg/d IV, + 5-FC, 100 mg/kg/d PO, or L-AmB, 3-6 mg/kg/d IV, or ABLC, 5 mg/kg/d IV, + 5-FC, 100 mg/kg/d PO for 4-6 wk. Consolidation therapy: FCZ or ITZ, 400 mg/d PO for 8 wk, followed by maintenance with FCZ, 200 mg/d PO, if disease free and CD4 count >200 μ /l | AmB-d, 0.7-1 mg/kg/d IV, + FCZ, 800 mg/d PO FCZ, \geq 800-1200 mg/d PO favorable, + 5-FC, 100 mg/kg/d PO |
| CNS infection (transplant recipient) | Induction therapy: LAmB, 3-6 mg/kg/d IV, or ABLC, 5 mg/kg/d IV, + 5-FC, 100 mg/kg/d PO for at least 2 wk. Consolidation therapy: FCZ, 400-800 mg/d PO for 8 wk. Maintenance therapy: FCZ, 200-400 mg/d PO for 6 mo-1 y | LAmB, 6 mg/kg/d, or ABLC, 5 mg/kg/d for 4-6 wk |
| CNS infection (non-HIV positive, nontransplant recipient) | Induction: AmB-d, 0.7-1 mg/kg/d IV, + 5-FC, 100 mg/kg/d PO for at least 4 wk, or AmB-d, 0.7-1 mg/kg/d IV for \geq 6 wk, or LAmB, 3-6 mg/kg/d IV, or ABLC, 5 mg/kg/d IV, + 5-FC, 100 mg/kg/d PO, if possible \geq 4 wk, or AmB-d, 0.7 mg/kg/d IV, + 5-FC, 100 mg/kg/d PO for 2 wk. Consolidation therapy: FCZ, 400-800 mg/d PO for 8 wk. Maintenance therapy: FCZ, 200 mg/d PO for 6 mo-1 y | |
| HISTOPLASMOSIS | | |
| Acute pulmonary (moderately severe to severe) | LAmB, 3-5 mg/kg/d IV, or AmB, 0.7-1 mg/kg/d IV for 1-2 wk, \pm corticosteroids, then ITZ, 200 mg PO BID for 12 wk | |
| Progressive disseminated histoplasmosis (moderately severe to severe) | LAmB, 3-5 mg/kg/d IV, or ABLC, 5 mg/kg/d IV; or AmB-d, 0.7-1 mg/kg/d IV for 1-2 wk; followed by ITZ, 200 mg PO BID for at least 1 y | |
| BLASTOMYCOSIS | | |
| Pulmonary (moderately severe to severe) | LAmB, 3-5 mg/kg/d IV, or AmB-d, 0.7-1 mg/kg/d IV, until clinical improvement; followed by ITZ, 200 mg PO BID for 6-12 mo | |
| EXTRAPULMONARY (DISSEMINATED) | | |
| CNS | LAmB, 5 mg/kg/d IV until clinical improvement, followed by an oral azole for at least 1 y (e.g., FCZ, 400-800 mg/d PO, or ITZ, 200 mg PO BID) | |
| Non-CNS (moderately severe to severe) | LAmB, 3-5 mg/kg/d IV, or AmB-d, 0.7-1 mg/kg/d IV for 1-2 wk, followed by ITZ, 200 mg PO BID for 12 mo | |

ABLC, amphotericin B lipid complex; AmB-d, amphotericin B deoxycholate; BID, twice daily; CNS, central nervous system; 5-FC, 5-fluorocytosine; FCZ, fluconazole; HIV, human immunodeficiency virus; ITZ, itraconazole; IV, intravenous; LAmB, liposomal amphotericin B; PO, per os.

Adapted from Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:291-322; Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45:807-825; Limper AH, Knox KS, Sarosi GA, et al. An official American Thoracic Society statement: treatment of fungal infections in adult pulmonary and critical care patients. Am J Respir Crit Care Med. 2011;183(1):96-128; Chapman SW, Dismukes WE, Proia LA, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis. 2008;46:1801-1812.

underutilized in patients with CNS cryptococcosis who are HIV-negative. Persistent elevations in ICP should be managed by sequential lumbar punctures.¹⁵⁷ If necessary, more invasive procedures, including insertion of a lumbar drain or placement of a ventriculoperitoneal shunt, should be performed.¹⁵⁷ The frequency with which lumbar punctures are performed depends on the initial opening pressure and symptoms. For patients with elevated baseline opening pressure, the pressure should be reduced by 50%, with subsequent lumbar puncture performed daily to maintain the ICP in the normal range.¹⁵⁷

Serum and CSF antigen titers are important in establishing the presumptive diagnosis and assessing the prognosis of CNS infection. The test measures cryptococcal polysaccharide capsule antigens but does not differentiate viable from nonviable organisms. Therefore, once therapy is started, treatment decisions should not be based on antigen test results.¹⁵⁷ A reduction in antigen titers during therapy is desired, but treatment decisions should be based on culture results.

Treatment of Histoplasmosis in Critically Ill Patients

Although there are no comparative studies, the efficacy of individual antimycotics for therapy of chronic and disseminated histoplasmosis has been well documented. AmB-d and itraconazole have proven efficacy. The efficacy of 6 weeks to 4 months of AmB-d therapy for chronic infection is approximately 75%; however, relapse is common. The efficacy of itraconazole ranges from 75% to 85%, but as is the case for AmB-d, relapse may be common. In vitro susceptibility of *H. capsulatum* to fluconazole is poor, and it is generally not used to treat this infection. Voriconazole and posaconazole are likely effective in the treatment of histoplasmosis, but data assessing their safety or efficacy for this infection are lacking.

The efficacy of AmB-d for therapy for disseminated histoplasmosis among immunocompetent patients is 70% to 90%. Therefore, AmB-d is recommended initially in severely ill patients. In a small study, all patients responded to itraconazole, 200 to 400 mg daily.¹⁸³ Once an adequate response is noted to AmB-d, therapy can be switched to itraconazole.¹⁸³ Few data exist concerning the efficacy of the lipid amphotericin B formulations as therapy for disseminated histoplasmosis in immunocompetent patients.

Treatment of Disseminated (Extrapulmonary) Blastomycosis in the Critically Ill

Disseminated blastomycosis and diffuse pulmonary infection are both associated with significant mortality. Treatment of these infections

produces cure rates ranging from 85% to 90%, and the effective agents cause little associated toxicity.⁹⁷ The optimal duration of therapy for the treatment of blastomycosis with existing antifungal agents is unknown and has been empirically derived from noncomparative studies and clinical experience. In cases of life-threatening infections or extrapulmonary disease and in patients who are severely immunocompromised or have already failed therapy with an azole, the risk of relapse is high.⁹⁷ Therefore, the duration of treatment is lengthy to prevent relapse. Patients can be switched to safer azole therapy when significant improvement is observed.⁹⁷

CONCLUSION

Invasive fungal infections are widespread in critically ill patients. Specifically in the ICU setting, *Candida* spp. are a common cause of nosocomial BSIs. There are many risks associated with the ICU environment or patients' underlying disease states that predispose them to infections with these pathogens. In addition, historically, because of the high mortality associated with BSIs caused by *C. albicans*, this species has been the primary fungal pathogen of concern. Although the epidemiology of *Candida* isolates in the ICU continues to shift, whether the changing epidemiology is a consequence of injudicious antifungal use is a matter of speculation and debate. Nonetheless, the steady increase in BSIs due to *C. glabrata*, a species with reduced susceptibility to antifungal therapy, is concerning. Furthermore, select populations of critically ill patients are at risk of developing life-threatening infections due to *Aspergillus* spp., *Fusarium* spp., and the Mucorales. These pathogens are angioinvasive and often respond poorly to antifungal therapy. The endemic mycoses (histoplasmosis, blastomycosis, and coccidioidomycosis) are not typically a concern in the ICU setting, but patients with severe infections due to *B. dermatitidis*, *H. capsulatum*, or *C. immitis* will often require intensive care.

Methods to perform antifungal susceptibility tests on a variety of pathogens, particularly *Candida* spp., are becoming routine in clinical practice. There is improved understanding of antifungal resistance and the pharmacodynamic actions of antifungal drugs. This understanding may ultimately lead to more rational use of antifungal agents and improved outcomes in infected patients. The advent of additional safer agents means that the available drugs differ sufficiently in terms of toxicity and potential for drug-drug interactions that clinicians have the luxury of choice when tailoring antifungal therapy to a specific patient.

KEY POINTS

Overview

1. Generally, fungal infections are more prevalent in ICUs than on the general medical wards. Although *Candida* spp. are the most commonly isolated fungi in critically ill patients, infections caused by other opportunistic fungal pathogens (i.e., *Aspergillus*, *Cryptococcus neoformans*, *Fusarium*, and Mucorales) are also a concern in selected critically ill populations.
2. New antifungal agents differ in mode and spectrum of activity, toxicity, and propensity to interact with other drugs. Antifungal therapy has to be tailored to the specific fungal pathogen and the needs of the patient.

Fungal Infections in the Critically Ill

1. *C. albicans* is the primary fungal pathogen in the ICU setting, but the prevalence of a given species may vary with age. For example, candidemia among neonates is predominantly due to *C. albicans*

and *C. parapsilosis*, rarely *C. glabrata* or other *Candida* spp. In adults, *C. albicans* and *C. glabrata* predominate.

2. Age differences in the isolation of specific species may have important repercussions for infection control, dosing, and selection of antifungal agents in older critically ill patients.
3. Bloodstream infections (BSIs) due to *C. glabrata* continue to become more prevalent.
4. In the ICU, *Candida* BSIs are common and difficult to detect, and consequently they carry a relatively poor prognosis. Although isolation techniques have improved, the attributable mortality rate associated with *Candida* BSIs is 35%, and *Candida* spp. are the only BSI pathogens that are an independent predictor of mortality. In surviving patients, candidemia adds approximately 1 month to the length of hospital stay.
5. Critically ill patients with hematologic malignancies are at high risk for infections due to *Candida*, *Aspergillus* spp., and

KEY POINTS—cont'd

Mucorales. Infections due to these pathogens are associated with high mortality.

Systemic Antifungal Agents

1. Amphotericin B deoxycholate (AmB-d) possesses a broad spectrum of activity and a long history of use with little acquired resistance, but its toxicity is significant, and it is potentially costly. In low doses for short courses, this agent is tolerable.
2. Lipid amphotericin B formulations are safer than AmB-d, but their cost may limit their use.
3. Azoles possess a broad spectrum of activity and are relatively safe, but they interact with a vast array of drugs that are commonly used in ICU populations.
4. Echinocandins are safe and interact with few drugs, but their spectrum of activity is limited primarily to *Candida* and *Aspergillus* spp.

Treatment of Fungal Infections in the Critically Ill

1. The paradigms of preventive antifungal therapy are prophylaxis, empiric, and preemptive therapy. There are few data to help

choose among these three approaches. *Empiric therapy* is the administration of antifungals to patients with persistent fever as the only symptom of a potential fungal infection. *Preemptive therapy* is the administration of antifungal treatment before the appearance of sepsis syndrome in patients with risk factors for infection and evidence of significant *Candida* colonization.

2. The treatment of CNS cryptococcosis evolved from a series of classic clinical trials. Elevations in intracranial pressure (ICP) occur in more than 50% of patients and contribute significantly to the morbidity and mortality of this infection. Therefore, in addition to antifungal therapy, elevations in ICP should be managed by sequential lumbar punctures. Serum and cerebrospinal fluid antigen titers aid in the presumptive diagnosis and assessing the prognosis of infection. A reduction in antigen titers during therapy is desired, but treatment decisions should be based on culture results.

ANNOTATED REFERENCES

Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Risk factors for hospital-acquired candidemia: a matched case-control study. *Arch Intern Med*. 1989;149:2349-2353.

This study was one of the first rigorous epidemiologic assessments of the risk factors that predispose patients to candidemia. Established risk factors have been borne out in subsequent analyses.

Pittet D, Li N, Woolson RF, Wenzel RP. Microbiological factors influencing the outcome of nosocomial bloodstream infections: a 6-year validated, population-based model. *Clin Infect Dis*. 1997;24:1068-1078.

This article provides compelling data concerning the importance of Candida spp. as bloodstream pathogens, as well as data regarding the crude and attributable mortality rates of Candida BSLs in the hospital. The study demonstrates that of all the microbial causes of BSLs, only Candida spp. are an independent predictor of mortality due to BSL.

Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis* 2006;43:25-31.

Inadequate antimicrobial treatment is an independent determinant of hospital mortality, and in companion publications, this group demonstrated the most common causes of inappropriate therapy for fungal BSLs are omission of initial empiric therapy and incorrect dosing of fluconazole. In this work, the authors link inadequate therapy to mortality. They demonstrate that delays in initiation of therapy of more than 24 hours were independently associated with mortality in patients with candidemia. The rate of development of newer and more potent antifungal agents is tailing off. Thus, this work, which has subsequently been corroborated, illustrated that current antifungal agents, if used properly, can perhaps help reduce mortality more than realized to date. In addition, it calls attention to the need to focus on early appropriate therapy as a strategy to reduce the significant mortality associated with candidemia.

Golan Y, Wolf MP, Pauker SG, Wong JB, Hadley S. Empirical anti-*Candida* therapy among selected patients in the intensive care unit: a cost-effectiveness analysis. *Ann Intern Med*. 2005;143:857-869.

Few studies have prospectively evaluated antifungal prophylaxis, and meta-analyses of these studies all produce slightly different conclusions. However, the meta-analyses all agree that in the ICU, targeted empiric therapy directed at high-risk ICU patients is probably a better strategy than general prophylaxis. However, even fewer studies have prospectively evaluated empiric therapy directed at high-risk ICU patients. This study provides a decision analytic model to evaluate the cost-effectiveness of empiric anti-Candida therapy given to such patients, defined as those with altered temperature (fever or hypothermia) or unexplained hypotension despite 3 days of antibacterial therapy in the ICU. In doing so, they found that although empiric caspofungin was the most effective strategy, it did not reduce mortality at an acceptable cost. Empiric amphotericin B, regardless of formulation, was the least effective strategy, owing to drug toxicity. The most effective strategy was empiric fluconazole because it reduced mortality at an acceptable cost.

Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. *Lancet* 2016;387(10020):760-769.

This was a phase 3, double-blind, multicenter, comparative-group study. Patients with suspected invasive mold disease were randomized in a 1:1 ratio to receive isavuconazonium sulfate or voriconazole. Isavuconazole was noninferior to voriconazole for the primary treatment of suspected invasive mold disease, was well tolerated, and had fewer drug-related adverse events.

■ References for this chapter can be found at expertconsult.com.

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Influenza is a zoonosis indigenous to waterfowl, with periodic introduction of the virus into domesticated poultry, humans, and other mammals. The consequences of host species transfer from birds to humans can be devastating, with substantial mortality rates and rapid transmission by the respiratory route with a potential for a global pandemic. The fate of influenza virus infection in human populations depends upon the virus virulence properties, immunologic differences from previous influenza outbreaks, fitness of the virus for replication and dissemination within humans, and status of the host immune defenses.¹

In the winter months, severe disease in individual patients is usually limited to those with vulnerabilities in host defenses, including the very young, the very old, and individuals with immunodeficiency or an underlying cardiopulmonary disease. The annual incidence rate varies each season depending upon the degree of antigenic "drift" (point mutations in coding regions of genes for major surface antigens) from one year to the next. However, influenza pandemics can occur following an antigenic "shift" (i.e., whole-scale reassortment of the influenza virus genome, with the expression of entirely new antigenic components), and these novel influenza hybrid viruses circulate throughout the susceptible global population. This set of events occurred in 2009 with the novel swine influenza virus strain, where almost everyone, including healthy young people, became susceptible to this new influenza infection and its complications.²

Even in a typical nonpandemic year, influenza viruses account for the deaths of hundreds of thousands of people worldwide and exact billions of dollars from society in terms of morbidity and lost productivity. Recent estimates from the United States indicate that at least 610,660 life-years are lost, with 3.1 million hospital days, 31.4 million outpatient visits, and \$10.4 billion in direct medical costs annually from influenza alone. The staggering amount expended for influenza care is \$16.3 billion in projected lost earnings and an estimated total cost burden (including lost-life years) amounting to \$87.1 billion.³ The global costs to society during a rather mild pandemic year such as 2009 have been estimated to be about \$374 billion.⁴ The costs of intensive care services required for managing the most severely ill influenza victims alone are enormous.²

PATHOGENICITY OF INFLUENZA VIRUSES

Influenza virus is a single-stranded RNA virus of the family *Orthomyxoviridae*. It affects birds and mammals and includes three genera, influenza virus A, B, and C, based upon their matrix proteins.^{1,5} Influenza A virus is more likely to reassort its genome with bird and mammal influenza viruses and has the greatest pandemic potential. Based upon the antibody response to two major antigenic proteins on the surface of the virus, hemagglutinin (HA) and neuraminidase (NA), influenza A is subdivided into different serotypes including H1N1 (responsible for Spanish flu in 1918, in addition to the 2009 flu pandemic), H2N2 (Asian flu of 1957), H3N2 (Hong Kong flu in 1968), H5N1 (the avian flu, often cited as the most recent pandemic threat), and H7N9, which circulated in China in 2012. A number of other influenza virus types are circulating in birds and mammals (H7N7, H1N2, H9N2, H7N2, H7N3, and H10N7). The two other forms include influenza B (which almost exclusively infects humans and

lacks pandemic potential) and influenza C (affecting humans, dogs, and pigs), which only rarely cause severe illness and epidemics in humans.⁶

The genome of influenza A virus consists of eight separate single-strand segments, each encoding a single major viral protein. The single-stranded RNA-based genome provides a high background mutation rate and gives the virus genetic plasticity. The multiple genome segments permit reassortment of large sequences of RNA, resulting in hybrid viruses when hosts are infected simultaneously by more than one virus strain. These events lead to the evolution of entirely novel viruses with new antigenic constituents (antigenic shift). As an example, the novel swine-origin influenza A/Mexico City/4/2009 (H1N1) outbreak strain was a quadruple-reassorted virus derived from gene segments originating from ducks, Eurasian swine, North American swine, and human-adapted influenza virus.⁷

Avian-adapted viruses can occasionally be transmitted to mammals, causing outbreaks in animals or giving rise to disease in human pandemics. Pigs are important "mixing vessel" hosts in shuttling avian influenza viruses to humans as they can carry both avian- and human-adapted influenza viruses.¹ Porcine mucous membranes express a mixture of sialic acid-coated glycopeptides linked in a favorable conformation to bind both avian- and human-adapted viruses. This is vitally important in the biology of influenza viruses as the initial event in influenza infection is an interaction of the HA receptor to binding sites on host epithelial tissues. Avian species primarily express α 2,3-linked sialic acid-galactose disaccharides on their epithelial surfaces, and avian-adapted influenza viruses preferentially bind to this linkage pattern. The human upper airways primarily express α 2,6-linked sialyl-galactose surface receptors, and seasonal influenza strains in humans bind readily only to α 2,6 linkages. Pigs, in contrast, normally express both α 2,3- and α 2,6-linked disaccharides on their mucous membranes. This biochemical arrangement facilitates simultaneous dual infections with avian- and human-adapted viruses and the attendant risk of hybrid viruses.^{1,7,8}

The lower airways and alveolar pneumocytes of humans actually express α 2,3-linked sialylated glycopeptides, and viruses that bind efficiently to α 2,3 linkages can cause severe pneumonia if deposited into the distal airways. Most seasonal influenza strains bind preferentially to α 2,6-linked disaccharide HA binding sites found in human upper airways. This usually leads to high transmission frequency by airborne droplet nuclei deposited into the upper airways but a relatively low risk of primary influenza pneumonia.⁹ The avian strain of H5N1 preferentially binds to α 2,3 linkages and is therefore poorly transmissible from person to person, but it has the potential to cause severe pneumonia if delivered to the lower airways. Poultry workers in Asia in close proximity to infected livestock can occasionally receive enough viruses deposited into the distal airways to cause severe influenza pneumonia with a high mortality rate (50%-70%).^{9,10}

Notably, the severe 1918 pandemic strain of H1N1 influenza expressed an HA that could bind with high affinity to both α 2,6- and α 2,3-linked sialyl-galactose moieties.^{11,12} The result of this unusual HA binding affinity was a highly transmissible virus with the capacity to replicate and spread in the upper airways and cause severe disease in the lower airways. Disturbingly, the HA of the 2009 outbreak strain of novel swine origin also bound with high affinity to both α 2,6 and α 2,3

TABLE 130-1 Pathogenicity Traits and Virulence Factors of Influenza Viruses

| VIRAL TRAIT | MECHANISM OF VIRULENCE | COMMENTS |
|---------------------------------|---|---|
| Epitope variations on HA and NA | Immune escape from recognition by preexisting antibodies within the population from previous virus exposure | Antigenic drift (point mutations) leads to epidemics; antigenic shift (reassorted genomes) leads to pandemics |
| Cleavability of HA | HA undergoes proteolysis by host-derived proteases before receptor binding | Readily cleaved HA is associated with avid binding and disease severity |
| Binding preference of HA | α 2,3-linked sialic acid receptor in alveoli and α 2,6 linkage in upper airways | Viruses that bind to the α 2,3 linkage or both α 2,3 and α 2,6 are more virulent |
| HA:NA ratio | NA cleaves sialic acid on glycopeptides on epithelium (binding site for HA) | Optimal ratio of NA and HA activity needed for high replication and release |
| NS-1 | This nonstructural protein inhibits host-derived interferons | Mutation or truncated variants are associated with loss of virulence |
| PB1-F2 | This peptide targets virus trafficking to mitochondria and induces apoptosis | Mutations or truncated forms of PB1-F2 associated with loss of virulence |
| NA inhibitor resistance | H275Y mutation blocks NA inhibitor binding site and oseltamivir activity | Commonly seen mutation is seasonal H1N1 but rare in the 2009 outbreak strain |
| M2 inhibitor resistance | S31N mutation blocks activity of amantadine | Now commonplace in both H3N2 and H1N1 |
| PB2 temperature range | Polymerase activity at lower (mammals) and higher (avian) temperature | Broad Pol temperature range aids transfer from bird to human hosts |

H275Y, histidine substitution for tyrosine at amino acid at position 275; HA, hemagglutinin; M, matrix protein; NA, neuraminidase; NS-1, nonstructural protein; PB, polymerase basic; Pol, polymerase; S31N, serine substitution for asparagine at amino position 31.

linkages. Fortunately, the virulence factors of the influenza virus (Table 130-1) resulted in an overall low case-fatality rate (<0.1%). A further mitigating factor against mortality in older populations during the 2009 outbreak was the presence of preexisting memory cells with B- and T-cell epitope recognition sites in people born before the early 1950s, induced by other H1N1 viruses circulating in the first half of the 20th century.¹³

CLINICAL MANIFESTATIONS AND COMPLICATIONS OF INFLUENZA

Classical seasonal influenza in adults is typified by a 4- to 5-day period of sudden-onset fever, chills, upper respiratory tract symptoms, headache, muscle pain, and weakness. Rhinitis is relatively uncommon, and diarrhea is more common with influenza than with most rhinovirus upper respiratory tract infections. Severe complications and death can occur, especially in infants, the elderly, and individuals with chronic medical conditions. Among the most severe complications are primary influenza pneumonia and secondary bacterial infection leading to respiratory failure.^{14,15} Influenza can also cause central nervous system, cardiac, skeletal muscle, kidney, and hepatic complications.^{5,15} Underlying pulmonary disease is a frequent risk factor, occurring in 18% of patients, most commonly asthma (7%),

followed by neurologic disease (12%) and hematologic or oncologic (9.9%) and cardiac conditions (4.6%).¹⁶ However, approximately half of those hospitalized (rates ranging from 1 to 5/1000) for influenza are otherwise healthy.¹⁴⁻¹⁶

In the absence of a pandemic, 11% to 19% of patients hospitalized with laboratory-confirmed influenza require treatment in the intensive care unit (ICU).¹⁵ The mean duration of mechanical ventilation is approximately 5 days; the sickest patients require treatment with advanced techniques for hypoxemia, such as high-frequency oscillatory ventilation (HFOV), extracorporeal membrane oxygenation (ECMO), prone positioning, and nitric oxide. These difficult-to-oxygenate patients have increased length of ICU stay and increased mortality.^{14,16,17}

An estimated 50 to 100 million people died during the 1918 pandemic. Death resulted from secondary bronchopneumonia, influenza-related lung disease with associated hypoxemia, and cardiac collapse.^{18,19} During the 1918 pandemic, there was unexplained increased influenza mortality in persons who were 20 to 40 years of age. This mortality increase may have been due to limited native immunity and/or a vigorous immune response directed against the virus in healthy young persons.¹⁸ The high mortality rate observed in the 1918 pandemic would certainly be reduced today as a result of better oxygen delivery, availability of ICUs, vaccines, antibacterial agents, and antiviral medications. However, the impact on hospital care and costs would be dramatic and necessitate extensive critical care management in modern ICUs that have a limited surge capacity to meet the sudden demand for critical care during a severe pandemic. Sophisticated ICU care is often out of reach to patients in many developing countries today, and case-fatality rates in these countries would still remain very high.²⁰

INFLUENZA A 2009 H1N1-RELATED EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Starting March 2009, a novel strain of a human-adapted influenza virus, influenza A (H1N1)pdm09 spread from an initial large outbreak in Mexico to virtually all countries worldwide. By September 27, 2009, there were over 340,000 cases with 4100 deaths worldwide.^{7,21} The World Health Organization issued the first phase 6 pandemic alert of the century, anticipating substantial influenza transmission and related disease. From June to September 2009, there were dramatic spikes in H1N1-related disease in Australia, New Zealand, and South America that breached the capacity for ICU care in some regions.²² Despite blunting of the North American spread of the pandemic by widespread deployment of an effective, inactivated, monovalent vaccine program,²³ modeling suggests as many as 61 million American cases, 274,000 hospitalizations, and approximately 12,500 deaths between April 2009 and April 2010.²⁴ Influenza A (H1N1)pdm09 remained the predominant isolate for several years after the initial pandemic event.

The events that transpired in Canada were illustrative of the influenza situation in much of the Northern Hemisphere in 2009. Among 168 critically ill Canadian patients with influenza A 2009 H1N1, with a mean age of 32 years, there was a possible predilection for more severe disease in women (67% of patients).²⁵ Pregnant women, in particular, suffered from a disproportionately high level of influenza disease severity.²⁵⁻²⁷ Nosocomial transmission was the mechanism of acquisition in approximately 10% of patients. Hospital-acquired transmission to healthcare workers occurred early in the outbreak, but healthcare-related infection occurred at a low incidence rate once the pandemic was recognized and appropriate infection-control safeguards were instituted. One or more comorbidities were observed in nearly all patients; most commonly, these were chronic lung disease such as asthma, chronic obstructive pulmonary disease, bronchopulmonary dysplasia (41%), obesity (33%, mean body mass index of 34.6 kg/m²), hypertension (24%), history of smoking (23%),

TABLE 130-2

Prognostic Indicators and Risk Factors for Severe Influenza Complications

| RISK FACTORS AND COMORBIDITIES | COMMENTS |
|---|---|
| Age <5 years | Children <2 years and those with chronic cardiopulmonary disease at greatest risk |
| Age >65 years | Poor vaccine response, poor host response to influenza infection |
| Chronic cardiopulmonary diseases | COPD, asthma, congestive heart failure |
| Metabolic disease and chronic liver disease | Diabetes mellitus and cirrhosis increase the risk of influenza complications |
| Chronic neurologic illness | Neurocognitive and neuromuscular diseases associated with increased complications |
| Pregnancy | Particularly women in the third trimester |
| Obesity | BMI >35 kg/m ² increased the risk of influenza complications in the 2009 outbreak |
| Hemoglobinopathy | Sickle cell disease patients at increased risk |
| Immunosuppression | Glucocorticoids, chemotherapy, HIV transplant recipients at increased risk |
| Children receiving salicylates | Increased risk of Reye syndrome |
| Aboriginal populations, poverty, poor access to healthcare services | Delayed treatment associated with increased risk of influenza complications |
| Secondary bacterial pneumonia | Bacterial pneumonia associated with longer ICU and hospital stays with more nosocomial complications and a greater mortality rate |

and diabetes (21%). Similar clinical findings and predisposing illnesses were reported in other regions of the world during the 2009 outbreak.^{21,22,28,29} Serious comorbid illness was observed in only 30% of patients. Notably, aboriginal Canadians have thus far been over-represented (26% of patients). A summary of clinical risk factors and comorbidities associated with severe influenza complications is found in Table 130-2.

The most common specific symptoms with influenza A 2009 H1N1 have included fever and respiratory symptoms in more than 90% of patients, with weakness and myalgias being less common. Several severe clinical syndromes associated with influenza A 2009 H1N1 infection may be seen, including:

- Rapidly progressive diffuse pneumonitis associated with severe, refractory hypoxemia in relatively healthy teens or adults and immunocompromised patients
- Decompensation of chronic underlying disease in patients with serious comorbidities including congestive heart failure, chronic renal failure, end-stage liver disease, poorly controlled diabetes, or immunocompromise
- Acute and prolonged exacerbation of chronic obstructive pulmonary disease and asthma in those with preexisting disease
- Bacterial pneumonia, frequently with gram-positive pathogens including *Streptococcus pneumoniae*, *Staphylococcus aureus*, and group A streptococci and superinfection on a background of mild or severe influenza A 2009 H1N1 infection
- Bronchiolitis and croup in infants and young children, who frequently require hospitalization but not ICU care

The typical clinical syndrome requiring ICU care among all age groups appeared to be a diffuse bilateral four-quadrant pneumonitis, which was often rapidly progressive. This process accounted for over 80% of ICU admissions in Canada and elsewhere and often

necessitated advanced ventilatory/oxygenation modalities including HFOV, inhaled nitric oxide, and/or ECMO therapy.^{25,30-33}

Patients who subsequently developed critical illness generally presented to the hospital within 4 days of symptom onset and required ICU admission within 1 day of hospital presentation for bilateral pulmonary infiltrates and hypoxic respiratory failure. The mean Acute Physiology and Chronic Health Evaluation II score was 20. Notable laboratory findings have included elevated creatine kinase levels and normal white blood cell counts.^{21,25,34} Concomitant presenting conditions included possible bacterial pneumonia (32.1%), hypotension requiring vasopressors (13.7%), and asthma or chronic obstructive pulmonary disease exacerbation (13.7%).

Over 80% of patients with H1N1-related acute lung injury (ALI) received mechanical ventilation; very few patients were successfully managed with noninvasive ventilation strategies alone. Oxygenation support included high concentrations of inspired oxygen (mean admission Pao₂/Fio₂, 147 mm Hg), positive end-expiratory pressure (PEEP), frequent use of HFOV (12%), nitric oxide (14%), neuromuscular blockade (30%), prone ventilation (5%), and occasionally, ECMO (7%). Medical therapies included NA inhibitors (90.5%), antibacterial agents (98.8%), and, despite uncertain efficacy, corticosteroids (50.6%).²⁵

Secondary bacterial pneumonia following ICU admission was found in 24% of cases, most commonly due to *S. aureus* and *S. pneumoniae*.^{25,35,36} The frequency of secondary bacterial infection was difficult to accurately determine owing to the widespread use of empiric antibacterial therapy in influenza patients with rapidly progressive respiratory failure. Overall mortality among critically ill patients at 90 days was 17.3% (similar to that reported in Australia).²² The median duration of ventilation was 12 days. The most common cause of death was severe acute respiratory distress syndrome (ARDS) and hypoxemia and complications thereof, secondary infection, sepsis, or multiorgan dysfunction syndrome. Characteristic radiographic changes of severe primary influenza pneumonia are shown in Figure 130-1, A and B.

Lung pathology in fatally infected patients who underwent autopsy revealed a diffuse alveolar filling process, often with early hyaline membrane formation that was sometimes accompanied by focal areas of hemorrhage.³⁷ The alveolar lining was usually thickened, with evidence of lymphocytic infiltrates and early organization with fibrosis. A typical lung tissue section of a patient with fatal influenza pneumonia is seen in Figure 130-2. The lung tissue in deaths occurring early in the presentation of influenza pneumonia often revealed diffuse immunohistochemical evidence of viral infection and intraalveolar hemorrhage.

In children, the median age of hospitalized patients was 5.0 years (range, 1 month to 17 years); 54.4% were females, and the mean PRISM III score was 9.^{14-16,25} One or more chronic comorbid illnesses were observed in 70.2% of patients: lung disease (44%), neurologic diseases (19%), immunosuppression or immunodeficiency (16%), history of prematurity (9%), and congenital heart disease (7%). Mechanical ventilation was used in 68% of children admitted to the ICU, and the median duration of ventilation was 6 days (range, 0-67 days).

CLINICAL AND LABORATORY DIAGNOSIS

Significant difficulties with definitive virologic diagnosis existed in the early phase of the 2009 influenza outbreak. Fever and upper respiratory symptoms were present in almost all patients who progressed to critical illness. However, shortness of breath, a symptom atypical of uncomplicated influenza virus infection, is suggestive of severe disease. Other clinical signs noted in patients with severe disease include hemoptysis, frothy pink sputum, and purulent sputum with diffuse lung crackles. Percutaneous oximetric assessment of oxygenation or arterial blood gas evaluation of Po₂ should be performed when assessing a patient with suspected severe influenza. The presence of relative hypoxia should trigger further assessment including a chest radiograph.

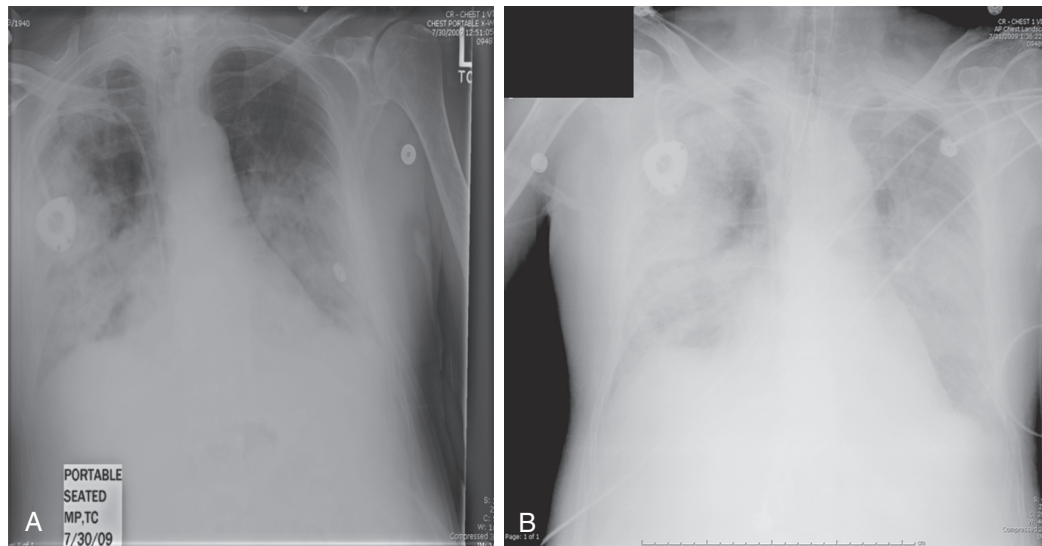


FIGURE 130-1 ■ **A**, Chest radiograph of a 70-year-old male with B-cell lymphoma and hypogammaglobulinemia, with primary influenza pneumonia at the time of ICU admission. Note Port-a-Cath in right anterior chest wall and diffuse pulmonary infiltrates, most prominently seen in both lower lung fields. **B**, Chest radiograph of same patient 3 days later; note diffuse alveolar filling process associated with profound hypoxemia. The patient expired despite oseltamivir and ventilatory support, with severe hypotension and acute kidney injury.

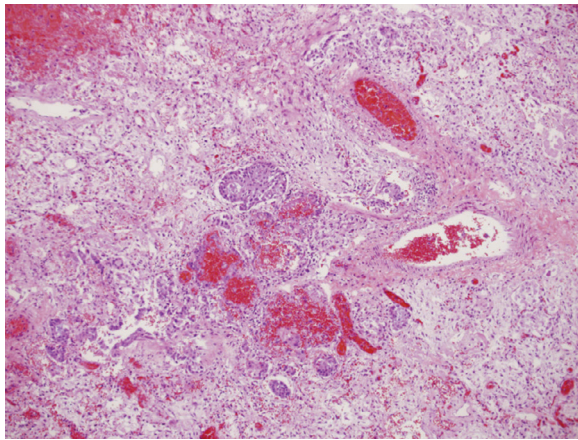


FIGURE 130-2 ■ Lung pathology of fatal case of primary influenza pneumonia in a previously healthy 20-year-old woman. Note diffuse alveolar filling, squamous metaplasia, lymphocytic infiltrates, focal hemorrhage, loss of ventilatable lung tissue. (Figure courtesy David Horn, MD.)

Laboratory findings typically found at presentation with severe disease include normal or low-normal leukocyte counts and elevated creatine kinase levels^{22,25,29} (Fig. 130-3).

Early laboratory diagnosis of influenza infection is greatly facilitated by the use of reverse transcriptase-polymerase chain reaction (RT-PCR).³⁸ This assay should be employed when available when evaluating a patient with suspected severe influenza. Immunofluorescent techniques, enzyme-linked immunoassays, and other rapid diagnostic tests of clinical specimens often lack diagnostic sensitivity.³⁸⁻⁴² Viral cultures require up to 1 week for processing. Although RT-PCR is the preferred definitive diagnostic technique and has very high sensitivity, the adequacy of the clinical specimen is essential. Standard nasopharyngeal swab samples are adequate but can be falsely negative. RT-PCR of

nasopharyngeal samples should be repeated in 48 to 72 hours if diagnostic suspicion remains. Paired nasopharyngeal and tracheal aspirates are useful for RT-PCR in intubated patients and may increase the diagnostic yield in critically ill patients.^{43,44}

SUPPORTIVE CARE

Almost all patients with severe infection in the ICU setting will have deficits in oxygenation and subsequently require ventilatory support.^{22,25,45} Shock and renal failure can occur during therapy as a consequence of efforts to optimize oxygenation through diuresis coupled with high intrathoracic pressures and limited venous return.^{25,29} Other important, but less frequently seen, disorders at presentation may include encephalitis (with or without obtundation or seizure activity), cardiac injury (myocarditis, pericarditis, or conduction defects), and rhabdomyolysis.¹⁷

Most critically ill patients with severe influenza will manifest evidence of ARDS; supportive care for severe hypoxemia with diffuse pulmonary disease and supplemental oxygenation and ventilation assistance are required.²⁵ During pandemics, patients are often relatively young compared with the age of patients in nonpandemic years, and much greater numbers can be expected to be in need of ventilatory support than during a usual flu season.^{18,22,25,30,31}

Primary influenza pneumonia is unusual in that patients often display a relative insensitivity to usual measures of oxygenation assistance with PEEP. Controlled ventilation with attention to a lung-protective strategy,⁴⁶ in combination with appropriate sedation and judicious use of neuromuscular blockade, is appropriate. Avoidance of volume overload (and judicious diuresis) may also be associated with reduced duration of ventilation and length of stay in the ICU for most patients with ALI and ARDS, and this strategy should be attempted for patients with influenza.^{31,47} Other ventilation measures (despite unproven benefit in other forms of ARDS) that might improve oxygenation for individual patients include prone positioning and inhaled nitric oxide.⁴⁸⁻⁵⁰ Unfortunately, HFOV failed as a rescue therapy for patients with severe ARDS in a recent randomized controlled trial,^{50,51} suggesting the probability of lack of utility in patients with influenza-related refractory hypoxemia. ECMO remains

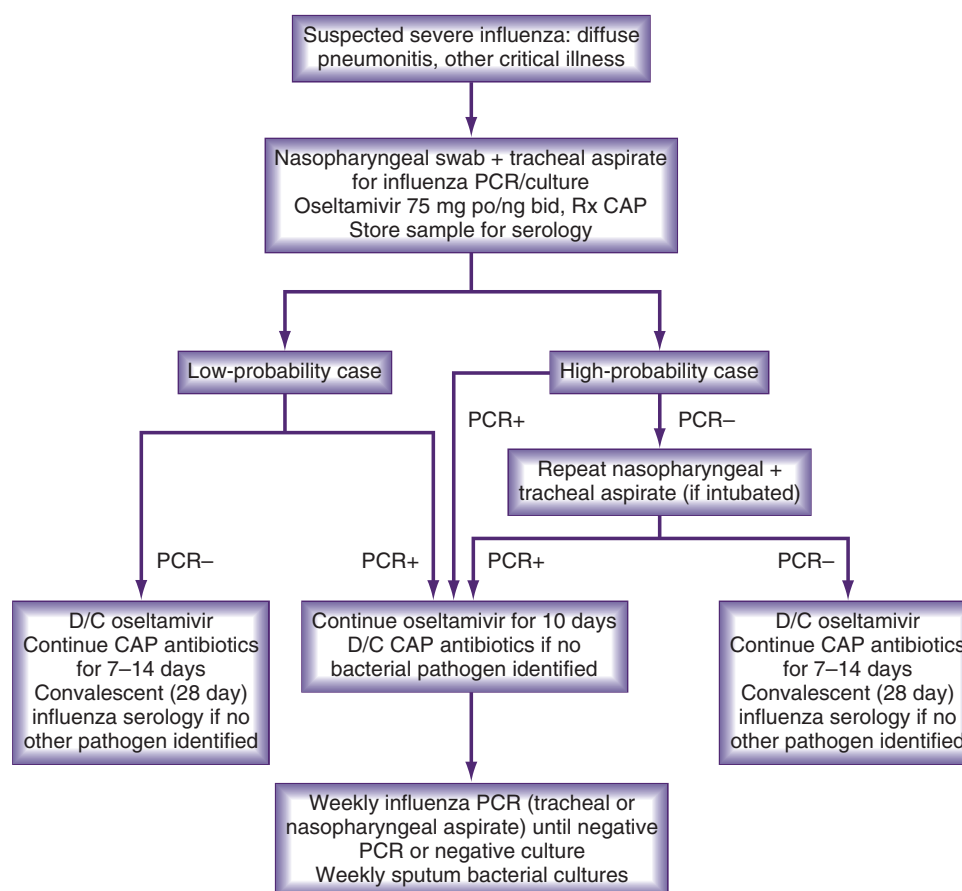


FIGURE 130-3 ■ Suggested algorithm in the workup and management of suspected severe influenza pneumonia in the critical care unit.

a controversial, albeit better supported, option to manage severe respiratory failure in influenza-associated ALI in adults.^{30-33,52} HFOV and ECMO might be considered as salvage therapy in centers familiar with these modalities in selected critically ill patients where other options do not exist.

■ ANTIVIRAL THERAPY

In severely ill patients with suspected influenza, early initiation of antiviral therapy is predicated on clinical presenting features and epidemiologic data. Therapy in such cases must not be delayed pending laboratory confirmation.^{22,25,53,54} Various influenza strains are circulating throughout the world, and susceptibility to currently available antiviral agents is isolate- and strain-specific. The 2009 H1N1 swine influenza variant was resistant to amantadine but sensitive to NA inhibitors including oseltamivir and zanamivir.⁵⁴ Rare oseltamivir-resistant strains were isolated during the 2009 H1N1 influenza A pandemic and remain very uncommon (1.2% frequency among U.S. influenza A(H1N1)pdm09 isolates to during the 2013-2014 season).^{55,56} In contrast, the seasonal H1N1 influenza A strains that predominated before the 2009 season and which persist currently at lower rates to date are often resistant to oseltamivir, yet many remain susceptible to zanamivir.⁵⁶⁻⁵⁸ At this time, only an oral form of oseltamivir and an inhaled form of zanamivir are available for routine use. Intravenous peramivir remains an option in severely ill patients.

Initiation of antiviral therapy within 48 hours of the onset of symptoms of seasonal influenza is associated with a 1-day or greater reduction in the duration of symptoms in ambulatory patients.^{56,59}

Oseltamivir therapy may reduce the risk of secondary bacterial superinfection.⁶⁰ Early therapy of severe influenza A 2009 H1N1 infections requiring ICU support with NA inhibitors appears to contribute to improved outcomes.^{53,54,61-63}

Fewer data are available to guide the optimal dose or duration of therapy for antiviral agents. Severe influenza infections, including those caused by the 2009 H1N1 strain, can represent a systemic infection in addition to a pulmonary infection,⁶⁴ favoring the use of a systemic rather than an inhaled antiviral agent. Despite concerns over inadequate gastrointestinal absorption of oseltamivir among critically ill patients, published studies indicate comparable blood levels in critically ill influenza patients in the ICU with those in normal volunteers.^{65,66} Available evidence suggests that an oseltamivir dose of 75 mg twice daily is adequate. While double or triple dose therapy is well tolerated, no study has suggested improved clinical response or survival in patients treated with these regimens^{53,67}; the only potential advantage appears to be accelerated viral clearance in one randomized, double-blinded, controlled study.⁶⁸

Viral shedding can be prolonged in hospitalized patients with seasonal or pandemic influenza. Among patients with pandemic influenza viral pneumonia (infiltrates and positive tracheal aspirate PCR), the median days for clearance while on oseltamivir therapy was 11.⁴³ NA-inhibitor therapy for longer than 5 days has been used in outbreak situations and in immunocompromised patients known to shed the virus for prolonged periods. The current World Health Organization (WHO) recommendations suggest continued antiviral therapy for critically ill patients with influenza pneumonia until adequate clinical response or infection resolution, but formal studies on optimal duration in this context are lacking.⁷⁰ The intravenous

NA inhibitor peramivir is now available in many countries. The recommended dose in adults is 600 mg of peramivir given intravenously once daily for 5 days.⁷¹

ADJUNCTIVE PHARMACOLOGIC THERAPY

Several potential adjunctive immunomodulatory or antiviral therapies for the treatment of severe influenza exist. Convalescent serum/plasma or hyperimmune globulin derived from patients who have recovered from influenza has been used for many decades. A series of studies were performed using convalescent plasma/serum during the 1918 pandemic; a recent meta-analysis showed that early, but not late, administration of such products may be associated with a significant survival benefit.⁷² Other case series suggest that similar therapy is of use in severe influenza A/H5N1 infection.^{73,74}

High-dose corticosteroid therapy has been advocated for a variety of infectious and inflammatory conditions.⁷⁵ The uncertain benefits and known risks of corticosteroids in the presence of ongoing infection warrant extreme caution before employing this strategy in primary influenza pneumonia. Although no randomized studies have been performed, retrospective analyses suggest prolongation of viral shedding, more frequent superinfections, and increased mortality.⁷⁶⁻⁷⁸

SECONDARY BACTERIAL PNEUMONIA

A majority of deaths from the 1918 influenza pandemic were the result of secondary bacterial infection.^{18,19} Similarly, a substantial number of deaths from the 1957 and 1968 pandemics were caused by bacterial co- or superinfection. The common pathogens in all series have been *S. pneumoniae*, group A streptococci, *S. aureus*, and *Haemophilus influenzae*. Given the frequency of secondary bacterial infection, clinicians should have a low threshold for considering antibacterial agents against these commonly observed pathogens.

Secondary bacterial pneumonia as a complication of viral pneumonia takes two forms: mixed viral/bacterial pneumonia and postinfluenza pneumonia during the convalescent phase of influenza. Postinfluenza pneumonia is generally attributable to damaged airways and poor mucociliary clearance mechanisms following severe influenza pneumonia.¹⁸ The early mixed form of bacterial pneumonia during ongoing viral replication in the airways is more complex, with possible synergism between the bacterial and viral pathogens. Apoptosis of pneumocytes is induced by the viral PB1-F2 protein that facilitates pneumococcal growth in the lung tissue.⁷⁹ Pneumococci bind to epithelial surfaces more readily if sialic acids have been cleaved by NA.⁸⁰ Viral NA from the influenza virus has been found to promote pneumococcal adhesion in lung tissues and increase lethality in experimental pneumococcal pneumonia.⁸¹ The early institution of effective antiviral agents with NA inhibitors might serve to decrease virus replication and decrease the risk of secondary pneumonia.⁶⁰

INFECTION CONTROL IN THE INTENSIVE CARE UNIT

Patients with suspected influenza should be managed using droplet precautions by healthcare professionals who should wear a standard surgical tie mask. There are different recommendations as to which face mask is optimal and whether N95 masks or similar personal respirators might be preferable to surgical tie masks. A recent study found limited to no additional protection of N95 masks in comparison to surgical masks, yet many still advocate their use during cough-inducing procedures when treating patients with influenza.⁸² Vaccines, when available against circulating strains of influenza, should be mandatory for all healthcare workers, unless specific contraindications exist. Healthcare workers should also consider appropriate gloves when they are likely to have contact with body fluids or touch contaminated surfaces, and they should wear gowns during procedures and patient-care activities where clothing might become contaminated. Protective eyewear is recommended when providing direct care in close proximity to the patient.⁸³ Patients with suspected influenza should be in single-patient rooms, if available, during the initial phase of hospital admission. If clinical demand exceeds the availability of single rooms, then cohorting patients with influenza into common rooms may be necessary. Influenza patients who must be transported outside a room should wear a mask if tolerated or, when necessary, an oxygen delivery system that limits the spread of aerosols.

With respect to infection prevention and control related to mode of ventilatory assistance, there is circumstantial evidence from the severe acute respiratory syndrome epidemic that noninvasive ventilation and HFOV may promote excess aerosolization of viral-laden particles and place surrounding patients and staff at risk. Limited evidence suggests that the process of endotracheal intubation, especially in an uncontrolled setting, is associated with an increased risk of acquiring infection; however, this risk is mitigated if adequate personal protective equipment is worn.^{84,85} HFOV circuits should be equipped with microbial filters and a scavenger system to the exhalation port to limit aerosol generation.

GLOBAL CRITICAL CARE COLLABORATION

The WHO does a superb job monitoring for outbreaks and antigenic shift and drift in influenza viruses in animals and human populations, but they are not equipped to perform ICU-based, international, clinical trials should a pandemic outbreak occur. A working group composed of members from the international critical care community has been formed, known as the *International Forum for Acute Care Trialists* (InFACT), to aid with global collaborative research in critical care during pandemics.⁸⁶ The impact of the InFACT initiative or similar cooperative groups will only be determined over time, but such organizations will attempt to more efficiently and more inclusively improve the care of critically ill patients in future international epidemics.

KEY POINTS

1. Influenza has exacted an enormous cost in human lives since antiquity and continues to cause annual epidemics and excess deaths to the present day.
2. Influenza A is responsible for periodic pandemics when influenza viruses from wild and domesticated bird species reassort with human-adapted viruses to generate new, hybrid viruses to which the entire human population is susceptible.
3. Specific antiinfluenza agents are available, particularly the neuraminidase inhibitors oseltamivir and zanamivir, but point mutations at the target site are increasingly common and induce resistance.
4. Secondary bacterial pneumonia following primary influenza pneumonia are common and are usually caused by pneumococci or *Staphylococcus aureus*.

Continued

KEY POINTS—cont'd

5. Supportive care and ventilatory assistance if needed can be lifesaving in severe influenza and often require prolonged ICU care for full recovery.
6. Until improved vaccines with long-term, cross-protective immunity become available, annual influenza vaccines remain mandatory for all healthcare workers to protect them and prevent nosocomial outbreaks caused by infected healthcare workers.
7. Droplet precautions and ventilatory equipment airway filters need to be followed when caring for influenza patients in critical care units, until they are no longer shedding viruses in respiratory secretions (usually 5-7 days but can be longer in critically ill and immunocompromised patients).

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Molinari NA, Ortega-Sanchez IR, Messonnier ML, Thompson WW, Wortley PM, Weintraub E, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine* 2007;25:5086–5096.

This paper presents a careful analysis of the direct costs to society in medical expenditures for the care of patients with influenza in one season throughout the United States. The costs are exceedingly high and argue strongly in favor of widespread use of annual influenza vaccines as a cost-savings measure.

Kumar A, Zyarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, et al. Critically ill patients with 2009 influenza A (H1N1) infection in Canada. *JAMA* 2009;302:1872–1879.

This report provides a detailed and valuable review of the impact of influenza upon critical care services and the relative values of various support measures in managing critically ill patients during an outbreak of pandemic influenza A (H1N1) in 2009.

Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Eng J Med* 2009;360:2605–2615.

This paper traces the fundamental virology, evolution, and epidemic behavior of the novel influenza A strain that caused a worldwide pandemic in 2009.

Moscona A. Global transmission of oseltamivir-resistant influenza. *N Engl J Med* 2009;360:953–956.

This report defines the molecular mechanisms responsible for development of resistance to the neuraminidase-inhibitor antiviral agents against influenza and explains why this is a major problem for oseltamivir rather than for a related antiviral agent, zanamivir.

Garten RJ, Davis CT, Russell CA, Shu B, Lindstrom S, Balish A, et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. *Science* 2009;325:197–201.

This paper provides the molecular details about the novel swine-origin quadruple reassorted influenza A H1N1 pandemic strain of 2009 and how it escapes immune clearance preexisting antibodies against currently circulating H1N1 strains. The virus possesses rapid human-to-human transmission potential but lacks many important virulence properties of many previous pandemic influenza viruses. These features explain its high transmissibility but rather low mortality rate.

Gamblin SJ, Haire LF, Russell RJ, Stevens DJ, Xiao B, Ha Y, et al. The structure and receptor binding properties of the 1918 influenza hemagglutinin. *Science* 2004;303:1838–1842.

This structural immunology paper analyzes the unique ability of the 1918 hemagglutinin to bind equally well to the α 2,3-linked sialic acid-galactose moieties covering avian epithelial surfaces and to the α 2,6-linked sialic acids typically found on human epithelial surface glycopeptides.

Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden F, et al. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis and institutional outbreak management: clinical practice guidelines of the Infectious Disease Society of America. *Clin Infect Dis* 2009;48:1003–1032.

This paper provides a useful review of the current existing evidence in support of a variety of diagnostic, therapeutic, and infection-control measures that are instituted when managing patients with influenza. This up-to-date guideline is a practical guide to optimal care of influenza in individual patients and in institutions during an outbreak.

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Many changes have occurred in the overall management and prognosis of patients with human immunodeficiency virus (HIV). The development of combination antiretroviral therapy (ART), in concert with chemoprophylaxis for opportunistic infections, has led to dramatic improvements in the morbidity and mortality of patients infected with HIV.^{1,2} However, those not known to be HIV-infected, those without access to medications, or those who are not responding to antiretroviral therapy may still present with AIDS-associated opportunistic infections and neoplasms.³

In this chapter, we discuss recent trends in the epidemiology and survival of HIV-infected patients admitted to an intensive care unit (ICU). Because *Pneumocystis jirovecii* pneumonia (PCP) continues to be an important cause of respiratory failure in HIV-infected patients and carries a high ICU mortality rate, we will also discuss diagnosis and treatment of PCP. Finally, we will examine problems unique to the ICU care of HIV-infected patients, particularly those related to combination ART.

INTENSIVE CARE TRENDS AMONG HIV-INFECTED PATIENTS

Epidemiology

Both the epidemiology of ICU admissions and views of the utility of ICU care for HIV-infected patients have undergone several shifts during the course of the AIDS epidemic. In the beginning of the epidemic, most patients with HIV infection admitted to the ICU had PCP, survival was poor, and ICU admission was often considered futile.⁴ Over the course of the epidemic, bacterial pneumonia, sepsis, and non-HIV-associated diagnoses have become increasingly common.⁴⁻⁷ With the widespread availability of combination ART, there have been continued changes in epidemiology and ICU mortality, and ICU care is again indicated for most patients. Unfortunately, with reports of antiretroviral resistance and transmission of multidrug-resistant HIV, ICU trends may shift again, with an increase in opportunistic infections and poor outcomes.⁸⁻¹⁰

The most extensive series documenting ICU epidemiology has come from San Francisco General Hospital, where researchers have tracked the trends in ICU diagnoses, admissions, and survival throughout the different eras of the AIDS epidemic. In the initial years (era I: 1981-1985), overall hospital mortality for those admitted to an ICU was 69%, and median survival was only 7 months.⁴ Owing to administration of corticosteroids in PCP and the initial development of ART, ICU mortality decreased over the next 10 years to 36.9%, a significant improvement from era I.⁴⁻⁷

Combination ART (era V: 1996-1999) brought about the most significant changes in mortality and admission rates.¹¹ The number of ICU admissions at San Francisco General Hospital decreased significantly from an average of 111 per year in era IV to 88.5 per year, and the survival rate increased to 71%. Respiratory failure was still the most common cause of ICU admission (40.7% of diagnoses), and PCP accounted for 10.7% of admissions compared with 17.6% in the preceding era. Shifts in ICU patient demographics reflected national trends in the HIV epidemic; whereas the majority of patients in previous eras had been white homosexual men, now African-Americans

accounted for 44.6% of ICU admissions, and women and intravenous (IV) drug users were also more commonly admitted.^{7,11} During era VI (2000-2004), as survival rates steadily increased, PCP was the most common cause of respiratory failure in patients not on ART, while obstructive airways disease was the most common among patients on ART.¹²

Exact mortality and admission rates are different in different centers, but overall trends of decreasing mortality and changes in the spectrum of diagnoses related to HIV are similar.^{13,14} In a 12-year, multicenter study of 6373 HIV-infected patients admitted to the ICU during the ART era, overall mortality decreased from 18.3% in the years 1999-2001 to 16.2% in 2008-2010.¹⁵

In most series, respiratory failure remains the leading cause of ICU admission in HIV-infected patients, although the percentage of respiratory admissions has declined. In the ART era, bacterial pneumonia has become more common, although PCP still accounts for many cases of respiratory failure.¹²⁻¹⁶ ICU admissions for severe sepsis have increased and are often associated with respiratory failure.^{16,17} HIV-infected patients with bacterial pneumonia are more likely to become bacteremic, and mortality approaches 68% in this setting.¹⁸

Non-AIDS-related diagnoses such as myocardial infarction, airway obstruction, and trauma are becoming more common, as are ART-associated diagnoses.^{16,19} In addition to respiratory failure, other comorbid conditions associated with HIV infection may be seen on admission to the ICU. These include cardiac disease, end-stage liver disease, and HIV-related renal disease. Combination ART has been associated with metabolic syndrome, dyslipidemias, and an increased risk of myocardial infarction.²⁰⁻²² End-stage liver disease due to viral hepatitis and HIV co-infection is a significant nonrespiratory problem seen in HIV-infected patients admitted to the ICU. Due to similar routes of infection, chronic hepatitis B virus has been reported in 10% and chronic hepatitis C virus (HCV) in 25% of HIV-infected individuals.²³ In the HIV Outpatient Study, the prevalence of HCV co-infection has decreased over time, from 36.7% in 1996 to 19.7% in 2007; however, HCV co-infection is associated with a higher ICU mortality than with HIV alone.^{24,25} HIV is a known risk factor for the accelerated progression of HCV to cirrhosis, and in addition to hepatotoxicity from co-infection, many antiretrovirals also elevate transaminase levels.^{26,27} Finally, end-stage renal disease secondary to HIV is a common complication. Despite the decreased incidence with the development of combination ART, it remains a significant problem, especially in HIV-infected African-Americans, who are at higher risk of developing HIV-associated nephropathy with progression to end-stage renal disease.²⁸⁻³¹

Prognostic Factors

Several key factors continue to impact mortality, and these factors seem not to have changed over the years. Mechanical ventilation, diagnosis of PCP, and vasopressor use have been associated with increased mortality.^{7,11,13,17} Conversely, admission for a non-AIDS-associated diagnosis, an albumin level greater than 2.6 g/dL, an Acute Physiology and Chronic Health Evaluation (APACHE) II score less than 13, and no need for mechanical ventilation were all associated with increased survival to hospital discharge.^{11,12}

INTENSIVE CARE TRENDS IN PNEUMOCYSTIS PNEUMONIA

Because PCP has historically been the most common cause of respiratory failure in patients with AIDS, more is known about ICU outcomes of those with PCP than for any other HIV-infected group. In the 1980s, patients with HIV and PCP who required intensive care had a mortality rate as high as 81%, rising to 87% if they required mechanical ventilation.⁴ Mortality due to PCP decreased to approximately 60% with the introduction of adjunctive corticosteroids in the mid-1980s and has continued to decline in the era of combination ART.^{5,32-34}

Despite improvement in PCP survival, a diagnosis of PCP remains a risk factor for overall mortality.^{12,35} In a study of HIV-infected individuals from 1998 to 2010, in-hospital mortality remained unchanged at 10.9% of HIV-infected patients admitted with PCP, despite advances in ART over those years.³⁶

Diagnosis and Treatment of *Pneumocystis Pneumonia*

Clinical Presentation

PCP most commonly occurs in patients with CD4 cell counts below 200 cells/ μ L, and the risk of PCP increases exponentially as the CD4 cell count further decreases below that level.^{37,38} Common symptoms and signs include fever, tachypnea, dyspnea with a nonproductive cough, and a chest examination that is normal or has a few dry rales.^{39,40} In the HIV-infected patient, symptoms have generally been present for days to weeks before the diagnosis is made. Approximately two-thirds of patients admitted to the ICU with PCP are unaware they are infected with HIV, so clinicians must remember to include PCP in their differential diagnosis of respiratory failure, even in individuals not known to have HIV.^{34,41}

Severe PCP is often similar in presentation and pathogenesis to acute respiratory distress syndrome (ARDS). The organism appears to cause a widespread capillary leak, and the chest radiograph usually resembles that in ARDS, with diffuse bilateral interstitial infiltrates. Less commonly, PCP results in focal airspace consolidation. Infiltrates are occasionally unilateral or asymmetric, and the pattern (interstitial and nodular) is more suggestive of the diagnosis than distribution of the abnormalities. However, about 10% to 15% of patients proven to have PCP initially have normal chest radiographs.⁴²⁻⁴⁴

Diagnosis

Although PCP may have a typical clinical and radiographic presentation, definitive diagnosis is encouraged, particularly in those who are critically ill. Many respiratory diseases in HIV have overlapping presentations, and prompt initiation of appropriate therapy is important to prevent clinical deterioration and avoid unnecessary drug side effects. The diagnosis of PCP is made by identifying the organism in the pulmonary secretions of a patient with a compatible clinical presentation. PCP may be diagnosed by examination of induced sputum,

which has a sensitivity of 79% and a negative predictive value of 61% in experienced hands.⁴⁵

When the sputum examination is negative or when it is not possible to obtain induced sputum, bronchoscopy with bronchoalveolar lavage is the procedure of choice, with a sensitivity of over 90% for diagnosis of PCP in an HIV-infected individual and an even greater yield when bilateral sampling is performed.⁴⁶⁻⁴⁸

In recent years, the search for noninvasive biomarkers in the diagnosis of PCP has yielded promising results. Detection of β -D-glucan in the serum has been shown to be both a sensitive and specific indicator of PCP in HIV-infected individuals.^{49,50} Interestingly, serum measurement of β -D-glucan is more sensitive and specific than bronchoalveolar lavage fluid measurement of the marker.⁵⁰ Although studies to date have been retrospective in nature, this biomarker shows promise in the risk stratification of HIV-infected individuals who may have PCP.

Treatment

A summary of treatment regimens in decreasing order of preference is given in Table 131-1. The treatment of choice for moderate to severe PCP is intravenous (IV) trimethoprim-sulfamethoxazole (TMP-SMX) for a total of 21 days.⁴⁰ Approximately 25% of patients will have therapy-limiting toxicity from TMP-SMX (Table 131-1), occurring between days 6 and 10 of treatment.⁵¹⁻⁵³

Intravenous pentamidine isethionate is an effective alternative for therapy in patients who cannot tolerate TMP-SMX or have failed treatment.⁴⁰ Because pentamidine is toxic to the pancreatic islet cells, initial hypoglycemia from a surge of insulin release followed by hyperglycemia from inadequate insulin may be seen, and the patient may progress to chronic diabetes mellitus. Adverse reactions may be seen in as many as 50% of patients treated with pentamidine.

Second-line therapy may be used if first-line therapies prove to be ineffective or have unacceptable side effects. If TMP-SMX has been the first-line agent, IV pentamidine or the combination of IV clindamycin with oral primaquine may be substituted.

The most profound improvement in PCP mortality occurred with the introduction of adjunctive corticosteroids.^{5,32,33} In a meta-analysis of six randomized controlled trials comparing adjunctive corticosteroids to standard care in HIV-infected patients with PCP, risk ratios for overall mortality were 0.54 (95% CI, 0.38-0.79) at 1 month and 0.67 (95% CI, 0.49-0.93) at 3 to 4 months in favor of corticosteroids.⁵⁴ It is recommended that patients with PCP and either a P_{aO_2} on room air of less than 70 mm Hg or an alveolar-arterial oxygen gradient greater than 35 mm Hg receive prednisone within 72 hours of initiating anti-*Pneumocystis* therapy to reduce mortality (Table 131-1).⁴⁰ For those patients unable to take oral medications, IV methylprednisolone may be substituted at 75% of the prednisone dose.⁴⁰

Treatment Failure

Worsening respiratory status with a decrease in arterial oxygenation is common 3 to 5 days after initiation of treatment. This is likely due to

TABLE 131-1 Treatment Regimens for Severe *Pneumocystis Pneumonia* in Decreasing Order of Preference

| AGENT | DOSE | SIDE EFFECTS |
|--|--|---|
| Trimethoprim-sulfamethoxazole | Trimethoprim, 15-20 mg/kg/d, with sulfamethoxazole, 75-100 mg/kg/d IV, divided q 6-8 h | Rash, nausea, bone marrow suppression, hyponatremia, hyperkalemia, nephrotoxicity, transaminitis |
| Pentamidine isethionate | 3-4 mg/kg/d IV | Nausea, hypotension, hypoglycemia or hyperglycemia, pancreatitis, bone marrow suppression, nephrotoxicity |
| Clindamycin-primaquine | Clindamycin, 900 mg IV q 8 h; primaquine, 30 mg PO daily | Nausea, diarrhea, rash, hemolytic anemia, methemoglobinemia, leukopenia |
| ADJUNCTIVE THERAPY | | |
| Prednisone if $P_{aO_2} < 70$ mm Hg or alveolar-arterial gradient > 35 mm Hg | 40 mg PO q 12 h for 5 days, 40 mg PO daily for 5 days, 20 mg PO daily for 11 days | Hyperglycemia, psychosis |

an inflammatory response to dead or dying organisms that may increase capillary permeability and pulmonary edema formation, and it may be inadvertently worsened by administration of excessive IV fluids. Given that patients' conditions may deteriorate and that symptoms may be prolonged, it is difficult to determine when a treatment regimen is failing and should be abandoned for an alternative. *Pneumocystis* has been shown to develop genetic mutations with exposure to sulfa- or sulfone-containing medications such as TMP-SMX and dapsone, although how these mutations impact outcome is still controversial.⁵⁵⁻⁵⁷ In general, treatment should be continued for 4 to 8 days before considering changing to a different agent.⁴⁰ It is also important to investigate alternative diagnoses including opportunistic pathogens, immune reconstitution inflammatory syndrome, and nosocomial organisms. Patients with PCP are also at increased risk of pulmonary edema, which may explain worsening respiratory status with increasing radiographic infiltrates. Repeat bronchoscopy is helpful to diagnose agents other than PCP, but it is not useful in determining whether PCP treatment is failing because *Pneumocystis* may persist in bronchoalveolar lavage fluid for several weeks.⁵⁸

Ventilation of the Patient with PCP

The pathophysiology of severe PCP resembles that of ARDS, and patients with PCP are at high risk for developing barotrauma and pneumothoraces, often heralding a fatal outcome. Low tidal volume ventilation as per the ARDSNet Ventilator Protocol has been shown to be associated with decreased mortality in HIV-infected patients with acute lung injury (OR, 0.76 per 1-mL/kg decrease; 95% CI, 0.58-0.99; $P = 0.043$), and is standard-of-care in HIV-infected patients with acute lung injury from PCP or other causes.^{35,59} Noninvasive positive-pressure ventilation has been found to lower the rate of intubation, decrease the incidence of pneumothorax, and improve ICU survival.⁶⁰

COMBINATION ANTIRETROVIRAL THERAPY AND THE ICU

Lactic Acidosis

The syndrome of severe hepatic steatosis and lactic acidosis in patients receiving ART was first described in the 1990s.^{61,62} The syndrome is most commonly associated with nucleoside reverse transcriptase inhibitors (NRTIs), particularly didanosine and stavudine, and results from the mitochondrial toxicity of these agents.^{63,64} The incidence of hyperlactatemia in patients taking NRTIs has been reported as high as 227 cases per 1000 person-years. Symptomatic lactic acidosis ranges from 1 to 25.2 cases per 1000 patient-years, with mortality as high as 77%.^{65,66} Risk factors for development of hyperlactatemia include older age, drug regimens containing stavudine or combined stavudine-didanosine, concomitant buprenorphine, creatinine clearance under 70 mL/min, and a nadir CD4 cell count less than 250 cells/ μ L.^{67,68} A case-control study identified female sex and obesity as risk factors for stavudine-related lactic acidosis.⁶⁷

Patients often present with abdominal pain, nausea, and vomiting and may have myalgias or peripheral neuropathies. Serum lactate levels are elevated, and hepatic steatosis and transaminitis occur frequently. Often, cessation of the ART results in resolution; however, some patients progress to life-threatening organ failure. An initial lactate level above 9 mmol/L has been associated with a higher risk of death, and some consider a level greater than 5 mmol/L life threatening.^{69,70}

In patients presenting with mild lactic acidosis, the offending agent should be switched to a safer alternative. Lactate levels should be closely monitored after changing the NRTI. For severe lactate acidosis, ART should be discontinued and supportive care administered.²⁷ Although data regarding treatment outcomes are not extensive, treatment with riboflavin, thiamine, and L-carnitine has reversed the toxicity in some case reports.^{27,69-72} One recommended regimen is to administer 50 mg of riboflavin daily with 50 mg/kg of L-carnitine and 100 mg of thiamine until the lactic acidosis resolves. The exact length

of treatment and the lactate level above which treatment is futile are unclear.

Immune Reconstitution

The immune reconstitution inflammatory syndrome (IRIS) leads to paradoxical worsening of an infection shortly after initiation of ART. This syndrome results from improvement in the immune system and a renewed inflammatory response directed against infectious agents.⁷³ Although this syndrome has been reported to occur in diseases such as tuberculosis, cytomegalovirus (CMV), and *Mycobacterium avium* complex, it usually results only in a symptomatic worsening of these conditions.⁷³⁻⁷⁵ A 2010 meta-analysis of 54 cohort studies of patients who developed IRIS found that it occurred in 16.1% of all patients and was associated with a 4.5% mortality, though mortality varied depending on the underlying pathogen and severity of immunodeficiency at the time of ART initiation.⁷⁶ There have been case reports of paradoxical worsening occurring during PCP, with patients experiencing increasing respiratory distress and hypoxemia and some requiring mechanical ventilation.⁷⁷⁻⁷⁹ All patients subsequently recovered, and there seemed to be some benefit from continuing or reintroducing corticosteroids.⁷⁹ Patients admitted to the ICU with a presumed paradoxical worsening of PCP should receive corticosteroids, and appropriate testing should be performed to rule out other infections or respiratory disorders causing clinical worsening.

Administration of Antiretroviral Therapy in the ICU

The question of whether to continue or initiate ART while HIV-infected patients are in the ICU is an unresolved issue in critical care. Traditionally, antiretroviral regimens have been discontinued while patients are in intensive care, and clinicians have been reluctant to initiate ART in this population. Many issues relating to the use of ART exist in the ICU, including possible poor gastric absorption of antiretroviral medications, the potential for drug interactions and side effects, and concern about patient compliance in continuing ART after discharge. There is also concern that initiating ART in a patient with borderline respiratory status might lead to respiratory failure through paradoxical worsening and immune reconstitution.

ART therapy is complicated in the ICU. Only zidovudine is available in an IV form. Other agents are available as liquids and therefore could be administered via a feeding tube (Box 131-1).⁸⁰ If physicians

BOX 131-1

List of Antiretroviral Agents Available in Nonpill Form

PROTEASE INHIBITORS

Amprenavir
Fosamprenavir
Lopinavir/ritonavir
Nelfinavir
Ritonavir
Tipranavir

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Abacavir
Didanosine
Emtricitabine
Lamivudine
Stavudine
Zidovudine (also intravenous)

NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR

Nevirapine

FUSION INHIBITOR

Enfuvirtide (subcutaneous injection)

choose to administer ART to an ICU patient, they need to be particularly aware of possible side effects including renal toxicity and hepatotoxicity, pancreatitis, and lactic acidosis.²⁷ Many common ICU medications such as benzodiazepines, fluconazole, pentamidine, and amiodarone may have dangerous interactions or altered metabolism when given with antiretrovirals.²⁷ Medications may also affect the serum levels of antiretrovirals, resulting either in toxic or subtherapeutic concentrations and increasing the risk of developing drug resistance.²⁷ Consultation with a specialist familiar with the many antiretroviral regimens is advised.

It is currently unclear whether the mortality benefits of ART administration in ICU patients outweigh the risks and difficulties. In a randomized controlled trial that compared deferring ART or initiating it within 14 days of treatment for an AIDS-related opportunistic infection or serious bacterial infection, early ART resulted in decreased progression of AIDS or death compared to deferred therapy (OR 0.51).⁸¹ In a retrospective cohort study of 278 HIV-infected patients admitted to the ICU in São Paulo from 1996 through 2006, beginning ART during the ICU stay was associated with reduced 6-month mortality, significantly less than patients not on ART while in the ICU (hazard ratio 0.55).⁸² Survival was worse in those who were previously on ART and had it stopped while in intensive care; however, use of ART in the ICU was associated with adverse events in 18% of patients. In patients with PCP admitted to the ICU during the ART era, mortality among patients who did not receive ART was 63%, whereas those patients either receiving ART at time of admission or started on ART in the ICU had a mortality rate of only 25%.⁸³ There have been several reports of improved cumulative survival (i.e., months to years post ICU discharge) among ICU survivors started on ART.^{17,35,84-86} Other studies, however, have not found that starting ART in the ICU improves ICU or in-hospital survival and that it may be associated with a higher incidence of subsequent antiretroviral resistance.^{34,81,87} One study of HIV-infected patients with respiratory failure found a trend toward worse outcome in those receiving ART in the ICU (30% mortality in those on ART vs. 15% in those not on ART).¹³

Given the lack of consensus guidelines for whether and when to initiate combination ART in the ICU, the decision to do so must be made on a case-by-case basis. A useful treatment strategy was described by Huang and colleagues.⁸⁸ In patients who are known to be HIV-infected and are already receiving combination ART, combination ART should be continued if the viral load is undetectable and there are no contraindications to continuing the drugs (e.g., drug toxicities, resistance, IRIS, difficulty in delivery or drug absorption). If the patient has a contraindication to ART, the entire regimen should be held so as not to foster resistance, and an HIV specialist should be consulted. In patients who are known to be HIV-infected but are not on ART or who are diagnosed with HIV on their ICU admission, consideration should be given to starting combination ART if the condition is an AIDS-associated condition, and an HIV specialist should be consulted. If the condition is not AIDS-associated and the CD4 count is greater than 200 cells, ART should probably be deferred until after the patient is discharged from the ICU, unless the ICU course is prolonged. The importance of consultation with an HIV specialist in these ART treatment decisions cannot be overemphasized.

METABOLIC ABNORMALITIES IN THE ICU

Metabolic Complications of Antiretroviral Therapy

Many drugs included in ART regimens have adverse effects on the metabolism of lipids and glucose. Patients treated with these drugs

commonly develop metabolic abnormalities including hyperlipidemia, hypercholesterolemia, glucose intolerance, and diabetes.⁸⁹⁻⁹¹ Conditions such as cardiovascular disease, dyslipidemia, insulin resistance, and osteoporosis have been associated with ART, and protease inhibitors have been specifically implicated in an increased relative risk of myocardial infarction (MI).^{20,21,92,93} In the landmark multicenter prospective study of 23,468 patients, the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study group reported that combination ART was independently associated with a 26% relative increase in the rate of MI per year of exposure in the first 4 to 6 years of use.²¹ In a follow-up study, the group showed that exposure to protease inhibitors was associated with increased risk of MI, likely related to dyslipidemia.²⁰ Other studies have reported that the NRTIs abacavir and didanosine are also associated with increased risk of cardiovascular disease, though not all studies support this association.^{94,95} A cohort of over 36,000 HIV-infected patients followed from 1993 to 2001 demonstrated no relationship between use of antiretroviral medications and cerebrovascular or cardiovascular events, but follow-up may have been too short to detect an effect.⁹⁶ A recent study of 81,322 veterans showed that when comparing people of similar cardiovascular risk profiles, HIV-infected veterans had a significantly greater risk of acute MI.⁹⁷ In general, HIV-infected patients admitted to the ICU with cardiac disease should be treated the same as the HIV-uninfected population, with interventions including cardiac artery bypass grafting as indicated. Data show that short-term outcome is equivalent, although HIV-infected patients have a higher long-term risk of requiring revascularization and higher risk of death at 1 year post acute MI.^{98,99} As HIV-infected patients live longer due to ART, clinicians can expect to see problems such as cardiac disease more frequently as the HIV-infected population ages.

Adrenal Insufficiency

Adrenal insufficiency (AI) is an important syndrome in the ICU that is more common among HIV-infected patients. The adrenal glands of patients with HIV may be damaged by infections such as CMV, neoplasms such as lymphoma, and drugs such as ketoconazole and rifampin.¹⁰⁰⁻¹⁰² At its most severe, AI can present as refractory hypotension and may lead to death if not recognized. Marik and colleagues studied adrenal function in 28 critically ill HIV-infected patients. In this study, depending on the criteria used, the rate of AI varied from 7% to 75%.¹⁰³ CMV infection was more common among the patients with AI. Clinicians should have a high degree of suspicion for adrenal insufficiency in HIV-infected patients, particularly in those with CMV, and should consider adrenocorticotrophic hormone stimulation testing. Patients with septic shock or early ARDS should be empirically treated for AI according to the Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock.¹⁰⁴

CONCLUSION

The outlook for ICU patients with HIV has improved dramatically since the beginning of the AIDS epidemic. Physicians caring for HIV-infected patients in the ICU need an understanding of both the HIV-associated and the non-HIV-associated conditions that can affect these patients. Knowledge of antiretroviral therapies and their side effects is also important because these therapies may lead directly to patients' ICU admissions and impact their morbidity and mortality. It is hoped that more information will become available to guide clinicians in the use of ART in the ICU and that survival will continue to improve.

KEY POINTS

1. Non-AIDS-related diagnoses have become more common since the introduction of combination antiretroviral therapy (ART).
2. Mortality from *Pneumocystis pneumonia* (PCP) can still be high, particularly if patients develop a pneumothorax while on mechanical ventilation.
3. Clinicians should have a high suspicion for PCP, because many patients will not be aware that they are HIV-infected before ICU admission.
4. Early bronchoscopy with bronchoalveolar lavage should be performed in patients with pneumonia who do not have a definitive microbiological diagnosis.
5. Trimethoprim-sulfamethoxazole is the treatment of choice for PCP, and corticosteroids should be given to those meeting established criteria.
6. Fatal lactic acidosis can develop as a result of antiretroviral medications. Treatment consists of drug discontinuation and supportive care.
7. Immune reconstitution syndrome after initiating ART can occasionally lead to respiratory failure, particularly in patients with PCP.
8. Administration of ART in the ICU is difficult, may lead to viral resistance, and is associated with many side effects and drug interactions; however, the association of ART with mortality in the ICU remains unclear.

ANNOTATED REFERENCES

- Barbier F, Coquet I, Legriel S, et al. Etiologies and outcome of acute respiratory failure in HIV-infected patients. *Intensive Care Med.* 2009;35:1678-1686.
- A retrospective study of 147 HIV-infected patients admitted to an ICU for acute respiratory failure (ARF) between 1996 and 2006, describing the etiologies of respiratory failure in this cohort. The most common cause of ARF was bacterial pneumonia ($n = 74$), followed by *Pneumocystis jirovecii* pneumonia (PCP; $n = 52$), other opportunistic infections ($n = 19$), and noninfectious pulmonary disease ($n = 33$). Two or more causes were identified in 33 patients. The 43 patients on ART more frequently had bacterial pneumonia and less frequently had opportunistic infections ($P = 0.02$). Noninvasive ventilation was needed in 49 patients and endotracheal intubation in 42. Hospital mortality was 19.7%. Factors independently associated with mortality were mechanical ventilation (OR, 8.48; $P < 0.0001$), vasopressor use (OR, 4.48; $P = 0.03$), time from hospital admission to ICU admission (OR, 1.05 per day; $P = 0.01$), and number of causes (OR, 3.19; $P = 0.02$). HIV-related variables (CD4 count, viral load, and ART) were not associated with mortality.
- Casolino E, Wolff M, Ravaud P, Choquet C, Bruneel F, Regnier B. Impact of HAART advent on admission patterns and survival in HIV-infected patients admitted to an intensive care unit. *AIDS.* 2004;18:1429-1433.
- This prospective observational cohort study of 426 HIV-infected patients admitted to an ICU between 1995 and 1999 examined ICU epidemiology and survival. The incidence of sepsis increased, while AIDS-related admissions decreased. Overall ICU survival was 77%, and cumulative survival rates after ICU discharge were 85.3% and 70.8% after 1 year and 2 years, respectively. While ICU survival was dependent on the non-HIV-associated prognostic indicators (SAPS II score > 40 , Omega score > 75 , and mechanical ventilation), long-term survival was associated with HIV disease stage and availability of combination ART.
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- This retrospective cohort study compared ventilator strategies in 148 HIV-infected patients with respiratory failure before and after the introduction of low tidal volume ventilation in 2000. Among all those with acute lung injury, lower tidal volume was associated with decreased mortality (adjusted OR, 0.76 per 1-mL/kg decrease; 95% CI, 0.58-0.99; $P = 0.043$). This study supports the use of a low tidal volume ventilation strategy in HIV-infected patients with acute lung injury and respiratory failure.
- Dickson SJ, Batson S, Copas AJ, Edwards SG, Singer M, Miller RF. Survival of HIV-infected patients in the intensive care unit in the era of highly active antiretroviral therapy. *Thorax.* 2007;62:964-968.
- This retrospective study of 102 HIV-infected patients admitted to the ICU between January 1999 and December 2005 reported an overall ICU and hospital survival of 77% and 68%, respectively. Factors predicting survival to ICU discharge included hemoglobin, CD4 cell count, APACHE II score, and mechanical ventilation. Use of combination ART was not associated with survival. Outcomes for HIV-infected patients were comparable to general medical patients.
- Muller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis.* 2010;10:251-261.
- A systematic review and meta-analysis describing the prevalence of IRIS in patients with different opportunistic infections. The overall prevalence of IRIS was 16.1% (11.1-22.9) in unselected patients starting ART, and 4.5% (2.1-8.6) of patients with any type of IRIS died. Meta-regression analyses showed that the risk of IRIS is associated with CD4 cell count at the start of ART, with a high risk in patients with fewer than 50 cells per μL . Occurrence of IRIS might therefore be reduced by initiation of ART before immunodeficiency becomes advanced.
- Powell K, Davis JL, Morris AM, Chi A, Bensley MR, Huang L. Survival for patients with HIV admitted to the ICU continues to improve in the current era of combination antiretroviral therapy. *Chest.* 2009;135:11-17.
- Sixth in a series of articles from San Francisco General Hospital documenting ICU epidemiology and mortality of HIV-infected patients throughout the course of the AIDS epidemic. In the most recent era of combination ART, respiratory failure remained the most common indication for ICU admission (42% overall). The proportion of patients with respiratory failure decreased each year from 52% to 34% ($P = 0.02$), and hospital survival ratios significantly increased during the 5-year period ($P = 0.001$). ART use at ICU admission was not associated with survival, but it was associated with higher CD4 cell counts, lower plasma HIV RNA levels, higher serum albumin levels, and lower proportions of patients with AIDS-associated ICU admission diagnoses and with *Pneumocystis pneumonia*.
- Walzer PD, Evans HE, Copas AJ, Edwards SG, Grant AD, Miller RF. Early predictors of mortality from *Pneumocystis jirovecii* pneumonia in HIV-infected patients: 1985-2006. *Clin Infect Dis.* 2008;46:625-633.
- This study is the largest retrospective study to date of 494 consecutive patients with 547 episodes of laboratory-confirmed PCP and identified risk factors for mortality on or soon after admission. Overall mortality was 13.5%. Multivariate analysis identified factors associated with risk of death, including increasing patient age (adjusted odds ratio [AOR], 1.54; 95% CI, 1.11-2.23; $P = 0.011$), subsequent episode of PCP (AOR, 2.27; 95% CI, 1.14-4.52; $P = 0.019$), low hemoglobin level at hospital admission (AOR, 0.70; 95% CI, 0.60-0.83; $P < 0.001$), low partial pressure of oxygen breathing room air at hospital admission (AOR, 0.70; 95% CI, 0.60-0.81; $P < 0.001$), presence of medical comorbidity (AOR, 3.93; 95% CI, 1.77-8.72; $P = 0.001$), and pulmonary Kaposi sarcoma (AOR, 6.95; 95% CI, 2.26-21.37; $P = 0.001$). Patients with a first episode of PCP were sicker (mean partial pressure of oxygen at admission \pm standard deviation, 9.3 ± 2.0 kPa) than those with a second or third episode of PCP (mean partial pressure of oxygen at admission \pm standard deviation, 9.9 ± 1.9 kPa; $P = 0.008$), but mortality among patients with a first episode of PCP (12.5%) was lower than mortality among patients with subsequent episodes of PCP (22.5%) ($P = 0.019$). While mortality decreased in the ART era, no patient was receiving highly active antiretroviral therapy before presentation with PCP, and none began highly active antiretroviral therapy during treatment of PCP; thus the trend toward improved outcome after June 1996 occurred in the absence of highly active antiretroviral therapy.
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■ EPIDEMIOLOGY

The World Health Organization (WHO) estimates that one-third of the world's population is latently infected with *Mycobacterium tuberculosis*.¹ From this pool, approximately 9 million active tuberculosis (TB) cases emerge annually, resulting in 1.5 million deaths and making TB the second leading cause of death by an infectious agent worldwide.^{2,3} The majority of TB cases (95%) occurs in the developing world. Incidence rates exceed 300 cases per 100,000 persons in most countries in sub-Saharan Africa as well as in Burma and Cambodia; rates are 100-300 cases per 100,000 persons in South Asia, rest of Southeast Asia, Russia and neighboring countries, several countries in South America, and many parts of Africa.^{1,4} Areas with the most cases per year include India (2.0 million cases per year) and China (1.3 million cases per year).

In the United States, the TB rate continues to decline, with 3 new cases per 100,000 reported in 2013, the lowest rate recorded since national reporting began in 1953.⁵ Foreign-born persons and racial/ethnic minorities bear a disproportionate burden of TB in the United States; for example, in 2013, the TB rate within foreign-born individuals—notably Hispanics and Asians—in the United States was 13 times higher than within U.S.-born persons.^{5,6} Among U.S.-born racial and ethnic groups, the greatest racial disparity in TB rates is seen in African-Americans, who have a TB incidence rate that is 6 times higher than U.S.-born whites.⁵ Other groups at increased risk of active TB include prisoners, homeless persons, and human immunodeficiency virus (HIV)-positive individuals.⁵

The acquired immunodeficiency virus (AIDS) epidemic has contributed significantly to the rise in TB cases worldwide, with approximately 1.5 million individuals with active TB per year co-infected with HIV.² HIV increases the risk of developing TB by 21-fold in countries where the prevalence of HIV is more than 1% in the general population.⁷

■ DRUG-RESISTANT TUBERCULOSIS IS A FORBIDDING PROBLEM

Drug-susceptible TB is readily curable provided adherence to medications is followed. However, TB due to *M. tuberculosis* strains with resistance to one or more first-line agents often requires a significantly longer course of antibiotics; second-line agents have more difficult-to-tolerate side effects, and the treatment of drug-resistant TB is significantly more challenging. More important, multidrug-resistant TB (MDR-TB)—defined as resistance to at least both isoniazid (INH) and rifampin (RIF), two of the most powerful first-line anti-TB drugs—is associated with significant increase in morbidity and mortality.⁸⁻¹⁰

It is estimated that of the 9 million new cases of TB per year worldwide, 500,000 are due to MDR-TB. While drug-resistant TB is increasing at an alarming rate worldwide, particularly in India and China,¹¹ the percent of MDR-TB cases in the United States decreased between 1991 and 2006 from 3.5% to 1.1%.^{12,13} MDR-TB disproportionately affects foreign-born individuals, accounting for 0.4% of TB cases occurring in U.S.-born persons and 1.3% in foreign-born individuals.⁶

Extensively drug-resistant tuberculosis (XDR-TB) is defined as resistance to INH, RIF, any fluoroquinolone, and to a second-line injectable (amikacin, kanamycin, or capreomycin). XDR-TB has

emerged with a wide geographic distribution including the United States and is associated with poorer treatment outcomes than MDR-TB, especially in those co-infected with HIV.^{11,14-19}

■ TUBERCULOSIS IN THE INTENSIVE CARE UNIT

TB patients requiring ICU care represent 1% to 3% of all patients with active TB. Most studies of TB patients requiring ICU admission are retrospective and frequently include a disproportionate number of HIV-positive individuals. TB should be considered in the differential diagnosis of critically ill patients, particularly in foreign-born individuals who emigrated from countries with a high prevalence of TB. With the increased use of tumor necrosis factor-alpha (TNF- α) antagonists and other immunosuppressive agents, ICU physicians are more likely to encounter patients with nonclassical features of TB. In this chapter, selected critical care issues in TB are discussed. Some disease forms, such as renal and peritoneal TB, are omitted because they are less likely to be seen in the ICU.

■ PULMONARY TUBERCULOSIS

Pulmonary disease is by far the most common manifestation of active TB and of TB requiring ICU admission. Pulmonary disease may be due to the progression of a primary infection or to reactivation disease.

Primary infection occurs following airborne implantation of tubercle bacilli into the lungs. *M. tuberculosis* is transported from the lungs to hilar lymph nodes via infected dendritic cells and then throughout the bloodstream, resulting in secondary occult infections at extrapulmonary sites (Fig. 132-1). While primary infection is usually asymptomatic in adults, it can present with fever, hilar adenopathy, lung infiltrates, pleural effusions, and even severe pulmonary disease that can mimic viral or bacterial pneumonia, potentially delaying the diagnosis of TB. In severely immunocompromised patients, primary TB may be aggressive and become disseminated. Pleural TB, which can present as pleuritis or empyema, is usually a manifestation of primary TB, although it may also occur with reactivation disease. Pleural biopsy specimens are more likely to yield positive cultures than pleural fluid.

In non-TB-endemic countries, most cases of active TB are due to the reactivation of latent TB infection (LTBI). Reactivation tends to occur within the first 2 years of the initial infection and occurs in about 10% of immunocompetent individuals with LTBI. Typically, reactivation TB is a subacute fibrocavitary pneumonia involving the upper lobes and/or superior segments of the lower lobes. However, reactivation TB can involve any organ system and can present in a fulminant fashion with respiratory failure.²⁰

Both primary and reactivation TB can cause bilateral alveolar infiltrates, hypoxic respiratory failure, and acute respiratory distress syndrome (ARDS).^{20,21} Consolidation is the most frequent radiographic pattern of patients with pulmonary TB who are admitted to the ICU.²² Since this radiographic pattern is highly nonspecific, chest x-rays are often not helpful in raising suspicion for TB. Nevertheless, in patients with active TB, consolidation on initial chest radiographs was found to be a stronger, independent predictor for in-hospital mortality than the presence of nodules, interstitial infiltrates, or cavities.²³ One possible reason for this is a delay in diagnosis as clinicians may be more

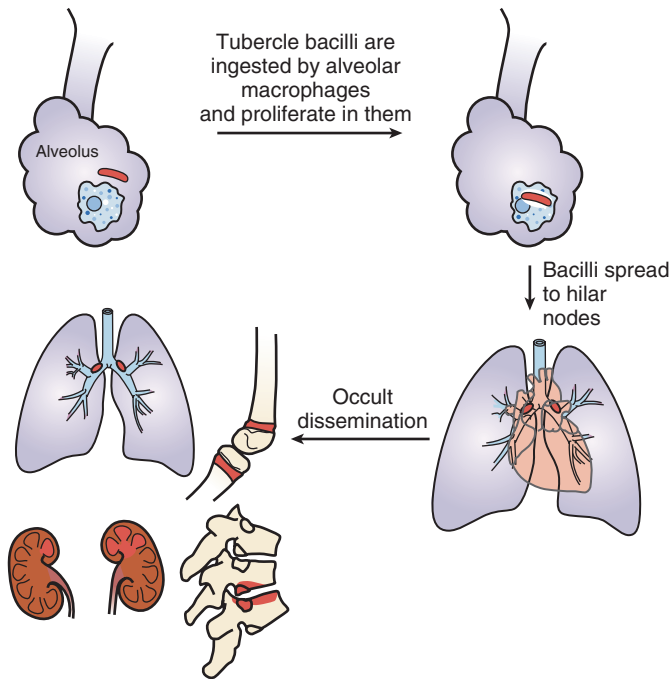


FIGURE 132-1 ■ Cartoon representation of a primary infection of TB and occult dissemination. Largely asymptomatic, dissemination of *M. tuberculosis* following primary infection occurs when infected mononuclear cells migrate throughout the body, particularly to the lung apices, kidneys, bone growth plates, and vertebrae, resulting in latent infection.

prone to favor nontuberculous bacterial pneumonia in the absence of cavitation or a miliary pattern. Another reason is that consolidation may be an indication of a suboptimal immune response to the infection. Pulmonary gangrene, which carries a mortality of up to 75%, can ensue when rapid progression of infiltrates causes vascular damage and death of lung tissue.²⁴ Other life-threatening complications of pulmonary TB include hemoptysis, spontaneous pneumothorax, broncho-pulmonary fistula, and empyema. Not unexpectedly, delayed recognition and treatment of nosocomial pneumonia complicating TB patients requiring mechanical ventilation have significant adverse effects on survival.^{25,26}

Perhaps the best safeguard to prevent missing a diagnosis of pulmonary or disseminated TB in critically ill patients is to maintain a high index of suspicion of it in at-risk individuals—for example, the foreign-born, immunosuppressed, and/or those known to have a history of untreated LTBI. Studies have shown that the presence of diffuse infiltrates consistent with ARDS and/or acute respiratory failure may cause physicians to inappropriately dismiss the diagnosis of TB.²⁷⁻²⁹ Older individuals (≥ 65 years old) or patients with AIDS may also have a delayed diagnosis of TB due, in part, to atypical presentations.^{30,31}

In-hospital mortality among TB patients who require ICU admission is high, at 26% to 67% and may be higher among those requiring mechanical ventilation, at 48% to 81%.^{23,25,26,32-36} Delayed initiation of anti-TB treatment has been shown to increase mortality.³⁶ Other risk factors for death among TB patients in the ICU are less specific to TB, such as severity of illness, hypoalbuminemia, anemia, lymphopenia, alcoholism, advanced age, and organ failure requiring life support including mechanical ventilation, renal replacement therapy, and use of vasopressors.^{23,25,26,32,33,37,38} Despite being a relatively rare cause of respiratory failure, pulmonary TB requiring ICU care carries a poor prognosis. Early recognition of the infection is essential in reducing mortality and preventing the nosocomial spread of *M. tuberculosis*.²⁹

DISSEMINATED TUBERCULOSIS

Disseminated, or “miliary,” TB is more likely to occur in the very young, the very old, and in patients with underlying diseases such as HIV. It may result from either primary or reactivation TB. Disseminated TB typically presents subacutely with symptoms present for days to months, but can manifest fulminantly with ARDS, septic shock, and multiorgan failure.^{39,40} Typical presenting signs and symptoms include fever, malaise, weight loss, dyspnea, and hypoxia.

The chest radiograph (Fig. 132-2, A) and CT scan (Fig. 132-2, B) show a typical miliary pattern manifested by a profusion of diffuse small (<2 mm) nodules that resemble the size and uniformity of millet seeds (Fig. 132-2, C). In some cases of disseminated disease, the chest x-ray may appear normal. Virtually any organ may be involved, including the adrenals, brain, meninges, liver, gallbladder, pancreas, eyes, urinary tract, and skin. Bone marrow involvement by TB commonly manifests with anemia, leukemoid reaction, and thrombocytosis. The diagnosis of miliary TB can be difficult. If disseminated TB is suspected, sputum smears should be obtained even if lung disease is not apparent. Biopsy and culture of affected tissue(s) such as the bone marrow are often required. Culture of blood, urine, and/or stool may be positive, especially in HIV-positive patients.⁴⁰

NEUROLOGIC TUBERCULOSIS

Tuberculous Meningitis

TB meningitis is rare, accounting for more than 1% of global TB cases, and with only 107 cases reported in the United States in 2013.⁴¹ It occurs via rupture of a subependymal tubercle that seeded and formed during primary infection or disseminated disease. Individuals at high risk of TB meningitis include very young children with primary TB and older patients with immunodeficiency disorders such as HIV. Most will have no known history of TB, but evidence of extrameningeal disease (e.g., pulmonary, urinary, etc.) can be found in about half of the patients.^{42,43}

TB meningitis is typically a subacute disease. Symptoms can be present for 1 day to 9 months with a median of 10 to 14 days prior to diagnosis.^{42,44} A prodromal phase of low-grade fever, malaise, headache, dizziness, vomiting, and/or personality changes may be present for 2 to 3 weeks before patients seek medical care. Typical findings at presentation include worsening headache, altered mental status, stroke, hydrocephalus, and cranial neuropathies. These clinical features are the result of basilar meningeal fibrosis and vascular inflammation.⁴⁵ Classic features of bacterial meningitis, such as stiff neck and fever, may be absent. When allowed to progress, seizures and coma may ensue.

The diagnosis of TB meningitis can be difficult and may be based only on clinical findings without definitive microbiological proof. The tuberculin skin test is positive in only about 50% of patients with TB meningitis. Certain clinical characteristics such as longer duration of symptoms (>6 days), moderate cerebrospinal fluid (CSF) pleocytosis, and the presence of focal deficits increase the probability of TB meningitis.^{46,47} Characteristic CSF findings of TB meningitis include

- Leukocytosis with predominance of lymphocytes. White blood cell counts are usually between 100 and 500 cells/ μ L. Lower white blood cell counts and neutrophil predominance may be seen very early in the course of the disease.
- Elevated protein levels, usually between 100 and 500 mg/dL
- Low glucose levels, typically less than 45 mg/dL

CSF samples should be sent for acid-fast smears, but this has low sensitivity. Because TB meningitis is a paucibacillary disease, centrifuging larger quantities of CSF (10–15 mL) from several lumbar punctures can increase the sensitivity. Culture is also associated with low sensitivity and can take weeks to become positive. A stereotactic biopsy can be performed if tissue samples are needed. Mycobacterial antigens by ELISA or radioimmunoassay have been detected in the

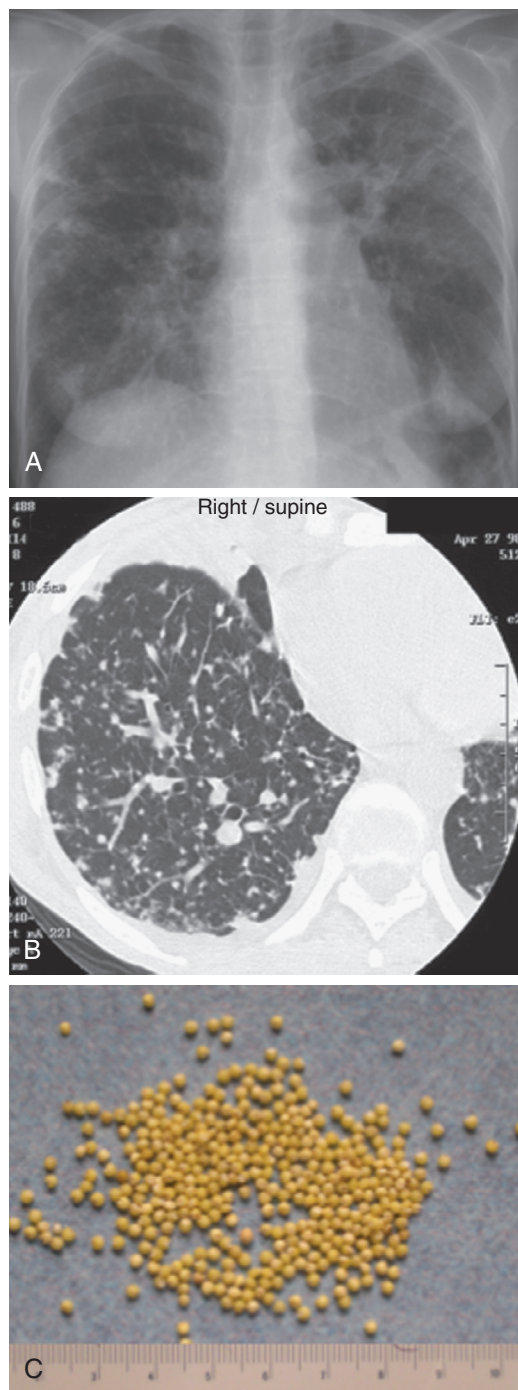


FIGURE 132-2 ■ Miliary TB. **A**, Chest radiograph of a patient with miliary TB. **B**, The chest CT scan of the same patient. Both show the characteristically small, less than 2-mm, nodules that are supposed to resemble **(C)** millet seeds. Note that millet seeds are approximately 2 mm in diameter.

CSF of patients with TB meningitis.⁴⁸ A large study cited sensitivities of 90% for interferon-gamma (IFN- γ) release assay, 82% for automated culture systems, 73% for Lowenstein-Jensen medium, 30% for adenosine deaminase, and 27% for Ehrlich-Ziehl-Neelsen acid-fast staining of the CSF.⁴⁹

In recent years, the use of nucleic acid amplification assays (NAAs) has been shown to aid in the diagnosis of TB meningitis. These tests can detect *M. tuberculosis* in a few hours. Their sensitivity is

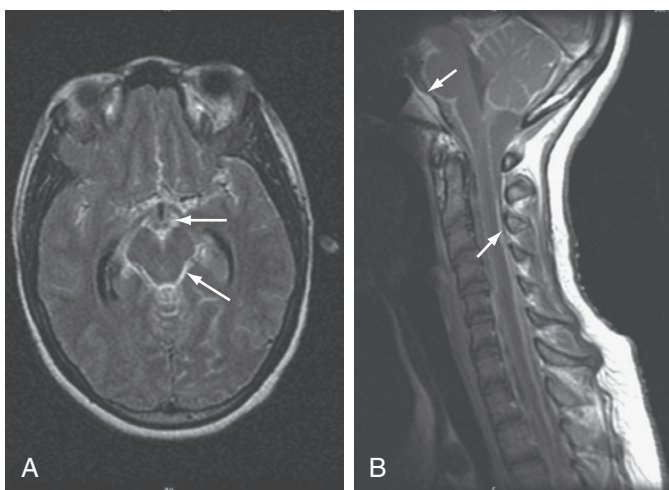


FIGURE 132-3 ■ Tuberculous meningitis. T1-weighted **(A)** transverse MRI of the brain and **(B)** sagittal MRI of the base of the brain and the spinal cord in a patient with tuberculous meningitis. Note the enhanced meninges (arrows) in the basilar regions of the brain, brainstem, and spinal cord.

56% to 62%, though it may be as high as 80% among HIV-infected patients, with a specificity of 95% to 98%.⁵⁰⁻⁵² Comparisons of NAAs and microscopy/culture using large volumes of CSF have indicated that the sensitivity of microscopy was similar to that of NAAs for the diagnosis of TB meningitis, and repeated testing gave the highest diagnostic yield.⁵³ The sensitivity of CSF microscopy and culture falls rapidly after the start of treatment, whereas mycobacterial DNA may remain detectable within the CSF up to a month after the start of treatment.⁵⁴ Given the high morbidity and mortality associated with TB meningitis, the most recent WHO recommendations include the use of Xpert MTB/RIF®, a NAA, to be used in preference to conventional microscopy and culture as the initial diagnostic test in patients with suspected TB meningitis.² Regardless of which diagnostic test is used, a negative test neither excludes the diagnosis nor obviates the need for continued empiric treatment if the clinical suspicion is high.⁵⁵

Magnetic resonance imaging (MRI) often reveals a basilar meningeal enhancement (Fig. 132-3) and/or hydrocephalus.⁴³ Hypodensities due to cerebral infarcts and ring- or nodular enhancing lesions can also be seen. MRI is superior to computed tomography for evaluating the brainstem and the extent of lesions.

The outcome of TB meningitis is improved by timely treatment. Thus, empiric treatment is warranted when risk factors and clinical features are suggestive of TB meningitis, even before microbiological confirmation. Chemotherapy for TB meningitis follows the model of short-course chemotherapy for pulmonary TB—an induction phase, followed by a continuation phase. However, unlike pulmonary TB, the optimal drug regimen and duration of each phase of treatment are not clearly established. INH and RIF remain the most essential drugs. INH penetrates the CSF freely and has potent early bactericidal activity.⁵⁶⁻⁵⁸ RIF penetrates the CSF less well (maximum concentrations around 30% of plasma), but the high mortality from RIF-resistant TB meningitis has confirmed its central role in the treatment of central nervous system (CNS) disease.⁵⁹ One study compared standard oral doses of RIF (450 mg) to higher doses of RIF (600 mg) administered intravenously. The higher dose RIF group had three times higher CSF concentrations than the standard oral dose group as well as improved mortality (35% vs. 65%).⁶⁰ INH, RIF, and pyrazinamide are considered mandatory at the beginning of TB meningitis treatment, and some centers use all three drugs for the duration of therapy.⁶¹ There are no data from controlled trials to guide the choice of the fourth drug. Most

authorities recommend either streptomycin or ethambutol, although neither penetrates the CSF well in the absence of inflammation, and both can produce significant adverse reactions. Therapy should be continued for 9 to 12 months.

Adjunctive corticosteroid treatment of TB meningitis has been recommended for more than 50 years, but there has been long-standing concern that corticosteroids may reduce the penetration of anti-TB drugs into the CNS.⁴⁵ A Cochrane systematic review and meta-analysis of seven randomized controlled trials involving 1140 participants (with 411 deaths) concluded that corticosteroids improved outcome in HIV-negative children and adults with TB meningitis but that the benefit in HIV-infected individuals remains uncertain.⁶² The results were heavily influenced by a study performed in 545 Vietnamese adults with TB meningitis, which observed that treatment with dexamethasone was associated with a significantly reduced risk of death.⁶³ However, there was no demonstrable improvement in the combined end point of death or severe disability at the 9-month follow-up. The survival benefit associated with corticosteroid therapy may have been due, in part, to a reduction in severe adverse events (9.5% vs. 16%), particularly hepatitis, that necessitated changes in anti-TB drug regimens. No mortality benefit from dexamethasone was evident in 98 HIV-infected patients included in the study.⁶³

Since there are no controlled trials comparing different corticosteroid regimens, the choice of regimen should be based on those found to be effective in published trials. One recommended regimen for adults is dexamethasone 12 mg a day for 3 weeks, followed by a gradual taper over the next 3 weeks.⁶⁴ In a large study from Vietnam, patients with mild disease received intravenous dexamethasone 0.3 mg/kg/day \times 1 week, 0.2 mg/kg/day \times 1 week, and then 4 weeks of tapering oral therapy.⁶³ For patients with severer TB meningitis, intravenous dexamethasone was given for 4 weeks (1 week each of 0.4 mg/kg/day, 0.3 mg/kg/day, 0.2 mg/kg/day, and 0.1 mg/kg/day), followed by 4 weeks of tapering oral dexamethasone therapy.⁶³

The prognosis of TB meningitis largely depends on the neurologic status at the time of presentation and time to treatment initiation. Most patients will die in 5 to 8 weeks if not treated. Various case series indicate a mortality rate between 7% and 65% in developed countries and up to 69% in underdeveloped areas.^{42,43,65} Neurologic sequelae occur in up to 50% of survivors.⁶⁵ Mortality risk is the highest in those who are elderly and with comorbidities, severe neurologic involvement on admission, and rapid progression of disease.

Other Central Nervous System Manifestations of Tuberculosis

Other CNS manifestations of TB include brain abscesses, intracranial tuberculomas, vasculitis, radiculomyelitis, and spinal arachnoiditis. These can occur in conjunction with TB meningitis but are less likely to be seen in the ICU when isolated. Intracranial tuberculomas are more common among pediatric patients, especially infants, and can occur in any region of the brain. They result from hematogenous spread of TB. Tuberculous radiculomyelitis is a paradoxical reaction to the treatment of TB meningitis and may respond to corticosteroids. Signs and symptoms include subacute paraparesis, radicular pain, bladder disturbance, and paralysis.⁶⁶

CARDIOVASCULAR TUBERCULOSIS

Tuberculous Pericarditis

Pericarditis is an uncommon, but important, manifestation of TB. In countries with a low incidence of TB, it is primarily a disease among the elderly and those with HIV, but it should be considered as a differential diagnosis of any patient with pericarditis and/or pericardial effusion. Tuberculous pericarditis can result from local spread from the lungs, tracheobronchial tree, lymph nodes, or adjacent bones or by disseminated infection. The onset is usually insidious. Presenting signs and symptoms can be nonspecific (fever, dyspnea, and weight loss)

and/or more specific to the pericardium, such as characteristic pericardial chest pain. Large hemorrhagic effusions may develop, resulting in cardiac tamponade. Pericardial inflammation and thickening may eventually cause constrictive pericarditis. The presence of both pericardial effusion and constrictive pericarditis is physiologically characterized by the continued elevation of diastolic pressure after pericardiocentesis. Such a finding should raise suspicion for tuberculous pericarditis.

The diagnosis of tuberculous pericarditis can be difficult to prove. Culture of pericardial fluid is positive in only 30% of cases, and pericardial biopsy has a yield of approximately 60%. Biopsy of the pericardium may reveal granulomatous changes consistent with TB or stain positive for acid-fast bacteria. The presence of elevated adenosine deaminase levels in the pericardial fluid has been shown to indicate tuberculous pericarditis, but confirmation is needed.⁶⁷ PCR holds promise as a more sensitive test in the diagnosis of tuberculous pericarditis.^{68,69} Many individuals are treated empirically for tuberculous pericarditis based on clinical suspicion, positive tuberculin skin test results, imaging studies, and exudative pericardial fluid with high protein and mononuclear white count. Treatment involves standard four-drug regimens as for other manifestations of TB. Prednisone 60 mg a day, tapered off over 11 weeks, is sometimes used in addition to anti-TB treatment and has been shown to reduce the need for operative intervention.⁷⁰ Further study of corticosteroid use in tuberculous pericarditis is ongoing.⁷¹ Pericardiectomy is sometimes necessary in the treatment of refractory or recurrent disease.

Other Cardiovascular Manifestations of Tuberculosis

In addition to the pericardium, TB may also affect the myocardium, endocardium, and epicardium (coronary arteries). These disorders are very rare. Tuberculous myocarditis occurs via direct spread from pericardial or mediastinal lymph nodes or from disseminated disease.⁷² Endocardial involvement may manifest as endocarditis or as mural thrombi with entrapped *M. tuberculosis*. TB may also affect the coronary arteries, resulting in coronary arteritis with granulomatous inflammation of the arterial wall and obliterative intimal fibrosis.⁷³

The aorta can be affected by TB, causing aortitis, aortointestinal fistula formation, or rupture.^{74,75} The pathogenesis of aortitis includes septic embolization from endocarditis, seeding of a preexisting aneurysm from bacteremia, or extension from a contiguous site of infection. Signs and symptoms include fever, abdominal or back pain, and a palpable abdominal mass. Blood cultures are positive for *M. tuberculosis* in approximately 15% of cases. CT findings include air in the aortic wall, a periaortic nodularity, a saccular aneurysm in a non-calcified aorta, and a rapidly increasing aortic diameter. A primary mycotic aneurysm of the aorta may be a sequela of chronic tuberculous aortitis.^{76,77}

TUBERCULOSIS IN HUMAN IMMUNODEFICIENCY VIRUS-POSITIVE PATIENTS

HIV is the most important host risk factor for active TB.⁷⁸ In many developing countries, TB is the most common opportunistic infection associated with HIV. The estimated annual risk of active TB among persons with LTBI in the general population is 12.9 per 1000 person-years. In contrast, rates of progression to active TB among HIV-infected persons with LTBI range from 35 to 162 per 1000 person-years. More recent estimates for reactivation TB in HIV-positive individuals shows a rate ratio of 57 (95% CI, 27-120) compared to HIV-negative individuals with LTBI.⁷⁹ Since TB may be an initial manifestation of HIV infection, all patients with TB should be tested for HIV. The WHO estimates that globally, 13% of TB patients in 2013 were co-infected with HIV and that HIV co-infected patients accounted for over 25% of deaths from TB.²

The mechanism of increased TB susceptibility in HIV-positive persons is incompletely understood. Unlike other AIDS-related opportunistic infections, the CD4⁺ count is not always a reliable predictor of increased risk of TB disease, albeit CD4⁺ lymphopenia would reduce IFN γ production, impairing macrophage and dendritic cell activation. Alveolar macrophages (AMs) are important components of an effective immune response to TB,⁸⁰ and AM apoptosis represents a critical host defense mechanism that promotes *M. tuberculosis* elimination. In this context, another possible mechanism by which HIV increases susceptibility to TB is that HIV-infected AMs have a reduced apoptotic response to *M. tuberculosis* compared to AMs from healthy individuals.^{81,82}

When the CD4⁺ count is above 350 cells/ μ L, pulmonary TB in AIDS patients is more likely to present with typical chest radiograph findings of upper lobe fibrocavitary disease.⁸³ However, as the CD4⁺ count decreases, pulmonary TB tends to manifest with more atypical radiographic manifestations, such as mediastinal adenopathy, diffuse miliary or nodular infiltrates, focal lower zone infiltrates, and lack of cavitation.⁸³ Among HIV-positive persons, death from TB was significantly associated with low CD4⁺ counts.²⁵ While co-infection with HIV is considered to contribute significantly to TB-related mortality, a study showed no difference in mortality in TB patients requiring ICU care between those who were HIV negative and those with advanced AIDS in a low-burden, resource-rich country where state-of-the-art intensive care is available, suggesting that the severity of illness has a greater influence on mortality than the HIV status per se.²⁵ Extrapulmonary TB is more common among HIV-positive patients, occurring in up to 70% of patients. Disease involving the lymph nodes is especially common. Other extrapulmonary manifestations include miliary disease, sepsis, and CNS disease.^{30,84} Empiric treatment may be necessary before the diagnosis is confirmed. If rapid diagnosis is needed, NAAs can be used, although they are more accurate in smear-positive cases.

After initiating highly active antiretroviral therapy (HAART) in severely immunosuppressed patients, those with subclinical or recently diagnosed TB may display a paradoxical reaction, where there is an apparent clinical worsening of TB while on appropriate anti-TB treatment.⁸⁵⁻⁸⁷ This phenomenon, also known by the more descriptive name of *immune reconstitution inflammatory syndrome* (IRIS), can manifest as early as 7 days after starting HAART. Signs and symptoms include fever, weight loss, and evidence of local inflammatory reactions such as lymphadenitis and worsening pulmonary disease such as increased pulmonary consolidation, nodules, and effusions. Histologically, a vigorous suppurative and necrotizing granulomatous reaction occurs, with or without caseation; cultures of infected material are almost invariably positive.

Treatment of TB in patients with HIV is similar to that in HIV-negative patients but is often complicated by drug interactions between TB medications and antiretrovirals.⁸⁸ Protease inhibitors and nonnucleoside reverse transcriptase inhibitors can either induce or inhibit activity of the P450-3A (CYP3A) system. RIF can increase the activity of CYP3A, leading to decreased levels of several antiretrovirals. Rifabutin is a less potent inducer of the CYP3A system and is associated with fewer drug-drug interactions, but dose adjustments may be needed. Despite these potential drug interactions, an RIF-based regimen should be used whenever possible. Patients with liver disease such as hepatitis C may be at increased risk of drug-induced hepatotoxicity. Another treatment issue in HIV-TB co-infection is that patients may fail to properly absorb the anti-TB drugs, which may increase the risk of treatment failure, relapses, and acquired drug resistance.⁸⁹

Because of the increased risk of RIF resistance, patients with HIV should *not* receive once weekly INH-rifapentine in the continuation phase of treatment. Twice weekly INH-RIF or INH-rifabutin should be avoided when the CD4⁺ cell count is less than 100 cells/ μ L. Treating drug-susceptible pulmonary TB in HIV-positive individuals for 9 months rather than the standard 6 months is associated with lower relapse rates.^{90,91} Recommendations regarding the treatment of TB in HIV patients are frequently revised as new drugs and information

become available. The following websites can assist with treatment decisions and information on drug-drug interactions:

- http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm
- <http://www.medscape.com/updates/quickguide>
- <http://www.nationaltbcenter.edu/>

If a patient develops IRIS while on HAART, it is generally recommended that HIV therapy be continued during TB treatment whenever possible because IRIS is usually self-limited. However, more severe IRIS may require the addition of corticosteroids and/or temporary discontinuation of HAART. Patients with the lowest CD4⁺ counts, less than 50 cells/ μ L, are at highest risk of severe IRIS with the initiation of HAART, though they also have the greatest mortality benefit with early HAART initiation.^{92,93} There is ongoing debate as to the safest time for the initiation of HAART following the start of TB treatment.^{92,94,95} The WHO currently recommends the initiation of HAART, for those not already on it, within 8 weeks of TB treatment initiation.

TUBERCULOSIS AND IMMUNOMODULATORY THERAPIES

TNF- α plays a central role in the pathogenesis of various inflammatory disorders and in the pathophysiologic response to many infections. TNF- α is produced predominantly by macrophages and lymphocytes and is active both as a membrane-bound and soluble protein.^{96,97} In several animal models, TNF- α plays an essential part in the host response to TB.⁹⁸ One mechanism by which TNF- α potentiates the host defense is by its ability to induce apoptosis of infected cells. Macrophage apoptosis helps contain *M. tuberculosis* by maintaining granuloma integrity, increasing the efficiency of antigen presentation, and promoting the killing of intracellular *M. tuberculosis*.⁹⁹ Administration of antibodies neutralizing TNF- α resulted in the reactivation of TB in a mouse model.¹⁰⁰ Interruption of the normal TNF- α -controlled response to TB reduces apoptosis, disrupts granuloma integrity, and predisposes to disseminated infection.

TNF- α antagonists are increasingly used for the treatment of various chronic inflammatory disorders. Currently licensed TNF- α antagonists fall into two main types: monoclonal neutralizing anti-TNF- α antibodies and soluble p75 subunits of the TNF- α receptor (TNF- α -R). The soluble TNF- α -Rs antagonize TNF- α function by acting as decoys to bind TNF- α . Four monoclonal anti-TNF- α antibodies (infliximab, adalimumab, certolizumab pegol, and golimumab) and two TNF- α -Rs (etanercept and abatacept) are in clinical use. Patients treated with TNF- α -blockers have a TB incidence rate of 1.17 per 1000 patient-years—12.2 times that of the general population¹⁰¹; almost all these cases are due to the reactivation of LTBI. A consensus statement reported that the relative risk for reactivation TB is increased 25-fold in individuals who use TNF- α antagonists compared to that in nonusers.¹⁰²

Important differences have emerged among the TNF- α antagonists in regard to the risks of reactivation TB. Consistently, the excess risk is associated with infliximab and adalimumab rather than etanercept. For example, compared with etanercept, infliximab is associated with a two- to seven-fold greater risk of TB, shorter time to TB onset (17 vs. 48 weeks), and a higher proportion of TB cases with disseminated or extrapulmonary disease (25% vs. 10%).^{103,104} It is not entirely clear why the neutralizing antibodies to TNF- α put people at greater risk of reactivation TB than soluble TNF- α receptors. Possible reasons include a longer duration of action of infliximab and adalimumab and their ability to bind to membrane-bound TNF- α with greater affinity than etanercept.⁹⁶ As a result, infliximab can induce death in T cells that express the membrane-bound TNF- α , whereas etanercept cannot. In addition, anti-TNF- α antibodies can inhibit T-cell activation and IFN- γ production, whereas etanercept cannot. Thus, the pharmacokinetic and biological differences between the two main types of TNF- α antagonists may account for the greater susceptibility to intracellular pathogens with the use of the anti-TNF- α antibodies.^{96,105} As might be anticipated, when anti-TNF- α antibodies are used in combination

with other immunosuppressive medications such as methotrexate or azathioprine, the risk of TB reactivation is higher than that with the use of anti-TNF- α antibodies alone.¹⁰⁶

Antagonists to other inflammatory cytokines are also being used in the management of patients with rheumatologic and inflammatory disorders. Interleukin-1 (IL-1) receptor antagonist (IL-1Ra) is the naturally occurring protein that prevents the action of IL-1 α and IL-1 β by competitively binding to IL-1R. Anakinra is a recombinant human form of IL-1Ra. In a case report, anakinra was associated with reactivation TB.¹⁰⁷

■ DIAGNOSIS OF TUBERCULOSIS

When TB is suspected, the first diagnostic test should be a microscopic examination and culture for mycobacteria of relevant body fluids or tissues. Several specimens are often required, especially for CNS disease.

Patients with suspected pulmonary TB should be placed in respiratory isolation until three sputa, collected by at least 8 hours between samples, are negative for acid-fast bacteria. Since patients with extrapulmonary disease may also have occult pulmonary disease, it is generally recommended that sputum smears be sent for these patients regardless of chest radiographic findings.

Since acid-fast smear does not differentiate between *M. tuberculosis* and nontuberculous mycobacteria, culture is used to confirm species and determine drug susceptibility. Simultaneous culture on both liquid and solid media is recommended. Liquid medium such as newer BACTEC systems allow growth of the organism in about 14 days, whereas growth takes 3 to 6 weeks on solid media (Lowenstein-Jensen or Middlebrook 7H11). Once sufficient growth is obtained, species identification can be obtained via conventional biochemical tests or more rapid tests such as nucleic acid probes, high-performance liquid chromatography, the NAP test (p-nitro- α -acetylamino- β -hydroxypropionophenone), or molecular tests. Only experienced laboratories should complete susceptibility testing on culture-positive specimens. Molecular fingerprinting by restriction fragment length polymorphism can be used to distinguish strain types when laboratory contamination is suspected.

Although rapid and inexpensive, acid-fast smear microscopy is limited by its poor sensitivity (approximately 50% sensitivity in culture-confirmed pulmonary TB cases) and suboptimal specificity (50%-80%) in settings where nontuberculous mycobacteria are commonly isolated.¹⁰⁸⁻¹¹⁰ NAAs have become a routine procedure in many settings because they can reliably detect *M. tuberculosis* in specimens

1 or more weeks earlier than culture.¹⁰⁹ Because of the increasing use of NAAs and the potential impact on patient care and public health, the Centers for Disease Control (CDC) and the Association of Public Health Laboratories made recommendations for using NAAs for laboratory confirmation of TB. The CDC recommends that NAAs be performed on at least one respiratory specimen from each patient in whom a diagnosis of TB is being considered but has not yet been established and for whom the test result would alter case management or TB control activities.^{111,112}

■ TREATMENT OF TUBERCULOSIS

Standard treatment of adults with drug-susceptible TB is a three- or four-drug regimen for at least 6 months.^{113,114} The typical course of therapy for drug-susceptible disease is 2 months of INH, RIF, pyrazinamide (PZA), and ethambutol (EMB) (initial phase), followed by 4 months of INH and RIF (continuation phase) (Tables 132-1 and 132-2). A 9- to 12-month regimen is suggested for TB meningitis, for pulmonary TB that is slow to respond to therapy such as those with

TABLE 132-1

Current Regimens for Treatment of Drug-Susceptible TB

| REGIMEN | INITIAL PHASE | CONTINUATION PHASE |
|--------------------------------|---|--|
| DAILY or 5 days per week | 8 weeks of INH, RIF, PZA, \pm EMB | 18 weeks of INH and RIF |
| INTERMITTENT | a) 2 weeks of daily INH, RIF, PZA, and EMB (or SM), then 6 weeks of INH, RIF, PZA, EMB BIW or TIW b) 8 weeks of thrice-weekly INH, RIF, PZA, and EMB (or SM) | 18 weeks of INH and RIF BIW 18 weeks of INH and RIF TIW |

The daily regimen is employed when patients self-administer their drugs. There is enough redundancy that, if patients miss some of their doses, the outcome will remain acceptable. The intermittent regimens are intended for DOT. Regimen (a) entails a total of 62 doses and has yielded over 95% success rates.¹²⁸ Regimen (b) involves 78 doses and has also resulted in success rates of approximately 95% in Hong Kong where it is the standard regimen.¹²⁹ BIW, twice weekly; EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; SM, streptomycin; TIW, thrice weekly.

TABLE 132-2 Dosages of First-line Antituberculosis Drugs (in Adults) and Major Adverse Effects

| DRUG | DAILY DOSAGE | TWICE OR THRICE WEEKLY DOSAGE | ADVERSE EFFECTS |
|---------------|---|--------------------------------------|--|
| Isoniazid | 5 mg/kg oral (max: 300 mg) | 900 mg BIW 600 mg TIW | Hepatitis, peripheral neuritis, drug-induced lupus, seizures, and hypersensitivity with rash and fever. Drug interactions with dilantin and disulfiram. Pyridoxine can decrease neurotoxicity. |
| Rifampin | 10 mg/kg oral (max: 600 mg) | 10 mg/kg 600 mg BIW 600 mg TIW | Orange body secretions, flu-like syndrome, hepatitis, pruritus, thrombocytopenia, nausea, anorexia, diarrhea, renal failure, and multiple drug interactions |
| Rifabutin* | 10 mg/kg oral (max: 300 mg) | 5 mg/kg | Neutropenia, uveitis, hepatotoxicity, orange discoloration of body fluids |
| Rifapentine** | 10 mg/kg once WEEKLY (max: 600 mg) | | Similar to rifampin |
| Pyrazinamide | 15-30 mg/kg oral (max: 2.0 gm) | 30-35 mg/kg | Hyperuricemia, hepatitis, rash, nausea, and anorexia |
| Ethambutol | 25 mg/kg initial 2 months, then 15 mg/kg oral | 50 mg/kg BIW 30 mg/kg TIW | Optic neuritis and gastrointestinal discomfort |

*Rifabutin and rifapentine are considered first-line agents when intolerance to rifampin precludes its use or concerning drug interactions exist.

**Rifapentine is only used in a once-weekly dose in HIV-negative patients with noncavitary and uncomplicated disease. It is not approved for use in children.

BIW, twice weekly; TIW, thrice weekly.

cavitary lesions and persistent sputum culture positivity even after 2 months of an appropriate four-drug regimen, or when PZA is not used in the induction regimen. EMB can be discontinued when drug-susceptibility studies show sensitivity to INH and RIF. Streptomycin can be used instead of EMB if resistance is unlikely or susceptibility is shown. The continuation phase can be daily therapy, twice weekly therapy, or thrice weekly therapy for drug-susceptible TB (see Table 132-1). See the HIV section for details of treating TB in HIV-positive patients. Specific guidelines including information on first- and second-line agents have been published by the CDC.¹¹⁵

When MDR-TB is suspected or confirmed, additional drugs that may be used include amikacin, a fluoroquinolone (levofloxacin, moxifloxacin), capreomycin, ethionamide, cycloserine, para-aminosalicylic acid, and/or linezolid.^{15a} In the absence of prospective, randomized trials, individual patient data meta-analyses have shown that treatment success for MDR-TB is associated with the use of fluoroquinolones, ethionamide, or prothionamide and a greater total number of effective drugs.⁸ Whenever possible, treatment for an MDR-TB strain should be guided by drug-susceptibility testing to EMB, PZA, and the second-line anti-TB drugs.¹¹⁶ While favorable results have been reported with new anti-TB drugs such as bedaquiline and delamanid, it is important to emphasize that efficacy was initially based on the surrogate end point of accelerated culture conversion and not on cure rate or survival¹¹⁷⁻¹²¹; indeed, in a phase 2 trial, there were significantly more deaths when bedaquiline was added to the standard regimen.¹²⁰ Local public health departments should be contacted to meet reporting requirements and will usually be responsible for treatment monitoring. Directly observed therapy should be implemented whenever possible. Patients with MDR-TB require longer therapy (generally 18 months of treatment after the last negative sputum culture). Surgical resection after 2 to 3 months of treatment may improve outcome.¹¹⁵

Parenteral therapy may be required in ICU patients and is recommended for patients with fulminant disease (Table 132-3). When delivered enterally, half of the ICU patients have subtherapeutic levels of RIF.¹²² INH and RIF are available in parenteral forms; EMB and PZA are not. Other active medications available for intravenous use include aminoglycosides, fluoroquinolones, and capreomycin. In patients with renal failure, dose adjustments are required for those taking EMB, PZA, cycloserine, an aminoglycoside, capreomycin, or a fluoroquinolone. INH and PZA should probably be withheld in the setting of severe liver failure. An expert in the treatment of TB should be consulted when treating complicated ICU patients or those with MDR-TB.

Corticosteroids are generally recommended in the treatment of several TB conditions including TB meningitis and pericarditis, as discussed above.¹²³ Their role in patients with respiratory failure due to TB and in patients with severe AIDS-associated TB has not been proven, but many have used corticosteroids for these conditions. Typical therapy includes prednisone at 40 to 80 mg per day, tapered over a few weeks.

RISK TO HEALTHCARE WORKERS

The awareness that caring for TB patients poses a risk to healthcare workers (HCWs) did not emerge until the 1950s and 1960s, when

TABLE 132-3

**Selected Parenteral Medications
Used in Treating Tuberculosis¹¹⁵**

| MEDICATION | PREPARATION | INITIAL DOSAGE IN ADULTS (MAXIMUM DOSAGE) |
|-----------------------|-------------|---|
| Isoniazid | PO, IV, IM | 5 mg/kg/day (300 mg) |
| Rifampin | PO, IV | 10 mg/kg/day (600 mg) |
| Streptomycin | IV, IM | 10-15 mg/kg/day or 750-1000 mg/day |
| Amikacin | IV, IM | Same as above |
| Kanamycin | IV, IM | Same as above |
| Capreomycin | IV, IM | Same as above |
| p-aminosalicylic acid | PO, IV | 8-12 g/day in 2 or 3 doses |
| Levofloxacin | PO, IV | 500-1000 mg/day |
| Moxifloxacin | PO, IV | 400 mg/day |

Notes: Table shows routine daily dosing. Dosages may differ in children and in patients in intermittent therapy. Persons over age 59 should receive the lower dose for aminoglycosides (750 mg).

IM, intramuscular; IV, intravenous; PO, oral.

studies established that *M. tuberculosis* infection was transmitted by the airborne route.¹²⁴ However, occupational transmission received little attention until numerous outbreaks of TB and MDR-TB occurred in U.S. and European hospitals in the late 1980s and early 1990s.¹²⁵ At that time, more than 20 HCWs became ill with MDR-TB, and at least 10 died.¹²⁶ Hundreds of HCWs may be latently infected with MDR-TB and thus represent a relatively large reservoir of individuals at risk of future reactivation MDR-TB.

Pulmonologists are at higher risk of occupational exposure to TB than other medical specialists. Atypical presentations of TB can put providers at increased risk when TB is not suspected and proper precautions are not taken.¹²⁷ Bronchoscopy requires close contact with patients and provokes coughing, which likely contributes to the tuberculin skin test conversion rate of 11% among pulmonary fellows.¹²⁷ DMF-HEPA respirators should be used when performing bronchoscopy on patients with known or suspected TB.¹²⁷

In HCWs with negative tuberculin skin test reactions who undergo repeat testing, an increase in reaction size of more than 10 mm within a period of 2 years should be considered a skin-test conversion indicative of recent infection with *M. tuberculosis*. Since tuberculin skin test conversion typically occurs 3 to 8 weeks after primary infection, skin testing should be performed at 3 weeks following exposure.

HCWs with potential exposure should be monitored for symptoms, and unless they are known to have a positive tuberculin skin test at baseline, skin testing or an IFN- γ release assay should be performed as soon as possible after the exposure to establish a baseline. If initial screening is negative, testing should be repeated 8 to 10 weeks following exposure, and if found to be positive, treatment for LTBI is recommended.

KEY POINTS

- Whereas pulmonary TB classically develops cavitary lung disease, it can present in many ways, including ARDS and respiratory failure.
- Tuberculous meningitis typically has a subacute presentation and has a high mortality rate, which is improved with prompt treatment.
- Tuberculous pericarditis is rare but can result in constrictive pericarditis or cardiac tamponade from a hemorrhagic effusion.
- Disseminated TB can affect nearly any organ and is most common in very young or old patients and those who are immunocompromised.

KEY POINTS—cont'd

5. Patients with HIV and those on anti-TNF therapies are at increased risk of developing active TB.
6. Culture remains the cornerstone of diagnosis of TB and is important for drug resistance testing. However, nucleic acid amplification assays can provide a much more rapid diagnosis and are especially recommended for use with CSF and other fluids where culture positivity is classically low, such as pericardial and pleural fluid.
7. Treatment of TB requires several drugs given over many months, though the exact regimen will vary depending on the site of disease and the susceptibility of the cultured organism.
8. Treating with a course of steroids is recommended to reduce morbidity and mortality from TB meningitis and TB pericarditis.

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Although the spectrum of possible “tropical” infections in a patient with exposures overseas may initially seem daunting, a detailed history of the patient’s travel itinerary, activities, and exposures can often significantly narrow the differential diagnosis (Table 133-1). This must include more than simply recording the countries to which the patient traveled. Exposures of a business traveler staying at hotels and dining in fine restaurants in a major city may differ dramatically from those of a student backpacking through rural areas of the same country. Knowledge of the diseases endemic in a given area and their incubation periods and drug resistance patterns is vital (Fig. 133-1 and Table 133-2). In addition, most nontropical infections are common in developing countries. Thus, although the differential diagnosis must be expanded to include tropical diseases, common illnesses seen in developing and industrialized countries must also be considered.

People prone to malaria can be divided into three groups: (1) nonimmune persons having no history of exposure to malaria—primarily tourists and young children, regardless of geographic origin—after the waning of maternal antibodies (around age 6 months); (2) immune or semi-immune persons residing in tropical countries who are repeatedly exposed; and (3) those originally from tropical countries but now residing elsewhere who, in the absence of continued exposure, have waning immunity. The degree of immunity may exert profound effects on the presentation and severity of illness. For example, a returning traveler may develop severe malaria at a relatively low parasitemic load, whereas a resident of sub-Saharan Africa with the same degree of parasitemia may be asymptomatic. Genetic differences in susceptibility may also exist, such as resistance to *Plasmodium vivax* in blacks because of the absence of Duffy antigen, which serves as the receptor, or the relative protection from severe malaria of any species afforded to those carrying the sickle cell trait.¹⁻³

In returning travelers, knowledge of pretravel vaccinations as well as prescribed and taken chemoprophylaxis (which often turn out not to be the same) is imperative. Nevertheless, these preventive measures do not confer 100% protection and should not be used to completely discard a given entity from the differential diagnosis. Both physicians and patients frequently err in the prescribing of and adherence to appropriate prophylactic regimens.^{4,5} Chemotherapy, complete or partial, may prolong the incubation period or alter the presentation of the illness. Those initially from tropical countries are often less likely to seek pretravel medical advice before making a home visit and also often have considerably more exposures to tropical pathogens during their visit than do short-term travelers from industrialized countries.⁶

People living in resource-poor tropical countries are more likely to have complicating health problems but less likely to have been previously diagnosed or controlled. Underlying conditions, such as diabetes, hypertension, malnutrition, chronic anemia, intestinal parasites, tuberculosis, human immunodeficiency virus (HIV), or hepatitis virus infection may be discovered at the time of acute illness.⁷ Infection with multiple tropical pathogens is common in those living in endemic areas. Thus finding a given pathogen cannot automatically be assumed to be the cause of the patient’s current illness.

■ EPIDEMIOLOGY

Malaria parasites are spread to humans by the bite of anopheline mosquitoes. Four species of *Plasmodium* commonly cause malaria in humans: *Plasmodium falciparum*, *P. vivax*, *Plasmodium ovale*, and *Plasmodium malariae* (see Table 133-2). A fifth species, *Plasmodium knowlesi*, is a zoonotic parasite of monkeys found to also cause disease in humans with exposure in the rainforests of Southeast Asia.^{8,9} Furthermore, evidence suggests that there may be distinct species of *P. ovale*.¹⁰ Malaria is the most common serious infection in tropical countries and in returning travelers, and it should therefore be considered in any patient reporting travel to malaria-endemic areas or with exposure to unscreened blood products (“transfusion malaria”) or blood-contaminated needles. Increased travel and immigration have resulted in increases in imported malaria in most industrialized countries.^{11,12}

The most prevalent and dangerous form of malaria is that due to *P. falciparum*. The risk of acquiring *P. falciparum* is highest in sub-Saharan Africa, in particular in West Africa¹³ and New Guinea, moderate in India, and comparatively low in Southeast Asia and Latin America.^{14,15} However, there is increasing recognition that *P. vivax*, the second most common cause of malaria and previously considered to be benign, can also cause severe disease and death.^{16,17} *P. vivax* malaria is especially frequent in travelers returning from Oceania, although the parasite exists in all malaria-endemic regions except Haiti and the Dominican Republic.^{18,19} The dormant liver stage parasites (hypnozoites) that characterize *P. vivax* sometimes result in primary disease or relapse even years after infection. *P. knowlesi*, found in rainforests of Southeast Asia, including parts of Cambodia, China, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Vietnam, can also cause severe disease in humans.²⁰⁻²³

Malaria is occasionally reported in individuals without reported travel, usually resulting from the carriage of malaria-infected passengers (who may be asymptomatic) or anopheline mosquitoes on aircraft arriving from endemic areas.²⁴ The parasite may then be secondarily transmitted by anopheline mosquitoes endemic in some industrialized countries, including the United States.

■ PATHOPHYSIOLOGY

P. falciparum accounts for the vast majority of severe malaria because of (1) its ability to infect red blood cells (RBCs) of all ages, resulting in overwhelming parasitemia (up to 70% of RBCs); (2) its induction of adherence of parasitized RBCs to the microvascular wall, with consequent obstruction; (3) its induction of severe metabolic derangements directly through glucose consumption and lactate production and indirectly through the induction of cytokines; and (4) the high prevalence of chloroquine resistance to *P. falciparum* in many parts of the world (see Table 133-2). Nonimmune persons and pregnant women are at greatest risk. Human genetic and parasite strain differences probably play roles in the ultimate course of any given malarial infection.

Unlike the other species of malaria, *P. falciparum* causes decreased RBC deformability and the production of small protrusions or “knobs”

Text continued on p. 937

TABLE 133-1 Some Tropical Diseases That May Merit Management in an Intensive Care Unit*

| DISEASE AND ORGANISM | DISTINGUISHING CLINICAL FEATURES | INCUBATION PERIOD | GEOGRAPHIC DISTRIBUTION | MODE OF TRANSMISSION AND TYPICAL RISK FACTORS |
|--|--|--|---|--|
| NONSPECIFIC FEBRILE SYNDROMES | | | | |
| African trypanosomiasis, hemolympathic stage (<i>Trypanosoma brucei gambiense</i> and <i>brucei rhodesiense</i>) | Lymphadenopathy, HSM, edema, rash; 30% have history of chancre, rarely DIC and thrombocytopenia | 3-21 days | Sub-Saharan Africa | Tsetse fly bite; camping, safari |
| Babesiosis (<i>Babesia</i> spp.) | Hemolytic anemia, HSM | 3-28 days | North America, Europe, sporadic cases worldwide | Tick bite; blood transfusion (rare); especially severe in asplenic persons |
| Brucellosis (<i>Brucella</i> spp.) | Subacute presentation over weeks/months, HSM, weight loss; may involve large bones, joints, and spine | 2-8 weeks | Worldwide, especially Mediterranean, Middle East, and Latin America | Ingestion of contaminated dairy products; respiratory, skin, or conjunctival inoculation from contact with farm animals; abattoir workers, butchers, farmers |
| Candidiasis, disseminated (<i>Candida</i> spp.) | May involve any organ; skin or mucosal lesions not always present | 1-4 weeks | Worldwide | Usually in IH or after administration of long-term antibiotics or maintenance of indwelling catheters |
| Cat scratch disease (<i>Bartonella henselae</i>) | Papule or eschar at the site of inoculation, regional lymphadenopathy, fever may be mild, may progress to CNS involvement or endocarditis | 1-2 weeks | Worldwide | Cat scratch or bite; severe disease most often seen in IH |
| Coccidioidomycosis (<i>Coccidioides immitis</i>) | May see pneumonia with cavities, meningeal, skin, and bone involvement, and eosinophilia | 1-4 weeks, often RD [†] in IH | Desert areas of the Americas | Inhalation of spores from soil; disseminated disease more common in Filipinos, blacks, Hispanics, IH, and in pregnancy |
| Echinococcal cyst, leak, or rupture (<i>Echinococcus</i> spp.) | Allergic symptoms: urticaria, pruritus, and anaphylaxis | Years | Worldwide | Ingestion of eggs in feces of infected carnivores such as dogs and wolves; raising of domestic livestock |
| Ehrlichiosis (<i>Ehrlichia</i> spp.) | Rash (<50%), leukopenia, thrombocytopenia, HSM; may progress to GI, renal, pulmonary, or CNS involvement | 7-21 days | Sporadic foci worldwide | Tick bite; camping, safari |
| Histoplasmosis, disseminated (<i>Histoplasma capsulatum</i>) | Mucocutaneous lesions, lymphadenopathy, HSM, DIC; any organ may be involved | 1-4 weeks, usually RD | Tropics worldwide | Inhalation of spores from soil; severe disease, usually IH |
| Leptospirosis (<i>Leptospira</i> spp.) | Icterus, jaundice, conjunctival suffusion, rash, HSM; may be biphasic; may develop hepatorenal syndrome, CNS involvement, or pulmonary disease with hemorrhage | 2-20 days | Worldwide | Contaminated urine of many types of small mammals, either directly or through soil or standing water; hunting; military exercises |
| Malaria (<i>Plasmodium falciparum</i> , <i>P. vivax</i> , <i>P. ovale</i> , <i>P. malariae</i> , and <i>P. knowlesi</i>) | See text | See Table 133-2 | See Fig. 133-1 and Table 133-2 | Mosquito bite; transfusion |
| Measles | Conjunctivitis, coryza, cough, rash, Koplik spots | 5-14 days | Worldwide | Person-to-person via aerosol |
| Melioidosis (<i>Burkholderia pseudomallei</i>) | May develop pneumonia or local suppurative infection, shock (especially if IH) | 2-21 days | Southeast Asia (especially Thailand), Australia, sporadic foci in tropics worldwide | Exposure to contaminated soil or infected animals, person-to-person (rare), often IH |
| Monkeypox (monkeypox virus) | Diffuse vesicular rash resembling chickenpox but involving palms and soles, lymphadenopathy | 3-21 days | Central and West Africa | Person-to-person as well as from exposure to infected small mammals and monkeys; exotic pets; rule out smallpox/bioterrorism |
| <i>Mycobacterium avium-intracellulare</i> , disseminated | Usually subacute, HSM, weight loss | Months-years | Worldwide | Environmental organism causing opportunistic infection in IH |
| Oroya fever (<i>Bartonella bacilliformis</i>) | Acute anemia, jaundice, HSM, lymphadenopathy | 2-3 weeks | Peru, Ecuador, Colombia | Sandfly bite; hiking, camping |
| Paracoccidioidomycosis (<i>Paracoccidioides brasiliensis</i>) | May involve lungs, bones, skin, lymph nodes, adrenal glands, or mucous membranes | 1-4 weeks, often RD | Tropical America | Inhalation of spores from soil; more severe in IH |
| Penicilliosis (<i>Penicillium marneffe</i>) | Mucocutaneous lesions, HSM, lymphadenopathy, may have skeletal or pulmonary involvement | Unknown, probably >1 week | Southeast Asia | Reservoir unknown, most often IH |
| Plague (<i>Yersinia pestis</i>) | Localized tender lymphadenitis ("bubo"), pneumonia, shock | 2-8 days | Worldwide | Flea bite or person-to-person; areas of heavy rat infestations, R/O bioterrorism |

Continued

TABLE 133-1 Some Tropical Diseases That May Merit Management in an Intensive Care Unit*—cont'd

| DISEASE AND ORGANISM | DISTINGUISHING CLINICAL FEATURES | INCUBATION PERIOD | GEOGRAPHIC DISTRIBUTION | MODE OF TRANSMISSION AND TYPICAL RISK FACTORS |
|---|---|--|--|--|
| Q fever (<i>Coxiella burnetii</i>) | HSM; may develop pneumonia, endocarditis, hepatitis, osteomyelitis, or neurologic abnormalities | 2-29 days | Worldwide | Inhalation of organism from products of infected livestock or pets, especially birth products but also milk, urine, and feces; farmers, ranchers |
| Rat bite fever (<i>Spirillum minor</i> or <i>Streptobacillus moniliformis</i>) | Peripheral rash, sometimes with desquamation, polyarthritides in <i>S. moniliformis</i> , eschar or ulcer at site of bite in <i>Spirillum minor</i> | 2-28 days | Worldwide, especially Asia and North America | Bite of rat or other animal that preys on rats; ingestion of food contaminated by rat |
| Relapsing fever (<i>Borrelia</i> spp.) | Recrudescence fever pattern, HSM, petechiae, epistaxis, neurologic abnormalities | 4-18 days | Worldwide (especially East Africa) | Body louse (<i>B. recurrentis</i>) or tick bite (various <i>Borrelia</i> species); conditions of poor hygiene, outdoor exposures, refugee camps, camping, safari |
| Rickettsiosis, spotted fever group (<i>Rickettsia rickettsii</i> , <i>R. conorii</i> , <i>R. africae</i> , <i>R. australis</i> , <i>R. sibirica</i> , <i>R. japonica</i> , <i>R. honei</i> , and <i>R. akari</i>) | Peripheral skin rash, eschar at site of tick bite may be seen ("tache noire"), may progress to GI, renal, pulmonary, or CNS involvement | 7-14 days | Worldwide (with circumscribed distributions of each specific organism) | Tick bite (mite for <i>R. akari</i>); camping, safari |
| Rickettsiosis, typhus group (<i>Rickettsia prowazekii</i> , <i>R. typhi</i> , and <i>R. felis</i>) | Centripetal rash (~50%), no eschar | 7-14 days | Worldwide, especially cold climates | Feces from infected louse (<i>R. prowazekii</i>) or flea (<i>R. typhi</i> and <i>R. felis</i>) rubbed into broken skin; crowding, poor hygiene, abundant rodents, refugee camps, and flea-infested cats |
| Scarlet fever (group A <i>Streptococcus pyogenes</i>) | Pharyngitis, "sandpaper" rash, cervical adenopathy | 1-4 days | Worldwide | Person-to-person via aerosolization/droplets |
| Schistosomiasis, Katayama fever (<i>Schistosoma</i> spp., especially <i>S. japonicum</i>) | Lymphadenopathy, HSM, eosinophilia | 1-2 months | Africa, Asia, Caribbean, Middle East, South America, Caribbean | Skin penetration of cercaria; swimming or bathing in contaminated water |
| Scrub typhus (<i>Orientia tsutsugamushi</i>) | Centripetal rash, conjunctival suffusion, lymphadenopathy, eschar at site of chigger bite (~50%), hearing loss in one-third of cases | 6-18 days | Asia, Australia, Pacific Islands | Chigger bite; outdoor rural or suburban exposures |
| Strongyloidiasis, disseminated (<i>Strongyloides stercoralis</i>) | Abdominal pain and distention, shock, pulmonary and CNS involvement common | 2-3 weeks; may be maintained via autoinfection for decades | Tropics worldwide | Skin contact with contaminated soil; military exercises; dissemination may occur in IH (AIDS, steroid treatment) |
| Toxic shock syndrome (<i>Staphylococcus aureus</i> , group A <i>S. pyogenes</i>) | Rash, extremity or abdominal pain, skin desquamation, soft-tissue infection (70%) | 2-10 days | Worldwide | Wound or vaginal colonization with toxin-producing bacteria; history of minor trauma (often without break in skin), previous surgery, or varicella infection; staphylococcal syndrome often associated with menses |
| Trench fever (<i>Bartonella quintana</i>) | Rash, HSM, shin pain; may develop endocarditis and angioma-like lesions | 1-2 weeks | Worldwide | Body louse bite; areas of crowding or poor sanitation, more severe in IH |
| Trichinellosis (<i>Trichinella</i> spp.) | Diarrhea followed by myalgias, periorbital edema, eosinophilia; may involve heart or CNS | 7-30 days | Worldwide | Ingestion of contaminated meat, including pork (<i>T. spiralis</i>), wild boar, horse, bear, and walrus |
| Tularemia, typhoidal form (<i>Francisella tularensis</i>) | Pulse-temperature dissociation, diarrhea (~40%); may develop pneumonia | 1-21 days | Sporadic foci worldwide, mostly Northern Hemisphere | Tick or fly bite or direct exposure to small mammals; hunting, camping, military exercises; R/O bioterrorism |
| Typhoid fever (<i>Salmonella typhi</i>) | Pulse-temperature dissociation, abdominal pain, rash, intestinal perforation and bleeding, HSM, 10% with extraintestinal manifestations | 8-28 days | Worldwide | Fecal-oral |
| Vibrio infection, nonepidemic type (<i>Vibrio vulnificus</i>) | Bullous skin lesions, DIC, thrombocytopenia, GI bleeding, shock | 1-2 days | Worldwide | Contaminated salt water or seafood; severe disease mostly in IH, history of alcoholism, liver disease |
| Viral hemorrhagic fever (dengue, yellow fever, Ebola, Marburg, Lassa, Junin, Machupo, and Rift Valley fever viruses, many others) | Capillary leak syndrome; may or may not exhibit frank hemorrhage, GI hemorrhage, shock | 3-21 days, depending on specific virus | Select areas worldwide | Depending on specific virus: exposure to rodent excreta, infected nonhuman primates, person-to-person, tick or mosquito bite, some unknown; R/O bioterrorism |

TABLE 133-1 Some Tropical Diseases That May Merit Management in an Intensive Care Unit*—cont'd

| DISEASE AND ORGANISM | DISTINGUISHING CLINICAL FEATURES | INCUBATION PERIOD | GEOGRAPHIC DISTRIBUTION | MODE OF TRANSMISSION AND TYPICAL RISK FACTORS |
|--|--|--|--|--|
| Viral hepatitis (hepatitis A, B, C, D, and E; Epstein-Barr virus; cytomegalovirus; others) | HSM, light-colored stools, dark urine, jaundice | 2 weeks-5 months, depending on specific organism | Worldwide | Fecal-oral or ingestion of seafood from contaminated sea beds (hepatitis A, E); percutaneous (blood exposure), sexual, or mother-to-child transmission (hepatitis B, C, D); hepatitis D requires co-infection with hepatitis B virus |
| Visceral leishmaniasis (<i>Leishmania</i> spp.) | Weight loss, HSM, neutropenia | Months-years | Tropics worldwide, especially Indian subcontinent, Middle East, and North Africa | Sandfly bite; military exercises, outdoor exposures |
| GASTROINTESTINAL SYNDROMES | | | | |
| Amoebic dysentery (<i>Entamoeba histolytica</i> , rarely other amoebae) | Abdominal pain and diarrhea, sometimes bloody, minority may develop amoeboma, toxic megacolon, peritonitis, or abscesses in solid organs (usually liver) | 2-4 weeks (usually longer for solid organ involvement) | Worldwide | Fecal-oral; may be transmitted through anal sex |
| Anthrax, gastrointestinal or oropharyngeal (<i>Bacillus anthracis</i>) | Abdominal pain and bloody diarrhea, neck swelling, pharyngitis, mucosal lesions, shock | 2-10 days | Worldwide | Ingestion of spores; exposure to domestic animals or animal byproducts; R/O bioterrorism |
| Ascending cholangitis (<i>Clonorchis sinensis</i> and <i>Opisthorchis</i> spp.) | May be recurrent and accompanied by pancreatitis | Months-years | Asia, former USSR | Ingestion of raw infected freshwater fish; sushi consumption |
| Bacterial dysentery (<i>Shigella</i> spp., <i>Campylobacter</i> spp., invasive and hemorrhagic <i>Escherichia coli</i> , non-typhi <i>Salmonella</i> spp., <i>Vibrio parahaemolyticus</i> , others) | Abdominal pain and diarrhea, sometimes bloody | 10 hours-7 days, depending on specific organism | Worldwide | Fecal-oral |
| Cholera (<i>V. cholerae</i>) | Copious "rice water" diarrhea, abdominal pain, severe hypovolemia, fever minimal or absent | 1-3 days | Tropics worldwide | Contaminated water or food, especially seafood; ceviche consumption |
| Clostridial gastroenteritis (<i>Clostridium difficile</i>) | Abdominal pain and diarrhea, sometimes with mucus or blood, toxic megacolon | ~1 week to months | Worldwide | Alteration of GI flora through previous antibiotic administration and/or GI manipulation |
| Eosinophilic gastroenteritis (<i>Angiostrongylus costaricensis</i>) | Mimics appendicitis or inflamed Meckel's diverticulum, right lower quadrant abdominal pain and mass, eosinophilia | Estimated 3-4 weeks | Latin America | Ingestion of larvae in undercooked mollusks, crustaceans, or frogs |
| Hemolytic uremic syndrome (<i>E. coli</i> O157:H7) | Bloody diarrhea followed by hemolysis and renal failure | 2-5 days | Worldwide | Ingestion of poorly cooked meat, fecal-oral |
| NEUROLOGIC SYNDROMES | | | | |
| African trypanosomiasis, meningoencephalitic stage (<i>Trypanosoma brucei gambiense</i> and <i>Trypanosoma brucei rhodesiense</i>) | Headache, HSM, cervical lymphadenopathy, somnolence, change in mental status, extrapyramidal and cerebellar signs | Months-years | Sub-Saharan Africa | Tsetse fly bite; camping, safari |
| Antiretroviral syndrome (human immunodeficiency virus-1) | Usually asymptomatic or mild flu-like illness, meningoencephalitis occurs rarely | 2-4 weeks | Worldwide | Sexual transmission or percutaneous blood exposure; unprotected sex, IV drug use |
| Arboviral encephalitides (eastern equine, Japanese encephalitis, West Nile, Murray Valley encephalitis, St. Louis encephalitis, and Venezuelan equine encephalitis viruses, many others) | Encephalitis, focal neurologic deficits, seizures, change in mental status | 3-21 days | Sporadic foci worldwide | Mosquito bite; seasonal |
| Bacterial meningitis (<i>Neisseria meningitidis</i> , <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> type B, <i>Listeria monocytogenes</i> , others) | Petechiae, ecchymoses, and bleeding suggest <i>N. meningitidis</i> | 2-10 days, depending on specific organism | Worldwide; <i>N. meningitidis</i> more frequent in African "meningitis belt" | Person-to-person, asymptomatic carrier states, seasonal fluctuations |
| Botulism (<i>Clostridium botulinum</i>) | Bilateral cranial nerve deficits with symmetric descending weakness, fever absent | 1-3 days | Worldwide | Toxin ingestion or wound contamination; home-canned foods, soil contamination |

Continued

TABLE 133-1 Some Tropical Diseases That May Merit Management in an Intensive Care Unit*—cont'd

| DISEASE AND ORGANISM | DISTINGUISHING CLINICAL FEATURES | INCUBATION PERIOD | GEOGRAPHIC DISTRIBUTION | MODE OF TRANSMISSION AND TYPICAL RISK FACTORS |
|---|---|---|--|--|
| Brain abscess (various bacteria, fungi, and parasites) | Focal neurologic signs | Days-months, depending on specific organism | Worldwide | Varies with infecting organism |
| Cryptococcosis (<i>Cryptococcus neoformans</i>) | Mild meningitis with low-grade fever, nonfocal neurologic exam, sometimes seizures or pulmonary involvement | 1-4 weeks | Worldwide | Inhalation of spores from soil and bird and bat excreta; usually IH |
| Eosinophilic meningitis (<i>Angiostrongylus cantonensis</i>) | Headache, meningitis, sometimes cranial nerve involvement, fever minimal | 1-7 days | Southeast Asia, South Pacific, sporadic foci worldwide | Ingestion of larvae in undercooked mollusks, crustaceans, or frogs |
| Gnathostomiasis (<i>Gnathostoma</i> spp.) | Migratory skin and subcutaneous swellings, epigastric pain and vomiting, eosinophilia, may invade any organ, especially CNS | Weeks-years | Southeast Asia, with sporadic cases from Central and South America | Consumption of raw freshwater fish, frogs, snakes, crustaceans, or poultry; sushi consumption |
| Herpes encephalitis (various herpesviruses) | Encephalitis, focal neurologic deficits, seizures, change in mental status, may show vesicular eruption | 2-20 days, depending on specific virus | Worldwide; herpes B virus via monkey exposure in Asia and North Africa (wild monkeys) or captive monkeys worldwide | Person-to-person, often more severe in IH; herpes B virus via bite or other exposure to monkeys of the genus <i>Macaca</i> ; person-to-person transmission reported; researchers, animal handlers |
| Mucormycosis (various fungi from the order Mucorales) | CNS infiltration with loss of consciousness, black exudate around mucous membranes of face, pulmonary infiltrates | 1-7 days | Worldwide | Inhalation of spores from soil, traumatic inoculation of wound; usually IH (diabetes mellitus or steroid use) |
| Neurocysticercosis (<i>Taenia solium</i>) | Seizures, headache, change in mental status, muscle pain | Years | Worldwide, especially Latin America and India | Ingestion of cysticerci in contaminated pork; areas where pigs roam freely |
| Paragonimiasis, cerebral (<i>Paragonimus</i> spp.) | Meningoencephalitis, often accompanied by pulmonary disease | Years | Sporadic foci worldwide, especially East Asia, Peru, Ecuador, and West Africa | Ingestion of raw infected crustaceans; sushi consumption |
| Poliomyelitis (poliovirus) | Acute flaccid paralysis, meningeal signs, muscle pain | 9-12 days | Sporadic foci in Africa, Asia, and eastern Mediterranean | Fecal-oral |
| Primary amebic meningoencephalitis (<i>Naegleria fowleri</i>) | Fulminant meningoencephalitis | 3-7 days | Sporadic foci worldwide | Entry of trophozoite through the nose; swimming in contaminated fresh warm water; hot springs |
| Rabies (rabies virus) | Change in mental status, autonomic instability, photophobia, aerophobia, paralysis | 20-90 days | Worldwide | Animal bite or bat exposure; spelunking, caring for injured animals |
| Schistosomiasis, CNS (<i>Schistosoma</i> spp.) | Encephalopathy, meningoencephalitis, transverse myelitis, seizures | Weeks-months | Africa, Asia, Caribbean, Middle East, South America, Caribbean | Skin penetration of cercaria; swimming or bathing in contaminated water |
| Tetanus (<i>Clostridium tetani</i>) | Diffuse muscle spasms, opisthotonos, trismus, autonomic dysfunction | 3-21 days | Worldwide | Soil contamination of wound, commonly involves umbilical stump in neonates |
| Tickborne encephalitis (tickborne encephalitis virus) | Encephalitis, focal neurologic deficits, seizures | 7-14 days | Central and East Asia, Europe, North Africa, North America | Tick bite |
| Toxoplasmosis, cerebral (<i>Toxoplasma gondii</i>) | Meningoencephalitis, HSM, focal neurologic deficits, seizures, change in mental status | Usually RD | Worldwide | Ingestion of cysts in undercooked meat or oocysts from exposure to cat feces; usually IH |
| Variant Creutzfeldt-Jacob disease (prion) | Change in mental status, myoclonus, spasticity, rigidity, extrapyramidal and cerebellar signs and symptoms, occasionally seizures | Months-years | United Kingdom, with sporadic cases elsewhere in Europe, Canada, and United States | Recipients of cadaveric transplants or injections of biomedical products derived from infected patients, contaminated surgical apparatuses, person-to-person(?), ingestion of contaminated beef or lamb(?) |
| Visceral larva migrans (<i>Toxocara canis</i>) | Cough, wheezing, HSM, eosinophilia; may develop CNS or other solid organ involvement | Weeks-years | Worldwide | Ingestion of eggs in puppy feces |

TABLE 133-1 Some Tropical Diseases That May Merit Management in an Intensive Care Unit*—cont'd

| DISEASE AND ORGANISM | DISTINGUISHING CLINICAL FEATURES | INCUBATION PERIOD | GEOGRAPHIC DISTRIBUTION | MODE OF TRANSMISSION AND TYPICAL RISK FACTORS |
|---|--|--|---|--|
| PULMONARY SYNDROMES | | | | |
| Anthrax, inhalation (<i>Bacillus anthracis</i>) | Pulmonary infiltrates with widened mediastinum, shock, CNS involvement | 2-60 days | Worldwide | Inhalation of spores, exposure to domestic animals or animal byproducts; R/O bioterrorism |
| Aspergillosis (<i>Aspergillus</i> spp.) | Pulmonary "fungus ball" (aspergilloma), transient infiltrates and allergic symptoms in allergic bronchopulmonary aspergillosis | 1-4 weeks | Worldwide | Inhalation of spores from soil |
| Bacterial pneumonia (<i>Streptococcus pneumoniae</i> , <i>Legionella pneumophila</i> , <i>Mycoplasma pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Chlamydia</i> spp., others) | Extrapulmonary findings frequent in Legionnaire's disease and psittacosis | 2-21 days, depending on specific organism | Worldwide | Person-to-person spread; Legionnaire's disease associated with colonized air/water systems; psittacosis associated with bird exposure |
| Blastomycosis (<i>Blastomyces dermatitidis</i>) | Subacute pneumonia; bone, skin, and GU tract involvement | 1-4 weeks, usually RD | Sporadic foci worldwide | Inhalation of spores from soil |
| Diphtheria (<i>Corynebacterium diphtheriae</i>) | Low-grade fever, cough, pharyngitis, oropharyngeal membrane, neck swelling, mucosal bleeding, myocarditis, polyneuritis | 3-7 days | Worldwide, especially temperate areas | Person-to-person through respiratory route and breaks in the skin |
| Eosinophilic pneumonia (various parasites, helminth, and filaria) | Eosinophilia, asthma-like condition, elevated IgE | Days-weeks, depending on specific organism | Worldwide, depending on specific organism | Lung passage of larvae or adult helminths, mosquito bite (filaria), filarial disease occurs primarily in those living in endemic areas with continued exposure |
| Hantavirus pulmonary syndrome (various hantaviruses) | ARDS, thrombocytopenia, leukocytosis, hemoconcentration, circulating immunoblasts | 1-5 weeks | Americas | Contaminated rodent urine or feces; outdoor exposures |
| Pertussis (<i>Bordetella pertussis</i>) | Low-grade fever, coryza, rhinorrhea, paroxysmal dry cough | 5-21 days | Worldwide | Person-to-person; adults vaccinated as children are susceptible to milder disease |
| Pneumocystosis (<i>Pneumocystis jiroveci</i>) | Dyspnea, dry cough, hypoxemia, often only mild findings on pulmonary auscultation and CXR | Usually RD | Worldwide | Inhalation; usually IH |
| Tuberculosis (<i>Mycobacterium tuberculosis</i>) | Upper lobe infiltrates and cavities; miliary TB, meningitis, and GU involvement also common | Usually RD | Worldwide | Person-to-person via aerosol/droplet; increased frequency and likelihood of extrapulmonary involvement in IH |
| Tularemia, pneumonic form (<i>F. tularensis</i>) | Pulse-temperature dissociation, diarrhea (~40%) | 1-21 days | Sporadic foci worldwide, mostly Northern Hemisphere | Tick or fly bite, or direct exposure to small mammals; hunting, camping, military exercises, R/O bioterrorism |
| Viral pneumonia (influenza, parainfluenza, respiratory syncytial, and SARS coronavirus, many others) | May be complicated by bacterial superinfection | Days-weeks, depending on specific organism | Worldwide, depending on specific organism | Person-to-person spread and zoonotic, depending on specific virus; contact with farms or live-animal markets, birds, or pigs (zoonotic influenzas); civet cats suspected to be a reservoir of SARS coronavirus |
| LOCALIZED INFECTIONS | | | | |
| Mycetoma (various fungi and bacteria) | Chronic swollen limb with nodules, sinus tracts, drainage of pus and "grains" | Weeks-months | Tropics worldwide | Traumatic implantation of organism into skin; soil exposure |
| Necrotizing fasciitis (group A <i>S. pyogenes</i> , <i>Clostridia</i> spp., <i>S. aureus</i>) | Rapid progression of edema, erythema, tenderness, bullae, necrosis, and gangrene | ~24 hours | Worldwide | Posttraumatic or surgical |

*Only diseases that typically have acute or subacute presentations and may cause severe disease are included. Diseases are classified by the most typical associated severe syndrome. In practice, significant variation may exist.

[†]Initial infection is usually asymptomatic or mild. Reactivation with severe disease may occur years later, usually in immunocompromised hosts.

ARDS, acute respiratory distress syndrome; CNS, central nervous system; CXR, chest x-ray; DIC, disseminated intravascular coagulopathy; GI, gastrointestinal; GU, genitourinary; HSM, hepatosplenomegaly; IgE, immunoglobulin E; IH, immunocompromised host; IV, intravenous; RD, reactivation disease; R/O, rule out; TB, tuberculosis; SARS, severe acute respiratory syndrome.

on parasitized RBC membranes that mediate their adhesion to the venular endothelium (Fig. 133-2). The rupture of schizont-stage parasites exposes glycosylphosphatidylinositol anchors on the parasite and RBC surface that induce macrophages and other inflammatory cells to release a host of inflammatory mediators including tumor necrosis factors (TNF), interleukin-1, and various kinins and reactive nitrogen intermediates.²⁵⁻²⁷ These cytokines play a role in the upregulation and

activation of endothelial adhesion molecules, such as ICAM-1 and E-selectin, enhancing cytoadherence of parasitized cells and mediating pathologic processes such as hypoglycemia, lactic acidemia, shock, gut mucosal damage, and increased permeability and neutrophil aggregation in the lung. The sum total of this cascade is sequestration of parasitized RBCs in the microvasculature where they are not only sheltered from removal but cause sluggish flow and obstruction, resulting in

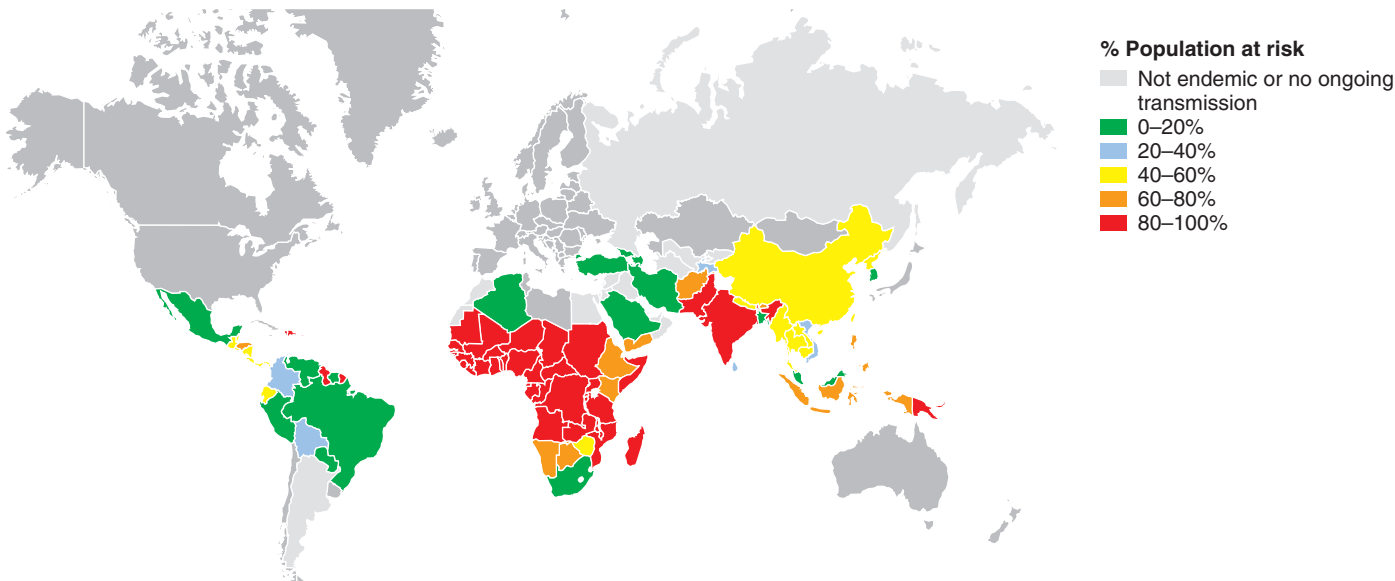


FIGURE 133-1 ■ Population at risk in malaria-endemic countries in the Western and Eastern hemispheres. The risk of malaria may vary within specific regions of each country. (From the World Health Organization 2013. Available at: <http://worldmalariaeurope.org>.)

TABLE 133-2 Features of the Five Species of Malaria Known to Cause Disease in Humans

| | PLASMODIUM FALCIPARUM | PLASMODIUM VIVAX | PLASMODIUM OVALE | PLASMODIUM MALARIAE | PLASMODIUM KNOWLESI |
|-----------------------------------|---|--|--|---|--|
| Incubation period (day) | 6-25 | 8-27 | 8-27 | 16-40 | 12 |
| Asexual cycle (hour) | 48 (tertian) | 48 (tertian) | 48 (tertian) | 72 (quartan) | 24 (tertian) |
| Relapse | No | Yes* | Yes* | No† | No |
| Chloroquine resistance | Yes‡ | Rare§ | No | No¶ | No |
| Characteristic on thin blood film | Rings predominate, multiply infected RBCs, high parasitemia, rings with thread-like cytoplasm, double nuclei, banana-shaped gametocytes | Enlarged RBCs, Schüffner's dots, trophozoite cytoplasm amoeboid, 12-24 merozoites in mature schizont | Oval RBCs with fringed edges, Schüffner's dots, trophozoites cytoplasm compact, 6-16 merozoites in mature schizont | Trophozoite cytoplasm compact (band forms), 6-12 merozoites in mature schizont, RBC unchanged | Similar to <i>P. malariae</i> , 8-10 merozoites in mature schizont, often in rosette pattern with central clump of pigment |

*Relapses may appear months to years after initial infection due to dormant hypnozoites in the liver.
†Although relapse does not occur, *P. malariae* can produce persistent infections that remain below detectable limits in the blood for 20 to 30 years or more.
‡*P. falciparum* resistance to sulfadoxine/pyrimethamine, mefloquine, halofantrine, and artemisinin has also been reported in some areas, along with partial resistance to quinine and quinidine.¹²⁸⁻¹³⁰
§*P. vivax* resistance to chloroquine has been reported in some areas of Southeast Asia, Oceania [Ethiopia, Madagascar], and South America.^{131-142,143}
¶Chloroquine-resistant *P. malariae* has also been reported in south Sumatra, Indonesia.¹⁴⁴
RBC, red blood cell.

impaired oxygen delivery and organ dysfunction.^{25,28} The most profound effects are usually on the cerebral capillaries, although a host of tissues may be affected, including the kidney, liver, spleen, placenta, intestine, lung, bone marrow, heart, and retina. Histopathologic changes are usually minimal, but ring hemorrhages and perivascular infiltrates sometimes develop at the sites of obstructed vessels, perhaps facilitated by thrombocytopenia because of splenic sequestration of platelets. Although subendocardial and epicardial hemorrhages have been noted at autopsy, myocarditis does not occur, and primary cardiac events are relatively rare in malaria.

However, in *P. vivax* infection, a very strong predilection for reticulocytes and the lack of cytoadhesive properties of the infected cells result in lower parasitemia and reduced microvascular obstruction and suggest different pathogenetic mechanisms to severe infection. A returning traveler exposed to *P. vivax* for a short period will rarely present a severe or fatal infection unless there is an underlying condition. However, in endemic regions, children with prolonged vivax infection due to frequent exposures and relapsing infections from the liver hypnozoites will present with profound anemia with subsequent high morbidity and mortality, particularly in the presence of

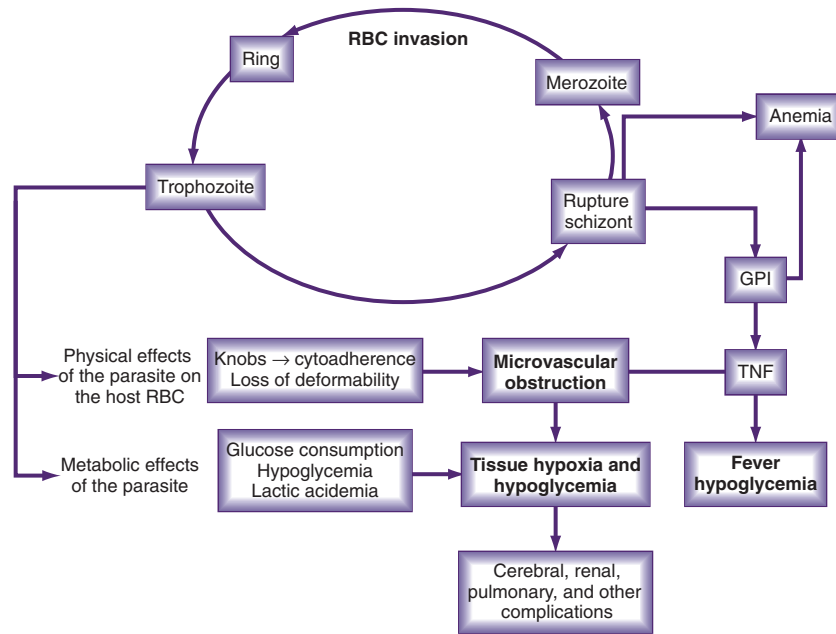


FIGURE 133-2 ■ Pathogenesis of severe and complicated *P. falciparum* malaria. GPI, glycosylphosphatidylinositol; RBC, red blood cell; TNF, tumor necrosis factor. (Modified from Krogstad D. Plasmodium species (malaria). In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 5th ed. Philadelphia: Churchill Livingstone; 2000.)

malnutrition and other causes of anemia.²⁹ Vivax anemia is further deepened by the splenic high removal rate of uninfected RBCs, although the removal mechanism is not fully understood.^{17,30}

CLINICAL PRESENTATION

Malaria infections are broadly classified into three clinical categories: (1) *asymptomatic parasitemia*, which generally does not require treatment for those living in endemic areas; (2) *uncomplicated malaria*, defined as parasitemia and fever without evidence of end organ damage or other signs of severe disease (these patients may often be treated as outpatients with oral antimalarials); and (3) *severe and complicated malaria*, defined as parasitemia and the presence of vital organ damage or other signs of severe disease. Patients with severe and complicated malaria require hospitalization, often in an intensive care unit (ICU), and parenteral antimalarials. This third category is the focus of this chapter.

Malaria classically produces three stages of symptoms, which progress over an 8- to 12-hour period, comprising a “paroxysm.” These correspond and are attributable to the period of schizont rupture and appearance of ring forms (merozoites) in the blood, accompanied by the release of numerous host inflammatory mediators. The paroxysm classically begins suddenly with a “cold stage” in which the patient experiences rigors and chills, often accompanied by headache, nausea, and vomiting. Intense peripheral vasoconstriction may result in pale, goose-pimpled skin and cyanosis of the lips and nail beds. Within a few hours, the “hot stage” ensues, with high fever, flushed skin, throbbing headache, and palpitations. The paroxysm concludes with the “defervescent stage,” consisting of a drenching sweat and resolution of the fever. The exhausted patient often then sleeps. Clinical deterioration with *P. falciparum* usually appears 3 to 7 days after the onset of fever.

Although a classic periodicity is described for different malarial species (see Table 133-2), this occurs only when the infection has persisted untreated long enough to allow for synchronization of schizont rupture. Furthermore, schizont rupture tends to be asynchronous in *P. falciparum* and in most primary infections of any *Plasmodium*

species. Therefore, malaria may often result in persistent spiking fevers, difficult to distinguish from fevers produced by many other infections. The absence of a classic paroxysm and periodicity should not be used to exclude the diagnosis. Paroxysms may be accompanied by cough, sore throat, myalgias, back pain, postural hypotension, abdominal pain, nausea, vomiting, diarrhea, and weakness. These are more common in children and may lead to misdiagnoses. Rash and lymphadenopathy are not typical of malaria and require another diagnosis.

Severe and Complicated Malaria

Although all species of malaria may produce severe consequences in a debilitated patient, potentially fatal malaria that merits attention in an ICU can be grouped into three categories: (1) severe complications of *P. falciparum*, and less commonly *P. vivax* and *P. knowlesi* in nonimmune children and adults, responsible for the vast majority of severe diseases worldwide (Table 133-3); (2) splenic rupture, which occurs most frequently with *P. vivax*; and (3) chronic nephrotic syndrome due to immune-complex nephritis associated with *P. malariae*, usually seen in children and often complicated by overwhelming bacterial infection.

Cerebral Malaria

This is the most frequent severe complication of *Plasmodium* infection, accounting for most fatalities and chronic sequelae. It is most frequent in children of 3 to 5 years of age. Strictly defined, *cerebral malaria* implies unarousable coma due to *P. falciparum*.^{31,32} Hyperpyrexia and febrile convulsions in young children may produce transiently altered mental status without true involvement of the cerebral microvasculature and thus technically do not constitute cerebral malaria. However, in clinical practice, seizures or persistent changes in sensorium that cannot be attributed to other disease processes should be considered cerebral malaria until proven otherwise. Although cerebral malaria is classically attributed to cytoadhesion and microvascular obstruction in

TABLE 133-3

Clinical and Laboratory Features That Classify a Patient as Suffering from Severe *Plasmodium falciparum* Malaria* According to the World Health Organization

CLINICAL FEATURES

Impaired consciousness (including unarousable coma); Glasgow coma score <11 in adults or a Bantyre coma score <3 in children
 Prostration: generalized weakness so that the patient is unable walk or sit up without assistance
 Multiple convulsions (more than two episodes in 24 hours)
 Pulmonary edema: radiologic evidence or oxygen saturation <92% on room air with a respiratory rate >30/min
 Respiratory distress (severe acidosis): rapid, deep, labored breathing
 Circulatory collapse or shock, systolic blood pressure <80 mm Hg in adults and <70 mm Hg in children, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
 Clinical jaundice plus evidence of other vital organ dysfunction
 Abnormal spontaneous and significant bleeding

LABORATORY FINDINGS

Hypoglycemia (blood glucose <2.2 mmol/L or <40 mg/dL)
 Metabolic acidosis; base deficit of >8 mEq/L, plasma bicarbonate <15 mmol/L or venous plasma lactate >5 mmol/L
 Severe normocytic anemia (hemoglobin ≤5 g/dL, hematocrit ≤15% in children <12 years of age (<7 g/dL and <20%, respectively, in adults) with a parasite count >10,000/μL
 Jaundice: plasma or serum bilirubin >50 μmol/L (3 mg/dL) with a parasite count >100,000/μL
 Hyperparasitemia: >10%
 Renal impairment: serum creatinine >265 μmol/L (3 mg/dL) or blood urea >20 mmol/L

Modified from Guidelines for the treatment of malaria 2015.3rd ed. Geneva: World Health Organization; 2010. Available at: <http://www.who.int/malaria/publications/atoz/9789241549127/en/>

*Comment:

For severe *P. vivax* malaria, the same criteria are used as for *P. falciparum* malaria but with no parasite density thresholds.

Likewise, severe *P. knowlesi* malaria is defined as for *P. falciparum* malaria but with two differences:

- *P. knowlesi* hyperparasitemia: parasite count >100,000/μL
- Jaundice and parasite count: >20,000/μL

(From the World Health Organization. Management of severe malaria—a practical handbook. 3rd ed. April 2013. Available at: <http://www.who.int/malaria/publications/atoz/9789241548526/en/>.)

the brain, other ongoing processes including hypoglycemia, metabolic acidosis, and impaired oxygenation due to anemia and pulmonary edema likely contribute.

The altered sensorium of cerebral malaria may develop gradually within a few days of onset of illness or manifest as persistent coma after a generalized convulsion. Compared with adults, children with cerebral malaria have a shorter history of fever before progressing to coma (average about 2 days). The most common neurologic picture is of a diffuse symmetric encephalopathy with hypertonia, opisthotonos, hyperreflexia, clonus, disconjugate gaze, absent abdominal reflexes, and extensor Babinski responses, sometimes with signs of frontal lobe release such as a pout reflex or bruxism. Hypotonia and acute cerebellar ataxia are sometimes seen as well, especially in India and Sri Lanka. Pupils are usually symmetric with intact pupillary, corneal, oculocephalic, and oculovestibular reflexes. There is usually no grasp reflex, and the gag reflex is normally maintained. Both decorticate and decerebrate posturing may occur.³² Nystagmus and a sixth nerve palsy have been noted, but papilledema and photophobia are almost never seen.³³

Convulsions may occur in up to 50% of cases of cerebral malaria. As a child ages above 3 to 4 years, seizures become more likely to represent cerebral malaria than febrile convulsions.³⁴ Although

generalized seizures are classically reported, partial motor seizures, with or without secondary generalization, may occur.³¹ Although often showing only diffuse cortical dysfunction, EEG studies may sometimes reveal underlying status epilepticus even when it is not clinically evident.³²

Pulmonary Edema and Acute Respiratory Distress Syndrome

Pulmonary edema, which may progress to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), is a frequent and typically the most lethal complication of malaria. It has been seen with infection by all malaria species.³⁴ In *P. falciparum* infection, evidence suggests that the mechanism may involve acute pulmonary hypertension precipitated by nitric oxide (NO) consumption by free plasma hemoglobin released from intravascular hemolysis.³⁵ Endothelial injury leading to increased alveolar permeability and noncardiogenic pulmonary edema may also contribute. Interstitial edema and inflammatory cell infiltrates are seen at autopsy, but sequestration of parasitized RBCs in the lung is uncommon.³⁶ Pulmonary complications occur in 5% to 30% of patients with severe malaria, especially pregnant women, nonimmune persons, and patients already suffering from other complications.³⁶ The onset may be any time during the course of illness, even if the patient appears to be improving and parasitemia has decreased. Symptoms include dyspnea and cough, with rapid progression to hypoxia and respiratory distress. In *P. vivax* infection, a cytokine-mediated inflammatory response in the pulmonary microvessels leads to increased alveolar permeability and fluid buildup. Because of a lower parasitic biomass, the effect of the hemolysis-associated NO depletion on pulmonary pressures is minimal.²⁹

Anemia and Hematologic Perturbations

Although some degree of anemia is common in all types of malarias, severe anemia (hemoglobin less than 5 g/100 mL) occurs mostly with *P. falciparum* owing to its high parasitemia and with *P. vivax*. In *P. falciparum* infection, severe anemia is most common and often severe in pregnant women and young children (<1 year), in whom it may be the presenting sign.³⁷ In addition to the acute hemolytic destruction of parasitized RBCs, the more chronic processes of removal of parasitized cells from circulation by the spleen and cytokine inhibition of erythropoiesis may contribute.³⁸ Nonimmune subjects may develop anemia within days after infection, whereas anemia usually develops more slowly in those who are semi-immune. The degree of anemia generally correlates with bilirubin level and level of parasitemia. It may be exacerbated by underlying glucose-6-phosphate dehydrogenase (G6PD) deficiency in the setting of administration of oxidant antimalarial drugs (e.g., quinine, sulfadoxine) and iron-deficiency anemia due to malnutrition. Significant jaundice and hemoglobinuria may result. Thrombocytopenia, although frequent, is not usually associated with bleeding or correlated with disease severity. Disseminated intravascular coagulation (DIC) is seen in less than 10% of severe cases. In *P. vivax* infection, profound anemia is seen in young children from high endemic areas and results from several pathogenetic processes including frequent hemolysis due to relapsing infection, increased fragility of infected and uninfected reticulocytes, high splenic removal rate of uninfected RBCs (four times higher than in *P. falciparum*), and recrudescence of chloroquine-resistant parasites.³⁰

Acute Kidney Injury

Acute kidney injury (AKI) is seen in about 30% of nonimmune adult patients with cerebral malaria but is uncommon in children. For unclear reasons, AKI is rare in semi-immune persons. AKI occurs mainly with *P. falciparum*, but it is also described with *P. vivax* and *P. malariae* and is generally a sign of poor prognosis.^{34,39} AKI is usually due to acute tubular necrosis, is oliguric in nature (<400 mL urine/24 h for adults), and is most often reversible. Renal ischemia due to

hypovolemia, renal vasoconstriction, microvascular obstruction, and pigment nephropathy from hemolysis may all contribute. Electrolyte abnormalities such as hyponatremia, hypocalcemia (usually related to albumin loss), hypophosphatemia, and metabolic acidemia, as well as fluid overload with pulmonary edema, may result.

Blackwater fever refers to a severe syndrome characterized by low or absent parasitemia, intravascular hemolysis, hemoglobinuria, and AKI. It is classically seen in people of northern European descent chronically exposed to *P. falciparum* and irregularly taking quinoline antimalarial drugs, quinine or quinidine, which together are known as *cinchona alkaloids*. The syndrome virtually disappeared after 1950 when chloroquine superseded quinine. However, it is now said to be resurgent, albeit with lower mortality, in relation to mounting chloroquine resistance and consequent increased use of quinine and the newer quinolines, such as mefloquine.⁴⁰

Hypoglycemia, Lactic Acidosis, and Other Metabolic Perturbations

Severe metabolic derangements are frequent, especially in pregnant women and young children. While sometimes asymptomatic in pregnancy, hypoglycemia (blood or plasma glucose <2.2 mmol/L) often causes convulsions and impaired consciousness and may be confused with cerebral malaria. Although the pathogenesis is still unclear, direct glucose consumption by the malaria parasite and cytokine inhibition of gluconeogenesis seem to be the main mechanisms. Decreased oral intake, depletion of liver glycogen, and insulin release stimulated by quinine or quinidine may also contribute.⁴¹ A meta-analysis showed hypoglycemia to be less frequent with artesunate treatment compared with quinine.⁴² Serum insulin levels are low, and lactate, alanine, and counterregulatory hormones are appropriately elevated. Although rarely clinically significant, mild hepatocellular damage may occur and be manifested by elevated hepatic transaminases and jaundice. At least theoretically, such hepatic dysfunction could result in impaired metabolic clearance of antimalarial medications and lactate and deficits in the production of coagulation factors and albumin.

Shock and Bacterial and Other Suprainfection

So-called *algid malaria*, referring to hypotension and shock, may resemble and indeed sometimes occur due to gram-negative sepsis from impaired flow in intestinal capillaries, with resultant mucosal erosion. Nontyphoidal salmonella septicemia is specifically associated with *P. falciparum*.⁴³ *Algid malaria* is often seen in the setting of hyperparasitemia, with concomitant hypoglycemia and lactic acidemia, and may progress to multiorgan system failure and death. As with most malarial complications, severe hemodynamic derangements are most often seen in nonimmune persons.⁴⁴ Whether bacteria are isolated or not, a classic septic shock picture is typical, with elevated cardiac index and decreased systemic vascular resistance.⁴⁵ Hemodynamic decompensation due to splenic rupture may mimic *algid malaria*.

A host of other infectious complications, including aspiration pneumonia and parvovirus infection, may be related to *falciparum* malaria. Malaria occurs with increasing frequency and severity in those who are HIV infected, especially during pregnancy, and can also transiently upregulate HIV replication.⁴⁶⁻⁵⁰ An association between severe malaria infection and hepatitis B surface antigen carriage has also been noted.⁵¹

Tropical Splenomegaly and Splenic Rupture

Splenomegaly is common in infection with all species of malaria. The *tropical splenomegaly syndrome*, also sometimes termed *hyperreactive malarial syndrome*, refers to a condition of massive splenomegaly, high titers of total serum immunoglobulin M and malaria-specific antibodies, and scanty or absent parasitemia. It is seen in individuals with a history of residence in an endemic area and can be associated with any malarial species. Host genetic factors appear to play a role.⁵²

Unlike virtually all the other complications of malaria that are most often associated with *P. falciparum*, acute splenic complications occur most commonly in *P. vivax*, especially with the first infection. Although the term *spontaneous splenic rupture* has traditionally been used, in reality a range of hematomas or tears of varying severity may occur. The rupture or tear usually occurs 2 to 3 months after infection, presumably as a result of increased intrasplenic tension, often precipitated by trauma of varying degrees or mechanical ventilation.⁵³ Over-eager examiners have been suggested to play a role, although no cases of clear palpation-induced rupture have been reported. Fever, tachycardia, vomiting, prostration, abdominal pain or guarding, tender splenomegaly, hypovolemia, and rapidly worsening anemia are common presenting features. Abdominal pain may be localized or diffuse, mild or severe. Shock may ensue. Diaphragmatic irritation after rupture may cause referred pain to the left shoulder, supraclavicular, or scapular regions ("Kehr's sign"). This is present in about one-half of cases and is said to have good specificity for rupture.

Malaria in Pregnancy and Children

Malaria is particularly dangerous in pregnant women and their fetuses are more susceptible to severe malaria with increased risk of pulmonary edema, hypoglycemia, severe anemia, infection premature delivery, low birth weight, and maternal and fetal death. Malarial parasites can often be found in the placenta and may impair oxygen and nutrient transport to the fetus. Disease is most severe in primiparae, especially if nonimmune. In contrast, women from endemic areas are usually asymptomatic, with the exception of the effects of anemia, again more severe in primiparae. Congenital malaria is rare except in infants born to nonimmune mothers.⁵⁴

DIAGNOSIS

Clinical

Malaria often presents with nonspecific signs and symptoms, so making a clinical diagnosis may be difficult. Although almost all patients have a history of fever, they may frequently be afebrile at the time of examination.⁵⁵ Physicians in industrialized countries who are unfamiliar with the disease may not initially include malaria in the differential diagnosis. Delayed diagnosis is frequent and associated with a poor outcome.^{6,56} Most patients with malaria will present within 1 month of exposure (See Table 133-2). Longer incubation periods may be seen in semi-immune persons or in those who have taken partial or inappropriate chemoprophylaxis. *P. vivax* and *P. ovale* infections can manifest later after months or even years after initial infection because of reactivation of liver hypnozoites.⁵⁷ The differential diagnosis includes most febrile illnesses found in the tropics (see Table 133-1). Babesiosis may present both clinically and microscopically similar to malaria in patients without travel to malaria-endemic areas. Cerebral malaria must be distinguished from bacterial meningitis, viral meningoencephalitis, metabolic coma, and intoxications by lumbar puncture.⁵⁸ In cerebral malaria, the cerebrospinal fluid (CSF) opening pressure is usually normal, although a few lymphocytes and moderate elevation of protein may be seen. High CSF lactate and low glucose indicate a poor prognosis.

Conventional Microscopy

Laboratory diagnosis has traditionally been made via the examination of thick and thin Giemsa-stained smears by light microscopy. This remains the standard method for diagnosing malaria. Thick smears are more sensitive in diagnosing malaria, whereas thin smears allow the identification of the specific parasite. Either smear can be used to quantify the level of parasitemia, but thick smears are theoretically more sensitive for this purpose.^{59,60} In addition to diagnosis, parasite quantification, and species identification, microscopy allows the monitoring of response to treatment (i.e., decreased parasitemia) and the

disease severity (i.e., presence of schizonts in *P. falciparum* infection).^{61,62} Simultaneous infections with multiple strains of *P. falciparum* are common in some areas of sub-Saharan Africa and also may occur with *P. vivax* in Southeast Asia and Latin America.^{63,64} Blood obtained by pricking a fingertip or earlobe is preferred because parasite densities are higher in these capillary-rich areas, although blood obtained by venipuncture collected in heparin or EDTA anticoagulant-coated tubes is acceptable if used shortly after being drawn (to prevent alteration in the morphology of white blood cells and malarial parasites).⁶⁵ Smears should be taken as soon as the diagnosis of malaria is considered, without waiting for manifestation of a classic paroxysm. Parasitemia may be undetectable in the early stages of the illness, in those with partial immunity, and in those who have previously self-administered antimalarials, a common practice in malaria-endemic areas.⁶⁶ Levels of parasitemia may fluctuate over time, necessitating repeated smears for diagnosis. Furthermore, *P. falciparum*-parasitized RBCs may be sequestered in the deep capillaries of the spleen, liver, and bone marrow. Although a blood film is unlikely to be falsely negative in a patient with severe disease, negative smears should not prevent prompt administration of antimalarial therapy if the diagnosis is strongly suspected.¹⁵ Conversely, asymptomatic parasitemia is common in children from endemic areas, and thus a positive smear does not necessarily signify a clinical case under these circumstances.

Considerable expertise at reading malarial smears may be necessary to detect and distinguish the parasites (see Table 133-2). *P. knowlesi* may often be misdiagnosed as *P. falciparum* or *P. malariae* owing to similar morphology. Superimposed platelets, particles of stain, pits in the slide, RBC inclusions such as Howell-Jolly bodies and those seen in siderocytes, and other intracellular pathogens such as *Bartonella* and *Babesia* must be distinguished from malarial parasites. Furthermore, alterations in parasite morphology may occur related to strain variation, drug pressure, and blood collection method.

Newer Laboratory Methods

Various new diagnostic techniques for malaria have been developed, including microscopy with fluorescent stains, dipstick antigen detection (i.e., rapid diagnostic test, RDT), DNA probes, polymerase chain reaction (PCR) assays, and automated blood cell analysis.^{59,60,67-71} Use of one of these new diagnostic modalities should be considered when a high suspicion of malaria remains despite repeatedly negative blood smears, especially if the microscopist has limited experience in reading malarial smears.⁶⁰ Each technique has unique advantages and disadvantages, but the sensitivity and specificity for *P. falciparum* is generally similar or better than conventional microscopy. Because of its greater sensitivity (as low as 5 parasites/ μ L), PCR may be a particularly valuable tool in nonimmune persons. PCR also allows evaluation for possible infection with multiple malarial strains and determination of drug resistance. A large number of malaria RDTs have been approved for use. RDTs are fast (usually with a result in less than 30 minutes) and easy to perform with sensitivities and specificities comparable to microscopy for *P. falciparum*. Sensitivity and specificity are lower for *P. vivax* and when the parasitemia is less than 100 parasites/ μ L, regardless of the species. RDTs based on the detection of the plasmodial lactate dehydrogenase antigen can be used to determine the efficacy of drug therapy since this antigen disappears rapidly after parasite clearance relative to other antigens detected by RDTs. False-negative malaria RDT results may occur because of a prozone-like-effect in high parasitemias.

RDTs cannot detect *P. knowlesi*-specific antigen, and cross-reaction with *P. falciparum* and *P. vivax* lactate dehydrogenase (pLDH) antibodies has been described. Microscopy is also not ideal, as *P. knowlesi* is often misdiagnosed as *P. malariae* or *P. falciparum* because of similar morphology.⁷²

Imaging

Computed tomography (CT) or magnetic resonance imaging (MRI) scanning of the abdomen is the usual diagnostic modality when splenic

rupture is considered, although ultrasonography, arteriography, bleeding scans, or exploratory laparotomy may sometimes be needed. Findings such as increased brain volume and, occasionally, brain swelling have been noted in CT and MRI studies in cerebral malaria, but these tests are generally unhelpful clinically and are indicated only to rule out suspected mass lesions when the diagnosis of cerebral malaria is uncertain.⁷³

CLINICAL MANAGEMENT

Indications for Admission to the Intensive Care Unit and General Management

Features that indicate severe disease meriting admission to an ICU and urgent intravenous (IV) therapy are noted in Table 133-3. In these critically ill patients, chloroquine-resistant *P. falciparum* should be assumed until proven otherwise. As per routine ICU management, the patient's breathing and circulatory status should first be rapidly assessed, the airway secured, and the neurologic status scored on the Glasgow Coma Scale or other appropriate scoring system.⁷⁴ For patients in profound shock, blood cultures should be drawn and broad-spectrum antibiotics begun unless the diagnosis of severe malaria has already been confirmed or if bacterial suprainfection is suspected. Unconscious patients should have a lumbar puncture to rule out bacterial meningitis.

Careful attention to fluid balance is imperative, especially considering the very poor prognosis once pulmonary edema or ARDS develops. Measurements of urine output and daily weights should be routinely performed. Monitoring of central venous pressure should be considered in critically ill patients. In patients with shock, initial effective fluid resuscitation with frequent monitoring, assessment of concomitant bacterial infection, and vasopressor support when required is the standard of care and should be initiated promptly. In patients with stable blood pressure and cardiac output, careful maintenance fluid therapy with regular assessment of tissue perfusion as therapeutic endpoints seems to be more beneficial than liberal fluid resuscitation to prevent the risk of capillary leak and acute pulmonary edema.⁷⁵

Hemofiltration or hemodialysis or peritoneal dialysis are indicated for AKI and may aid not only through improved fluid and electrolyte balance and control of acidemia but also via removal of circulating cytokine mediators of inflammation.⁷⁴ Although observations are limited, the quinolones appear not to be dialyzed.⁷⁷ Cautious transfusion of packed cells is usually indicated when the hematocrit falls below 20% or hemoglobin is less than 7 g/dL. In addition to improved oxygen transport, blood transfusion may reduce the parasite load and cytokine mediators of inflammation.^{55,78} Concurrent administration of diuretics may be warranted to avoid fluid overload. Use of low-dose dopamine and epinephrine has not been associated with significant improvement in renal oxygen metabolism or function.⁷⁹

Increasing respiratory distress may indicate the onset of ALI or ARDS. Arterial blood gas measurements may reveal hypoxemia, and chest x-rays bilateral infiltrates. Supplemental oxygen and mechanical ventilation may be required. In accordance with the National Institutes of Health ARDS Network Trial, lung-protective ventilation, with tidal volume of 6 mL/kg predicted body weight and plateau pressures less than 30 cm H₂O are indicated for improved survival.³⁶ Extracorporeal oxygenation has also been employed.⁸⁰ Metabolic acidosis should be treated by improving pulmonary gas exchange, correcting hypovolemia and hypoglycemia, and treating associated septicemia. Careful monitoring of serum potassium with appropriate supplementation is warranted, especially when correcting acidosis. Blood glucose should be checked frequently, especially in pregnant patients, and 50% dextrose administered when needed. Results of studies on the efficacy of continuous IV infusion of 5% dextrose have been mixed.^{81,82} Quinoline-induced hypoglycemia may be prevented by administering somatostatin analogs followed by glucagons.⁸³ Acute seizures may be treated with IV benzodiazepines or intramuscular (IM) paraldehyde, and prolonged seizures terminated with phenytoin.³² However, prophylactic

anticonvulsants with phenobarbital are not recommended and may be harmful.⁷⁵ Although the risk of bleeding is low, aspirin should be avoided in the presence of thrombocytopenia. Many patients with splenic rupture can be managed conservatively with supportive therapy, although splenectomy may be necessary.⁵²

In late pregnancy, fetal monitoring should be begun prior to initiation of quinoline therapy so that the effects of the disease can be distinguished from those of drug toxicity. Early obstetric intervention should be considered for the benefit of both mother and fetus. Although fetal distress is usually the result of placental insufficiency, it may sometimes be related to high maternal temperature and hypoglycemia. Thus these parameters should be carefully monitored and treated accordingly. Fluid balance is particularly crucial in pregnant patients; the sudden increase in peripheral vascular resistance postpartum may precipitate pulmonary edema. In young children prone to febrile convulsions, extra efforts should be made to control fever by the use of acetaminophen, cooling blankets, and baths.

Antimalarial Chemotherapy

Because delay of therapy is associated with increased mortality, empirical parenteral treatment should be implemented immediately in all suspected cases of severe malaria after obtaining appropriate blood specimens. Infection with chloroquine-resistant *P. falciparum* should be assumed unless specifically ruled out. Treatment regimens for severe *P. falciparum* are also effective for the more infrequent cases of severe malaria due to other species.

Two classes of medicines are indicated for parenteral treatment: artemisinin derivatives (artesunate, artemether, and others) and cinchona alkaloids (Table 133-4). Two large randomized trials showed artesunate to be superior to quinine for severe malaria in both adults and children.^{75,84,85,86} Intravenous or IM artesunate is the first-line drug recommended by the World Health Organization (WHO) for severe malaria and should be administered for at least 24 hours even if there is early improvement. If IV or IM artesunate is not available, IM artemether should be considered. After 24 hours, if patients are able to tolerate oral therapy, they may be transitioned to one of three recommended artemisinin-based combination therapies (ACTs) for a total of 3 days (see Table 133-3). If not possible to treat with one of the three recommended ACT regimens, oral artesunate can be combined with either clindamycin or doxycycline, or oral quinine plus either clindamycin or doxycycline can be used for a total of 7 days' course for both drugs. Doxycycline is preferred to other tetracyclines because it can be given once daily and does not accumulate in renal failure. Doxycycline is contraindicated, and thus clindamycin is preferred, in children and pregnant women (see Table 139-3). The dosage of artemisinin compounds does not need to be adjusted for patients with AKI or hepatic dysfunction.

Despite its use in most part of the world, artesunate is not licensed in many industrialized countries. In the United States, artesunate has the "investigational new drug" status and is available only through request to the Centers for Disease Control and Prevention (CDC) (770-488-7788).^{87,88} If no artemisinin drug is available, parenteral quinine or quinidine gluconate can be used as an alternative.^{85,86} Since IV quinine is also unavailable in the United States, quinidine gluconate is often used.⁸⁹ Cinchona alkaloids may also be considered in patients infected in Southeast Asia, where resistance to artemisinin compounds has been documented, and should be coadministered with artemisinin compounds.^{90,91} Chloroquine and sulfadoxine/pyrimethamine are no longer recommended for treatment of severe malaria.

Adverse Effects of Therapy

Side effects associated with artemisinin compounds are infrequent and generally mild and include abdominal pain, diarrhea, contact dermatitis, decreases in reticulocyte and neutrophil counts, and elevated hepatic transaminases.⁹² Severe allergic reactions and cerebellar dysfunction have been rarely reported.⁹³ In nonimmune adult travelers with high parasitemia, delayed hemolysis has been described after

administration of parenteral artesunate, and thus patients treated with this compound should be monitored for anemia for 1 month posttreatment.^{94,95}

Side effects of quinine and quinidine, known as *cinchonism*, are common and typically include nausea, vomiting, headache, dysphoria, vasodilation, tinnitus, and changes in auditory and visual acuity. These alterations are dose related and reversible. Less common side effects include rash, urticaria, angioedema of the face, pruritus, agranulocytosis, hepatitis, blackwater fever, and psychiatric disorders. Overdoses are associated with depressed respiration, circulatory collapse, and central nervous system (CNS) alterations including seizures and coma, which may be difficult to distinguish from cerebral malaria.⁹⁶ Simultaneous use of two quinolines or retreatment with the same quinoline within a short period may predispose to severe side effects.⁹⁷ The cinchona alkaloids are metabolized in the liver and excreted in the urine. Monitoring blood levels is recommended for persons with impaired renal or hepatic function, and dose reduction is necessary in those with severe renal impairment. Quinine metabolism appears to be decreased in children with kwashiorkor but increased in those with marasmus.⁹⁸

Although rarely clinically significant, prolongation of the electrocardiographic QT interval with IV quinoline therapy is common.⁹⁹ Severe conduction abnormalities may occur along with hypotension, blindness, and deafness.^{75,87-99} Dysrhythmias and hypotension may also result from overly rapid infusion. Coma may result when serum quinoline levels exceed 20 mg/L. Cardiac monitoring should be performed with IV quinoline use, especially with quinidine, which although more potent against the malarial parasite is also generally more toxic.⁹⁹ Infusion rates of quinidine should be decreased if the QT interval increases by more than 25% of its baseline level.

Quinoline-induced stimulation of insulin release may elicit significant hypoglycemia, especially in pregnancy.^{82,100} Hypophosphatemia may also be precipitated by both quinoline and IV dextrose, causing CNS dysfunction.⁵⁵ Levels of digoxin, mefloquine, neuromuscular blocking agents, and oral anticoagulants may all be increased with quinoline administration. Quinine can cause hemolysis in patients with G6PD deficiency. Because of their curare-like effect on skeletal muscle, quinolines are contraindicated in patients with myasthenia gravis. An extensive list of drug interactions reported for recommended antimalarial drugs is available in the WHO guidelines for treating malaria.⁷⁴

Ancillary Therapies

Various ancillary therapies have been proposed for severe malaria. In most cases, controlled data are not available to judge their efficacy. Exchange transfusion and erythrocytapheresis have been employed in cases of severe malaria with high parasitemia with apparent benefit.¹⁰¹⁻¹⁰⁴ However, a study encompassing 25 years of experience treating U.S. patients with severe malaria by exchange transfusion concluded that there was no survival benefit.¹⁰⁵ Treatments such as heparin, prostacyclin, desferrioxamine, pentoxifylline, low-molecular-mass dextran, urea, high-dose corticosteroids, aspirin, anti-TNF antibody, cyclosporine A, dichloroacetate, adrenaline, hyperimmune serum, *N*-acetylcysteine, and bolus administration of albumin are not recommended since their effectiveness is not proven or they have shown to be detrimental in severe malaria.^{41,74}

Laboratory Monitoring

Findings in severe malaria may include profound hemolytic anemia and thrombocytopenia, leukocytosis with a left shift (although milder cases may show leukopenia), prolonged coagulation times (with increased fibrin split products and diminished fibrinogen reflecting DIC), hyponatremia, hypoalbuminemia, hypophosphatemia, hypoglycemia, lactic acidemia, and elevated hepatic enzymes, LDH, bilirubin, blood urea nitrogen (BUN), and creatinine. Urinalysis may reveal proteinuria, RBCs and RBC casts, and hemoglobinuria. Coagulation

TABLE 133-4 Treatment Guidelines for Severe *Plasmodium falciparum* Malaria

| DRUG | DOSE | COMMENTS |
|-----------------------------------|--|--|
| ARTEMISININ COMPOUNDS | | |
| Artesunate | 2.4 mg/kg IV bolus at 0, 12, 24 hours, then daily until patient is able to transition to the following oral regimen: | Artesunate has “investigational new drug” status in the United States and is available only on request to the CDC (770-488-7788). Eligibility requirements include inability to take oral medications, high levels of parasitemia, clinical evidence of severe malaria, intolerance of or contraindication to quinidine, failure of quinidine therapy, and lack of rapid access to quinidine. ⁸⁸ Where available, artesunate rectal suppositories (10 mg/kg) may be used in children <5 years of age if IV or IM administration is not possible. Doxycycline is contraindicated in children <8 years of age and in pregnancy. Atovaquone/proguanil is packaged in the United States in fixed-dose combination tablets of 250 mg atovaquone/100 mg proguanil for adults and 62.5 mg atovaquone/25 mg proguanil for children. Safety of atovaquone/proguanil in pregnancy has not been established. |
| Artemether | 1. Artemether + lumefantrine: tablets containing 20 + 120 mg, 40 + 240 mg of artemether and lumefantrine, respectively <ul style="list-style-type: none"> Adults ≥35 kg: 80 + 480 mg twice daily for 3 days Children: <ul style="list-style-type: none"> 5 to <15 kg: 20 + 120 mg twice daily for 3 days 15 to <25 kg: 40 + 240 mg twice daily for 3 days 25 to <35 kg: 60 + 360 mg twice daily for 3 days | |
| | 2. Artesunate + amodiaquine: A fixed-dose combination tablet containing 25 + 67.5 mg, 50 + 135 mg, 100 + 270 mg of artesunate and amodiaquine, respectively <ul style="list-style-type: none"> Adults ≥36 kg, 200 + 540 mg daily for 3 days Children: <ul style="list-style-type: none"> 4.5 to <9 kg: 25 + 67.5 mg daily for 3 days 9 to <18 kg: 50 + 135 mg daily for 3 days 18 to <36 kg: 100 + 270 mg daily for 3 days | |
| | 3. Dihydroartemisinin (DHA) + piperazine (PPQ): Tablets containing 20 + 160 mg, 40 + 320 mg of DHA and PPQ, respectively <ul style="list-style-type: none"> Adults: <ul style="list-style-type: none"> 36 to <75 kg: 120 + 960 mg daily for 3 days ≥75 kg: 160 + 1280 mg daily for 3 days (no data on dose recommendation >100 kg) Children <ul style="list-style-type: none"> 5 to <7 kg: 10 + 80 mg daily for 3 days 7 to <13 kg: 20 + 160 mg daily for 3 days 13 to <24 kg: 40 + 320 mg daily for 3 days 24 to <36 kg: 80 + 640 mg daily for 3 days | |
| | 4. Artesunate or quinine PO to complete 7 days plus doxycycline, 100 mg PO BID × 7 days | |
| | 5. Artesunate or quinine PO to complete 7 days plus clindamycin, 20 mg base/kg/d PO, TID × 7 days | |
| | Initial dose: 3.2 mg/kg IM (anterior thigh); maintenance dose: 1.6 mg/kg IM daily until patient is able to transition to oral regimen as described earlier for artesunate | |
| CINCHONA ALKALOID REGIMENS | | |
| Quinine dihydrochloride | 20 mg salt/kg IV or IM on admission, then 10 mg/kg q 8 h. Can be given IM if IV administration is not possible. One of the following drugs should also be given concurrently: <ol style="list-style-type: none"> ACT as listed earlier. Doxycycline as listed earlier. If patient unable to take PO, give 100 mg IV q 12 h and switch to PO when possible. Avoid rapid IV administration. Clindamycin as listed earlier. If patient unable to take PO, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV q 8 h and switch to PO when possible. Avoid rapid IV administration. | The infusion rate of IV quinine should be rate controlled and not exceed 5 mg salt/kg per hour. The drug is usually diluted in 5% dextrose and infused over 4 hours. IV quinine is not available in the United States. When administering IM, the dose should be split and diluted to a concentration of 60-100 mg/kg and delivered to each thigh. Reduce the quinine dose by one-third (to 10 mg salt/kg q 12 h) after 48 hours in patients with severe renal and/or hepatic dysfunction. Doxycycline is contraindicated in children <8 years old and in pregnancy. |
| Quinidine gluconate | 6.25 mg base/kg (= 10 mg salt/kg) IV on admission over 1-2 hours, then 0.0125 mg base/kg minute (= 0.02 mg salt/kg per minute) continuous infusion. An alternative regimen is 15 mg base/kg (= 24 mg salt/kg) loading dose IV infused over 4 hours, followed by 7.5 mg base/kg (= 12 mg salt/kg) infused over 4 hours q 8 h, starting 8 hours after the loading dose. A second drug should be given concurrently as listed earlier for quinine. | The loading dose should be omitted if the patient received >40 mg/kg quinine in the preceding 48 hours or mefloquine in the previous 12 hours. Reduce the dose by one-third after 48 hours in patients with severe renal and/or hepatic dysfunction. |

BID, Twice a day; CDC, Centers for Disease Control and Prevention; DHA, dihydroartemisinin; IM, intramuscular; IV, intravenous; PO, by mouth; PPQ, piperazine; q8h, every 8 hours; TID, thrice a day.

defects and thrombocytopenia often correlate with the degree of parasitemia. The level of parasitemia should be monitored via blood smear every 12 hours after initiation of therapy. A decrease of 75% should be noted within 48 hours. If this does not occur, drug resistance should be suspected, and the regimen should be changed accordingly (see Table 133-4).

PROGNOSIS

Case fatality rates of severe malaria vary by geographic context and quality of care from 2% to 50%.^{31,32,115-117} More studies of treatment with artemisinin compounds in endemic areas generally report case fatality

rates of 10% to 19%.^{85,86} The case fatality associated with imported cases of *P. falciparum* malaria requiring ICU admission has been estimated to be between 4% and 29%.¹¹⁸ Factors that correlate with a poor prognosis include the infecting species and resistance profile, choice of parenteral therapy, CNS involvement, pulmonary edema, shock, hypoglycemia, lactic acidosis, renal failure, severe anemia, younger age, pregnancy, and treatment in a rural health facility as opposed to an ICU.^{55,119-126} There is a semiquantitative relationship between the level of parasitemia and risk of death, especially in nonimmune patients.

Although less than 10% of adults with cerebral malaria have persistent neurologic sequelae, this number may be as high as 40% in

children, especially if associated with hypoglycemia.^{81,115} Commonly seen sequelae include psychosis, hemiparesis, cerebellar ataxia, and extrapyramidal rigidity.^{31,32} Children who survive without obvious neurologic sequelae then appear to develop normally neuropsychologically.¹²⁷ A postmalaria neurologic syndrome, usually associated with mefloquine use, of an acute confusional state, psychosis, convulsions, and tremors has been described but is usually self-limited.³²

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KEY POINTS

1. A detailed history of patients' travel itinerary, activities and exposures, and any pretravel prophylaxis, as well as their general knowledge of the prevalent diseases and their incubation periods and drug resistance patterns in the region of travel are imperative when evaluating patients with exposures overseas.
2. Most "nontropical" infections are also common in developing countries and thus need to be considered.
3. Assessing patients' immune status based on their history of exposure to malaria is essential in directing the diagnostic workup and management.
4. Infection with multiple tropical pathogens is common in those living in endemic areas.

Risk of Infection and Uncomplicated Malaria

1. Malaria is the most common serious infection in most tropical countries, as well as in returning travelers, and therefore should be considered in any patient reporting travel to malaria-endemic areas or exposure to unscreened blood products ("transfusion malaria") or blood-contaminated needles.
2. Malaria classically produces a three-stage "paroxysm" progressing over an 8- to 12-hour period, consisting of rigors and chills ("cold stage"), followed by fever ("hot stage"), and subsequently sweating with resolution of all symptoms ("defervescent stage"). In practice, neither the classic paroxysm nor the periodicity is invariably seen.

Severe and Complicated Malaria

1. The overwhelming majority of severe and complicated malaria is due to *P. falciparum* in nonimmune children, adults, and pregnant women, but *P. vivax* and *P. knowlesi* can also cause severe disease.
2. The risk of acquiring *P. falciparum* is highest for those traveling to sub-Saharan Africa (especially West Africa) and New Guinea, moderate in India, and comparatively low in Southeast Asia and Latin America. *P. vivax* is widely distributed, with the highest risk in Oceania. *P. knowlesi* is restricted to Southeast Asia.
3. The most frequent severe complication is cerebral malaria, mostly seen in children and manifesting as coma, convulsions, changes in sensorium, or focal neurologic signs. Other severe complications include severe anemia (especially in young children and pregnant women), hypoglycemia, lactic acidosis, AKI, pulmonary edema, ARDS, shock, and bacterial suprainfection.
4. Potentially severe complications due to non-*falciparum* malaria include splenic rupture and severe anemia (*P. vivax*) and chronic nephrotic syndrome (*P. malariae*).

Diagnosis

1. Malaria often presents with nonspecific signs and symptoms, and the differential diagnosis is broad, so making a clinical diagnosis may be difficult.
2. The vast majority of malarial cases present within 1 month of exposure. *P. vivax* and *P. ovale* infections can present months, or even years, after infection because of the possibility of dormant forms (hypnozoites) in the liver.
3. Laboratory diagnosis is traditionally made through microscopy of thick and thin Giemsa-stained smears. Low or fluctuating parasitemias or altered parasite morphology may complicate diagnosis, especially with an inexperienced microscopist. Asymptomatic parasitemia is common in children from endemic areas.
4. Various new diagnostic techniques for malaria (e.g., dipstick antigen detection, PCR) have been developed, with sensitivities and specificities for *P. falciparum* generally similar or better than conventional microscopy. Use of one of these new modalities should be considered when the diagnosis of malaria is unclear.
5. Radiographic imaging of the abdomen is indicated when splenic rupture is suspected.

Clinical Management

1. Patients with evidence of severe or complicated malaria should be assumed to have chloroquine-resistant *P. falciparum* and admitted to the ICU for aggressive supportive care and urgent antimalarial drug therapy. Therapy should consist of IV artesunate followed by oral ACT for 3 days. Parenteral artesunate should be given for at least 24 hours and until the patient is able to tolerate oral medication. Acceptable alternatives to parenteral artesunate/ACT include IM artemether, IV quinidine gluconate, or IV quinine (transitioned to oral artesunate or quinine according to the same aforementioned criteria) given simultaneously with oral/IV doxycycline or clindamycin for 7 days.
2. Artemisinin compounds are usually well tolerated. Side effects with cinchona alkaloid therapy are frequent but are usually mild, dose related, and reversible.
3. Many patients with splenic rupture can be managed conservatively with supportive therapy, although splenectomy may be necessary.
4. The hemoglobin/hematocrit, electrolytes, platelet count, glucose, lactate, arterial blood gas, BUN/creatinine, liver function and coagulation enzymes, and level of parasitemia in response to therapy should be monitored closely.
5. The case fatality rate of severe malaria treated in an ICU is estimated to be 9%.

ANNOTATED REFERENCES

Cox-Singh J, Davis TM, Lee KS, et al. *Plasmodium knowlesi* malaria in humans is widely distributed and potentially life threatening. Clin Infect Dis 2008;46:165–171.

P. knowlesi has been misdiagnosed as *P. malariae* in humans. In this study, 960 blood samples from hospitalized malaria patients and 54 archival blood samples previously diagnosed as *P. malariae* in Malaysian Borneo, in addition to 5 archival samples from peninsular Malaysia, were subjected to nested PCR. *P. knowlesi* was detected in 27.7% of samples from hospitalized patients, 83.7% of archival samples in Borneo, and 100% of samples from peninsular Malaysia. Since *P. knowlesi* is frequently misdiagnosed and has been implicated in severe disease, all patients with *P. malariae* contracted in Southeast Asia should be treated for severe *falciparum* malaria.

Griffith KS, Lewis LS, Mali S, et al. Treatment of malaria in the United States: a systematic review. JAMA 2007;297:2264–2277.

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Mishra SK, Newton C. Diagnosis and management of the neurological complications of *falciparum* malaria. Nat Rev Neurol 2009;5:189–198.

*This review article summarizes the pathogenesis, symptoms, and sequelae of the neurologic complications of *falciparum* malaria. First-line and adjuvant therapies are also discussed.*

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*The acute respiratory distress syndrome is a dangerous complication of severe *falciparum* malaria. Mechanisms of pathogenesis are proposed but not well understood. This review article details the difficult management of fluid balance and mechanical ventilation in the setting of respiratory compromise in severe malaria.*

Stauffer WM, Cartwright CP, Olson DA, et al. Diagnostic performance of rapid diagnostic tests versus blood smears for malaria in US clinical practice. Clin Infect Dis 2009;49:908–913.

*The diagnosis of malaria is difficult in countries where few cases are seen, and clinicians and laboratorians are thus unfamiliar with the disease. This prospective study of 852 blood samples compared testing by standard thick and thin smears with a rapid antigen capture assay. The sensitivity of rapid diagnostic test was 97% and 100% for all malaria and *P. falciparum*, respectively, compared to 85% and 88% by Giemsa-stained thick blood smear. Rapid diagnostic tests are recommended, especially, for inexperienced microbiologists.*

■ References for this chapter can be found at expertconsult.com.

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Acute infections with viruses produce a variety of clinical manifestations with a wide spectrum of clinical severities. Viral upper respiratory tract infections in immunocompetent hosts are usually trivial, although they may be life-threatening and associated with subsequent lower respiratory tract infection and disseminated disease in immunocompromised hosts. Respiratory virus infections, including those responsible for MERS and SARS, are described elsewhere in this book.

Viral infections can affect virtually every organ system and have a variety of clinical manifestations. These are described below.

VESICULAR RASH

Poxviruses Including Smallpox and Monkeypox

Poxviruses are double-stranded DNA viruses that are relevant because of concerns regarding possible bioterrorism with smallpox.^{1,2} Additionally, outbreaks of monkeypox infection in humans have been detected, albeit rarely.³ The poxviruses and their major clinical manifestations are listed in Table 134-1. In general, a common feature of poxviruses is that they cause vesicular skin eruptions.

Smallpox

The last case of endemic smallpox occurred in Somalia in 1977, and it was declared in 1980 that the disease was eradicated.⁴ The virus (variola) has been maintained in some laboratories—the last known case of laboratory-acquired smallpox occurred in the United Kingdom in 1978. In part, as a result of this accident, the number of laboratories that retained the virus was reduced from 76 to 2. These laboratories are at the Centers for Disease Control and Prevention (CDC) in Atlanta in the United States and the Vektor Institute in Novosibirsk in Russia. It is not known if all the other laboratories destroyed their stocks of viruses—therefore, the potential exists for a deliberate release of variola as an act of bioterrorism.^{1,5}

The incubation period for smallpox is 7 to 17 days (mean, 10-12 days).⁴ A prodromal phase consisting of the abrupt onset of severe headaches, backaches, and fever occurs. The fever often reaches 40°C and then subsides. This is followed by a rash; initial lesions are small, red macules, which become vesicles over the next 2 to 3 days. The lesions first appear on the face and extremities and then cover the entire body including the palms and soles of feet. Subsequently, these lesions may umbilicate and crust.

The rash of smallpox could be confused with monkeypox, generalized vaccinia and eczema vaccinatum, chickenpox, coxsackievirus infection, herpes simplex virus (HSV) infection (especially eczema herpeticum), rickettsialpox, insect bites, drug eruptions, and acne. A classic feature of smallpox is that the lesions are all at the same stage of development. In contrast, chickenpox has individual lesions present at different stages of development. With chickenpox, fever occurs with the onset of the rash.

It is well known that smallpox is associated with significant mortality; however, it is not clear what the likelihood of mortality would be in patients who receive good supportive care, such as that which exists in modern intensive care units (ICUs). There are many reasons for the mortality associated with smallpox. Substantial amounts of fluid and protein are lost by febrile patients with numerous weeping lesions. In

some patients, death may occur before the appearance of any rash since this prodromal period is associated with significant viremia. A hemorrhagic form of smallpox is also associated with high mortality.⁴ Encephalitis occurs in less than 1% of infected patients. Secondary bacterial infections of the skin lesions may occur and are heralded by a second temperature spike.⁴ Although cough is not usually a prominent symptom of smallpox, secondary bacterial pneumonia may occur, particularly in patients with severe disease.

The CDC recommends an algorithmic approach for the diagnosis of smallpox. Patients are subdivided into low-risk, moderate-risk, and high-risk groups depending on a variety of variables (Boxes 134-1 and 134-2). Patients at low or moderate risk of smallpox should undergo polymerase chain reaction (PCR) testing of the skin lesion for varicella-zoster virus (VZV) infection, HSV, and enterovirus. Patients at moderate risk undergo consultation by infectious disease or dermatology specialists. Electron microscopy should be performed if PCR for these viruses is negative. If rapid testing for VZV and HSV is negative for moderate-risk patients, the adequacy of specimen collection should be confirmed. If there is ongoing clinical suspicion of smallpox, local and state health departments should be consulted. For patients at high risk of smallpox, all testing should be performed at the CDC. This testing should include variola real-time PCR, *Orthopoxvirus* real-time PCR, and nonvariola *Orthopoxvirus* real-time PCR, in addition to tests for VZV, HSV, and enteroviruses.

There is no approved treatment for smallpox.⁴ Prevention of secondary cases is crucial. A suspected case of smallpox should be managed in a negative-pressure room. Additionally, strict respiratory and contact isolation is essential (detailed instructions are available at <http://www.bt.cdc.gov/agent/smallpox>).⁴

Vaccinia

Vaccinia is the poxvirus used in smallpox immunizations. The primary vaccination results in a vesicle at the site of vaccination, usually within 3 to 5 days. This vesicle becomes pustular or is surrounded by induration or congestion 6 to 8 days after vaccination. In rare cases, a generalized rash characterized by multiple small, vesicular lesions occurs. Occasionally, severe complications result from smallpox vaccinations. If vaccinia is administered to patients with an immunologic deficiency, progressive necrosis at the site of vaccination may occur (vaccinia necrosum). Second, lesions may spread to other parts of the body. Such cases may be fatal. Patients with eczema may develop dissemination of vaccinia virus in the abnormal skin, leading to a generalized rash (eczema vaccinatum or Kaposi varicelliform eruption). Vaccinia immunoglobulin (0.6 mL/kg every 24 hours) can be prescribed for disseminated infection.

Encephalitis due to vaccinia may occur 1 to 2 weeks after vaccination and is associated with a mortality of 10% to 30%. Myocardial infarction, pericarditis, myocarditis, and dilated cardiomyopathy have been observed after smallpox vaccinations. In 2003, 37,901 potential bioterrorism first responders received the smallpox vaccine in the United States. There were 822 reports of adverse events; 100 of the 822 were serious, resulting in 85 hospitalizations, 2 permanent disabilities, 10 life-threatening illnesses, and 3 deaths. Among the 100 serious adverse events, 21 cases were myocarditis and/or pericarditis, 10 cases were ischemic cardiac events, 2 cases were generalized vaccinia, and 1 case was postvaccinial encephalitis. Serious adverse events were

TABLE 134-1 Common Clinical Manifestations of Poxviruses

| VIRUS | CLINICAL MANIFESTATIONS |
|--------------------|---|
| Variola (smallpox) | Diffuse vesicular rash; systemic disease |
| Monkeypox | Vesicular rash |
| Vaccinia (cowpox) | Vesicular rash; postinfectious encephalitis |
| Parapoxvirus | Orf (localized vesicular lesion) |
| Molluscipoxvirus | Molluscum contagiosum |
| Tanapox virus | Vesicular rash |

BOX 134-1 Criteria for the Suspicion of Smallpox in Patients with Acute Generalized Vesicular or Pustular Rash**MAJOR SMALLPOX CRITERIA**

Febrile prodrome

>101°F, 1-4 days before rash onset, with headache, backache, or abdominal pain

Firm, deep-seated, well-circumscribed vesicles/pustules

Lesions in the same stage of development in any one area of the body

MINOR SMALLPOX CRITERIA

Centrifugal distribution

First lesions in the pharynx, oral mucosa

Patient appears "toxic"

Slow evolution of the rash

1-2 days each stage: macule, papule, vesicle

Lesions on palms and soles

BOX 134-2 Categorization of Risk of Smallpox from Clinical Criteria***HIGH RISK OF SMALLPOX**Febrile prodrome *and*Classic smallpox lesion *and*

Lesions in the same stage of development

MODERATE RISK OF SMALLPOXFebrile prodrome *and* one other *major* smallpox criterion *or*Febrile prodrome *and* four *or* more minor smallpox criteria**LOW RISK OF SMALLPOX**No febrile prodrome *or*Febrile prodrome *and* fewer than four minor smallpox criteria

*The major and minor criteria are listed in Box 134-1.

more common among older revaccinees than in younger first-time recipients.⁶

From December 2002 to January 2004, the U.S. Department of Defense vaccinated 578,286 military personnel with vaccinia.⁶ Thirty cases of suspected contact transfer of vaccinia were reported.⁶ *Contact transfer* is the spread of vaccinia from a recipient of the smallpox vaccine to another person. This spread occurs because the live virus used in the vaccine is present on the skin at the site of the vaccination. Spread of the virus to other parts of the body (autoinoculation) also can occur via the same mechanism. No cases of vaccinia necrosum or eczema vaccinatum were observed in the people with contact transfer of the virus.

Monkeypox

Monkeypox was first recognized in 1958 as a disease of primates. Subsequently, the disease was recognized in rodents. Beginning in

1970, cases in humans were reported in Central Africa.⁷ In 2003, cases occurred in the United States in residents of the Midwest who had contact with imported prairie dogs.³ Patients developed vesicular skin lesions and fever/sweats. Although case fatality rates of 4% to 22% have been observed in outbreaks of the infection in Africa, none of the 11 patients in the American outbreak died.³

Herpesviruses

HSV, VZV, and herpes B virus are all capable of causing vesicular skin rash and other systemic manifestations of disease. The herpesviruses are large, enveloped DNA viruses that exhibit lifelong latent infection.^{8,9} The eight known human herpesviruses are HSV types 1 and 2; VZV; cytomegalovirus (CMV); human herpesvirus (HHV) types 6, 7, and 8; and Epstein-Barr virus (EBV).

Herpes Simplex Virus

HSV infections are found worldwide. Characteristically, HSV-1 is associated with orolabial disease, and HSV-2 is associated with genital infection, although this is not a rigid distinction. Primary infections (first infections with HSV-1 or HSV-2) are usually associated with mucosal lesions and systemic signs and symptoms. Mucosal and cutaneous lesions are vesicular and usually localized, although disseminated infection may occur rarely. Patients with atopic eczema or severe burns may develop extensive infections.

Primary HSV infections may have severe complications. Aseptic meningitis may occur and is more common with HSV-2. Meningeal symptoms usually start 3 to 12 days after the onset of genital lesions. Transverse myelitis and autonomic nervous system dysfunction may also occur in conjunction with primary genital HSV infection. HSV encephalitis in adults usually is not associated with primary infection. Potentially, reactivation of latent HSV-1 infection in trigeminal or autonomic nerve roots may be associated with the extension of virus into the central nervous system (CNS) via the enervation of the middle cranial fossa. Occasionally, patients with primary HSV infection develop hepatitis, pneumonia, or thrombocytopenia. These complications may be life-threatening and require ICU admission.

By virtue of the establishment of latency, HSV-1 or HSV-2 may reactivate. HSV reactivations may be less severe than primary infections. In immunocompromised hosts, however, reactivation of HSV-1 or HSV-2 may be associated with disseminated infection or severe local esophagitis, hepatitis, or pneumonia. Neonatal herpes, occurring in infants of mothers with primary or reactivated infection at the time of delivery, carries a high risk of disseminated fatal infection.

HSV-1 encephalitis is frequently seen in the ICU and is characterized by confusion or coma, accompanied by cerebrospinal fluid (CSF) lymphocytosis. Magnetic resonance imaging (MRI) of the brain may show temporal lobe lesions. Testing of CSF by PCR for HSV-1 is typically positive.

Diagnosis of HSV-1 or HSV-2 infections causing vesicular skin lesions can be suspected clinically by the presence of multiple vesicular lesions on an erythematous base, occurring in the orolabial or anogenital areas. A precise diagnosis can be established easily by PCR on scrapings from the lesions. Results can be available within hours of specimen collection.

Varicella-Zoster Virus

Primary VZV infections cause chickenpox, whereas reactivated infections cause shingles (zoster). Chickenpox is characterized by multiple vesicular lesions, whereas shingles is characterized by a unilateral vesicular eruption with a dermatomal distribution. Immunocompromised patients with shingles may develop disseminated cutaneous infection that may resemble chickenpox.

Chickenpox is usually associated with fever, constitutional symptoms, and a vesicular skin rash. Most skin lesions are small vesicular lesions with an erythematous base. Successive crops of lesions occur over 2 to 4 days, so lesions at all stages from fresh vesicles to crusted lesions are present simultaneously.

Secondary bacterial infections of vesicular lesions are relatively common, with infections involving *Staphylococcus aureus* and *Streptococcus pyogenes* being the most common. One manifestation of secondary bacterial infection is the occurrence of fever after the fever associated with the onset of chickenpox has subsided. Severe infection often results in toxic shock syndrome.^{10,11}

Chickenpox is associated with pneumonia in 1 in 400 cases of infection.^{12,13} A larger proportion of people may have some pulmonary involvement, but it is typically asymptomatic. Pregnant women and immunocompromised patients are at high risk of life-threatening pneumonia. Chickenpox pneumonia is generally manifested by cough and shortness of breath 3 to 5 days after the onset of the rash. Chest radiography typically shows a reticulonodular infiltrate. Respiratory failure may occur.

Neurologic complications of chickenpox include encephalitis, acute cerebellar ataxia (1 in about 4000 cases),¹⁴ and cerebral angiitis. Encephalitis due to VZV is less common than pneumonia but nevertheless may be life-threatening. The typical manifestation is onset of headaches followed by depression occurring in adults within 2 weeks of the chickenpox. Acute cerebellar ataxia is more common in children 1 to 3 weeks after the onset of chickenpox. Ataxia and slurred speech may occur but usually with complete resolution.

As with HSV infections, the rash of chickenpox or shingles can usually be diagnosed confidently on clinical grounds or confirmed by PCR of scrapings of skin lesions. PCR can also be performed on CSF to diagnose VZV encephalitis.¹⁴

Herpes B Virus (*Cercopithecine Herpesvirus 1*)

Herpes B virus (cercopithecine herpesvirus 1) infection is a relatively benign disease in monkeys. However, herpes B virus infection in humans, usually occurring from monkey bites or scratches, is a severe and potentially fatal disease. Monkeys of the *Macaca* genus (rhesus and cynomolgus monkeys) are considered to be at the highest risk. An incubation period of 2 to 14 days is usually observed after the bite or scratch. Initial symptoms are nonspecific but include fever, malaise, and headache. A cluster of small vesicles may occur at the bite site. Severe encephalomyelitis may ensue, with death occurring in days. In the United States, only one reference laboratory is equipped to identify the virus. Prompt and exhaustive cleaning of wounds, followed by early initiation of acyclovir or valacyclovir, may prevent the occurrence of severe disease. Additional information with contacts is available at <http://www.cdc.gov/niosh/docs/99-100/>.^{15,16}

FEVER IN IMMUNOCOMPROMISED PATIENTS

Numerous viruses can cause fever as a presenting symptom. In the absence of specific manifestations such as pneumonia or encephalitis, viral infections are rarely life-threatening. The onset of fever in immunocompromised individuals may, however, be the harbinger of severe overwhelming viral infection.

Cytomegalovirus

CMV infection is a classic cause of severe infection in immunocompromised hosts, especially transplant recipients and patients with human immunodeficiency virus (HIV) infection.¹⁷⁻¹⁹ Infection can be primary or due to reactivation. The risk of end organ CMV infection depends on the degree of immunosuppression and whether the infection is primary or reactivated. For solid organ transplant recipients, there is a significant risk of primary infection in patients who were seronegative for CMV before transplantation and received an organ from a seropositive donor.^{17,19}

The organs commonly affected by CMV infection include the esophagus, colon, retina, and lungs. Virtually any organ can be infected, including the CNS. Some patients present with fever, malaise, and hematologic abnormalities, without specific end organ abnormalities.

Given the high risk of CMV infections in solid organ transplant recipients, strategies should be employed to prevent CMV infections.^{17,20,21} Two options are prophylaxis or preemptive therapy. *Prophylaxis* implies the administration of preventive therapy to all persons at risk.¹⁷ In contrast, *preemptive* therapy is the administration of antiviral therapy only to persons at highest risk, as determined by a positive result on a regularly monitored blood test for CMV infection.¹⁷ Such therapy is given even if the patient is asymptomatic. Detection of CMV by PCR is used most often for early detection of CMV infection.

Epstein-Barr Virus

Primary EBV infection may be associated with fever, malaise, and hematologic abnormalities in immunocompromised patients (and also in some immunocompetent individuals). EBV infection may be associated with the development of malignancies such as posttransplant lymphoproliferative disorder.²²⁻²⁴ In some transplant populations, regular quantitative monitoring of EBV in peripheral blood by PCR is performed to determine the risk of significant EBV infection.²⁵

Human Herpesvirus 6

HHV-6 is a ubiquitous viral infection that usually occurs in infancy. Primary HHV-6 infection and possibly reactivation of infection in immunocompromised patients can be associated with serious disease.^{26,27} HHV-6 seems to have neurotropism—in addition to fever, HHV-6 infection may be associated with confusion, coma, and seizures.^{28,29} Occasionally, CSF examination is normal except for increased protein and the finding of HHV-6 by PCR.

Human Herpesvirus 8

HHV-8 is associated with Kaposi sarcoma, primary effusion lymphoma, and Castleman syndrome.^{30,31} It may be transmitted via organ allograft in solid organ transplantation. Primary infection in immunosuppressed patients may be associated with high fever, thrombocytopenia and other severe cytopenias, and mental state abnormalities.³² Detection of HHV-8 by PCR in whole blood can establish the diagnosis.

West Nile Virus and Zika Virus

In the 1990s, West Nile virus infection was detected in North America for the first time.^{33,34} Although many cases of infection were directly from the vector of infection (mosquitoes), other cases were via blood transfusion or organ allograft.^{35,36} West Nile virus exhibits neurotropism; infected patients may experience confusion and headaches in addition to fever and other more general symptoms.

Although Zika virus was described some decades ago, it has come to significant attention in 2015 and 2016. Most infected patients have minor symptoms with rash and fever. However, some adult patients may have more significant infection. In utero transmission may result in microcephaly and significant developmental problems in the child.

Adenovirus

Adenoviruses have a myriad of presentations in immunocompetent and immunocompromised hosts. Adenovirus infection in immunocompetent individuals is rarely associated with severe disease.³⁷ Although adenovirus infection in immunocompromised hosts may have trivial manifestations, severe diseases may certainly occur. In recipients of hematologic stem cell transplantation, adenoviruses may cause interstitial pneumonitis, hepatitis including ascending cholangiohepatitis, hemorrhagic cystitis, nephritis, hemorrhagic colitis, CNS disease, and disseminated disease.³⁷ In solid organ transplant recipients, the primary site of adenovirus disease is usually related to the transplanted organ. Clinical manifestations of adenovirus infections described in solid organ transplantations include pneumonia, hepatitis, nephritis, hemorrhagic cystitis, enteritis, and disseminated disease.³⁷

Adenovirus infection in patients with HIV may cause pneumonia, hepatitis, meningoencephalitis, nephritis, and gastrointestinal and disseminated disease.³⁷

Polyomaviruses

The most commonly encountered polyomaviruses are JC virus and BK virus. JC virus may be associated with progressive multifocal leukoencephalopathy, a progressive and ultimately fatal neurologic disease occurring in profoundly immunosuppressed individuals, such as patients with advanced HIV infection. BK virus is associated most commonly with renal infection in renal transplant recipients.³⁸ This infection is usually not accompanied by systemic manifestations such as fever. Infected patients have steadily rising serum creatinine. This presentation may be mistaken for acute rejection. Treatment with augmented immunosuppression is contraindicated, however, in patients with BK virus–associated nephropathy. Instead, immunosuppression should be minimized.

■ VIRAL HEMORRHAGIC FEVERS

Hemorrhagic fevers may be due to Filoviridae, Bunyaviridae, Arenaviridae, or Flaviviridae. Dengue hemorrhagic fever is not discussed in this chapter because it is reviewed in detail elsewhere in this book.

Marburg and Ebola Virus Hemorrhagic Fevers

Marburg virus and Ebola virus are members of the *Filovirus* genus. Marburg virus appears to have originated in Uganda and Western Kenya, where it infected monkeys and subsequently humans. *Marburg* refers to a town in Germany where monkeys from Uganda infected medical researchers, who subsequently infected hospital staff. The major subtypes of Ebola virus have occurred in Central Africa. An additional subtype (Reston) was discovered in Reston, Virginia, among infected monkeys imported from the Philippines.³⁹ The source of this infection has not been definitively determined.

Marburg and Ebola virus infections have an incubation period of 5 to 10 days and begin with the abrupt onset of fever, myalgia, and headache. Somnolence and delirium usually follow. Most patients have abdominal pain and diarrhea. Many have a maculopapular rash on the trunk. Hemorrhagic manifestations such as bleeding around needle puncture sites and from the mucous membranes become prominent. Most patients have significant thrombocytopenia, leukopenia, and elevated transaminase levels. Viral culture, serology, and PCR have all been used to establish the diagnosis. At present, management is purely supportive. Additionally, strict contact isolation precautions are necessary.

Hanta Fever and Crimean-Congo Hemorrhagic Fever

Hantavirus and Crimean-Congo hemorrhagic fever (CCHF) virus (CCHFV) are from the Bunyaviridae family of viruses. Hantaviruses cause hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). There are several human pathogenic strains of hantavirus. The subtypes Hantaan, Dobrava, and Seoul cause moderate to severe HFRS in Asia and Europe, whereas Puumala causes a mild form of HFRS.⁴⁰ Unlike other Bunyaviridae, hantaviruses do not appear to have an arthropod vector and are usually transmitted via aerosols of virus-contaminated rodent urine or feces. The incubation period is typically 2 weeks. Initially, patients develop fever, headache, dizziness, blurred vision, abdominal pain, and back pain. Petechiae may be evident on the palate and the trunk; most patients have significant thrombocytopenia. After 4 to 7 days, significant hypotension can occur. In patients who survive, oliguria and mucosal hemorrhage occur, followed by polyuria. Sin Nombre virus and Andes virus cause HPS in North America and South America, respectively.⁴⁰

CCHF is a severe hemorrhagic fever with a mortality rate ranging from 3% to 30%; it has been described in parts of Africa, Asia, Eastern Europe, and the Middle East.⁴¹ It has the most extensive geographic distribution of medically important tickborne viral diseases. CCHF occurs through tick (*Hyalomma* spp.) bites, by contact with blood or tissues from viremic livestock, and after contact with patients with CCHF during the acute phase of infection.⁴¹ Patients have severe thrombocytopenia, disseminated intravascular coagulation, and extensive bleeding, with increased levels of liver enzymes, creatinine phosphokinase, and lactate dehydrogenase. Diagnosis is made by enzyme-linked immunoassay (ELISA) and PCR. The clinical course of CCHF is composed of an incubation period (3–7 days), a prehemorrhagic period (3–7 days) characterized by flu-like symptoms, a hemorrhagic period (2–3 days), and a convalescence period. Supportive therapy is the most essential part of the management of CCHF. Ribavirin (30 mg/kg as an initial dose, then 15 mg/kg 6-hourly for 4 days, then 7.5 mg/kg 8-hourly for 6 days) is the recommended antiviral agent for severe CCHF, although its mechanism of action is unknown.⁴¹

Lassa Fever and South American Hemorrhagic Fevers

Lassa fever and South American hemorrhagic fevers are due to the Arenaviridae. Lassa fever occurs in West Africa. South American hemorrhagic fevers occur in Argentina, Bolivia, and Venezuela. Lassa fever is transmitted via rodents, but subsequent nosocomial transmission has been extensive. Many cases of Lassa fever are only mildly symptomatic. Some patients develop high fever, pharyngitis, and retrosternal chest pain accompanied by significant mucosal bleeding. Hypotension, renal failure, and pulmonary edema may follow. Serology can be used to establish the diagnosis, but the virus is also easily isolated from blood during the first week of illness, when viremia is often striking.⁴² Use of ribavirin has been associated with a decrease in mortality.⁴²

South American hemorrhagic fevers (Argentine, Bolivian, and Venezuelan) usually present with unremitting fever accompanied by a variety of nonspecific symptoms. Petechiae are often present on the palate and the skin, especially the axilla; mucosal bleeding may result. Pulmonary edema may occur. Management is extremely difficult owing to the combination of hypotension and refractory pulmonary edema. The diagnosis can be established by serologic tests. No specific therapy is available.

2009 PANDEMIC INFLUENZA A AND AVIAN INFLUENZA A

The rapid dramatic increase in the frequency of severe illness due to the 2009 influenza A(H1N1) has affected intensive care facilities around the world.^{43–45} Suggested risk factors for severe illness associated with the 2009 H1N1 infection include age (<5 years or ≥65 years), pregnancy, chronic cardiovascular conditions, chronic lung disorders, diabetes, immunosuppression, morbid obesity, hemoglobinopathy, chronic renal disease, chronic hepatic disease, and a long history of smoking.⁴⁶ Therapy with neuraminidase inhibitors (e.g., oseltamivir, zanamivir) is especially important for patients with such risk factors, as well as pregnant women. Epidemiologic studies estimated the case fatality ratio to be 0.05% to 0.5%.⁴⁷ However, as more than three-quarters of cases of the 2009 influenza A(H1N1) pandemic occurred in persons younger than 30 (with a peak in the group aged 10 to 19 years), years of life lost are estimated to be 3 to 5 times higher than for typical seasonal influenza and of the same order as the 1968 pandemic.⁴⁷

Avian influenza A(H5N1) virus remains a cause for concern. The first human case of influenza A(H5N1) virus infection was documented in Hong Kong in 1997.⁴⁸ Since its reemergence in 2003, it has caused human cases in 15 countries (e.g., China, Egypt, Indonesia, Iraq, Nigeria, Thailand, Turkey, Vietnam) around the world.^{49–53} The cumulative number of cases of avian influenza A(H5N1) virus infections

reported to the WHO as of June 8, 2010, was 499, with 295 subsequent deaths representing a mortality rate of approximately 60% (http://www.who.int/csr/disease/avian_influenza/country/en/). Although it has limited ability for human-to-human transmission, the continued circulation of influenza A(H5N1) virus increases the possibility of the reassortment of this virus with other circulating human influenza A viruses and increases the threat of a global influenza pandemic.⁵⁰

HENDRA AND NIPAH VIRUSES

These paramyxoviruses have been associated with deaths due to encephalitis or an acute pulmonary syndrome in Australia (Hendra virus) and Malaysia, Singapore, India, and Bangladesh (Nipah virus). The reservoir for these closely related viruses appears to be fruit bats. Viral transmission appears to occur from bats to horses (Hendra virus) or pigs (Nipah virus). Humans exposed to ill horses or pigs have developed the fatal infection. In Bangladesh, nosocomial transmission of Nipah virus may have occurred.

OTHER ACUTE VIRAL SYNDROMES

Many viruses can cause aseptic meningitis, encephalitis, pneumonia, or hepatitis. These viruses are summarized in [Tables 134-2, 134-3, and 134-4](#).

ANTIVIRAL DRUGS

Since the advent of HIV infection, there has been an increase in the development of drugs active against viruses. This section describes the currently available antiviral drugs, with the exception of drugs for HIV and viral hepatitis.

Acyclovir

Acyclovir is a deoxyguanosine analog that inhibits viral DNA polymerase. When incorporated into viral DNA, it acts as a chain terminator. Acyclovir has its greatest clinical utility against HSV-1, HSV-2, and

VZV. It has some activity against CMV, but it is far inferior to ganciclovir for infections with this virus. Acyclovir-resistant HSV has been well described, whereas acyclovir-resistant VZV is rare. Acyclovir is available in oral and intravenous (IV) forms. It penetrates the CSF reasonably well, and CSF levels are about 50% of plasma levels.⁴³ Dosing for acute mucosal HSV infections is 200 mg, five times a day, administered orally, and for VZV infections is 800 mg, five times a day, administered orally. In HSV encephalitis, the usual dose is 10 mg/kg given IV every 8 hours. Dose reduction is required in the presence of renal dysfunction. In the absence of appropriate reduction in dosage for renal dysfunction, neurotoxicity is observed, usually manifesting as confusion, hallucinations, and occurrence of tremors. As acyclovir can cause crystalline nephropathy, patients receiving the drug should be well hydrated.

Valacyclovir

Because the bioavailability of orally administered acyclovir is low, valacyclovir (the L-valyl ester prodrug of acyclovir) was developed. It is usually administered twice daily for HSV infections and three times daily for VZV infections. Valacyclovir is also used for the prevention of CMV disease in renal transplant recipients.⁵⁴

Famciclovir

Famciclovir lacks antiviral activity but is the prodrug of penciclovir, which is active against HSV and VZV. Similar to acyclovir, penciclovir is an inhibitor of viral DNA synthesis. In general, acyclovir-resistant strains are also resistant to penciclovir. Dose adjustment of famciclovir is needed in renal insufficiency.

TABLE 134-2 Viruses That Cause Aseptic Meningitis or Encephalitis

| VIRUS | IMPORTANT CLINICAL FEATURES |
|------------------------------|---|
| Enteroviruses | Common cause of aseptic meningitis; rapid diagnosis available via PCR of CSF |
| HSV | In adults usually due to reactivation; rapid diagnosis available via PCR of CSF |
| VZV | Uncommonly may cause encephalitis after chickenpox |
| HHV-6 | Causes encephalitis in transplant recipients |
| JK virus | Causes progressive multifocal leukoencephalopathy |
| Japanese encephalitis | Endemic in parts of Asia |
| St. Louis encephalitis | Outbreaks have occurred in all U.S. states |
| West Nile virus | Now common in U.S. and Canada |
| Tickborne encephalitis | Several foci of infection |
| Nipah virus | Zoonosis occurring in Malaysia, Singapore, India, and Bangladesh |
| Hendra virus | Zoonosis occurring in Australia |
| Rabies virus | Well-known zoonosis |
| California encephalitis | La Crosse virus is responsible for most cases |
| Human immunodeficiency virus | May cause acute encephalitis |

CSF, cerebrospinal fluid; HSV, herpes simplex virus; HHV-6, human herpesvirus 6; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

TABLE 134-3 Viruses That Cause Pneumonia

| VIRUS | IMPORTANT CLINICAL FEATURES |
|-----------------------------|--|
| Respiratory syncytial virus | Common cause of infection in infants |
| Influenza | Well-known cause of respiratory infection |
| Parainfluenza virus | Croup and pneumonia |
| Measles virus | Leading cause of pneumonia in children in underdeveloped nations |
| Coronaviruses | Severe acute respiratory syndrome |
| CMV | Important cause of pneumonia in immunosuppressed hosts |
| VZV | Pneumonia can complicate chickenpox |
| Adenovirus | Ubiquitous virus; severe pneumonia in immunosuppressed hosts |
| Hantavirus | Severe pneumonia in immunocompetent hosts |
| Hendra virus | Zoonosis in Australia |

CMV, cytomegalovirus; VZV, varicella-zoster virus.

TABLE 134-4 Viruses That Cause Hepatitis

| VIRUS | IMPORTANT CLINICAL FEATURES |
|-------------------|---|
| Hepatitis A virus | Fecal-oral transmission |
| Hepatitis B virus | Parenteral, sexual, vertical transmission |
| Hepatitis C virus | Parenteral transmission |
| Hepatitis D virus | Requires coinfection with hepatitis B |
| Hepatitis E virus | Fecal-oral transmission |

Ganciclovir

Similar to acyclovir, ganciclovir is a deoxyguanosine analog. It has activity against HSV and VZV. Its primary use has been in the treatment or prevention of CMV infections. Ganciclovir acts by inhibiting viral DNA polymerases. Patients with end organ disease due to CMV are treated initially with ganciclovir, 5 mg/kg IV every 12 hours. Alterations in dose and frequency are required in patients with renal dysfunction. Typically, maintenance therapy is given at a reduced frequency (e.g., once per day) in patients who have received 2 to 3 weeks of induction therapy. Myelosuppression is the major toxicity of ganciclovir. Neutropenia typically begins to occur in the second week of ganciclovir therapy. Regular monitoring of hematologic parameters is mandatory for patients receiving ganciclovir. CNS abnormalities such as headaches and confusion have been well described in patients receiving ganciclovir. In addition to an IV preparation, ganciclovir is available in an orally administered form. This form may be useful as a prophylaxis against CMV infections.¹⁷ Ganciclovir also can be administered into the eyes via an ocular implant.^{55,56} Ganciclovir is less active against acyclovir-resistant HSV strains than against acyclovir-susceptible strains. Resistance of CMV to ganciclovir has been well described, and mutations in the *UL97* phosphotransferase gene are generally associated with ganciclovir resistance.^{17,57} Risk factors for ganciclovir resistance include prolonged exposure to ganciclovir (usually several months), ongoing active viral replication due to severe immunosuppression, lack of prior CMV immunity, and inadequate antiviral drug delivery with oral ganciclovir.¹⁷

Valganciclovir

The oral bioavailability of ganciclovir is poor. Valganciclovir, a prodrug of ganciclovir, can be used to enhance bioavailability. Valganciclovir is widely used as a prophylaxis against CMV infections.¹⁷ However, a meta-analysis demonstrated that valganciclovir for CMV prevention in solid organ transplant patients had no superior efficacy and significantly higher risk of absolute neutropenia, CMV late-onset disease, and CMV tissue-invasive disease compared to other standard therapies (e.g., valacyclovir, ganciclovir).⁵⁸ A recent study has suggested the safety and efficacy of valganciclovir for preemptive therapy and treatment of CMV disease in solid organ transplant recipients.⁵⁹

Foscarnet

Foscarnet is used most frequently in patients with CMV infection refractory to or intolerant of ganciclovir. Foscarnet also has activity against HSV and VZV, including acyclovir-resistant and ganciclovir-resistant strains. Although foscarnet and ganciclovir may have synergistic activity against CMV, there is no proven usefulness of their combination in therapy.⁶⁰ Use of the combination of ganciclovir and foscarnet is associated with greater toxicity than use of ganciclovir alone.⁶⁰ Foscarnet is available in an IV formulation only. Toxicity is common with foscarnet. Nephrotoxicity is a major dose-limiting side effect. Electrolyte abnormalities are also common, especially hypocalcemia, hypophosphatemia, hypomagnesemia, and hypokalemia, which may be symptomatic. Foscarnet may produce painful genital ulcerations; saline loading may diminish the likelihood of nephrotoxicity or genital ulceration.

Cidofovir

Cidofovir is a nucleotide analog that is active against many herpesviruses and other DNA viruses, including polyomaviruses, poxviruses, and adenovirus. It is active against acyclovir-resistant and ganciclovir-resistant HSV and CMV. Cidofovir is administered via IV once a week or once every 2 weeks. Its use is accompanied by high rates of nephrotoxicity. Neutropenia occurs in 20% of patients receiving this drug.

Ribavirin

Ribavirin has found wide use as part of a combination therapy for hepatitis C virus infection, but it is discussed here in the context of its use against other viruses. In vitro, ribavirin has activity against a wide range of DNA and RNA viruses. Ribavirin (aerosolized) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of bronchiolitis and pneumonia due to respiratory syncytial virus. It has been used systemically in the treatment of some hemorrhagic fevers. Systemic ribavirin administration is associated with hemolytic anemia. Use of aerosolized ribavirin is controversial because of the drug's teratogenicity. Healthcare workers may potentially be exposed to the drug when it is used in conjunction with mechanical ventilation; use of aerosol containment systems are thus recommended.

Antiinfluenza Drugs

Amantadine, rimantadine, zanamivir, and oseltamivir are used in the treatment of influenza and for postexposure prophylaxis. Amantadine and rimantadine are active only against influenza A virus, whereas zanamivir and oseltamivir are active against influenza A and B viruses. In patients who have not received reduced doses of amantadine or rimantadine in the setting of renal dysfunction, serious neurotoxic reactions (including confusion and seizures) have been observed. Extensive experience with oseltamivir has been gained in recent years, and the drug has been found to be generally safe.

IV formulations of zanamivir or peramivir are now available on a compassionate-use basis for treating seriously ill patients, and peramivir was recently authorized for emergency use in hospitalized patients in the United States and licensed for use in Japan.⁴⁶ The efficacy of IV peramivir appeared to be similar to that of oseltamivir for seasonal influenza, but peramivir is less active for oseltamivir-resistant viruses than for oseltamivir-susceptible viruses. Thus IV zanamivir is the preferred option for seriously ill patients with suspected or documented oseltamivir resistance.⁴⁶

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KEY POINTS

1. For a generalized vesicular rash, scraping the base of the lesion and using polymerase chain reaction (PCR) to detect herpesviruses can assist in the rapid diagnosis of chickenpox or disseminated herpesvirus infections.
2. Cytomegalovirus (CMV) infection should be rapidly excluded as a cause of fever in an immunocompromised patient by way of detection of CMV DNA in peripheral blood by PCR.
3. Travelers from Africa, Asia, or South America who present with thrombocytopenia and fever should be assessed for Dengue and the viruses that cause hemorrhagic fevers. Strict contact isolation should be considered.
4. Herpes simplex virus (HSV), varicella-zoster virus (VZV), and enteroviruses can be detected by PCR of cerebrospinal fluid, enabling a rapid diagnosis.
5. Dosage adjustment is necessary for most commonly used antiviral agents in patients with renal dysfunction. Failure to adjust dosage may lead to adverse effects such as neurotoxicity.

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■ References for this chapter can be found at expertconsult.com.

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Antibiotic-associated colitis was recognized soon after antibiotics were introduced in the 1940s, but the cause was not known until 1978 with the original reports of the role of *Clostridium difficile* as the agent in nearly all cases of antibiotic-associated pseudomembranous colitis (PMC) and ~20% of those with antibiotic-associated diarrhea. Subsequent work has identified the pathophysiology, epidemiology, diagnostic methods, and treatment for *C. difficile* infection (CDI).¹ CDI has emerged as a major challenge to healthcare systems, and it is also increasingly recognized as a community-associated pathogen.²⁻⁴ Prevention of CDI and the management of patients with multiple recurrences and life-threatening infections remain key areas for improvement.

ETIOLOGY

The consequences of *C. difficile* ingestion, usually as spores from contaminated hands, the environment, or possibly food, are varied. At one extreme the individual may simply excrete *C. difficile*, while at the other, life-threatening PMC with toxic megacolon may occur. In between these extremes, asymptomatic colonization (or carriage), diarrhea, or colitis may result. The mortality rate following CDI can be 15% to 20% (particularly for cases defined by the presence of free toxin; see below), which partly reflects the underlying comorbidities and frailty of many patients with this disease.⁵⁻⁷ There are occasional cases of antibiotic-associated colitis due to other pathogens (*Staphylococcus aureus*, *Klebsiella oxytoca*, enterotoxin-producing strains of *Clostridium perfringens*, or *Salmonella*), but most cases are either due to *C. difficile* or have no cause identified. Direct effects of antibiotics on gut peristalsis or the microbiome likely account for a considerable proportion of the remainder.¹

PATHOPHYSIOLOGY

There are six relevant issues:

1. Colonization with *C. difficile*: this organism is found in the colonic flora of 2% to 3% of healthy adults and 10% to 20% of hospitalized patients, which can increase further in long-stay elderly subjects.¹
2. Toxin production: *C. difficile* produces two toxins, A and B. Early studies implicated toxin A as the major enteric toxin based on animal studies that showed florid colitis with injection of toxin A into bowel loops. However, more recent studies established that toxin B is critical for clinical expression.⁸ Most strains of *C. difficile* produce both toxins, but about 1% to 2% produce only toxin B. Some strains also produce a binary toxin that may enhance virulence, but this remains controversial.^{9,10}
3. Antibiotic exposure: this is the most important identifiable risk and reflects the impact of the inducing agent on gut bacteria, typically reducing diversity and key components of the microbiome, which to date are poorly characterized. This creates an opportunity for *C. difficile*, already present in the gut or soon to be acquired, to convert from the spore to vegetative form, with replication and toxin production. Virtually every antibiotic has been implicated in CDI, but the most frequent culprits are clindamycin and broad-spectrum cephalosporins. *C. difficile* resistance to an antibiotic in some cases confers a selection advantage. For example, fluoroquinolones are also associated with increased CDI risk and may have promoted the emergence and selection of clones such as ribotype 027/NAP-1/BI,

which is significantly associated with poor outcome, including treatment failure, recurrence, need for surgical intervention, and mortality.¹¹⁻¹³ Notably, determining which antibiotic has caused CDI is problematic, as patients frequently receive multiple agents over weeks. Cumulative antibiotic exposure exponentially increases the risk of CDI.¹⁴

4. Epidemiology: *C. difficile* is relatively infrequent in ambulatory persons, but rates of colonization and disease are much higher as a result of exposure to the hospital environment. *C. difficile* now represents an important and potentially lethal nosocomial pathogen. Nursing homes are another setting in which there is clustering of vulnerable patients with high rates of antibiotic use where *C. difficile* may be endemic or epidemic.¹ In the period 2001-2006, the ribotype 027/NAP-1/BI strain emerged as an important epidemic agent of *C. difficile* in Canada, the United States, and Europe.^{3,11,15} This strain has declined in some countries (e.g., Western Europe and possibly North America) but is causing major problems in others (e.g., Germany, Eastern Europe).^{3,4,5,16}
5. Age: there is increasing susceptibility to the development of *C. difficile* colitis with age, possibly due to immunosenescence. However, age may simply be a proxy measure of multiple comorbidities that are known to exacerbate CDI risk.⁷
6. Immunologic susceptibility: patients may harbor toxigenic strains of *C. difficile* with no clinical expression despite extensive antibiotic exposure. One reason for this paradox is the apparent immune protection due to the presence of neutralizing antibody to toxins A and B. This observation accounts for the increasing interest in monoclonal antibodies to toxins A and/or B for treatment and in vaccines for prevention.^{1,17}

CLINICAL SIGNS AND SYMPTOMS

The typical presentation of CDI is watery diarrhea associated with cramps. Other common features are fecal leukocytes, endoscopy showing PMC or colitis, characteristic changes on computed tomography (bowel wall thickening restricted to the colon, often associated with ascites), fever, leukocytosis, and hypoalbuminemia (particularly in those with recurrent infections). Nearly all cases of CDI are associated with diarrhea, but paradoxically, patients with very severe cases may not have diarrhea because of ileus. An important indicator of CDI and its severity is the white blood cell (WBC) count; the average WBC is about 15,000 cells/mL, but it may be much higher, with counts over 20,000 or even 50,000 cells/mL. This strongly supports the diagnosis of CDI and predicts severe disease.¹⁸

DIAGNOSIS

Clinical diagnosis alone of CDI is unreliable, so laboratory testing of symptomatic patients is needed. The great majority of patients tested for CDI are not confirmed to have the illness. The diagnosis is based on detection of *C. difficile* (culture, enzyme immune assay [EIA] for glutamine dehydrogenase, or polymerase chain reaction [PCR] for toxigenic *C. difficile*) or its toxins (by EIA or cytotoxin assay). The most accurate way of diagnosing CDI is using a combination of tests that includes the detection of free fecal toxin.^{6,19} The relative merits of different testing methods are shown in Table 135-1.

TABLE 135-1 Diagnostic Tests for *Clostridium difficile* Infection

| TEST | WHAT DETECTED | TIME | ASSESSMENT |
|-----------------|---------------------------------|----------|--|
| Culture | <i>Clostridium difficile</i> * | 3-4 days | Nonspecific; uncommonly used in routine diagnosis. |
| Culture-toxin | Toxigenic <i>C. difficile</i> * | 3-4 days | Test for toxin after culture for clostridia; sometimes used in Europe. |
| Cytotoxin | Free toxin A/B | 2-3 days | Formerly gold standard, but slow and rarely used now in routine diagnosis. |
| EIA toxin A & B | Toxins A and B | Hours | Variable kit performance; not as sensitive as cytotoxin testing. False-positives do occur. |
| EIA GDH | <i>C. difficile</i> | Hours | Detects <i>C. difficile</i> but not specific; good screening test, particularly when used with a toxin test. Such algorithms are becoming the most common diagnostic method, especially in Europe. |
| Toxin B gene | Toxigenic <i>C. difficile</i> * | Hours | Detects toxigenic <i>C. difficile</i> ; sensitive. Has become widely used, especially in North America. However, use of these tests alone leads to overdiagnosis of CDI, notably as patients with diarrhea (due to another cause) may well be colonized by toxigenic <i>C. difficile</i> . |

*About 50% to 60% of *C. difficile* strains produce toxin. CDI, *Clostridium difficile* infection; EIA, enzyme immune assay; GDH, glutamine dehydrogenase.

TREATMENT

If possible, the implicated antibiotic(s) should be discontinued. If there is a need for continued systemic antibiotic treatment, a drug should be selected that is unlikely to cause CDI (e.g., narrow-spectrum β -lactams, macrolides, aminoglycosides, antistaphylococcal drugs, tetracyclines). There are three main choices at present for treatment of CDI: metronidazole, vancomycin, and fidaxomicin, all usually given by mouth.^{1,20} Metronidazole was often preferred because it is less expensive. However, recent evidence shows that oral vancomycin is superior to metronidazole. This has been demonstrated on an intention-to-treat basis²¹ and in severe CDI,¹⁹ usually defined as having a WBC over 15,000 cells/mL or elevated creatinine to $1.5 \times$ baseline.^{20,22} Other markers of serious disease are albumin less than 2 mg/dL, admission to the ICU for CDI, and PMC on endoscopy or radiologically.²³ Vancomycin is superior to metronidazole, likely because of its pharmacology. Vancomycin is not absorbed and so achieves higher sustained gut lumen concentrations than metronidazole. Fidaxomicin is also primarily nonabsorbed and has a similar initial cure rate to vancomycin, but it is associated with an approximate 50% reduction in recurrence rate compared with the latter (12% vs. 20%-25%).^{24,25} Fidaxomicin is considerably more expensive than vancomycin (or metronidazole), but it may be cost-effective for patients at increased risk of recurrence (e.g., patients with multiple comorbidities, those receiving concomitant systemic antibiotic therapy alongside CDI treatment, and those with recurrent CDI).^{26,27}

Variable proportions of recurrences are caused by relapse, typically within the first 2 weeks after treatment cessation, or reinfection. This likely reflects the continued deleterious effects of systemic antibiotics on the gut microbiome with superimposed changes caused by the drug used to treat the CDI. In such circumstances, persistent spore colonization may progress to germination and further toxin production with new onset of symptoms. Thus, narrower spectrum CDI therapeutics (such as fidaxomicin) are associated with less microbiome disruption or reduced diversity and hence a lower risk of recurrence.

Most patients improve with resolution of diarrhea in 3 to 5 days. Patients who are seriously ill (megacolon, septic shock, WBC > 30,000/mL, lactate > 5 μ M) and fail to respond to standard treatment should be considered for surgical intervention (colectomy or diverting loop ileostomy).^{23,28} Toxic megacolon markedly impairs delivery of vancomycin given orally to the site of infection. In such circumstances, vancomycin can be administered rectally via a catheter or enema. Although some patients are severely ill with signs of sepsis, it is perhaps surprising that bacteremia due to enteric bacteria is rare. *C. difficile* bacteremia as a complication of CDI has not been reported. Most seriously ill patients respond to standard management of sepsis, with particular attention to rehydration, while attempting to control disease with oral or rectal vancomycin and IV metronidazole with or without IV vancomycin.²⁹

Recurrence of CDI is a therapeutic challenge, especially in patients with multiple episodes. There is increasing use of fecal microbiota transplantation in such cases, delivered either via the mouth or rectum, with impressive reported efficacy.^{30,31} Screening of donors is necessary, and long-term safety remains a potential concern given the far-reaching effects of the gut microbiome.

There are several CDI treatment options in advanced clinical trials, including targeted antibiotics, a monoclonal antibody to toxin B, and tailored collections of gut microbiome-based bacteria.¹

PREVENTION

Prevention of *C. difficile* includes surveillance to detect increasing rates, emergent strain types, and outbreaks or epidemics; methods to prevent transmission of *C. difficile*; and strategies to prevent unnecessary exposure to antibiotics, especially those most likely to induce CDI.

It has long been believed that the great majority of CDI cases occurring in hospitals represents transmission of *C. difficile* from patients with the disease to at-risk recipient patients. However, a large, 3.5-year-study from the UK using highly discriminatory whole genome sequencing found that only 35% of all CDI cases were closely related to prior cases; less than a fifth (19%) were closely genetically related and involved hospital contact.³² Just under half (45%) of CDI cases in the study population were genetically distinct from all previous cases, which suggests that there is a large reservoir of strains causing infection. The modes of transmission and precise sources of the strains causing CDIs that are not closely linked to previous cases require further understanding. Possibilities include asymptomatic or transiently symptomatic *C. difficile* carriers, infants, food, and environmental niches.

The key measures to prevent horizontal transmission are hand hygiene with soap and water, barrier precautions, use of private rooms or cohorting of case patients as soon as they become symptomatic and until diarrhea resolves, and disinfection of environmental surfaces using sporicidal agents such as chlorine-containing agents or vaporized hydrogen peroxide. Patients with CDI should ideally have their own commode and room or be cohorted until diarrhea resolves. The decision to stop barrier precautions or transfer the patient should not be based on *C. difficile* testing, as there is no appropriate test to determine treatment response.

Avoidance of unnecessary antibiotic use with antibiotic stewardship programs is an important general practice principle and especially so in controlling CDI. When surveillance indicates an epidemic is occurring, it is important to define the associated antimicrobials. Published reports indicate control of epidemics through restraining or eliminating use of clindamycin, cefotaxime, or fluoroquinolones.²² Identification of the ribotype of the implicated strain may facilitate epidemiologic

investigations in outbreaks. However, this requires stool culture for *C. difficile*, which for most hospital laboratories requires referral of the strain to a typing reference center. One such system in the UK has been associated with a large decline in national CDI rates.³³

Investigational approaches to prophylaxis against CDI include vaccines and antibiotic sequestration or inactivation.¹

CONCLUSION

C. difficile has emerged as a major nosocomial pathogen that is usually associated with antibiotic use and that may cause a devastating colitis. It is optimally diagnosed by testing that includes the detection of fecal

toxin, and it usually responds rapidly to a combination of discontinuing the implicated antibiotic and adding oral vancomycin or fidaxomicin. Important issues for the intensivist in dealing with this nosocomial pathogen are (1) an understanding of the management guidelines for the patient with CDI who is critically ill and (2) the need for implementing careful infection-control procedures in all cases.

Acknowledgment

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KEY POINTS

1. Most cases of healthcare-associated infective diarrhea are caused by *C. difficile*.
2. Major complications of CDI are severe disease with ileus or toxic megacolon, sepsis, and recurrent disease.
3. Risks for CDI are advanced age, multiple comorbidities, exposure to antibiotics, and being in a hospital or chronic care facility. Antibiotics with the greatest risk are fluoroquinolones, second- and third-generation cephalosporins, and clindamycin.
4. The preferred diagnostic approach for CDI is a combination of a screening test (e.g., EIA to detect glutamine dehydrogenase or PCR to detect toxigenic *C. difficile*) plus a direct toxin detection test.
5. The usual management of CDI is to (a) discontinue the implicated antibiotic, (b) treat with oral vancomycin or fidaxomicin, and (c) maintain contact precautions to avoid nosocomial spread.
6. The ribotype 027/NAP-1/BI strain became epidemic in North America and Europe in the early to mid-2000s. This strain is promoted by fluoroquinolone use and causes severe disease, contributing to the increasing rates of CDI and mortality.
7. The intensivist is likely to see CDI as complication of antibiotic use in seriously ill patients; treatment is usually straightforward if the diagnosis is considered.
8. The intensivist may also see complicated cases, with critical disease indicated by a leukemoid reaction, renal failure, sepsis, ileus, or megacolon. These patients may require IV metronidazole, rectal vancomycin, and consideration of surgical intervention.

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Anemia remains common in the critical care population, affecting more than 50% of patients at some point during their intensive care unit (ICU) stay. There are a multitude of causes of anemia including issues with losses and production that may be disease-related, patient-related, and even iatrogenic. This chapter will explore the problem of anemia in the euvolemic critically ill patient, its causes and effects, and the use and risk of red blood cell (RBC) transfusions in the management of this common problem with a focus on evidence-based studies. Particular emphasis will be placed on randomized controlled trials (RCTs) and systematic reviews, where available. The physiologic effects of anemia are covered elsewhere. A review of resuscitation practices and transfusion guidelines in patients suffering from hemorrhagic shock and/or trauma (i.e., the hypovolemic hemodynamically unstable patient) is also out of the scope of this chapter.

ANEMIA

According to the World Health Organization (WHO), anemia is defined as a hemoglobin level of <130 g/L in men and <120 g/L in nonpregnant women.¹ In the critical care population, modest anemia is generally accepted to be a hemoglobin level of ≤100 g/L in both men and women.

Epidemiology

Among all admitted ICU patients, the vast majority will experience an appreciable drop in hemoglobin. Large observational studies of this population have demonstrated the significance of this problem. In a 2006 European study of over 1000 sequential patients, anemia, as defined by a hemoglobin level of <130 g/L in men or <115 g/L in women, was observed in more than 80% of the patients, and by the time of discharge almost a quarter of them had a hemoglobin level of <90 g/L.² Similar observations were made in a 2004 North American critical care study that involved 4892 patients.³ In this report, 70% of the patients developed a hemoglobin level of <120 g/L within 2 days of ICU admission, and 50% had a hemoglobin level of <100 g/L.

Anemia develops early post ICU admission and on average within the first 2 days. In nonbleeding patients, an average hemoglobin drop of 5.2 g/L/day has been observed, with the largest decline seen in the first days following admission.⁴

Etiology

The significant drop in hemoglobin seen in ICU patients is the result of many factors, including problems with decreased production and increased losses. Production issues include a blunted erythropoietin response during critical illness, lack of substrate availability (including iron, vitamin B12, and folate), and the presence of renal failure (which may accentuate these but is also an independent risk factor of anemia).^{5,6} Anemia due to blood loss can be subdivided into disease-related and secondary causes. Disease-related causes of anemia include traumatic blood loss, coagulopathy, hemolysis, and gastrointestinal losses. Other secondary losses are primarily iatrogenic and include losses due to diagnostic sampling, vascular cannulation, renal replacement therapy, and surgical procedures. Daily diagnostic sampling can be an important contributor to anemia: when the average volume of blood taken per draw exceeds 10 mL, it results in an average of 40 mL of blood loss per day.⁷

Morbidity and Mortality Associated with Anemia

Although preclinical work has demonstrated that anemia becomes intolerated in healthy animals only under conditions of extreme hemodilution (hemoglobin concentration as low as 50 g/L),⁸ this is not necessarily true in humans. In a retrospective observational study of 300 consecutive anemic patients who declined RBC transfusion, no deaths were observed in those with postoperative hemoglobin levels between 71 and 80 g/L.⁹ However, in patients with postoperative hemoglobin levels between 41 and 50 g/L, mortality was 34%. Previous work in a similar population demonstrated that patients with a preoperative hemoglobin level of <60 g/L had significantly higher morbidity and mortality.¹⁰

Despite the theoretic rheologic benefits of hemodilution created during euvolemic anemia, cardiac output must increase to maintain oxygen delivery. This supply/demand balance is particularly stressed in the critically ill patient population where cardiac and peripheral oxygen consumption has increased. In patients with ischemic heart disease, coronary flow may be fixed, thereby creating a mismatch between blood supply and oxygen demand. In a large retrospective administrative database study of over 75,000 patients over the age of 65 with myocardial infarction, lower hematocrit (Hct) levels were associated with significantly higher rates of shock and heart failure, in-hospital and 30-day mortality and increased length of hospital stay.¹¹ These results should be interpreted with caution as retrospective studies are often limited by confounding factors.

Summary of Anemia Epidemiology and Clinical Impact

Anemia in critical care populations is common and is often caused by many simultaneous processes. Its physiologic effects impact not only oxygen delivery to vital organs and tissues but also increase cardiac workload as a consequence of natural compensatory mechanisms. These effects may be further accentuated in certain high-risk populations. Although anemia appears to be a risk factor for both morbidity and mortality, whether augmentation of hemoglobin levels with red blood cell transfusion can improve outcomes (and at what threshold this should occur) is less clear and is the focus of the discussion ahead.

RED BLOOD CELL TRANSFUSION

Epidemiology

Several large observational studies demonstrate that RBC transfusion is commonplace across ICUs in North America and Europe. In the American CRIT study,³ a cohort of 4892 patients from 284 ICUs in 213 hospitals were observed. Of these, 44% received at least one RBC transfusion during their ICU admission, with a mean pretransfusion hemoglobin level of 86 g/L (±1.7 g/L). This was similar to the European ABC Study (3534 patients, RBC transfusion rate 37%)⁷ and, more recently, a Scottish observational study involving 1023 sequential ICU admissions, where RBC transfusions occurred in 39.5% of patients.²

In the euvolemic critically ill patient, improving oxygen delivery is the most common reason for administering an RBC transfusion.¹² Specifically, in the CRIT study,³ low hemoglobin, active bleeding, and hemodynamic instability/hypotension were the most common

indicators for transfusion (90%, 24%, and 21%, respectively). These observations were consistent with the findings of the European ABC study,⁷ where active bleeding (56%) and anemia with diminished physiologic reserves (28%), altered tissue perfusion (17%), or ischemic heart disease (8%) were the most common reasons for transfusion.

Physiologic and Oxygen Transport Effects of RBC Transfusion

The negative effects of anemia on oxygen delivery, as described above, are clear. Although the improved delivery of oxygen following RBC transfusions in these patients has been demonstrated in several studies, an increase in oxygen uptake and consumption by the end organs and tissue beds is less evident and is not a consistent finding.

It is thus evident that despite a strong physiologic rationale to treat anemia in critically ill patients, particularly those with evidence of end-organ ischemia, studies have failed to demonstrate reliable benefits with respect to oxygen utilization. Furthermore, there are risks associated with RBC transfusions, and these risks are summarized in the next section.

Risks

Risks from RBC transfusions can result from infectious and non-infectious complications (Table 136-1). Complications from massive transfusions, including coagulopathies, electrolyte disturbances, acid-base imbalances, temperature dysregulation, and citrate toxicity are also of significant importance but are beyond the scope of this chapter.

Infectious Complications

Due to significant enhancements in donor screening and blood testing, the direct transmission of infection through contaminated blood supply is exceedingly rare and presented in Table 136-1.

TABLE 136-1

Complications Associated with Allogeneic RBC Transfusion

| | COMPLICATION | RISK PER RBC UNIT TRANSFUSED |
|-----------------------------|---|------------------------------|
| Infectious complications | Symptomatic bacterial sepsis | 1:250,000 |
| | Death from bacterial sepsis | 1:500,000 |
| | Hepatitis: | |
| | A | 1:2 million |
| | B | 1:153,000 |
| | C | 1:2.3 million |
| | HTLV | 1:4.3 million |
| | HIV/AIDS | 1:7.8 million |
| | West Nile virus | <1:1 million |
| | Parasitic infection | 1:4 million |
| Noninfectious complications | Urticarial reaction | 1:100 |
| | Febrile nonhemolytic reaction | 1:300 |
| | Transfusion-associated circulatory overload | 1:700 |
| | Transfusion-related acute lung injury | 1:10,000 |
| | Delayed hemolytic transfusion reaction | 1:7000 |
| | Acute hemolytic transfusion reaction | 1:40,000 |
| | Anaphylactic reaction | 1:40,000 |
| | Posttransfusion purpura | Rare |

AIDS, acquired immune deficiency syndrome; HTLV, human T-cell lymphotropic virus; HIV, human immunodeficiency virus; RBC, red blood cell

(Data from Callum JL, Lin Y, Pinkerton PH, et al. *Bloody Easy 3: blood transfusions, blood alternatives and transfusion reactions: a guide to transfusion medicine*. 3rd ed. Ontario Regional Blood Coordinating Network. 2011.)

Noninfectious Complications

Noninfectious complications of RBC transfusions are far more common (see Table 136-1). These represent a spectrum from relatively benign (fever) to more severe (acute lung injury) and imminently life-threatening (hemolytic reactions).¹³ The exact mechanisms by which these occur are not understood but are likely at least in part attributable to host immune and inflammatory responses. Central to immune-mediated reactions are donor interleukins and the tumor necrosis factor as well as antibodies or activated neutrophils, fragments of cellular membranes, and soluble human leukocyte antigen, which play important roles in transfusion-induced immunomodulation (TRIM). TRIM is purported to predispose patients to infections and cancer recurrence.¹⁴⁻¹⁶ Many Western countries across Europe and North America have adopted leukoreduction programs to reduce the effects of TRIM. TRIM may facilitate indirect infectious complications from RBC transfusions like healthcare-associated infections that occur downstream from the point of transfusion.

Evidence from Systematic Reviews. A recently published systematic review and meta-analysis (20 randomized trials, 7456 patients, published 2014)¹⁷ evaluated the risk of healthcare-associated infections linked to RBC transfusions and compared different transfusion strategies (liberal vs. restrictive strategy). They found that although a restrictive transfusion strategy was not significantly associated with fewer overall healthcare-associated infections, there was a significant risk reduction in serious infection rates (defined by the specific trials themselves) even when controlling for leukoreduction (number needed to treat 48, 95% CI: 36-71). Interestingly, this significance was not observed in a subgroup analysis of critically ill patients (2 studies, 1475 patients, $P = 0.104$). A systematic review of randomized trials to study the effect of restrictive versus liberal transfusion strategies to guide RBC transfusions was conducted by the *British Medical Journal*, a subgroup meta-analysis of 8 trials deemed lower risk of bias by the authors (5107 patients). The authors also showed a lower associated risk of infection with a restrictive transfusion strategy (RR 0.73, 95% CI: 0.55-0.98).¹⁸

In modern medicine, changes in donor screening and blood testing have led to a significant decline in direct RBC transfusion-related infections over the past 30 years. The leading cause of RBC transfusion-related morbidity and mortality is from transfusion-related acute lung injury (TRALI). The clinical picture of TRALI is difficult to distinguish from other causes of acute lung injury (ALI). A definite diagnosis of TRALI requires (1) no pretransfusion evidence of ALI; (2) new ALI occurring during or within 6 hours of RBC transfusion; and (3) no other likely direct or indirect confounding causes for lung injury.¹³ Given these strict diagnostic criteria and the fact that in the critically ill there are often confounding causes for ALI, the clinical importance of this complication is likely underestimated.¹⁹ This pathophysiologic process is secondary to increased lung endothelial permeability to inflammatory mediators and fluid, as a result of neutrophil activation in the recipient brought on by donor antibodies. A significant association has been found between the incidence of TRALI and the use of female donor plasma, particularly from female donors post pregnancy, as a result of increased human neutrophil antibodies.^{19,20} Incidence of TRALI has decreased since policy changes use male-only donated plasma.²¹

Complications Related to Age of Blood

Red blood cell storage encompasses the numerous physiologic and morphologic changes that occur in RBCs during storage, over time, and potentially as a consequence of the medium in which they are stored.²² These include biochemical changes such as a depletion of 2,3-DPG (causing a reduction in oxygen unloading), and adenosine triphosphate (intracellular energy stores), S-nitroso hemoglobin, and calcium. Biomechanical changes include membrane phospholipid loss and redistribution, protein oxidation and lipid peroxidation, release of free hemoglobin, and microvesicle formation, which lead to RBC membrane deformation, changing the typical biconcave

shape to permanently deformed spherocytocytes.²³ Consequently, the rheologic properties of blood are altered, potentially affecting the normal passage of these deformed RBCs through the capillary microvasculature.

The effect of the age of blood on clinical outcome has been reported in several observational studies, suggesting potential harm associated with older blood. These findings, however, were not validated in more rigorous study designs.

Evidence from RCTs. The Canadian-led Age of Blood Evaluation (ABLE) international randomized trial (published 2015) was conducted to study the effect of blood storage time on clinical outcome. ABLE included 2430 patients from 64 centers across Canada and Europe and tested the effect of transfusion of fresh (stored <8 days) RBCs compared to standard-issue RBCs (oldest available compatible blood) on 90-day mortality and clinically important morbidity.²⁴ The investigators found no significant difference in the primary outcome of 90-day mortality among those patients who received fresh RBCs (mean age 6.1 ± 4.9 days) compared to those who received the older units (mean age 22.0 ± 8.4 days). Further, there were no appreciable differences between the two groups in all of the secondary outcomes including major illnesses, duration of life supports (respiratory, hemodynamic, and renal), and length of hospital stay or transfusion reactions.

We await the results of a similar study currently being conducted by an Australian group called the TRANSFUSE-RCT (standard issue transfusion versus fresher red blood cell use in intensive care) (NCT01638416). In this large multicenter study, the investigators are aiming to recruit 5000 ICU patients to test the effect of transfusion of the freshest available versus the oldest available RBC and its effect on 90-day mortality.

RBC TRANSFUSION THRESHOLDS IN THE CRITICALLY ILL AND THE EVIDENCE-BASED STUDIES TO SUPPORT THEM

Evidence from Observational Studies

There are a multitude of observational studies examining the use of, indications for, and potential benefit or harm of RBC transfusions in several euolemic nonbleeding critical care populations.

Evidence from Systematic Reviews of Observational Studies. A 2008 systematic review of 45 of these observational studies demonstrated an association between RBC transfusions and poor outcomes including an increased risk of death, infection, organ dysfunction, and acute respiratory distress syndrome.²⁵ More recently, a systematic review of large-scale observational studies of mixed medical, surgical, ICU, and trauma patient populations (minimum 1000 patients) published between 2006 and 2010 demonstrated that RBC transfusions (as compared to no transfusion) were associated with adverse events, including mortality.²⁶ All of these studies, however, are subject to potential bias (most frequently the inability to effectively adjust for confounding by indication) significantly limiting the interpretation and generalization of the results.

Evidence from Randomized Controlled Trials

In guiding RBC transfusions of the critically ill, the rigorously designed TRICC trial remains the most influential.²⁷ This RCT included 838 ICU patients with a hemoglobin concentration of ≤ 90 g/L within 3 days of admission who were randomized to either a restrictive or liberal (70 g/L vs. 100 g/L) transfusion threshold strategy. The investigators found no significant difference in 30-day mortality between the groups (18.7 vs. 23.3%, $P = 0.11$). Further, subgroup analyses showed that 30-day mortality was significantly lower in the less sick subpopulation (patients with an APACHE II score of <20) and in those critically ill patients who were less than 55 years of age.

Evidence from Systematic Reviews. Several systematic reviews of randomized trials of RBC transfusion in critical care and other

populations exist. A comprehensive 2012 Cochrane Systematic Review by Carson et al.²⁸ examined transfusion thresholds and other strategies to guide transfusion (19 RCTs). A restrictive transfusion strategy significantly decreased the exposure risk for RBC transfusion. Although the authors found that a restrictive RBC transfusion threshold was associated with reduced hospital mortality (5 studies, RR 0.77, 95% CI: 0.62-0.95), no statistical significance was observed for 30-day mortality (11 studies, RR 0.85, 95% CI: 0.70 to 1.03). Furthermore, there was no statistically significant reduction in medical complications including pneumonia (5 studies), pulmonary edema (5 studies), stroke (5 studies), cardiac (7 studies), or venous thromboembolic events (3 studies). The authors also noted the lack of literature to guide transfusion practices in certain patient populations like those with acute cardiac ischemia. More recently, a systematic review of restrictive versus liberal transfusion strategies for RBC transfusion by Holst et al. included 31 trials from a number of different clinical settings.¹⁸ They concluded that a restrictive strategy resulted in less RBC transfusion and was not associated with less risk of death, either overall or in any of the population subgroups (Fig. 136-1). Differences in overall mortality or fatal or nonfatal myocardial ischemia were also not observed.

This suggests that a restrictive RBC transfusion strategy leads to fewer transfusions, decreasing exposure risks, and appears to not be associated with worse clinical outcomes and may in fact result in better outcomes as compared to a liberal transfusion strategy. Although a liberal RBC transfusion strategy has not been shown to be beneficial, certain critical care populations were either minimally or not included in these studies. The effect of such strategies on these subpopulations has remained in question.

TRANSFUSION THRESHOLDS FOR SPECIFIC SUBPOPULATIONS

There are certain critical care subpopulations with distinct physiology or pathophysiologic processes that are underrepresented in the trials discussed above, limiting the generalization of the existing evidence to guide their anemia management with RBC transfusions. A specific focus on septic shock, cardiac ischemia, and neurocritical care follows.

RBC Transfusion Thresholds in Septic Shock—Evidence from RCTs

A more liberal approach to RBC transfusions was suggested in septic shock patients with evidence of hypoperfusion/end-organ ischemia. This was based on the significant effect on survival when introduced as part of an early goal-directed therapy bundle demonstrated in the Rivers et al. RCT ($n = 263$, published 2001).²⁹ In this study, a target Hct $>30\%$ as part of a bundle of care was pursued in a specific subset of patients (depending on each patient's course through the treatment algorithm). Although 68% of patients in the intervention arm received an RBC transfusion, it was administered according to a bundle of care. As such, the direct effect of transfusion strategy on outcome cannot be ascertained. Interestingly, since then, two other RCTs of a goal-directed therapeutic approach to patients with severe sepsis/septic shock ($n = 1341$ and 796 , both published 2014), using similar strategies as the one published by Rivers et al., failed to demonstrate the same survival benefit.^{30,31} Transfusion rates in the intervention arm of both of these studies were under 15%.

The specific effect of transfusion strategies on outcome in septic shock has recently been tested (liberal vs. restrictive) in the TRISS RCT (published 2014).³² In this multicenter RCT of 1005 ICU patients, the effect of a liberal (Hb trigger <90 g/L) versus a restrictive (Hb trigger <70 g/L) transfusion strategy in patients with septic shock on 90-day mortality was examined. They found no appreciable difference in the primary outcome between the two groups (RR 0.94, 95% CI: 0.78-1.09) as well as no significant difference in ischemic events or use of life supports. Similarly, no important differences were found in subgroup analyses for age, chronic cardiovascular disease history or illness severity. It can thus be concluded that in septic shock patients,

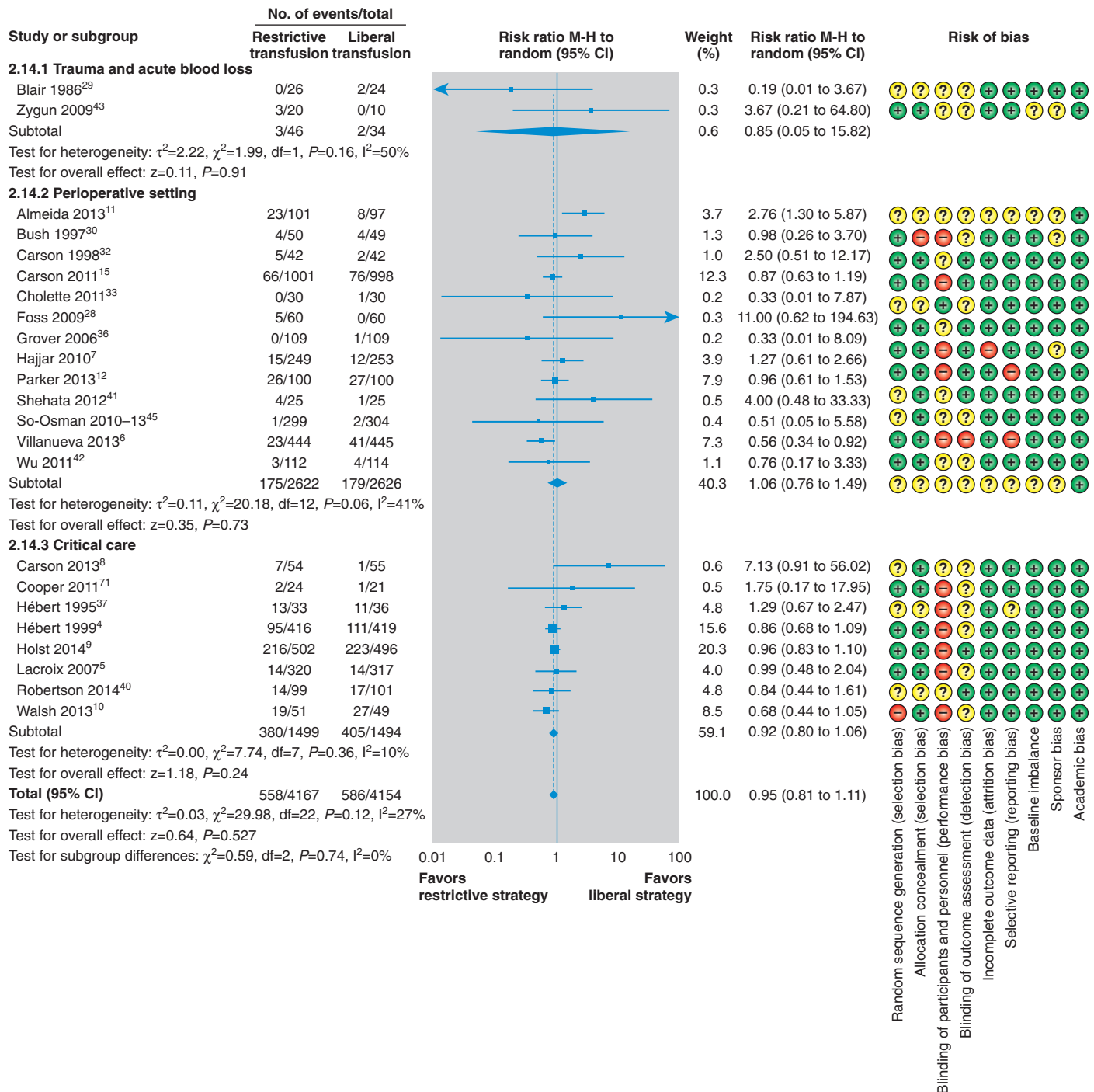


FIGURE 136-1 ■ Forest plot of the effect of restrictive versus liberal transfusion strategy on mortality stratified by patient population, presented as risk ratios with 95% confidence intervals and presented with risk of bias assessment. The size of square represents the weight of the trial in the pooled analysis. (From Holst L, Petersen M, Haase N, Perner A, Wetterslev J. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. *BMJ* 2015;350:h1354.)

a restrictive strategy imparts no increased risk of mortality or negative outcome over a liberal strategy but is associated with fewer RBC transfusions. Indeed, the most recent edition of Surviving Sepsis Guidelines suggests a hemoglobin transfusion trigger of <70 g/L “once tissue hypoperfusion has resolved and in the absence of extenuating circumstances.”³³

RBC Transfusion Thresholds in Patients with Ischemic Heart Disease—Evidence from RCTs

As described above, the increased oxygen demands placed on the heart in the face of anemia may not be met by supply, propagating ischemic

processes. In a subgroup analysis of patients with cardiovascular disease ($n = 357$) enrolled in the TRICC trial,³⁴ no significant difference in clinical outcome (including hospital and 30-day mortality and length of stay) were found between the restrictive (Hb trigger of 70 g/L) and liberal (Hb trigger of 100 g/L) transfusion strategies. An insignificant trend toward harm (increased mortality) in the restrictive strategy group was observed in those patients with severe ischemic heart disease ($n = 257$).

This finding was challenged in the more recent FOCUS RCT (published 2011) of high-risk patients undergoing hip surgery ($n = 2016$, patients ≥ 50 years of age with a history of or risk factors for cardiovascular disease) randomized to either a restrictive (Hb trigger of 80 g/L) or a liberal (Hb trigger of 100 g/L) transfusion strategy.³⁵ The investigators found no difference between the groups for the primary outcome of death or inability to walk across the room without human assistance at 60 days. However, in a higher risk population of patients with acute coronary syndrome or stable angina undergoing angiography, a small pilot RCT³⁶ ($n = 110$, published 2013) of a restrictive (Hb trigger < 80 g/L) versus a liberal (Hb trigger < 100 g/L) transfusion strategy, a trend toward a decrease in the primary composite outcome of death, myocardial infarction, or unscheduled need for revascularization at 30 days was observed in the liberal strategy group (risk difference: 15.0%, 95% CI: 0.7-29.3%, $P = 0.054$).

Evidence in RBC transfusion strategies in the cardiovascular surgery population is more conflicting. In the TRACS noninferiority trial³⁷ ($n = 502$, published 2010), involving patients who had undergone cardiac surgery, a restrictive ((Hct) trigger $< 24\%$) compared to a liberal (Hct trigger $< 30\%$) transfusion strategy was noninferior with respect to their primary composite outcome of 30-day all-cause mortality and severe morbidity (10% vs. 11%). Most recently, a large multicenter RCT of patients aged 17 years or older and undergoing nonemergency cardiac surgery ($n = 2007$, TITRe2 trial published 2015) examined the effect of a liberal (Hb trigger < 90 g/L) versus restrictive (Hb trigger < 75 g/L) transfusion strategy on a composite of serious infections or ischemic events (including heart, brain, gut, or acute kidney injury) at 3 months.³⁸ Although there was no significant difference in the primary outcome between the two groups, a significant increase in mortality was observed in the restrictive arm (hazard ratio 1.64, 95% CI: 1.00-2.67, $P = 0.045$). Although the authors are careful to not overinterpret these secondary findings, they strengthen the call for further large pragmatic trials in this population.

A review of these findings support the claim that not all critical care populations are the same and that there may exist higher risk populations in which a restrictive transfusion strategy may not be safe, and potentially harmful, compared to a liberal strategy. There is an ongoing need for further study.

RBC Transfusion Thresholds in Neurocritical Care Patients—Evidence from RCTs and Systematic Reviews

The decreased oxygen delivery associated with anemia may have more significant effects on the brain injury population, including those patients with stroke, traumatic brain injury, and subarachnoid hemorrhage (SAH). Evidence to guide RBC transfusions in these populations is lacking, and whether obtaining a higher hemoglobin value is beneficial has not been adequately tested. In the TRICC trial, only 67 patients with a primary neurologic diagnosis were included in the original trial.²⁷ A subgroup analysis of these limited patients showed no difference in outcome between the liberal and restrictive transfusion strategies.³⁹

A recent systematic review of comparative studies of RBC transfusion in a neurocritically ill population (6 studies, no meta-analysis, published 2012)⁴⁰ found only one additional small RCT in an adult population (in addition to the subgroup analysis of TRICC presented above). This small RCT included 44 patients with SAH who were

randomized to either a liberal (Hb trigger of < 115 g/L) or a restrictive (Hb trigger < 100 g/L) RBC transfusion strategy.⁴¹ The study was underpowered to detect any clinically relevant outcome and used triggers that are higher than those currently practiced, which resulted in the majority of the patients receiving at least one RBC transfusion in both arms. There are no RBC transfusion strategy trials specific to an ischemic stroke population. Consequently, the aforementioned systematic review concluded that insufficient information existed to guide clinical practice.⁴⁰

Since this systematic review, a factorial design RCT of 200 patients with traumatic brain injury was published (2014).⁴² It aimed to test the effect of 2 hemoglobin transfusion threshold strategies (a liberal vs. a restrictive strategy—Hb thresholds of 100 g/L and 70 g/L, respectively) and erythropoietin versus placebo on favorable outcome as measured by the Glasgow Outcome Scale (GOS) at 6 months. No statistically significant difference between the two transfusion strategy groups was found ($P = 0.28$), but fewer thromboembolic events in the restrictive threshold group were reported (OR 0.32, 95% CI: 0.12 to 0.79). This study does not completely answer the clinical question of utility of liberal transfusion strategies in this patient population, as the study was underpowered to detect smaller yet clinically important outcome differences between the two transfusion groups (the study was powered to detect a 20% absolute increase in favorable outcome (GOS score) in the liberal transfusion arm compared to the restrictive arm). Further, although RBC transfusion rates differed in the two groups, the difference in median hemoglobin level was less than 20 g/L by day 9 (first data points presented) and increasingly smaller by days 16, 23, and 30.

Although these studies do not demonstrate specific harm by maintaining a restrictive transfusion strategy, it remains unclear if any benefits result from a more liberal strategy in these unique patient populations. Further rigorous study with RCTs is needed.

CONCLUSIONS—SUMMARY OF RBC TRANSFUSION THRESHOLD EVIDENCE AND PRACTICAL STRATEGY

Given the current evidence that exists to guide RBC transfusion strategies in the critically ill, it seems evident that in most populations a restrictive practice imparts no specific harm and may even be better than a liberal RBC transfusion strategy. As such, in the hemodynamically stable, euvolemic ICU patient, a transfusion hemoglobin trigger of 70-80 g/L is optimal. Careful consideration to individual cases must be taken in specific populations, including patients with cardiovascular disease and brain injury in which there is a need for more evidence to guide whether a more liberal strategy may be more appropriate.

KEY POINTS

1. Anemia is common in ICU and may negatively affect organ function and patient outcome.
2. RBC transfusions may improve oxygen delivery but not necessarily oxygen utilization and are not without significant risk.
3. In most hemodynamically stable critically ill populations, a restrictive RBC transfusion strategy (hemoglobin trigger of 70-80 g/L) is at least as good as and perhaps better than a liberal strategy.
4. Certain subpopulations of the critically ill such as those with cardiac or neurologic disease may benefit from a more liberal trigger, but further research is still needed.

ANNOTATED REFERENCES

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Good review article.

Napolitano LM, Corwin HL. Efficacy of red blood cell transfusion in the critically ill. *Crit Care Clin* 2004;20:255–268.

This article evaluates the literature on the efficacy of RBC transfusions in the critically ill. It concludes that RBC transfusions do not improve tissue oxygen consumption consistently in critically ill

patients; it is not associated with improvements in clinical outcome and may result in worse outcomes in some patients. Specific factors that identify patients who will improve from RBC transfusions are difficult to identify, and lack of efficacy of RBC transfusions likely is related to storage time, increased endothelial adherence of stored RBCs, nitric oxide binding by free hemoglobin in stored blood, donor leukocytes, host inflammatory response, and reduced red cell deformability. Taken together, these studies generally support conservative RBC transfusion strategies in critical care to reduce the risk of transfusion-related adverse effects.

■ References for this chapter can be found at expertconsult.com.

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Blood component therapy has had a central role in the development and practice of numerous medical advances, especially in modern surgery. It is only in more recent years that blood transfusion is no longer regarded as essential for a wide range of medical and surgical conditions.¹ It is now possible for most uncomplicated major surgery to be conducted without allogeneic blood component therapy. *Blood component transfusion* is generally supportive therapy for the correction of one or more hematologic deficiencies until the basic disease process can be controlled or corrected. During the past decade there has been a shift from a donor focus to one of patient blood management in blood component therapy. Standard of care for the role of allogeneic blood component therapy in clinical medicine addresses the three-pillar matrix of patient blood management.² Attention to accurate diagnosis of the hematopoietic deficiencies, minimizing blood loss, and tolerance of deficiencies, within limits, is important. Before considering transfusion there should be appropriate consideration of the range of therapeutic options available and their potential hazards.³

Blood component therapy and its immediate endpoints are part of a medical management process. Although appropriate endpoints may be achieved in terms of measurable parameters or immediate clinical response, the clinician needs evidence that these traditional surrogate endpoints are relevant and correlate with clinical outcome for the patient. In many areas of transfusion medicine, evidence from prospective randomized trials is not available, and the clinician must base therapy on a good understanding of the problem in terms of pathophysiology and indicators of severity. Transfusion medicine decision making can be difficult, and there is ongoing debate regarding the indications for various allogeneic blood components.⁴ Unnecessary allogeneic transfusion can be avoided or minimized by giving attention to the clinical time frame, hematologic defect, alternatives, and knowledge about blood components and the potential hazards. The concept of transfusion alternatives can be challenged as inappropriate, as most of the so-called alternatives are indeed optimal patient management. There is now good evidence supporting a restrictive red cell transfusion policy in hemodynamically stable patients with hemoglobin levels above 7 gm/dL.^{5,6} In managing a patient's oxygen-carrying capacity, a three-pillar approach—optimizing red cell mass, minimizing blood loss, and tolerating anemia in the short term—results in avoidance of allogeneic transfusion in most uncomplicated elective surgical cases.² This can be achieved by identifying patients at high risk of bleeding, giving attention to surgical and anesthetic techniques (e.g., controlled hypotension, hypothermia prevention, reduction of venous pressure at the operative site), and using pharmacologic agents to minimize blood loss. Autologous methodologies including perioperative hemodilution, blood salvage, fibrin glue, and platelet fibrin gel may all have a part to play.

GUIDELINES FOR BLOOD COMPONENT THERAPY

The following is a brief summary of the guidelines for use of commonly available blood components. Fig. 137-1 illustrates the general approach to the decision to transfuse blood components, with the emphasis on patient blood management and how blood component therapy fits into a more comprehensive approach to clinical management. This move from a blood product focus to a patient focus

has resulted in the development of patient blood management guidelines.⁷

Red Blood Cell Concentrates

Appropriate and inappropriate use of red blood cell (RBC) transfusions in acute medicine has received considerable attention in recent years; however, identifying the benefits of RBC transfusion in many circumstances has been difficult.^{8,9} The question of the lowest safe hematocrit remains controversial. In an otherwise stable patient, the transfusion of RBC concentrates is likely to be inappropriate when the hemoglobin level is above 100 gm/dL. Their use may be appropriate when hemoglobin is in the range 70 to 100 gm/dL if there are other defects in the oxygen transport system. The decision to transfuse should be supported by the need to relieve clinical signs and symptoms of impaired oxygen transport and to prevent morbidity and mortality, ultimately to improve clinical outcomes. The transfusion of RBC concentrates is likely to be appropriate when hemoglobin is less than 70 gm/dL and the anemia is not reversible with specific therapy in the short term, but lower levels may be acceptable in patients who are asymptomatic, especially in the younger age group.

Platelet Concentrates

Prophylactic transfusion of platelet concentrates is indicated in patients with bone marrow failure when the platelet count is (1) less than $10 \times 10^9/L$ and there are no associated risk factors for bleeding or (2) less than $20 \times 10^9/L$ in the presence of additional risk factors. However, recent evidence suggests lower levels may be tolerated if there is no clinical evidence of hemostatic failure.¹⁰⁻¹²

In patients undergoing surgery or invasive procedures, the platelet count should be maintained at greater than $50 \times 10^9/L$. In patients with qualitative defects in platelet function, platelet count is not a reliable indicator for transfusion, and transfusion decisions and monitoring of efficacy should be based on the setting and clinical features. The wide use and increasing range of antiplatelet medications is a challenge, especially in the perioperative setting. The role of ex vivo point of care platelet function testing in predicting hemorrhage is promising.¹³

Platelet transfusions are indicated in hemorrhaging patients in whom thrombocytopenia is secondary to marrow failure and is considered a contributory factor to the bleeding. In massively hemorrhaging patients, platelet transfusions in conjunction with correcting plasma coagulation factor deficits are indicated when the platelet count is less than $50 \times 10^9/L$ or less than $100 \times 10^9/L$ in the presence of diffuse microvascular bleeding. The transfusion of platelet concentrates is not generally considered appropriate when thrombocytopenia is due to immune-mediated destruction, in patients with thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, or in uncomplicated cardiac bypass surgery.

Fresh Frozen Plasma and Cryoprecipitate

Fresh frozen plasma is widely used, but there are limited specific indications for its use, and there is a dearth of evidence for efficacy in most clinical settings. The use of fresh frozen plasma may be appropriate in patients with a coagulopathy who are bleeding or are at risk of bleeding

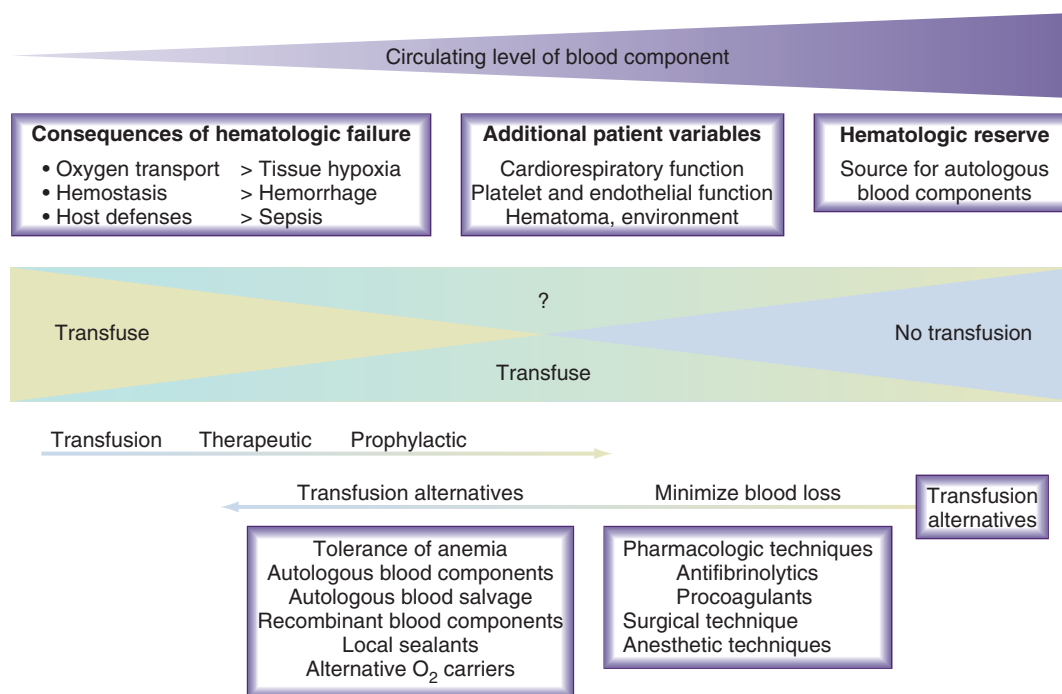


FIGURE 137-1 ■ Overview of blood management and where blood component therapy may be appropriate.

when a specific therapy or factor concentrates are not appropriate or are unavailable. Fresh frozen plasma is generally indicated in acutely hemorrhaging patients, usually as an inclusion in a massive transfusion protocol. There is poor evidence for the prophylactic use of fresh frozen plasma in many clinical settings.¹⁴⁻¹⁸ Fresh frozen plasma is rarely indicated in vitamin K deficiency or reversal of warfarin therapy, because concentrates are now generally available.^{19,20} The use of fresh frozen plasma is generally not considered appropriate in cases of hypovolemia, in plasma exchange procedures in treatment of immunodeficiency states, or prophylactically in nonbleeding coagulopathic intensive care unit (ICU) patients prior to invasive procedures.²¹

Cryoprecipitate contains factor VIII, fibrinogen, factor XIII, von Willebrand factor, and fibronectin and is principally indicated for fibrinogen deficiency or dysfibrinogenemia when there is clinical bleeding, invasive procedures, trauma, or acute disseminated intravascular coagulation (DIC).

Plasma-Derived Products

Table 137-1 summarizes commonly used fresh and plasma-derived blood products. Fibrinogen concentrate instead of cryoprecipitate is having an increasing role in the management of hypofibrinogenemic states, depending on local availability.

Recombinant Blood Products

Development and introduction of recombinant blood components continue to be one of the most exciting advances in transfusion medicine. Recombinant growth factors (cytokines) such as erythropoietin and granulocyte stimulating factor have had a major impact on managing anemia and neutropenia. There are further promising recombinant cytokines in development that could have a role in countless clinical conditions, especially as antiinflammatory and tissue-protecting agents. Recombinant hemostatic factors have improved the management of hemophilia. Recombinant activated factor VII (rFVIIa) was originally developed for treating hemophiliac patients with coagulation factor inhibitors. However, it is having an impact on the

management of a range of hemostatic disorders. Factor VIIa initiates the extrinsic coagulation pathway only when complexed to tissue factor at sites of injury. Its wider use has had a checkered history and although it may have a role in a range of hemostatic disorders, evidence in terms of safety and efficacy has been conflicting. It has been difficult to establish a sound evidence base outside the hemophilia setting for the use of rFVIIa, with most experience being observational and anecdotal.

Blood Substitutes

Efforts have been ongoing for many years to develop substitutes for RBCs and platelets, but results have been disappointing, and safety concerns have plagued clinical development.

TRANSFUSION MANAGEMENT OF MASSIVE ACUTE HEMORRHAGE

In recent years, there has been a reappraisal of guidelines for the use of blood components in acutely hemorrhaging patients.²² Guidelines are more focused on managing critical bleeding and avoiding the massive transfusion coagulopathy quagmire in which a patient spirals down into the “triad of death”: coagulopathy, acidosis, and hypothermia. Advances in patient retrieval, resuscitation protocols, techniques for rapid and real-time diagnosis, trauma teams, and early “damage-control” surgery have improved the management of acutely hemorrhaging patients. There is also greater attention and research being directed toward the nature of clear fluids and the importance of plasma viscosity, colloid oncotic pressure, and functional capillary density.

Patients are now surviving increasingly larger volumes of blood transfusion, but sepsis, acute lung injury, and multiorgan failure remain challenges. Although blood transfusion may be life saving for exsanguinating patients, it is increasingly recognized that transfusion may be an independent risk factor for delayed morbidity and mortality. Transfusion can be minimized with tolerance of hypotension until hemorrhage is controlled and lower hemoglobin levels are accepted. The immediate posttransfusion function of stored red cells and

TABLE 137-1 Blood Products

| BLOOD PRODUCT | MAIN INDICATIONS |
|--|---|
| Whole blood* | Rarely indicated in acute hemorrhage unless other blood products are unavailable |
| Red blood cell concentrates* | Hemorrhage and anemia |
| Leukocyte-depleted blood* | In patients having febrile reactions, to avoid leukocyte immunization in selected patients (especially patients with hematologic malignancy). Universal prestorage leukodepletion is more widely used and has the added benefit of minimizing storage lesions. |
| Platelet concentrates* | Thrombocytopenia due to marrow hypoplasia or platelet functional defect |
| Granulocyte concentrates* | Occasionally in patients with sepsis associated with profound and prolonged neutropenia secondary to marrow suppression |
| Fresh frozen plasma* | Specific or multiple plasma protein deficiencies (especially coagulation) |
| Cryoprecipitate* | Hypofibrinogenemia and rarely in factor VIII and von Willebrand disease, when concentrates are unavailable ³¹ |
| 4% or 5% albumin solutions† | Plasma volume expansion. Use is controversial, and the role of albumin solutions in critically ill patients remains under deliberation. ³² |
| Concentrated albumin† | Severe hypoalbuminemic states with complicating hypovolemia |
| Concentrate of coagulation factors II, VII, IX, and X† | Vitamin K–dependent factor II, IX, and X deficiency and reversal of oral vitamin K antagonists |
| Specific factor concentrates† | Factor VIII and IX concentrates have an established role in management of hemophilia, but others are in the process of establishing their clinical efficacy and indications. ^{26,33,34} Fibrinogen concentrates for hypofibrinogenemia and dysfibrinogenemia ²⁶ Antithrombin concentrates are available for thrombophilia due to antithrombin deficiency and are increasingly recommended in other disorders in which antithrombin may be depleted (e.g., DIC, MODS). ³⁵ |
| Gamma globulin† | Generally used intravenously for replacement in hypogammaglobulinemia or in high dosage as an immune-modulating therapy ^{36,37} |
| Specific immune gamma globulins† | Rhesus prophylaxis, specific infection prophylaxis and treatment ³⁸ |

*Fresh products.

†Fractionated plasma products.

DIC, disseminated intravascular coagulation; MODS, multiorgan dysfunction syndrome.

hemoglobin in delivering oxygen to the microcirculation and in oxygen unloading is also being questioned, with the storage age of RBCs possibly being associated with poorer clinical outcomes. Recent animal data point to the immediate clinical benefit of transfused red cells in treating hypovolemic shock relating more to reconstitution of the macrocirculation, with potentially adverse effects on the functional capillary density in the microcirculation.

A protocol approach to blood component therapy has been a controversial issue, with advocates for correcting hemostatic defects when they are identified and those for up-front protocol component therapy with fixed ratios of red cells, platelets, and fresh frozen plasma. The recent PROPPR randomized controlled trial compared equal numbers of fresh frozen plasma, platelets, and RBCs (1:1:1) to half as much fresh frozen plasma and platelets as RBCs (1:1:2). There was no significant difference in mortality at 24 hours or at 30 days, although

exsanguination in the first 24 hours, a secondary outcome, was significantly decreased in the 1:1:1 group versus the 1:1:2 group, and more patients achieved hemostasis. This is probably the best evidence available supporting a 1:1:1 ratio.²³ Ironically, as 1:1:1 is leukodepleted “reconstituted” whole blood, this raises the perennial question of the role for whole blood and fresh whole blood in the critical bleeding setting.²⁴

With better understanding of coagulopathy and the importance of hypofibrinogenemia and hyperfibrinolysis, there is a reanalysis of the approach to blood component therapy. Failure of hemostasis is common in acutely bleeding patients and may be complex and multifactorial. Accumulating evidence supports the view that the pathophysiology of coagulopathy, when occurring in the context of critical hemorrhage, should be viewed as related to the primary insult or initiating event. A secondary coagulopathy may compound the problem in the resuscitated patient, such as massive stored blood transfusion, hemodilution, hypothermia, and continuing tissue hypoxia. The primary mechanisms of coagulopathy relating to the initiating event may relate to trauma, hypoxia, pregnancy, sepsis, envenomation, or antithrombotic agents. In all circumstances there is activation or inhibition of some aspect of the hemostatic system, and therapy is better informed if these varied mechanisms are better understood. Frequently, complex tests are required for definitive diagnosis, but the urgency of the situation cannot always wait for the results, and therapy may be initiated on clinical evidence with minimal laboratory information.

Many trauma patients have coagulopathy at presentation related to hypovolemic shock and not consumption or dilution.²⁵ Activation of the protein C system and hypofibrinogenemia due to secondary hyperfibrinolysis are important. In the massively transfused patient, thrombocytopenia and impaired platelet function are the most consistent significant hematologic abnormalities, correction of which may be associated with control of microvascular bleeding. The level of fibrinogen is now recognized to be of greater importance than previously thought.²⁶ A problem with clotting time standard screening tests of coagulation function is that they do not provide information about the formation of the hemostatic plug, its size, structure, or stability. Global tests of hemostatic plug formation and stability such as thromboelastography are of increasing use. With ongoing bleeding and associated microvascular oozing, various approaches may be taken. Having ensured that all identifiable hemostatic defects have been corrected, questions then arise as to the role of fresh blood and recombinant activated factor VII.²⁷

HAZARDS OF ALLOGENEIC TRANSFUSION

Allogeneic blood transfusion is a tissue transplant that is probably associated with the greatest range of potential hazards of any medical intervention and should only be used in circumstances in which there is good evidence that clinical outcomes will be improved. The pathophysiology of transfusion reactions can be divided broadly into the following four categories. More detailed discussion of the complications of allogeneic blood transfusion are discussed in other chapters.

1. Reactions may occur due to *immunologic differences* between the donor and recipient, resulting in varying degrees of blood component incompatibility. In general, for a reaction to occur, the recipient needs to have been previously immunized to a cellular or plasma antigen.
2. A wide range of *infectious agents* may be transmitted by allogeneic blood component therapy.
3. *Alterations in blood products due to preservation and storage* may result in quantitative or qualitative deficiencies in the blood components that reduce transfusion efficacy and expose the patient to potentially adverse consequences from substances that accumulated during storage (Table 137-2).^{28,29}
4. *Clinical, technical, and clerical errors* resulting from incorrect patient identification, failure of cold chain management, or administration errors may result in a range of hazards. Included in this

TABLE 137-2

Red Blood Cell Storage Lesions and Possible Clinical Consequences

| STORAGE LESION | POTENTIAL CLINICAL CONSEQUENCES |
|---|---|
| Alterations in red blood cell structure and function | |
| ATP depletion | Echinospherocyte formation, increased osmotic fragility, impaired RBC deformability with adverse effects on oxygen transport and delivery |
| Microvesiculation and loss of membrane lipid, lipid peroxidation and hemolysis, and irreversibly damaged RBCs | Reduced RBC viability and cell death Hyperbilirubinemia, LDH, increased serum iron, free radical generation (?), hyperkalemia |
| Reduced 2,3-DPG | Increased hemoglobin affinity for oxygen and impaired unloading |
| Decreased CD47 antigen (integrin-associated protein) expression | Reduced posttransfusion survival due to premature clearance post transfusion |
| RBC adhesion to endothelial cells | Adverse effects on microcirculatory hemodynamics |
| Storage temperature | Hypothermia unless pretransfusion warming |
| Additives | |
| Citrate | Hypocalcemia, acid-base imbalance, initial acidosis alkalosis |
| Glucose | Hyperglycemia |
| Sodium | Hypernatremia |
| Cytokines: IL-1, IL-6, IL-8, TNF | Fever, hypotension, flushing |
| Enzymes: Myeloperoxidase, elastase, arginase, secretory phospholipase A ₂ | Transfusion-related immunomodulation, neutrophilia |
| Reactive proteins: Defensins, annexin, soluble HLA, Fas ligand, soluble endothelial cell growth factor, and others | Proinflammatory, potential “priming” for ARDS, TRALI, and MODS |
| Histamine and kinin accumulation | Hypotension, anxiety, flushing, pain syndromes, proinflammatory |
| Microaggregates and procoagulants | Blockade of reticuloendothelial system Risk factor for development of ARDS, MODS, TRALI Activation of hemostasis > DIC (?), VTE (?), arterial thrombotic events (?) |

ARDS, acute respiratory distress syndrome; ATP, adenosine triphosphate; DIC, disseminated intravascular coagulation; 2,3-DPG, 2,3-diphosphoglycerate; HLA, human leukocyte antigen; IL, interleukin; LDH, lactate dehydrogenase; MODS, multiorgan dysfunction syndrome; RBC, red blood cell; TNF, tumor necrosis factor; TRALI, transfusion-related acute lung injury; VTE, venous thromboembolism.

group are patients who are at particular risk from lung injury and circulatory overload due to comorbidities such as cardiac compromise, poor clinical assessment of fluid and volume status, and sepsis.

In terms of causation of an adverse clinical event, the possible role of transfusion can be classified broadly into three categories on the basis of probability³⁰ (Fig. 137-2). Hemovigilance programs focus on the adverse events that are included within categories 1 and 2 but do not address the question of the appropriateness of the clinical indication for the transfusion.

1. **Definite—unifactorial.** The well-understood and well-reported hazards of transfusion (i.e., immunologic, technical, infectious) are

generally unifactorial, with a 1:1 well-understood deterministic causal relationship between the blood component transfused (usually a specific individual unit) and the adverse consequence for the patient. ABO blood group incompatibility, transfusion-related infection transmission, transfusion-associated graft-versus-host disease, and transfusion-related lung injury due to donor leukoagglutinins are examples in this category.

2. **Probable—oligofactorial.** Some adverse consequences of transfusion result from interaction with other insults, pathophysiology, or host factors, but the contribution of the transfusion can usually be specifically identified in a deterministic manner. Fever, allergic reactions, hypotensive reactions, pulmonary edema, some cases of transfusion-related lung injury, hyperbilirubinemia, and cytomegalovirus transmission are examples of this category.
3. **Possible—multifactorial.** Transfusion may contribute to a complication or poor clinical outcome. In these circumstances, a causal implication for transfusion is probabilistic (i.e., a risk factor), and it is not necessarily the major factor. Transfusion-induced immunomodulation and the clinical consequences of storage lesions fall into this category.

Blood Storage Lesions and Potential Clinical Consequences

Blood is altered from the moment of its initial collection and subsequent storage. Physical and biochemical characteristics may be of particular importance when large volumes are infused rapidly. Warming of all rapid blood transfusions should minimize the possibility of hypothermia. Patients receiving massive blood component therapy are likely to be seriously ill and have multiple problems. Potential adverse effects must be considered in conjunction with the injuries and multiorgan dysfunction. It is not always possible to define complications caused or aggravated by massive blood transfusion.

The storage lesions progressively increase until the time of expiry, and the extent of these changes is determined by the specific blood component, preservative medium, container, storage time, and storage conditions. Storage results in quantitative and qualitative deficiencies in blood components, which may reduce the efficacy of a transfusion. Quantitative deficiencies may result in reduced RBC survival, failure to achieve anticipated endpoints, and excessive donor exposure, increasing immunization and infection risks. Qualitative deficiency includes decreased membrane flexibility and increased adhesion to endothelium, which may impair microcirculatory hemodynamics. Reduced 2,3-diphosphoglycerate decreases hemoglobin oxygen affinity, impairing oxygen unloading.

In parallel with these storage changes is an accumulation of degenerate material (e.g., microaggregates, microparticles, and procoagulant material), release of vasoactive agents, cytokine generation, and hemolysis (Fig. 137-3). Many of the changes occurring during storage are related to the presence of leukocytes (especially granulocytes) and can be minimized by prestorage leukoreduction. The clinical significance of storage lesions continues to be debated. In some cases, the effects are widely accepted; in others, further studies are needed. There is evidence that the storage lesion is clinically significant in several respects. Transfusion may result in significant increases in unconjugated bilirubin and lactic dehydrogenase, neutrophilia, and saturation of serum iron. The transfusion of biologically active lipids in stored blood may be associated with the development of acute lung injury in patients with predisposing conditions. Blood transfusion has been shown to be an independent risk factor for the development of postinjury multiorgan failure and acute respiratory distress syndrome, and this relationship may be stronger with the age of the transfused blood. There is an increased rate of infection associated with transfusion of old blood after severe injury, suggesting that transfusion-related immunomodulation may not be related only to allogeneic transfusion, but contributed to by the storage lesion. Further information about the storage lesion and the possible clinical implications is summarized in Table 137-2. Hyperbilirubinemia warrants a special mention.

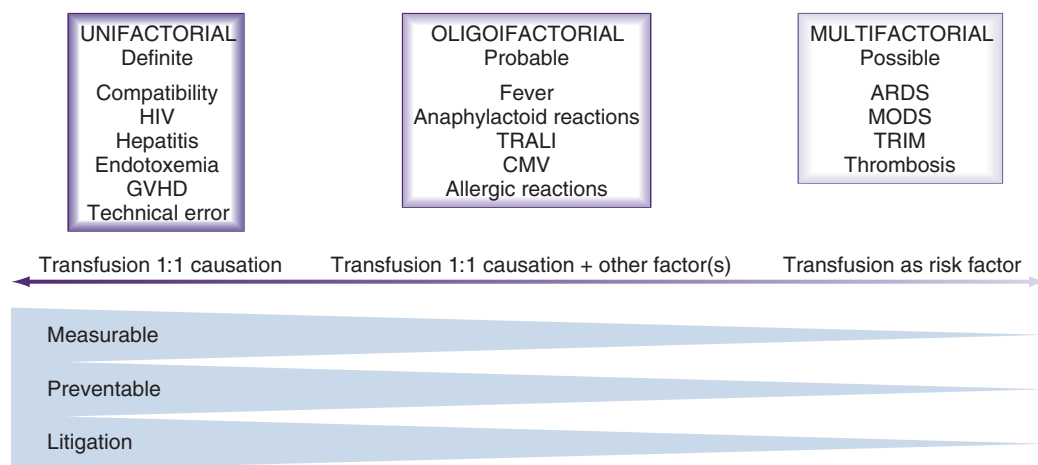


FIGURE 137-2 ■ Hazards of allogeneic blood transfusion. ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; MODS, multiorgan dysfunction syndrome; TRALI, transfusion-related acute lung injury; TRIM, transfusion-related immunomodulation.

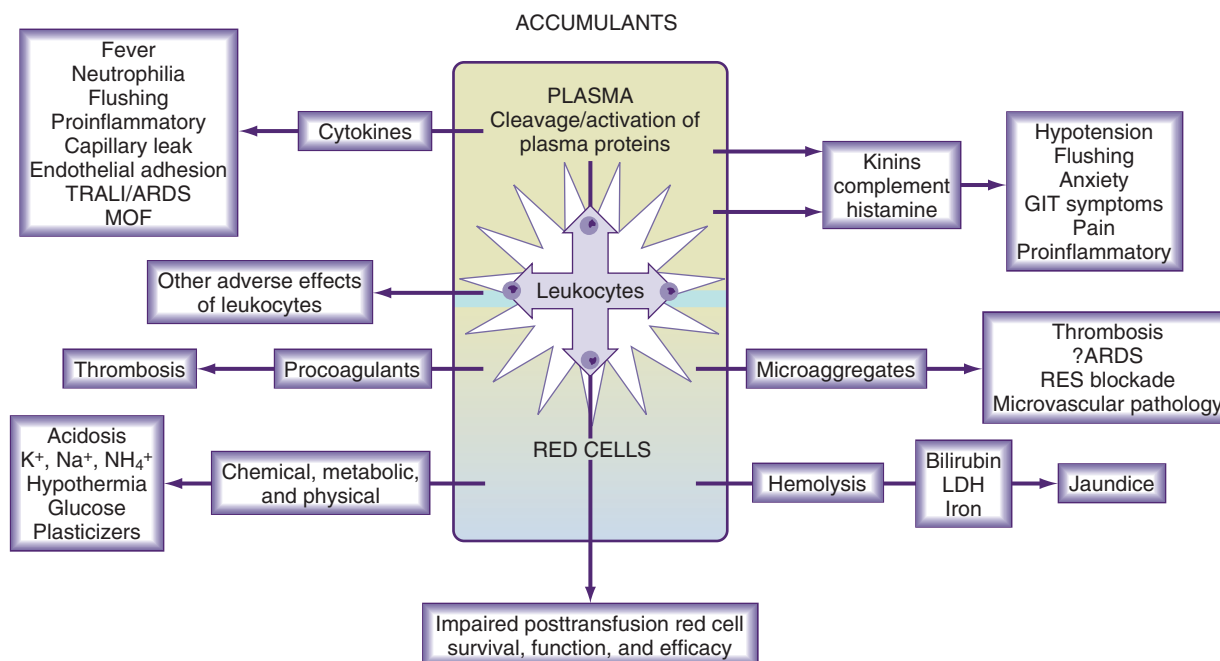


FIGURE 137-3 ■ Red blood cell storage lesions. ARDS, acute respiratory distress syndrome; GIT, gastrointestinal tract; LDH, lactate dehydrogenase; MOF, multiple organ failure; RES, reticuloendothelial system; TRALI, transfusion-related acute lung injury.

Hyperbilirubinemia is common after massive blood transfusion because a significant proportion of RBCs transfused may not survive, and the resulting bilirubin load causes varying degrees of hyperbilirubinemia. If the patient has been hypovolemic and shocked, biliary transport functions may be impaired, particularly in the presence of sepsis or multiorgan dysfunction. An important rate-limiting step in bilirubin transport is the energy-requiring process of transporting conjugated bilirubin from the hepatocyte to the biliary canaliculus. Bilirubin from destroyed transfused RBCs may be conjugated, but delayed excretion may lead to conjugated hyperbilirubinemia. A hemolytic transfusion reaction and resorbing hematoma also have to be considered as possible causes of hyperbilirubinemia.

Allogeneic Transfusion as an Independent Risk Factor for Poorer Clinical Outcomes

In recent years, experimental and clinical studies have identified blood transfusion as an independent risk factor for morbidity and mortality as well as increased admission rates to ICUs, increased length of hospital stay, and additional costs. The implication of RBC transfusion as part of the problem rather than optimal therapy has challenged long-held views about the safety of allogeneic blood transfusion. It has generally been assumed that blood transfusion can only be of *benefit* to the bleeding or anemic patient, with immunologic and infection transfusion hazards well understood and minimized. There is increasing

evidence that transfusion-related immunomodulation (TRIM) and the transfusion effects of storage lesions may be responsible for poorer clinical outcomes in a range of clinical settings. There is also an association of transfusion with a higher incidence of venous thromboembolism. The case for the association between blood transfusion and poorer outcomes is strengthening, and evidence for the efficacy of many transfusions is being reassessed, as are studies supporting restrictive red cell transfusion policies as not jeopardizing clinical outcomes. Until these concerns are resolved, a precautionary approach should be adopted, with avoidance or minimization of allogeneic transfusion and the use of appropriate patient blood conservation techniques whenever possible.⁹

BASIC IMMUNOHEMATOLOGY

RBC serology is a specialized area of knowledge, and it is not possible to expect clinicians to have more than a basic working knowledge essential for patient safety.

Regular and Irregular (Atypical) Antibodies

The regular alloantibodies (isoagglutinins) of the ABO system are naturally occurring agglutinins present in all ABO types (except AB), depending on the ABO group. Group O people have anti-A and anti-B isoagglutinins, group A people have anti-B, and group B people have anti-A. Group A cells cause the most common and most dangerous ABO-incompatible hemolytic reactions.

Atypical antibodies are not normally present in the plasma but may be found in some people as naturally occurring antibodies or immune antibodies. Immune antibodies result from previous exposure due to blood transfusion or pregnancy. Naturally occurring antibodies are generally of minimal clinical significance. In contrast, many of the immune atypical antibodies are of major clinical significance, and their recognition is the *raison d'être* for pretransfusion compatibility testing and antenatal antibody screening. Blood group antigens vary widely in frequency and immunogenicity. The D antigen of the Rhesus (Rh) blood group system is common and highly immunogenic. When an Rh-negative (i.e., D-negative) patient is exposed to D-positive blood, there is a high likelihood of forming an anti-D antibody. For this reason, the D antigen is taken into account when providing blood for transfusion, in contrast to the numerous other RBC antigens that are less common or less immunogenic. Beyond the Rh(D), and sometimes the Kell (K) blood group antigens, it is not practical or necessary to take notice of other blood group antigens unless an atypical antibody is detected during antibody screening procedures.

Antibody Screen

On receipt of a blood sample by the transfusion service, the RBCs are ABO and Rh(D) typed, and the serum is screened for atypical antibodies. This screen consists of testing the patient's serum with group O screening cells. The screening panel consists of RBCs obtained from two group O donors containing all common RBC antigens occurring with a frequency of greater than approximately 2% in the community. If an atypical antibody is detected on the antibody screen, further serologic investigations are done to identify the specificity of the antibody. These investigations are time consuming and when possible should be carried out electively.

Crossmatch (Compatibility Test)

The crossmatch is the final compatibility test between the donor cells and the patient's serum. The crossmatch test tends to be overemphasized to the detriment of the antibody screen. With sophisticated knowledge of serology, the emphasis in the supply of compatible blood is now concentrated on the steps before the final compatibility crossmatch.

As precompatibility testing has assumed the major role in the selection of blood for transfusion, there has been a rethinking of policies relating to the supply of blood for elective transfusions. Whenever elective surgery is planned for a patient who is likely to require blood transfusion, the transfusion service must receive a clotted blood sample well before the anticipated time of surgery. Precompatibility testing should be carried out during routine working hours when facilities are geared for large workloads and enough staff are available to handle all contingencies. With computerization, electronic crossmatching is increasingly accepted as the standard for releasing compatible blood for patients with negative antibody screens.

When urgent clinical and laboratory decisions are made under conditions of stress, it is frequently difficult for all involved personnel to appreciate the difficulties of others. The decision to give uncrossmatched or partially crossmatched blood or to wait for crossmatch-compatible blood is not easy, and certain basic serologic considerations may clarify for the clinician some of the problems faced by the serologist. Depending on the degree of urgency and extent of previous knowledge about the patient's RBC serology, blood can be provided with varying degrees of safety. When a patient is exsanguinating and likely to die, however, giving ABO-compatible, uncrossmatched blood, especially if the antibody screen is negative, is safe and appropriate therapy.

Group O Rh(D)-negative donors are referred to as "universal" blood donors and are ABO compatible with all recipients. The blood is also screened for high-titer A or B hemolysins. The transfusions should be given as RBC concentrates and used only in emergencies. Group O Rh(D)-positive blood can be used in exsanguinating patients, but if the recipient is of childbearing age, every attempt should be made to give Rh(D)-negative blood until the patient's blood group is known.

Transfusion of blood of the correct ABO type circumvents the isoagglutinin problems alluded to earlier. Simple as this approach may seem, its safety depends on meticulous attention to grouping. Previous blood group information such as a "bracelet" group or "unofficial" group written in the patient's records may be incorrect, and there may be considerable risk if blood is administered on the basis of this information alone.

KEY POINTS

1. An evidence-based approach to blood component transfusion has resulted in many long-standing transfusion dogmas assuming clinical efficacy of the labile allogeneic blood components (red cells, platelets, and fresh frozen plasma) in improving clinical outcomes.
2. The decision to transfuse red blood cell concentrates should be supported by the need to relieve clinical signs and symptoms of impaired oxygen transport and to prevent morbidity and mortality, with the aim of improving clinical outcomes.
3. Allogeneic blood transfusion may be an independent risk factor for adverse clinical outcomes.
4. The development of clinical practice guidelines for the use of blood components should focus on patient blood management, and transfusion of allogeneic blood should no longer be the default decision in the context of clinical uncertainty.
5. The classic symptoms and signs of an acute hemolytic transfusion reaction include apprehension, flushing, pain (e.g., infusion site, headache, chest, lumbosacral, abdominal), nausea, vomiting, rigors, hypotension, and circulatory collapse.
6. A clinician needs a basic working knowledge of red blood cell serology to ensure patient safety.

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Thomson A, Farmer S, Hofmann A, Isbister J, Shander A. Patient blood management—a new paradigm for transfusion medicine? *Vox Sang ISBT Science Series.* 2009;4:423–435.

This article reviews patient blood management, describing the evolution of transfusion medicine from a product focus to a problem-based patient focus.

Ganter MT, Pittet JF. New insights into acute coagulopathy in trauma patients. *Best Pract Res Clin Anaesthesiol.* 2010;24:15–25.

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Zubair AC. Clinical impact of blood storage lesions. *Am J Hematol.* 2010;85:117–122.

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Buddeberg F, Schimmer BB, Spahn DR. Transfusion-transmissible infections and transfusion-related immunomodulation. *Best Pract Res Clin Anaesthesiol.* 2008;22:503–517.

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Venous thromboembolism (VTE) is a common complication of serious illness and is associated with considerable morbidity and mortality in hospitalized patients. It represents the third most common cause of vascular death, after myocardial infarction and stroke, and is the leading preventable cause of death in hospitalized patients.^{1,2} Within the United States, there are approximately 600,000 to 900,000 cases annually with an overall mortality rate ranging between 15% and 53%.³ Within the ICU, patients with VTE are more likely to have a longer duration of mechanical ventilation (9 vs. 6 days; $P = 0.02$), ICU stay (17.5 vs. 9 days; $P = 0.005$), and hospitalization (51 vs. 21 days; $P < 0.001$). These patients also have significantly higher in-hospital mortality (56% vs. 38%).⁴ Recognizing that ICU patients often have multiple risk factors for VTE, increased attention has been placed upon the identification of risk factors, development of clinical prediction scores, and preventative strategies.

RISK FACTORS FOR VENOUS THROMBOEMBOLISM IN MEDICAL-SURGICAL ICU PATIENTS

Medical-surgical ICU patients demonstrate a higher risk of VTE than patients managed on medical or surgical ward services.⁵ Established risk factors for VTE may be classified within three general categories: stasis, vascular injury, and hypercoagulable state. Several clinical risk factors have been identified that may contribute significantly to the development of VTE. These factors may exist prior to ICU admission (e.g., acute and chronic illness, recent surgery, or trauma) or may be acquired during the admission (e.g., use of sedatives/paralytics and thrombin-generating invasive procedures). Observational studies in this patient population have identified several VTE risk factors to include female sex, previous VTE events, central venous catheterization, and comorbid conditions (e.g., malignancy).^{6,7} More recent prospective studies have further described these risk factors. In a prospective cohort study of 261 medical-surgical ICU patients, four independent risk factors were identified for ICU-acquired VTE: personal or family history of VTE (HR 3.9; 95% CI, 1.5-10), end-stage renal disease (HR 3.7; CI, 1.3-11.2), platelet transfusion (HR 3.2; 95% CI, 1.2-8.5), and vasopressor administration (HR 2.8; 95% CI, 1.1-7.2).⁴ These studies assist in characterizing VTE as a multifactorial disease process with both fixed and modifiable risk factors. Understanding these risk factors can aid in the development of effective preventative strategies as well as inform the role of screening and surveillance in this patient population.

PREVALENCE AND INCIDENCE

The prevalence and incidence of VTE in medical-surgical ICUs vary greatly among patient populations and are influenced by whether these events were clinically diagnosed or detected by screening methods. The prevalence of VTE at the time of admission in medical and surgical ICUs ranges from 7.5% to 10.7% in cross-sectional studies that have employed systemic screening methods.^{9,10} Based upon data from earlier longitudinal studies that utilized systematic screening with either lower extremity Doppler ultrasound or radioactive iodine fibrinogen scanning, the incidence of developing VTE (specifically DVT) during ICU

admission has ranged between 8.8% and 40%. More recent studies have identified a lower incidence of VTE events, suggesting a range between 9.8% and 26.6%.^{6,11,12} These findings may be due in part to changes in thromboprophylaxis practice.^{8,13,14} Both prevalence and incidence rates may be considerably higher in neurosurgical, trauma, and acute spinal cord injury patients.^{15,16}

PREVENTION

Patients admitted to medical-surgical ICUs are considered higher risk for VTE and should be evaluated thoroughly for early thromboprophylaxis within the first 24 hours of admission. In a retrospective observational study of 175,665 critically ill patients, ICU and in-hospital mortality were both significantly lower in those receiving thromboprophylaxis within 24 hours of admission than in those who did not (6.3% and 10.6% vs. 7.6% and 11.2%, respectively). The attributable mortality effect of omitting early thromboprophylaxis was 3.9% (95% CI, 2.2-5.6), 8.0% (95% CI, 5.6-10.4), 9.4% (95% CI, 6.4-12.4), and 15.4% (95% CI, 11.1-19.9) for patients with multiple trauma, sepsis, metastatic disease, and cardiac arrest, respectively.¹⁷ While no formally, prospectively validated risk assessment models exist, several empirically generated or data-derived risk models have been developed, to include the Padua Prediction Score, IMPROVE risk score, and GENEVA risk score (Tables 138-1, 138-2, and 138-3). For critically ill patients at moderate to high risk of VTE and low risk for bleeding, thromboprophylaxis with subcutaneous low-molecular-weight heparin (LMWH) or subcutaneous low dose unfractionated heparin (UFH) is recommended. For critically ill patients who are either bleeding or at high risk for major bleeding, mechanical thromboprophylaxis with graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) devices are recommended until the bleeding risk decreases, at which time transition to pharmacologic thromboprophylaxis may be substituted.¹⁸ Although it is common practice to insert inferior vena cava (IVC) filters in high-risk trauma patients who may also have a high risk of bleeding, there are no high-quality data to support this practice. A meta-analysis of controlled observational studies suggests a reduction in PE and fatal PE with no effect on the rates of DVT.¹⁹ Table 138-4 outlines a generalized approach to VTE prevention in medical-surgical ICUs.

DIAGNOSIS

Clinical Evaluation and Prediction

Clinical evaluation, including risk factor consideration, physical examination, laboratory/imaging studies, and cardiovascular monitoring, are integral to the assessment of a patient's risk for early mortality and to providing optimal management.^{20,21} However, evaluation for VTE can be challenging within the ICU. Often, patients may be mechanically ventilated or demonstrate altered mentation that does not allow for the timely identification of symptoms. Many patients may also have comorbid conditions that confound or complicate the diagnostic process.

Classification of patients into pretest probability categories corresponding to their likelihood of VTE, whether assessed by clinical judgment or by a validated prediction rule, allows the selection of the

TABLE 138-1 Padua Prediction Score⁵⁹

| | |
|---|----|
| Active cancer | +3 |
| Previous VTE | +3 |
| Decreased mobility | +3 |
| Thrombophilia | +3 |
| Previous trauma or surgery within the past month | +2 |
| Age ≥ 70 | +1 |
| Heart and/or respiratory failure | +1 |
| Ischemic stroke or acute myocardial infarction | +1 |
| Acute rheumatologic disorder and/or acute infection | +1 |
| Obesity | +1 |
| Hormonal therapy | +1 |

Score < 4: Low risk for VTE**Score ≥ 4 : High risk for VTE****TABLE 138-2 IMPROVE Risk Assessment Model⁶⁰**

| | |
|----------------------------|----|
| Previous VTE | +3 |
| Known thrombophilia | +2 |
| Lower limb paralysis | +2 |
| Active malignant condition | +2 |
| Immobilization | +1 |
| Intensive care unit stay | +1 |
| Age > 60 years | +1 |

Score 0-2: Low risk for VTE**Score ≥ 3 : High risk for VTE****TABLE 138-3 Geneva Score (Revised)⁶¹**

| | |
|---|----|
| Age > 65 years | +1 |
| Previous DVT or PE | +3 |
| Surgery or lower limb fracture within 1 month | +2 |
| Active malignant condition | +2 |
| Unilateral lower limb pain | +3 |
| Hemoptysis | +2 |
| Heart rate | |
| <75 beats/min | 0 |
| 75-95 beats/min | +3 |
| ≥ 95 beats/min | +5 |
| Pain on lower limb deep venous palpation and unilateral edema | +4 |

Score 0-3: Low probability (8%)**Score 4-10: Intermediate probability (28%)****Score ≥ 11 : High probability (74%)**

Data from Nendaz M, Spirk D, Kucher N, et al. Multicentre validation of the Geneva Risk Score for hospitalised medical patients at risk of venous thromboembolism. Explicit ASsessment of Thromboembolic Risk and Prophylaxis for Medical PATients in SwitzErland (ESTIMATE). *Thromb Haemost* 2014;111:531.

most appropriate diagnostic pathway. Several clinical prediction rules have been developed to assist in the objective evaluation of pretest probability for VTE. Of the existing prediction rules, the Wells score is one of the most extensively validated and most commonly used score to identify patients according to their probability of VTE²²⁻²⁵ (Table 138-5). Despite extensive validation and widespread use, the Wells score has not been evaluated in critically ill patients, and its role in the diagnosis of VTE remains unclear within this patient population.

TABLE 138-4 Generalized Approach to VTE Prevention in the ICU⁶²

| BLEEDING RISK | VTE RISK | RECOMMENDATION |
|---------------|------------------|--|
| Low | Moderate | Low-dose unfractionated heparin or low-molecular-weight heparin |
| Low | High | Low-molecular-weight heparin |
| High | Moderate or high | Graduated compression stockings or intermittent pneumatic compression devices; may transition to low-dose unfractionated heparin when risk decreases |

TABLE 138-5 Well's Score²²

| | |
|--|------|
| Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins) | +3 |
| An alternative diagnosis is less likely than PE | +3 |
| Heart rate > 100 beats/min | +1.5 |
| Immobilization for more than 3 days or surgery in the previous 4 weeks | +1.5 |
| Previous DVT/PE | +1.5 |
| Hemoptysis | +1 |
| Malignancy (on treatment, treated in the past 6 months, or palliative) | +1 |

Dichotomous (Two-tier):**Score ≤ 4 : PE unlikely****Score > 4: PE likely****Three-tier:****Score 0-1: Low risk****Score 2-6: Medium risk****Score ≥ 7 : High risk**

Data from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;83:416-420.

Diagnostic Testing

Several laboratory and imaging modalities have been suggested to assist in the diagnosis of VTE. D-dimer is a fibrin degradation product present during clot degeneration and is a marker of thrombotic disease. Enzyme-linked immunosorbent assays (ELISA) are widely used to quantify plasma D-dimer concentration in patients and demonstrate favorable performance characteristics for excluding VTE in patients with low to moderate probability of pulmonary embolism (sensitivity 0.95; 95% CI, 0.85-1.0).²⁶ However, most patients in the ICU setting would be less likely to be classified as low probability, which considerably limits its clinical utility. Additionally, there is evidence to suggest that the specificity in hospitalized patients may be lower. In a prospective study of 239 medical ICU patients, D-dimer was negative in only 16% of patients, and three of these patients were subsequently diagnosed with VTE.²⁷ Given these limitations, D-dimer should be used with caution in the ICU, and patients with a high pretest probability for VTE should be evaluated by an alternative diagnostic modality.

Computed tomography pulmonary angiography (CTPA) has become the primary diagnostic test for pulmonary embolism (PE). It may also provide additional information such as the assessment of the right ventricular (RV)/left ventricular ratio to identify RV overload, enabling estimation of the severity of PE in addition to a positive diagnosis.²⁸ Based upon data from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II study, in patients with a moderate or high clinical probability of PE, the positive predictive values of CTPA were 92% and 96%, respectively.²⁹ However, CTPA does have diagnostic limitations and may not be able to reliably exclude PE when the clinical probability is high. In patients with a high pretest probability of PE, the negative predictive value is only 60% and further

evaluation may be required.²⁹ When evaluated specifically in ICU and trauma populations, CTPA demonstrated similar performance characteristics.^{30,31}

The results of the Prospective Investigation Study of Acute Pulmonary Embolism Diagnosis (PISA-PED) suggest that perfusion scanning, combined with clinical assessment, may reduce the need for angiography and provide a viable diagnostic alternative.³² This technique may be appealing in certain patient populations, such as renal insufficiency or pregnancy, and may circumvent limitations (e.g., contrast agents, ionizing radiation exposure) associated with CTPA.³³ Based upon data from the PIOPED II study, in patients with a high clinical suspicion for PE and high-probability V/Q scan, the clinical probability of PE was 96%. However, in patients with a high clinical suspicion for PE and low-probability V/Q scan, the clinical probability of PE was still 40%. In patients with all other combinations of clinical suspicion and scan results, the probability of PE ranged from 6% to 88%.³⁴ In these situations, clinical judgment must be used, and additional diagnostic modalities should be considered. To limit the possibility of nondiagnostic results, V/Q scans should ideally be used in patients with a normal chest radiograph. However, patients with concurrent cardiopulmonary processes are common in ICU populations (e.g., pneumonia, atelectasis, pulmonary edema, pleural effusion), thereby potentially limiting its diagnostic utility in some patients. Additionally, transport and image acquisition time are higher for V/Q, thus making it a less attractive option for unstable ICU patients.

As approximately 50% to 70% of patients with confirmed PE have a proximal DVT, lower extremity Doppler ultrasound may be a useful adjunctive diagnostic study.^{20,35,36} In patients with symptomatic proximal DVT, meta-analysis suggests a pooled sensitivity of 97% (95% CI, 96-98). In asymptomatic patients, a pooled sensitivity of 62% (95% CI, 53-71) was reported.³⁷ Unfortunately, many critically ill patients may be sedated and unable to report typical symptoms or may have bilateral lower extremity swelling, thus potentially reducing the sensitivity in this population. Two-point complete compression ultrasonography (CCUS) has been proposed as an alternative technique for rapid and/or serial bedside assessment of DVT. In a prospective study of 2098 patients with symptomatic DVT, similar diagnostic accuracy was observed in patients undergoing whole leg Doppler ultrasonography and CCUS.³⁸ CCUS may also provide useful prognostic information that may assist in risk stratification. In a prospective cohort of patients diagnosed with acute symptomatic PE who subsequently underwent CCUS screening, patients with concomitant DVT had an increased all-cause mortality (HR 2.05; 95% CI, 1.24-3.38, $P = 0.005$) and PE-specific mortality (HR 4.25; 95% CI, 1.61-11.25; $P = 0.04$) compared with those without DVT.³⁶

Transthoracic echocardiography (TTE) can be a useful adjunct in the diagnosis and management of VTE; however, as the reported sensitivity of TTE for the diagnosis of PE is approximately 60% to 70%, a negative result cannot reliably exclude PE.²⁰ Nevertheless, in patients with suspected PE presenting with shock or hypotension, the absence of echocardiographic signs of RV overload or dysfunction practically excludes PE as a cause of hemodynamic instability.²⁰ In addition, echocardiography can identify the presence of a concurrent RV thrombus, which is a marker of worse prognosis (14-day mortality: 21% vs. 11%; 3-month mortality: 29% vs. 16%), as well as provide insight into RV function and pulmonary artery pressures.³⁹ As such, TTE may be a useful adjunctive diagnostic modality to assist in the confirmation/exclusion of PE as well as provide useful diagnostic information for risk stratification.

RISK STRATIFICATION

In patients with confirmed PE, initial risk stratification is based upon clinical assessment of hemodynamic status.^{18,20} Assessment of hemodynamic status is used to guide diagnostic and treatment decisions.

High-risk (or massive) PE results in hemodynamic instability and represents a life-threatening emergency, which may be associated with an in-hospital mortality rate in excess of 50%.³ The American College

of Chest Physicians (ACCP) define hemodynamically unstable PE as PE associated with shock or hypotension (systolic blood pressure <90 mm Hg) or systolic pressure drops of ≥ 40 mm Hg for >15 minutes if not caused by new-onset arrhythmia, hypovolemia, or sepsis.^{18,20} The ACCP definition also includes patients at risk of developing hypotension.¹⁸

In hemodynamically stable patients, the purpose of further risk stratification is to differentiate those patients who are normotensive and have a low risk of all-cause mortality (low-risk or nonmassive PE) from those patients with preserved systemic arterial pressure who possess increased risk of PE-related adverse clinical events (intermediate-risk or submassive PE). Prognostic models, laboratory testing, and imaging studies may assist with classification of patients into these categories.²⁰

Identification of patients with PE who have a low risk of complications associated with PE and its therapy may assist in determining the appropriate disposition of patients to ICU or medical-surgical ward services. Risk stratification models can accurately identify patients at low risk of death within the first 3 months after the diagnosis of PE. Two clinical models commonly used for estimating prognosis in patients with PE are the Pulmonary Embolism Severity Index (PESI) and the Geneva Score, which have both been extensively validated, and may assist in the risk stratification of these patients⁴⁰⁻⁴³ (Table 138-6 and 138-7).

Identification of patients at high risk for complications associated with PE can assist in the selection of patients for escalation of PE therapy (e.g., transfer to the intensive care unit for observation and/or consideration of thrombolysis). RV dysfunction, induced by the increased load caused by pulmonary obstruction and the release of vasoconstrictive substances in response to reduced blood flow in the pulmonary vasculature, is associated with a poor prognosis.^{18,20,44} Myocardial injury is also associated with short-term mortality and adverse outcomes in patients with acute PE.²⁰ Markers of RV dysfunction (via echocardiography, spiral computed tomography, or brain

TABLE 138-6 Pulmonary Embolism Severity Index⁴⁰⁻⁴²

| VARIABLE | ORIGINAL PESI | SIMPLIFIED PESI |
|---|---------------|-----------------|
| Age > 80 years | Age in years* | +1 |
| Male sex | +10 | |
| History of cancer | +30 | +1 |
| History of heart failure | +10 | +1 [†] |
| History of chronic lung disease | +10 | |
| Pulse ≥ 110 beats/min | +20 | +1 |
| Systolic blood pressure < 100 mm Hg | +30 | +1 |
| Respiratory rate ≥ 30 breaths/min | +20 | |
| Temperature < 36°C | +20 | |
| Altered mental status | +60 | |
| Arterial oxyhemoglobin saturation level < 90% | +20 | +1 |
| Original PESI: Class I (≤ 65): Very low mortality risk (0-1.6%), Class II (66-85): Low mortality risk (1.7-3.5%), Class III (86-105): Moderate mortality risk (3.2-7.1%), Class IV (106-125): High mortality risk (4-11.4%), Class V (>125): Very high mortality risk (10-24.5%) | | |
| Simplified PESI: | | |
| Score 0: Low mortality risk (1%) | | |
| Score ≥ 1: High mortality risk (10.9%) | | |

*The patient's age in years is added to the scores for each predictor to calculate a total score.

†Merged into one category: chronic cardiopulmonary disease.

TABLE 138-7 Geneva Pulmonary Embolism Prognostic Index⁶⁴

| | |
|---------------------------------------|----|
| Active cancer | +2 |
| Systolic blood pressure < 100 mm Hg | +2 |
| Concomitant DVT at diagnosis | +1 |
| Previous VTE | +1 |
| Congestive heart failure | +1 |
| Arterial PaO ₂ < 60 mm Hg | +1 |
| Score 0-2: Low mortality risk | |
| Score ≥ 3: High mortality risk | |

Data from Wicki J, Perrier A, Perneger TV, et al. Predicting adverse outcome in patients with acute pulmonary embolism: a risk score. *Thromb Haemost* 2000;84:548.

natriuretic peptide testing) and myocardial injury (via cardiac troponin T or I) are able to assist in the identification of intermediate-risk patients with PE.^{20,45,46} At present, no single test is sufficient to provide a positive predictive value for PE-specific mortality to guide the initiation of escalation of therapy. However, recent studies have suggested that evaluation utilizing combined diagnostic testing may provide useful prognostic information. In a prospective study of 591 normotensive patients with PE, evaluation using a two-test strategy, cardiac troponins/TTE or cardiac troponins/CCUS, in high-risk patients (per PESI risk stratification) demonstrated a positive predictive value for 30-day PE-related mortality of 20.7% and 24.4%, respectively.⁴⁷ Therefore, a combined diagnostic testing strategy may be helpful in further risk stratifying patients within this intermediate-risk group and improve prognostication. Recently, a simple four-factor prediction score for the identification of normotensive patients with acute PE at high risk of adverse PE-related clinical events (intermediate risk) has been developed and validated^{48,49} (Table 138-8).

TREATMENT

Treatment of VTE is guided by risk stratification, and first-line therapy varies depending on hemodynamic status.

Low-Risk Hemodynamically Stable PE

For low-risk hemodynamically stable patients, parenteral anticoagulation with subcutaneous LMWH, subcutaneous or intravenous UHF, or subcutaneous fondaparinux followed by bridging therapy to a vitamin K antagonist (VKA) is the cornerstone of standard treatment. VKA therapy may begin on the first or second day of heparin therapy and should overlap for a minimum of 5 days.^{18,20} More recently, several direct oral anticoagulants (rivaroxaban, apixaban, edoxaban, and dabigatran) have been approved for the treatment of hemodynamically stable VTE and provide an alternative treatment option in selected patients.⁵⁰⁻⁵²

Intermediate-Risk Hemodynamically Stable PE

Standard treatment of intermediate-risk PE is similar to patients with low-risk PE. However, the consideration of escalation of therapy in a selected subgroup of patients at higher risk for complications associated with PE remains controversial. While there is evidence that thrombolytic therapy in selected intermediate-risk patients with PE may result in both an acute and long-term improvement in pulmonary artery pressures as well as RV function, there has been no definitive evidence of mortality benefit in this patient population.⁵³ In the Pulmonary Embolism Thrombolysis Study (PEITHO), intermediate-risk normotensive patients with evidence of RV dysfunction on TTE or CTPA as well as myocardial injury indicated by positive cardiac troponins demonstrated improvements in the primary composite outcome

TABLE 138-8 BOVA Risk Score^{48,49}

| | |
|--------------------------------|----|
| SBP 90-100 mm Hg | +2 |
| Elevated cardiac troponin | +2 |
| RVD (echocardiogram or CTPA) | +2 |
| Heart rate ≥ 110 beats per min | +1 |

30-day PE-related mortality:

Stage I (0-2 points): Low risk (3.6%)

Stage II (3-4 points): Intermediate risk (5.0%)

Stage III (>4 points): High risk (15.5%)

30-day PE-related complications:

Stage I (0-2 points): Low risk (4.2%)

Stage II (3-4 points): Intermediate risk (10.8%)

Stage III (>4 points): High risk (29.2%)

(death from any cause or hemodynamic collapse within 7 days) when treated with heparin/tenecteplase versus heparin/placebo (2.6% vs. 5.6%; OR 0.44; 95% CI, 0.23-0.87; $P = 0.02$). However, there was no statistically significant difference in the rate of all-cause mortality between the groups at 7 days (1.2 vs. 1.8%, $P = 0.42$) and 30 days (2.4% vs. 3.2%, $P = 0.42$). Additionally, the tenecteplase group demonstrated increased rates of both stroke (2.4% vs. 0.2%, $P = 0.03$) and extracranial bleeding (6.3% vs. 1.2%, $P < 0.001$).⁵⁴ While a recent meta-analysis suggests a potential mortality benefit in intermediate-risk patients, particularly those less than 65 years of age, the analysis was heavily influenced by the PEITHO trial, in which the primary outcome was driven primarily by clinical deterioration and rescue thrombolysis.⁵⁵ This suggests that a more reasonable approach may be close monitoring of these patients, reserving reperfusion therapy for those who demonstrate clinical deterioration.

High-Risk Hemodynamically Unstable PE

In patients with hemodynamically unstable PE, in which restoration of pulmonary arterial flow is urgently required due to the risk of RV failure, thrombolytic therapy with intravenous streptokinase, urokinase, or recombinant tissue plasminogen activator (tPA) is suggested and is associated with a significant reduction in the composite outcome of recurrent PE or death compared with heparin monotherapy.^{18,20,56} In a prospective single-center registry of patient with acute PE who underwent thrombolytic therapy, 91.8% of patients demonstrated improvement in hemodynamic stability and RV dysfunction.⁵⁷ However, the use of thrombolytic agents in acute PE has been associated with a greater overall rate of major bleeding (9.2% vs. 3.4%; OR 2.73; 95% CI, 1.91-3.91) and intracranial hemorrhage (1.5% vs. 0.2%; OR 4.63; 95% CI, 1.78-12.04).⁵⁵ Short infusion times (2 hours) are preferred over prolonged infusions (24 hours) as shorter infusion times are associated with more rapid clot lysis and a reduced risk of bleeding.¹⁸ Upon completion of thrombolytic infusion, full anticoagulation with heparin is typically performed prior to transition to a VKA.

In patients with hemodynamically unstable PE in whom thrombolytics are contraindicated or have failed or in those experiencing shock that is likely to cause death before systemic thrombolysis can take place, catheter-assisted thrombus removal may be considered.^{18,20} Several techniques have been proposed, to include rheolytic thrombectomy, aspiration thrombectomy, ultrasound-accelerated thrombolysis, and catheter-directed tPA. While several of these techniques show promise, there is insufficient evidence to support any one individual technique at this time.

In patients with hemodynamically unstable PE who have failed both systemic and catheter-directed thrombolysis or are experiencing shock that is likely to cause death before thrombolysis can take effect, surgical pulmonary embolectomy should be considered, although the evidence supporting these recommendations is limited.^{18,20} In a recently

published retrospective review of twenty patients with acute PE and RV dysfunction who had contraindications to thrombolysis, 95% of patients undergoing pulmonary embolectomy survived to hospital discharge.⁵⁸ Surgical pulmonary embolectomy may be a viable option for a selected patient population with contraindications to thrombolysis or profound clinical instability.

Indications for IVC filters for the treatment of acute PE are currently the same as in other populations. Evidence-based guidelines recommend their use in patients who cannot receive anticoagulant therapy, those who develop significant bleeding while on anticoagulation, and those who develop recurrent thrombosis on therapeutic anticoagulation.¹⁸

KEY POINTS

1. VTE is a common complication of serious illness, and medical-surgical ICU patients are likely to have multiple fixed and modifiable VTE risk factors.
2. Implementation of thromboprophylaxis in appropriately selected patients is vital to reduce the incidence of VTE and its associated complications including death, prolonged ventilation, and prolonged hospital and ICU stay.
3. Clinical prediction scores in conjunction with diagnostic testing (e.g., CTPA, V/Q, CCUS, TTE) can assist in the timely and accurate diagnosis of patients with suspected VTE.
4. Risk stratification based upon hemodynamic stability and risk for VTE-associated complications is used to determine treatment strategies.
5. High-risk hemodynamically unstable patients should be considered for immediate systemic and/or catheter-directed thrombolytic therapy. The role for escalation of therapy in intermediate-risk hemodynamically stable patients with significant risk for VTE-associated complications remains unclear.

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OVERVIEW OF EFFECTIVE COAGULATION

The classic cascade model of coagulation, although still widely taught and utilized, is out of date. According to this model, coagulation can be initiated by the activation of either the “extrinsic” or “intrinsic” pathway, which converge on factor X and generate thrombin with the subsequent formation of fibrin. This outdated model fails to explain many clinical scenarios, and the current understanding of the biochemistry of hemostasis is far more nuanced and complex. The cell-based model of coagulation emphasizes the important roles of tissue factor (TF)-bearing cells and platelets in hemostasis.¹⁻² This model regards thrombus formation as the result of overlapping processes: initiation, amplification, and propagation.²

Initiation occurs on the surface of a TF-expressing cell (typically fibroblasts, immunostimulated endothelium cells, and monocytes). This interaction of TF with plasma leads to the TF-FVIIa complex, which in turn, promotes localized FXa, FIXa, and thrombin generation that can serve to activate platelets. The localization of activated platelets at the site of injury allows for diffusion of FIXa to activate the intrinsic pathway, creating a much larger burst of thrombin (*amplification*). The platelet surface is well suited for the task of bringing together von Willebrand factor (vWF), coagulation factors, and fibrinogen. This activated surface allows further *propagation* to occur with continued activation of the intrinsic pathway of coagulation.²

The complex interplay of the vascular endothelium, coagulation enzymes, vWF, and platelets cannot be evaluated by any current laboratory analysis. Further, disease processes have their own unique pattern of disturbances of the hemostatic system.¹⁻⁶

BASIC CONDITIONS NECESSARY FOR PROPER HEMOSTASIS

Bleeding can be the primary reason for admission or a secondary insult while in the intensive care unit (ICU). Although coagulopathy may be the driver of or an important contributor to bleeding, an anatomic source of bleeding may require imaging studies, endoscopy, or surgical exploration as the most important initial evaluation.

Ionized calcium is a necessary cofactor in the coagulation cascade. Citrate anion is capable of binding (chelating) ionized calcium, and this is how the citrate component of ACD (acid citrate dextrose) buffer leads to anticoagulation. Massive resuscitation of patients with citrated blood products can lead to hypocalcemia. Repletion of calcium should be part of the resuscitation when patients require massive transfusion.⁷

Hypothermia may be a deliberate therapeutic maneuver or an accidental occurrence associated with surgery, trauma, or exposure. Body temperatures less than 33°C lead to slowing of the enzymatic reactions in the coagulation cascade.⁶ Platelet activation is maintained at temperatures down to 33°C, but at higher temperatures, conformational changes occur in platelets that decrease their adhesion.^{6,8} The localization of platelets to the site of injury is necessary for amplification and propagation of coagulation, and decreased adhesion may contribute to clinical bleeding observed between 33°C and 37°C.⁶

Acidosis has an equally important effect on the coagulation system. The optimal pH for proteolytic activity of coagulation enzymes is well above physiologic pH.⁹ A blood pH of 7.2 decreases the activity of the

FXa/FVa complex by 50%.⁹ Fibrinogen degradation increases in an acidemic environment, and fibrinogen levels drop.¹⁰ The coagulopathy associated with acidemia is not corrected with infusion of bicarbonate.¹¹ Ensuring the appropriate environment for proper function of coagulation factors and platelets is as important as correcting detectable coagulopathy.

LABORATORY ANALYSIS OF COAGULATION

Traditional Measures of Coagulation

Traditional measures of coagulation include the prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, and platelet count. These are the most widely available and utilized tests and will be discussed first.

Both the PT and aPTT are measures taken from the acellular plasma component of a citrated blood sample that has been centrifuged. PT uses thromboplastins to activate FVII and the extrinsic pathway.¹² Most laboratories will report an international normalized ratio (INR) based on a correction in relation to the International Reference Preparation. PT will be prolonged in the setting of deficient or inactive factors VII, X, V, and II. The aPTT uses partial thromboplastins to activate the intrinsic pathway.¹² The aPTT will be prolonged in settings of deficient or inactive factor XII, XI, IX, VIII, X, and II; high molecular weight kininogen; and/or kallikrein. These tests are helpful for identifying factor insufficiencies or the presence of circulating inhibitors but cannot assess the overall risk of hemorrhage.¹³ Additionally, in patients who have suffered large volume hemorrhage with clinical coagulopathy, different commercially available tests variably identify dilutional coagulopathy.¹⁴

Fibrinogen level can be measured with quantitative immunochemical methods. Most laboratories, however, report a fibrinogen level that is derived from a functional analysis of fibrinogen activity. The most basic assessment of fibrinogen activity is the thrombin time (TT). For this assay, thrombin is added to plasma and the time to stable clot formation is recorded. Quantitative analysis of fibrinogen modifies the TT by diluting the patient's plasma and adding higher levels of thrombin. The time to clot formation is correlated to a standard dilution chart and converted to a concentration. Using this assay, the reporting of a low fibrinogen concentration can reflect true hypofibrinogenemia or the presence of a dysfunctional form of the protein. Fibrinogen is vital for the formation of a stable thrombus, and unlike PT/aPTT, fibrinogen levels have been shown to be predictive of procedural bleeding.¹⁵⁻¹⁷

Platelet count does not provide a functional assessment of platelets, but thrombocytopenia can exacerbate bleeding; very low platelet levels are associated with spontaneous hemorrhage. Significant spontaneous bleeding with intact endothelium is unlikely to occur unless the platelet count is less than 5000/ μ L.¹⁸ Randomized trials comparing prophylactic transfusion triggers of 10,000/ μ L to 20,000/ μ L showed no difference in bleeding.¹⁸ Suggested trigger levels are 50,000 for patients having procedures or with active bleeding and 100,000 for neurologic surgical procedures, though these are consensus levels without supportive data.¹⁸ Although a low platelet count is helpful in evaluating the bleeding patient, a normal platelet count does not preclude platelet dysfunction.

Measures of Platelet Function

Many bleeding patients have a normal platelet count but might have platelet dysfunction caused by uremia, cardiopulmonary bypass, or other predisposing factors. Other bleeding patients have a platelet count that is only slightly less than normal, and the decision whether to transfuse platelets is unclear. Fortunately for clinicians, numerous laboratory tests measure platelet function. The most commonly used tests rely on a platelet agonist (e.g., adenosine diphosphate [ADP], epinephrine, ristocetin, thrombin receptor agonist peptide [TRAP]), exposure to shear stress, or both to activate platelets. These tests monitor the rate of platelet aggregation through changes in light transmission, light scattering, electrical impedance, platelet aggregation on a plate, or occlusion of a tube.^{19,20}

The platelet function analyzer (PFA-100, Dade Behring, Miami, FL) utilizes citrated whole blood exposed to high shear stress within a capillary tube coated with collagen and either ADP or epinephrine. It subsequently monitors flow rate and reports a closure time.²¹ The test is sensitive to vWF deficiency and can be used to monitor for deficiency or response to desmopressin.¹⁹ The test is sensitive to both thrombocytopenia (platelet count < 100,000/ μ L) and anemia (hematocrit < 30%), so results should be interpreted with a complete blood count.^{21,22} Since both anemia and thrombocytopenia are common in ICU patients, the usefulness of this method in the context of critical illness is limited.

The Multiplate Analyzer (Verum Diagnostica, Munich, Germany) exposes platelets in multiple channels to platelet activators, and aggregation is monitored through changes in electrical impedance.²³ This test is extensively used to monitor the effect of platelet antagonism with aspirin and P2Y₁₂ antagonists (e.g., clopidogrel, prasugrel) with the ASPI test and ADP test, respectively. TRAP acts as the most active stimulator of platelets and is used as a control in antiplatelet monitoring. For intensivists, decreased response to TRAP is an excellent test for overall platelet function. The Multiplate system has been evaluated in both cardiac surgery and trauma.²³⁻²⁵ Unlike the whole blood clotting assays that will be discussed next, the benefit of dedicated platelet function assays is their ability to reliably detect the effect of platelet antagonists.²⁰

Whole Viscoelastic Hemostatic Assays

With further elucidation of the cell-based model of hemostasis, the desire has arisen for testing approaches that evaluate the interplay of the enzymatic and cellular components of coagulation. The following tests assess the interaction of coagulation factors and platelets: rotational thromboelastography (ROTEM; ROTEMVR) (TEM International, Munich, Germany) and thromboelastography (TEG; TEGVR) (Haemonetics, Braintree, MA, USA).

Both TEG and ROTEM are viscoelastic tests of hemostasis in whole blood that measure time to clot formation, strength, and dissolution kinetics.²⁷ TEG relies on a rotating cup of whole blood with a pin on a torsion wire suspended in the cup. As a clot forms, the rotation of the cup is transmitted to the wire. In the ROTEM assay, the cylindrical cup containing blood is held steady while a suspended pin in the sample oscillates at a constant force.²⁷ Although a minor change, the ROTEM system is less sensitive to external motion, which enhances its ability to be used in a point-of-care setting.

Newer TEG and ROTEM systems differ from traditional TEG in their utilization of activators to accelerate the process for timely acquisition of data. Both assays provide similar data on clot formation and kinetics, but the values are not interchangeable because of differences in the methods. As they are trademarked enterprises, the nomenclature differs. The initial time to clot formation (CT in ROTEM and R for TEG) is the time it takes for the tracing to reach 2 mm. The clot formation time (CFT) in ROTEM and the kinetics time (K) in TEG are measured as the time for the tracing to increase from 2 mm to 20 mm. The angle is created from the developing curve from the point of clot initiation. Maximal clot firmness (MCF) in ROTEM and maximal

amplitude (MA) in TEG are the peak amplitudes and a measure of overall clot strength. Lysis at 30 and 60 minutes after MA is recorded in TEG, and the Lysis Index 30 is the percent reduction from MCF 30 minutes after CT in ROTEM.²⁷

The TEG system has two channels and ROTEM has four. The presence of multiple channels allows simultaneous evaluation of clot formation with multiple activators or inhibitors. The standard ROTEM analysis includes INTEM (activation with phospholipid and ellagic acid), EXTEM (activation with tissue factor), and FIBTEM (activation with cytochalasin D followed by tissue factor). Additional tests can include heparinase before ellagic acid (HEPTEM) and aprotinin followed by tissue factor (APTEM).

The CT of an INTEM assay provides data similar to an aPTT. The CT with the EXTEM assay provides data similar to a PT/INR. HEPTEM gives the data of the INTEM without the effect of circulating heparin. These data points are available within minutes and help guide therapy with fresh frozen plasma, prothrombin complex concentrates, vitamin K, or activated factor VII.

The CFT, alpha angle, and MCF are all sensitive to deficiencies in platelet or fibrinogen activity (due to dilution or dysfunction). Further differentiation of platelet and fibrinogen contributions to dysfunction can be obtained by including the FIBTEM analysis. The addition of cytochalasin D inhibits platelets, thus assessing the component of clot strength from fibrin alone. A FIBTEM MCF >12 largely precludes clinically important bleeding secondary to fibrinogen dysfunction or dilution. Measures of lysis take longer to obtain but can alert the clinician to coagulopathy from fibrinolysis.

A Cochrane review in 2011 determined that both TEG- and ROTEM-guided algorithms reduced bleeding without other significant improvements in patient outcome.²⁸ Further trials showing improvements in bleeding, transfusion, and patient-centered outcomes have come out since that review.²⁹ Further data and experience with TEG and ROTEM will likely lead to greater availability and exposure to these tests.

Disseminated Intravascular Coagulation (DIC) Scores

DIC is a syndrome resulting from diffuse hemostatic activation leading to small vessel thrombosis and, eventually, consumptive coagulopathy.³⁰ As activation of the hemostatic system and abnormal lab values are present in almost all critically ill patients, simple scoring systems for identifying patients with DIC have been created and validated.³¹ The International Society of Thrombosis and Haemostasis DIC scoring system uses points assigned as follows for routine lab results in patients with disease states associated with DIC: platelet count (>100,000/ μ L, 0; <100,000/ μ L, 1; <50,000/ μ L, 2); fibrin-related markers (no increase, 0; moderate increase, 1; strong increase, 2), PT (<3 sec, 0; >3 sec but <6 sec, 1; >6 secs, 2); fibrinogen level (>1.0 g/L, 0; <1.0 g/L, 1).³¹ A score of 5 or greater has a sensitivity of 93% and specificity of 98% for diagnosing DIC.³¹ Although current management of DIC is supportive and directed at the underlying disease process, having a simple diagnostic tool allows for accurate risk stratification.

Monitoring Anticoagulation

Unfractionated Heparin (UFH), Low Molecular Weight Heparin (LMWH), and Fondaparinux

UFH, LMWH, and fondaparinux all require the activation of antithrombin for their anticoagulant effect. UFH and LMWH are mixtures of negatively charged glycosaminoglycans, whereas fondaparinux is a synthetic polysaccharide.³² UFH can be reliably monitored with the aPTT until higher plasma concentrations are achieved, at which point an activated clotting time (ACT) test is necessary to accurately assess anticoagulation. Protamine titration assays are available with ACT systems, allowing accurate assessment of residual heparin effects. PT is typically not affected by heparin at low concentrations because

polybrene, a heparin neutralizing substance, is used in most commercial thromboplastins. LMWH and fondaparinux do not uniformly affect the aPTT, and anti-Xa assays calibrated to the particular agent are necessary for monitoring.³²

Vitamin K Analogs (VKA)

The most commonly used VKA is coumadin. The degree of anticoagulation is reliably measured with the international normalized ratio (INR) of the PT.

Non-vitamin K Oral Anticoagulants (NOAC): Dabigatran, Apixaban, Rivaroxaban

Dabigatran is a direct inhibitor of free and clot-bound thrombin. It can prolong both the aPTT and PT. Unfortunately, the effect on different commercial assays varies widely.³² The thrombin time (TT) is exquisitely sensitive to low concentrations of dabigatran and can be used to exclude residual activity.^{32,33} For quantification of drug levels, dilute TT and ecarin clotting times can be used.^{32,33}

Apixaban and rivaroxaban are direct Xa inhibitors.^{32,33} Although both can alter the PT and aPTT, this effect is not reliable, and normal values do not preclude clinically relevant drug concentrations.³³ Activity can be reliably measured with anti-Xa assays that are calibrated for the drug in question, and negative anti-Xa assays preclude clinically relevant concentrations.³³

Direct Thrombin Inhibitors: Argatroban, Bivalirudin

Direct thrombin inhibitors reliably prolong both the aPTT, PT, INR, and ACT. For therapeutic monitoring, the aPTT or ACT can be used.³⁴ As argatroban prolongs the INR, it should be discontinued while transitioning to coumadin if the INR is greater than 4 with an aPTT within goal.³⁴

KEY POINTS

1. The classic cascade model of coagulation inadequately explains in vivo hemostasis. The cell-based model emphasizes the role of tissue-factor-bearing cells and platelets in initiation, amplification, and propagation.
2. Patient temperature, pH, and serum calcium should be monitored in the bleeding patient.
3. aPTT, PT, INR, platelet count, and fibrinogen assays are widely available and are standard in the workup of coagulation. The INR does not accurately predict bleeding. Platelet count cannot assess platelet function.
4. Platelet function assays are available for detecting platelet dysfunction due to disease or antiplatelet agents.
5. ROTEM and TEG allow for evaluation of whole blood clotting. These tests assess coagulation factor activity, platelet function, fibrinogen activity, and fibrinolysis.
6. DIC scores are determined using widely available lab tests and have good sensitivity and specificity.
7. Heparin, argatroban, and bivalirudin can be monitored with ACT and aPTT. Coumadin is monitored with INR. LMWH, fondaparinux, apixaban, and rivaroxaban can all be monitored using anti-Xa assays with normalized curves for the specific agent. Dabigatran activity can be ruled out with a normal TT.

■ References for this chapter can be found at expertconsult.com.

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Patients in an intensive care unit (ICU) often have received or require anticoagulation for multiple reasons that include acute thrombotic issues, mechanical valves, venous thromboembolic prophylaxis, atrial fibrillation, and ischemic cardiovascular disease. The types of anticoagulation and need for therapy vary depending on whether patients have arterial or venous thromboembolic issues. These issues are important in critically ill patients and have important perspectives for management. The concept of anticoagulation and the various therapeutic approaches have rapidly changed over recent years with the advent of many new anticoagulation agents that will be considered here.¹ In addition, there are important links between coagulation and other important physiologic responses including inflammation that are beyond the scope of this review.

ICU patients are anticoagulated for both thrombosis treatment and thromboprophylaxis. As initially mentioned, this includes a broad spectrum of potential indications. Although multiple therapeutic agents prevent or treat thrombosis in pathologic states, it is important to consider that all anticoagulation agents can cause bleeding. Thus, causes of bleeding in an ICU setting often are due to an acquired hemostatic defect due to alterations in the physiologic equilibrium of procoagulant and anticoagulation balances. Under normal physiologic states in healthy patients, anticoagulation is favored due to a multitude of mediators and vascular endothelial cells.¹ After vascular injury due to metabolic causes, surgery, or trauma, patients also develop procoagulant changes that alter this complex balance.¹ As a result, hemostasis and coagulation are far more complex than the simplified coagulation cascades that most clinicians have learned or considered.²⁻⁵ There is a complex equilibrium among blood cells, platelets, coagulation factors, natural inhibitors of coagulation, and the fibrinolytic system.⁶

In ICU settings, patients may receive anticoagulants for venous thromboembolism (VTE) that include deep vein thrombosis (DVT) and pulmonary embolism (PE) for either prevention or therapy.³ Patients may also have additional problems that include acute coronary syndromes, percutaneous coronary interventions (PCIs), or with an acute ischemic stroke that are arterial issues. Arterial thrombi are mediated by platelet responses, and important interactions exist in hemostasis and thrombus formation.^{4,7} With an arterial injury, injury or rupture of an atherosclerotic arterial plaque serves as a procoagulant focus for clot formation due to platelet adhesion, activation, and aggregation with the clinical end result of myocardial infarction or stroke.^{8,9} Platelets normally circulate in an inactivated state, but following activation as described, they express glycoprotein IIb/IIIa receptors that allow fibrinogen to bind, cross-link platelets, aggregate, and form a thrombus.⁹ Vascular injury causes thrombin formation but also platelet activation and the formation of the platelet-fibrinogen plug. Since platelets have a pivotal role in the pathogenesis of thrombosis after plaque rupture, antiplatelet agents including aspirin, thienopyridines (clopidogrel, prasugrel, ticagrelor), and the glycoprotein IIb/IIIa inhibitors reduce adverse events that are associated with plaque rupture.^{10,11,12}

Patients therefore commonly present in the ICU with underlying hemostatic disorders because of preexisting preoperative anticoagulation or antiplatelet therapy.¹³ All therapies that prevent clot from forming in pathologic states also interfere with normal hemostasis, an important mechanism to protect patients from exsanguination.^{14,15}

Multiple anticoagulation agents are administered in the ICU setting that include low-molecular-weight heparins (LMWHs), oral

anticoagulants (vitamin K antagonists (VKAs)/warfarin and the new target-specific oral agents apixaban, dabigatran, edoxaban, or rivaroxaban), platelet inhibitors (the thienopyridines clopidogrel, prasugrel, or ticagrelor), or direct thrombin inhibitors (r-hirudin, bivalirudin, argatroban).^{1,16-18} This review will focus on current pharmacologic anticoagulation therapies ICU patients may receive and the therapeutic perioperative and prohemostatic pharmacologic approaches that are used to treat or prevent bleeding in this setting.

■ ANTICOAGULATION

The basis of anticoagulation is modulating clot formation by inhibiting both thrombin activation and platelet activation.^{17,19-21} Thrombin is a critical component of hemostasis (stopping bleeding) and a critical procoagulant in coagulation. Thrombin catalyzes the formation of fibrin from soluble fibrinogen, but also activates factors V and VIII, and platelets.⁴ Activated platelets adhere to injured vascular endothelium through a von Willebrand factor bridge between the vasculature and the platelets. Platelets also, when activated, express IIb/IIIa receptors where fibrinogen binds, causing aggregation, but also facilitate the further generation of thrombin.²² There are also complex humoral amplification pathways that link both inflammatory and coagulation responses to generate thrombin and prothrombotic effects.^{14,23} Thus, anticoagulation is based on inhibiting thrombin activation, platelet activation, and/or both. Thrombin is a potent procoagulant that generates fibrin from soluble fibrinogen, activating factors V and VIII, and activating platelets. Activated platelets adhere to injured vascular endothelia, express IIb/IIIa receptors, aggregate, and further increase thrombin generation. Current and future anticoagulants used to prevent clot formation will be considered.

■ HEPARIN

Heparin, the most commonly used anticoagulant, especially in an ICU setting, is isolated from porcine intestine where it is stored in the mast cell granules. Unfractionated heparin (UFH) is a combination of 3000- to 30,000-Dalton (da) fragments.²⁴ Heparin binds to antithrombin III (also called antithrombin/AT), increasing the rate of thrombin-AT complex formation, but also inhibits other steps in coagulation.²⁴ Heparin anticoagulation has major advantages in an ICU setting as it can be rapidly reversed with protamine, has a short half-life of ~1 hour, and one of the few anticoagulants that can be readily administered in patients with renal dysfunction that may otherwise prolong the half-lives of most agents.²⁵ One of the major side effects of UFH is heparin-induced thrombocytopenia (HIT) that can occur in ~1% to 5% of ICU patients, especially postoperatively and following cardiac surgery with cardiopulmonary bypass.²⁶

Low-Molecular-Weight Heparins (LMWH)

Low-molecular-weight heparins (LMWHs) are purified from UFH, with an average molecular weight of ~5000 da.²⁰ LMWHs have a longer half-life, are only partially reversible with protamine, and in patients with renal dysfunction, the effects can be greatly prolonged and should be avoided in this setting.^{18,20,23} Commonly used LMWHs include enoxaparin and dalteparin.

Heparin-Induced Thrombocytopenia (HIT)

Heparin-induced thrombocytopenia (HIT) is a serious, prothrombotic effect of heparin that develops in 1% to 3% of heparin-treated patients. HIT is an interesting paradigm where an anticoagulant produces an increased risk of thrombosis.^{26,27} The pathophysiology of HIT is due to a heparin-platelet factor 4 immunoglobulin G (IgG) antibody that binds and activates platelets and is associated with increased thrombotic morbidity and mortality.^{26,28} HIT should be suspected whenever the platelet count drops >50% from baseline after starting heparin (or sooner if there was prior heparin exposure) and/or new thrombosis occurring during, or soon after, heparin treatment, with other causes excluded. When HIT is strongly suspected, with or without complicating thrombosis, heparins should be discontinued, and a nonheparin alternative anticoagulant such as a direct thrombin inhibitor (argatroban) should be initiated immediately.^{26,29,30} Bivalirudin is also commonly used off-label, especially in this setting, and for HIT positive patients requiring extracorporeal membrane oxygenation (ECMO).^{31,32}

SYNTHETIC XA INHIBITORS (FONDAPARINUX)

Fondaparinux, a synthetic pentasaccharide with specific antiXa activity, has a long half-life with renal clearance and should be avoided in patients with renal dysfunction.¹⁸ Because of this, it is not commonly used in an ICU setting.

DIRECT THROMBIN INHIBITORS: PARENTERAL AGENTS

An important major class of anticoagulants used primarily for HIT or HIT patients suspected to need anticoagulation are the direct thrombin inhibitors that include bivalirudin, argatroban, and desirudin. Lepirudin is no longer available clinically. All of these parenteral direct thrombin inhibitors also vary in their binding affinities for thrombin and immunogenicity. All of the agents, except argatroban, are polypeptides, so there is a potential but rare risk for antibody formation and hypersensitivity responses.¹⁶ Bivalirudin and argatroban are most often used in an ICU setting and will be considered separately.

Bivalirudin

Bivalirudin is a polypeptide with a molecular weight ~4000 da, approved as an anticoagulant for patients undergoing PCI with provisional use of glycoprotein IIb/IIIa inhibitor, with or at risk of HIT or HIT and thrombosis syndrome undergoing PCI, and with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).³²⁻³⁴ It has also been used off-label as a replacement for heparin with ECMO. With normal renal function, the half-life is ~20 minutes but can be prolonged in patients with renal dysfunction.

Argatroban

Argatroban is an injectable, synthetic, small-molecular-weight (~500 da) direct thrombin inhibitor approved for prophylaxis or treatment of thrombosis in adult patients with HIT or as an anticoagulant in adult patients with or at risk for HIT undergoing PCI. However, for PCI, bivalirudin is currently used in this setting. The half-life is 40-50 minutes, and levels are not affected by renal dysfunction.³⁵ Patients with HIT often also present with acute renal failure, and all of the other agents used for acute HIT therapy are proteins that are renally eliminated. Argatroban is hepatically eliminated so no dose adjustments are required in patients with renal dysfunction. Also antigenicity is not an issue due to its low molecular weight.³⁶ We reported a study of 87 suspected HIT patients in the cardiothoracic ICU of which 47 patients (54%) were treated with argatroban, and 40 patients (46%) were not treated with argatroban. We concluded that clinical suspicion of HIT as detected by clinical probability score and thrombotic complications

should prompt immediate cessation of heparin and initiation of an alternative anticoagulant such as argatroban.³⁷

Desirudin

Desirudin (another recombinant hirudin) is approved in the United States for the prophylaxis of DVT, which may lead to PE in patients undergoing elective hip replacement surgery. Of note, desirudin has also been studied extensively for in patients with stable angina undergoing PTCA. Because desirudin is primarily eliminated by the kidneys, patients with renal impairment require monitoring, and activated partial thromboplastin time (aPTT) can be used. However, this agent is seldom used, especially with all of the newer oral anticoagulation agents available.¹⁸

ORAL ANTICOAGULANTS

Vitamin K Antagonists (VKAs): Warfarin

Warfarin is the only oral VKA agent available in the United States.¹⁸ Warfarin is an effective anticoagulation agent by inhibiting vitamin K epoxide reductase that converts the vitamin K-dependent coagulation proteins (factors II [prothrombin], VII, IX, and X) to their active form as a posttranslational modification. One of the reasons that warfarin's onset is so slow is that it takes several days to decrease coagulation factors to the ~20% to 40% level that is required for a therapeutic INR of 2-3.

Managing warfarin in the ICU setting is complicated and often bridged initially. However, in the bleeding patient, vitamin K will not immediately reverse the anticoagulant effect, and additional therapies are needed as detailed in the guidelines for perioperative management by Douketis in the ACCP guidelines and summarized in Perioperative Management of Antithrombotic Therapy.³⁸ The ACCP guidelines also recommend use of a four-component prothrombin complex concentrate (e.g., Kcentra/Beriplex, CSL Behring [King of Prussia, PA]; or Octaplex, Octapharma [Lachen, Switzerland]) for urgent warfarin reversal when required for bleeding or surgical interventions.³⁸ Additional considerations for warfarin reversal are reviewed below.

New Oral Agents: Apixaban, Dabigatran, Edoxaban, and Rivaroxaban

The new target-specific oral anticoagulation agents have a rapid onset with therapeutic anticoagulation within hours of administration.³⁹ Dabigatran is an oral direct thrombin inhibitor, and apixaban, edoxaban, and rivaroxaban are direct factor Xa inhibitors similar to LMWH but independent of antithrombin.¹⁸ Edoxaban has been recently approved and will not be further discussed. The new agents require dose adjustments for renal failure and will be considered separately.^{18,40}

Apixaban

Apixaban is a factor Xa inhibitor anticoagulant approved for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and for the prophylaxis of DVT, which may lead to PE in patients who have undergone hip or knee replacement surgery, for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy. If bleeding occurs and measurement of its effects is needed, then using a specific calibrated anti-Xa assay, similar to what is used for LMWH, is needed. However, measuring the effects of the Xa inhibitors can be difficult.⁴¹ The formulation can be crushed and given through a feeding tube if needed in the ICU setting.

Dabigatran Etxilate

Dabigatran etexilate is an oral, direct thrombin inhibitor currently approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, for the treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for

5 to 10 days, and to reduce the risk of recurrence of DVT and PE in patients who have been previously treated. Dabigatran has a rapid onset of action and no requirement for routine coagulation monitoring. Dabigatran's effects can be measured best by tests similar to any direct thrombin inhibitor, including aPTT values, thrombin times, diluted thrombin times, or ecarin clotting times.⁴⁰ A specialized assay that uses a diluted thrombin time is helpful for specific measurement of levels when needed and sensitive to lower levels. However, the aPTT is still a good screening test.⁴² Dosing should also be adjusted for patients with renal dysfunction. The capsule is specially formulated and cannot be altered or crushed for administration in an ICU setting. A specific monoclonal antibody is in clinical trials for acute reversal of dabigatran and will be discussed later.⁴³

Rivaroxaban (Xarelto)

Rivaroxaban is a direct-acting oral factor Xa inhibitor, which unlike heparins, does not require antithrombin.⁴² Rivaroxaban has the broadest indications of all of the new agents that include reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; for the treatment of DVT and PE and for the reduction in the risk of recurrence of DVT and of PE; and for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery. If bleeding occurs and measurement of its effects are needed, then using a specific calibrated anti-Xa assay, similar to what is used for LMWH, is needed.⁴¹ The formulation can be crushed and given through a feeding tube, if needed, in the ICU setting.

ICU Management of the Oral Anticoagulants

In the ICU, oral therapy often is not feasible, and parenteral agents need to be considered. In renal failure, heparin and argatroban are most often used, and bivalirudin offers an alternative, but all of these agents require monitoring. However, for urgent reversal or management of the bleeding patients, significant concerns have been expressed about the new agents, but despite the extensive use of LMWH in the ICU, there is no antidote available and it accumulates in renal failure.

In the United States, warfarin is still a problem for clinicians because the balanced prothrombin complex concentrates (PCCs) that contain all four factors (II, VII, IX, and X), like KCENTRA for immediate INR reversal, are not readily used by clinicians but are recommended in recent ACCP guidelines.^{38,44} Vitamin K takes days to work, ~4 units of fresh frozen plasma (FFP) is required with transfusion risk issues and volume overload, and FFP never restores the INR to baseline but usually to ~1.4 to 1.6, which is the baseline INR for FFP.⁴⁴

Managing Bleeding with the New Oral Anticoagulants

If patients are acutely bleeding, the new agents as mentioned can be evaluated with specialized tests that should be measured in such patients. For dabigatran, thrombin times (TT) and a diluted thrombin time and ecarin clotting times (used in Europe) are the most sensitive. The aPTT can measure its effects although not as sensitive as a thrombin time.⁴⁵ The aPTT potentially provides a qualitative assessment of anticoagulation. Although there currently is no specific antidote to antagonize the anticoagulant effect of all of the agents, with normal renal function, these agents have a relatively short duration of effect, are direct acting, and drugs should be discontinued when risks of bleeding exceed risks of thrombosis.

With bleeding, patients should be hemodynamically and hemostatically resuscitated, and therapy should be multimodal as outlined previously.⁴² Dabigatran can be dialyzed in patients with renal impairment, but this is not practical in a patient in shock. In instances of life-threatening bleeding, prohemostatic agents such as PCCs can be considered.⁴⁵ For apixaban and rivaroxaban prolongation of most standard hemostatic tests are too variable, and specialized tests evaluating anti-Xa are required.⁴⁶ Our data and others report PCCs completely reverses the anticoagulant effect of rivaroxaban in anticoagulated

patients.^{47,48} Animal data suggest PCCs may actually reverse bleeding and should be considered part of a multimodal approach. However, new specific reversal strategies are in active development.

Of note is that the French Study Group on thrombosis and hemostasis have proposed perioperative management strategies.⁴⁹ They suggest for procedures with low hemorrhagic risk a therapeutic window of 48 hours (last administration 24 hours before surgery, restart 24 hours after). For procedures with medium or high hemorrhagic risk, they suggest stopping therapy 5 days before surgery to ensure complete elimination in all patients. Treatment should be resumed only when the risk of bleeding has been controlled. In patients at high thrombotic risk (e.g., those in atrial fibrillation with a history of stroke), bridging with heparin is proposed. They suggest prohemostatic agents should not be given for prophylactic reversal due to their uncertain benefit-risk.⁴⁹

The major concerns in the ICU are emergency procedures or major bleeding. However, there is increasing information available to facilitate managing patients receiving new oral anticoagulants (NOACs).⁴² Important management of the NOACs is discontinuing its use, but if reversal is required, specific therapeutic approaches should be considered and include the application of PCCs for reversal and/or bleeding. PCCs in the United States are available in four components (KCENTRA) or three components (Profilnine and Bebulin). The 3-component PCCs are deficient in factor VII. We have reported the ability of PCCs to reverse rivaroxaban anticoagulation, and there are increasing reports on their off-label use in bleeding cardiac surgical patients.^{48,50,51}

Despite concerns about NOACs and bleeding, most studies suggest patients fare better on NOACs compared to warfarin.⁵² In one study of 27,419 patients treated up to 3 years, 1034 patients had 1121 major bleeds. The 30-day mortality after the first major bleed was 9.1% in the dabigatran group compared to 13.0% in the warfarin group, and dabigatran-treated patients required a shorter ICU stay compared to warfarin.⁵²

Novel Reversal Strategies for NOACs

Currently, there are no specific reversal strategies available for any of the NOACs although there are three specific reversal agents in development.⁵³ For factor Xa reversal, PRT064445 (andexanet alfa) is a recombinant mimetic of factor Xa that binds to all factor Xa inhibitors and lacks catalytic activity. In current studies involving anticoagulated volunteers, andexanet alfa dose-dependently reversed factor Xa inhibition (clinicaltrials.gov: NCT01758432). For dabigatran reversal, a Fab antibody fragment directed against dabigatran (BI 655075; idarucizumab) is under development in clinical trials, and the FDA granted breakthrough therapy designation to idarucizumab in June 2014 with an ongoing clinical trial: REVERSE-AD (NCT02104947). Two types of patients are being studied: those with serious bleeding and those requiring urgent surgery or intervention. The first data have been reported.⁴³ The third agent is PER977 (aripazine), a cationic small molecule designed to bind all Xa inhibitors including LMWH. Idarucizumab for dabigatran reversal was approved by the FDA in 2015 and is available in most medical centers (<https://www.praxbind.com/>).

■ PLATELET INHIBITORS

In patients with ischemic cardiovascular disease and/or atherosclerotic vascular disease, inhibiting platelet activation is critical in managing these patients.⁵⁴ Platelet inhibitors/antiplatelet agents should also be considered as anticoagulants, but they pose increased risks for bleeding. The antiplatelet agents differ in their modes of action, potency, onsets of action, and indications. Aspirin is an irreversible platelet cyclooxygenase and thromboxane A₂ inhibitor but is also a relatively weak antiplatelet agent,⁵⁵ and resistance can occur.⁵⁶ More potent antiplatelet agents include the P2Y₁₂ receptor and IIb/IIIa receptor antagonists (abciximab, tirofiban, eptifibatide). Clopidogrel, prasugrel, and ticagrelor have become the mainstays of therapy and inhibit platelets by selectively and irreversibly binding to the P2Y₁₂ receptor

to inhibit the adenosine diphosphate–dependent mechanism of glycoprotein IIb/IIIa–receptor expression and platelet activation.^{55,57,58} Clopidogrel is the major agent used with the least knowledge available about how to manage these patients or monitor its effects, and resistance can occur because it is a prodrug and requires metabolism to be transformed to its active metabolite. Dual antiplatelet therapy with aspirin and clopidogrel is standard care following revascularization by PCI with stent insertion. This so-called dual therapy is recommended for up to 4 weeks after intervention for bare-metal stents and for 6–12 months after intervention for drug-eluting stents.⁵⁴ Vincenzi noted a 45% complication rate and a mortality of 20% in patients undergoing noncardiac surgery after coronary artery stenting.⁵⁹ Discontinuation of antiplatelet drugs appeared to be of major influence on outcome. They prospectively evaluated 103 patients receiving stents within 1 year before noncardiac surgery. Antiplatelet drug therapy was not, or only briefly, interrupted. Heparin was administered to all patients. Of 103 patients, 44.7% developed complications after surgery; 4.9% of the patients died. All but two (bleeding only) adverse events were of cardiac nature. Most complications occurred early after surgery. The risk of suffering an event was 2.11-fold greater in patients with recent stents (<35 days before surgery) compared with PCI more than 90 days before surgery.⁵⁹ The clopidogrel package insert suggests if a patient is to undergo elective surgery and an antiplatelet effect is not desired, it should be stopped 5 days before surgery. However, if patients bleed, therapy or monitoring its effects has not been established. Further, the risk compared to the benefit of stopping clopidogrel needs to be weighed against the risk of stent thrombosis, and the need for surgical intervention as well. Prasugrel has an advantage of increased potency and potentially a lower rate of “resistance,”⁶⁰ one of the potential problems for clopidogrel.⁵⁸

ICU/PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTIC THERAPY BASED ON GUIDELINES

Recent guidelines from the American College of Chest Physicians in 2012 have been reported.³⁸ In patients requiring VKA interruption before surgery, they recommend stopping VKAs 5 days before surgery instead of a shorter time before surgery (Grade 1B). In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, they suggest bridging anticoagulation instead of no bridging during VKA interruption (Grade 2C); in patients at low risk, they suggest no bridging instead of bridging (Grade 2C). In patients who require a dental procedure, they suggest continuing VKAs with an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure instead of alternative strategies (Grade 2C).

In moderate- to high-risk patients who are receiving acetylsalicylic acid (ASA) and require noncardiac surgery, they suggest continuing ASA around the time of surgery instead of stopping ASA 7 to 10 days before surgery (Grade 2C). In patients with a coronary stent who require surgery, they recommend deferring surgery >6 weeks after bare-metal stent placement and >6 months after drug-eluting stent placement instead of undertaking surgery within these time periods (Grade 1C); in patients requiring surgery within 6 weeks of bare-metal stent placement or within 6 months of drug-eluting stent placement, they suggest continuing antiplatelet therapy perioperatively instead of stopping therapy 7 to 10 days before surgery (Grade 2C).³⁸ In all patients, relative risk versus benefit must be considered when managing patients.

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Hematopoietic stem cell transplantation (HSCT) is used to treat an ever-increasing array of disorders, including hematologic and lymphoid cancers, selected solid tumors, and nonneoplastic diseases including autoimmune disorders, amyloidosis, and aplastic anemia. The main indications for autologous transplant include multiple myeloma and lymphomas. Allogeneic transplants are most commonly performed for acute and chronic leukemia, lymphoma, and myelodysplastic syndrome. The most common graft source is peripheral blood; other graft sources include bone marrow and cord blood. A conditioning regimen is employed before transplantation to eradicate malignant cells and, in allogeneic transplantation, to induce immunosuppression that permits engraftment. The conditioning regimen can be myeloablative, reduced-intensity, or nonmyeloablative. Some patients are also given total body irradiation for myeloablation and immunosuppression.

Following HSCT, the immune system recovers along predictable patterns depending on the underlying disorder, stem cell source, and complications such as graft versus host disease (GVHD). Recovery occurs faster in autologous recipients, in those who receive peripheral blood stem cell grafts, and after nonmyeloablative conditioning. The posttransplant period is divided into three phases: preengraftment, early post transplant, and late post transplant. The preengraftment phase (0-30 days) is characterized by neutropenia and breaks in the mucocutaneous barriers. The early postengraftment phase (30 to 100 days) is dominated by impaired cell-mediated immunity. The impact of this cell-mediated defect is determined by the development of GVHD and the corresponding immunosuppressive medications. The late posttransplant phase (>100 days) is characterized by defects in cell-mediated and humoral immunity, as well as function of the reticuloendothelial system in allogeneic transplant recipients.

■ INDICATIONS FOR ICU ADMISSION

Reflecting the multitude of potentially life-threatening complications that can punctuate the posttransplant course, the ICU is a common setting for care of HSCT recipients. Reported rates of admission to the ICU vary widely in the published literature, ranging from 5% to 55% with an overall rate approximating 16%.¹ Pulmonary complications represent the most common reason for ICU admission, accounting for approximately 60% of cases.² Pneumonia and sepsis-induced acute respiratory distress syndrome (ARDS) are common causes of hypoxemic respiratory failure in HSCT recipients. Noninfectious pulmonary complications also can lead to respiratory failure and ICU admission. Finally, airway compromise due to mucositis occasional prompts ICU admission during the preengraftment period.

The second most common reason for ICU admission in this patient population is hemodynamic compromise secondary to sepsis, accounting for approximately 20% of admissions.² Other common reasons are cardiac arrhythmias (8%-17% of cases), intracranial bleeding (2%-5% of cases), seizures (11% of cases), gastrointestinal bleed (5% of cases), and acute renal failure (less than 5% of cases).²

■ COMMON INFECTIOUS COMPLICATIONS REQUIRING ICU CARE

Infectious complications are more common in patients who have undergone allogeneic transplantation since these recipients require the administration of immunosuppressive agents after transplantation to prevent or treat GVHD. In addition, GVHD itself causes an immunodeficient state by involving mucosal surfaces, the reticuloendothelial system, and bone marrow. The use of alternative hematopoietic precursor sources, such as mobilized peripheral blood stem cells, and cytokines, such as hematopoietic cell colony-stimulating factors, have shortened the period of neutropenia and decreased the frequency of infectious pulmonary complications. Additionally, effective prophylactic strategies have evolved that have further reduced the incidence of infections, in particular *Pneumocystis jiroveci* and cytomegalovirus. Nonetheless, pneumonia remains the leading cause of death following HSCT.

Bacterial Pneumonia

Bacterial pneumonia may occur at any time in the posttransplantation period but is particularly prevalent during the preengraftment period of profound neutropenia. Gram-negative pathogens, especially *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, predominate in the first 100 days, while gram-positive organisms such as *Streptococcus pneumoniae* cause the majority of late infections. *Legionella* species have been reported to be an important cause of nosocomial pneumonia in some centers.

Bacterial pneumonia is commonly heralded by fever, but respiratory symptoms and signs may be absent in the neutropenic host. Presumably because of the paucity of neutrophils, chest x-ray abnormalities may be subtle or absent as well. In one series, the use of high-resolution CT imaging revealed evidence of pneumonia in more than 50% of febrile neutropenic patients with normal chest radiographs.³ Broad-spectrum antibiotics (with anti-*Pseudomonas* activity) should be initiated expeditiously in all suspected cases of bacterial pneumonia and in febrile, neutropenic patients without an identified site of infection.

Aspergillus

Invasive aspergillosis represents one of the most devastating complications of HSCT and remains one of the leading cause of infectious deaths in this group. There is a bimodal distribution of cases, and risk factors for each period are somewhat distinct. Both allogeneic and autologous recipients are at increased risk for invasive aspergillosis during the preengraftment phase, when neutropenia is the prevailing risk factor. Allogeneic HSCT recipients experience a second, postengraftment period of vulnerability coincident with the development of chronic GVHD and the attending physician needs to administer immunosuppressive agents.

Invasive aspergillosis is confined to the lungs in the majority of cases, but sinusitis and central nervous system involvement also occur with some frequency. Cough and dyspnea are the most common presenting symptoms. Pleuritic chest pain and hemoptysis are important albeit nonspecific clues to the presence of invasive aspergillosis, reflecting the tendency of the organism to invade blood vessels and cause pulmonary infarction. Fever may be absent in up to two-thirds of patients.

Initial radiographic findings include single or multiple nodules, cavities, and subsegmental or segmental consolidation. CT imaging is more sensitive in detecting abnormalities and can do so at an earlier stage of infection. A highly characteristic CT finding is the halo sign, a rim of low attenuation representing edema or hemorrhage that surrounds a pulmonary nodule. In one study, the halo sign was present in over 90% of neutropenic patients with invasive pulmonary aspergillosis when CT scans were performed at the onset of fever.⁴

Establishing a definitive diagnosis of invasive pulmonary aspergillosis remains difficult, and up to 30% of cases are unrecognized antemortem.⁵ The recovery of *Aspergillus* species from respiratory tract cultures is highly suggestive of invasive infection in the HSCT population, with a positive predictive value of 82%,⁶ but sensitivity is only 35% to 57%.^{7,8} Transthoracic fine-needle aspiration of accessible focal lesions has a yield of 50% to 67%.^{8,9} An enzyme-linked immunosorbent assay that detects galactomannan, a fungal cell wall component released during invasive disease, has been introduced into clinical practice as a diagnostic tool, albeit with its own limitations. Among HSCT patients with proven or probable cases of invasive aspergillosis included in a meta-analysis, the pooled sensitivity, specificity, and positive and negative predictive values of serum galactomannan testing were 82%, 86%, 65%, and 65%.¹⁰ There are conflicting data on whether galactomannan testing of bronchoalveolar lavage (BAL) performs better than that of serum, with reported sensitivity ranging from 50% to 90% and specificity from 73% to 94%.^{11,12}

Voriconazole is the treatment of choice for invasive aspergillosis, based on demonstration of superior efficacy and less toxicity compared to amphotericin B.¹³ A recent multicenter registry of HSCT recipients documented partial or complete response at 12 weeks in 64% of patients with invasive aspergillosis, the majority of whom were treated with voriconazole alone or in combination with an echinocandin.¹⁴ The mortality rate at this time point was 36%, a dramatic reduction from rates in excess of 80% reported in the 1990s. Surgical resection of localized disease is sometimes used as an adjunct to antifungal therapy in refractory cases.

CMV

The risk of CMV pneumonia is far greater following allogeneic compared to autologous HSCT, a consequence of the need to administer immunosuppressive drugs for GVHD prophylaxis in association with the former procedure. The vast majority of episodes of CMV disease result from reactivation of latent virus in seropositive recipients. Seronegative patients who receive stem cells from a seropositive donor have a lower risk of posttransplantation CMV disease than do seropositive recipients, a situation that contrasts with that seen following solid organ transplantation. In the preprophylaxis era, onset of CMV pneumonia almost invariably occurred between engraftment and day 100. The use of prophylaxis has dramatically reduced the incidence of CMV pneumonia to approximately 5% among allogeneic HSCT recipients but has also shifted the onset of disease to later in the posttransplantation course.

The clinical presentation of CMV pneumonia is not distinctive. Nonproductive cough, fever, and hypoxemia are typical, with rapid progression to respiratory failure in some cases. The chest radiograph most often demonstrates bilateral interstitial opacities, but focal or diffuse consolidation and nodular opacities may also be seen. Ground-glass opacities are commonly demonstrated by high-resolution CT. The diagnosis of CMV pneumonia is most definitively established by demonstration of viral inclusion bodies in specimens obtained by

either transbronchial lung biopsy or BAL, but the yield of both of these techniques is low. In association with compatible clinical and radiographic features, detection of virus in BAL fluid by rapid culture technique or PCR is considered diagnostic in this patient population. However, in cases lacking the classic features, these results must be interpreted with caution since viral shedding into the respiratory tract can occur in the absence of invasive disease. Identification of a high viral load in peripheral blood provides additional supportive evidence in the appropriate setting.

The combination of ganciclovir and high-dose intravenous immunoglobulin or CMV-specific immunoglobulin has become the standard of care for treatment of CMV pneumonia, though the need for the immunoglobulin preparations has recently been challenged.¹⁵ Foscarnet is reserved for patients unable to tolerate ganciclovir and those infected with ganciclovir-resistant strains.

Community Respiratory Viruses

As a group, the community respiratory viral pathogens—respiratory syncytial virus (RSV), influenza A and B, and parainfluenza—account for the majority of non-CMV viral respiratory infections in both autologous and allogeneic HSCT recipients. With the exception of parainfluenza virus, which occurs year-round, the other viruses occur predominantly in the late fall, winter, and early spring. Among patients with RSV infection, the risk of pneumonia approaches 80% for those who are less than 1 month post transplant or still in the preengraftment stage but falls to less than 40% for those beyond this critical period.¹⁶ Once pneumonia develops, mortality from untreated RSV infection approximates 80%. Uncontrolled trials suggest that a combination of aerosolized ribavirin and intravenous immunoglobulin may decrease pneumonia-related mortality when initiated prior to the onset of respiratory failure.^{17,18} Progression to pneumonia occurs considerably less frequently with influenza, though postinfluenza bacterial pneumonias are a concern. The neuraminidase inhibitors zanamivir and oseltamivir are commonly administered, but their efficacy in treatment of influenza pneumonia in HSCT recipients has not been established.

COMMON NONINFECTIOUS COMPLICATIONS REQUIRING ICU CARE

Acute Pulmonary Edema

Acute pulmonary edema is a common but potentially overlooked cause of pulmonary dysfunction during the neutropenic phase following HSCT. Noncardiogenic pulmonary edema has many contributory factors including total body radiation, induction drugs, aspiration, transfusion-related acute lung injury, and sepsis. Patients who develop hydrostatic/cardiogenic pulmonary edema have often received large volumes of fluid for medications, total parenteral nutrition, and multiple blood product transfusions. Cardiac dysfunction resulting from chemotherapeutic agents used during induction can also contribute to volume overload, as can renal impairment.

Engraftment Syndrome and Periengraftment Respiratory Distress Syndrome

Engraftment syndrome is characterized in its full expression by a combination of fever, erythrodermatous rash, diarrhea, diffuse capillary leak, and noncardiogenic pulmonary edema occurring coincident with neutrophil recovery.¹⁹ This syndrome has been described most frequently following autologous HSCT, with a reported incidence of 7% to 53%.^{20,21} A similar presentation following allogeneic transplantation has been described but must be distinguished from acute GVHD. Periengraftment respiratory distress syndrome (PERDS) refers exclusively to the pulmonary component of engraftment syndrome. Recent studies suggest that pulmonary involvement occurs in one-third of patients with engraftment syndrome.²²

The etiology of engraftment syndrome is poorly understood; release of proinflammatory cytokines during engraftment is postulated to play a principal role. The use of granulocyte colony-stimulating factor may increase the incidence and severity of the engraftment syndrome, and discontinuation of this agent is recommended in patients who develop this complication.

Signs and symptoms of PERDS begin within 5 days following neutrophil engraftment. Dyspnea is universally present, accompanied by hypoxemia of varying severity. Frank respiratory failure requiring mechanical ventilator support develops in approximately one-third of patients with PERDS. The majority of patients are febrile; other clinical features of engraftment syndrome may be present, including a maculopapular rash, hypoalbuminemia, ascites, and peripheral edema. Bilateral pulmonary infiltrates are seen on chest x-ray and CT scan but are nonspecific. The diagnosis of PERDS is based on the presence of compatible clinicoradiographic features, onset in the periengraftment period, and the exclusion of infection, volume overload, diffuse alveolar hemorrhage (DAH), and other entities that share similar features. Treatment with high-dose corticosteroids has been associated with rapid clinical improvement, even among patients requiring mechanical ventilation.^{19,23}

Diffuse Alveolar Hemorrhage (DAH)

In the context of HSCT, DAH is considered to be a manifestation of widespread alveolar injury of noninfectious etiology. DAH occurs with a frequency approximating 5% among both autologous and allogeneic HSCT recipients and is encountered in up to 40% of HSCT patients admitted to the ICU.²⁴ DAH is most commonly observed within the first month, often during the periengraftment phase, but later onset is encountered in up to 42% of cases.²⁴ Age > 40 years, total body irradiation, and renal insufficiency have been identified as risk factors.²⁵ Although thrombocytopenia is common, platelet counts are not lower than those found in patients without DAH, and aggressive platelet transfusion does not result in improvement in respiratory status.²⁵

The pathogenesis of DAH in HSCT recipients remains obscure. Postmortem investigations have shown that the majority of patients with DAH have evidence of diffuse alveolar damage.^{25,26} It is likely that DAH, like idiopathic pneumonia syndrome (IPS) and PERDS, is part of a spectrum of acute lung injury induced by conditioning chemotherapy, radiation, and occult infection. The fact that many cases occur at the time of engraftment suggests that neutrophil influx into the lung may accentuate the injury and in some way precipitate hemorrhage.

Patients present with dyspnea, nonproductive cough, fever, and diffuse pulmonary infiltrates, but hemoptysis is notably rare. An otherwise unexplained drop in hemoglobin provides an important clue to the presence of DAH. The majority of patients require ICU admission and mechanical ventilation. Diagnosis centers on the bronchoscopic demonstration of progressively bloodier BAL fluid from at least three lobes or greater than 20% hemosiderin-laden macrophages in the BAL fluid, and the exclusion of underlying infection.

With supportive therapy alone, mortality rates of 80% to 100% have been reported.^{25,27} Onset of DAH within the first 30 days of transplantation and autologous HSCT are associated with the most favorable outcomes, with mortality rates in the range of 30% in association with each of these factors compared to 70% in association with late-onset DAH or allogeneic transplantation.²⁸ Death is usually a result of superimposed multisystem organ failure or sepsis rather than respiratory failure from refractory hemorrhage.²⁴ Retrospective case series and anecdotal reports suggest that high-dose corticosteroids may improve the survival rate but there are no prospective, randomized trials.^{27,29} There are reports of allogeneic HSCT recipients with DAH successfully treated with recombinant factor VIIa.^{30,31}

Idiopathic Pneumonia Syndrome

The term *idiopathic pneumonia syndrome (IPS)* applies to HSCT patients presenting with widespread alveolar injury in the absence of

BOX 141-1 Criteria for Diagnosing Idiopathic Pneumonia Syndrome

- I. Evidence of widespread alveolar injury
 - Multilobar infiltrates on routine chest radiographs or computed tomography
 - Symptoms and signs of pneumonia (cough, dyspnea, tachypnea, rales)
 - Evidence of abnormal pulmonary physiology
 - Increased alveolar to arterial oxygen difference
 - New or increased restrictive pulmonary function test abnormality
- II. Absence of active lower respiratory tract infection based upon
 - Bronchoalveolar lavage cultures, cytology, polymerase chain reaction, and other studies negative for significant bacterial, viral, and fungal pathogens
 - Transbronchial biopsy if condition of the patient permits
- III. Absence of cardiac dysfunction, acute renal failure, or iatrogenic fluid overload as etiology for pulmonary dysfunction

Modified from Panoskaltis-Mortari A, Griesse M, Madtes DK, et al. An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. *Am J Respir Crit Care Med.* 2011;183:1262-79.

an identifiable infectious etiology. More recently, the definition was updated to additionally require exclusion of cardiac dysfunction, renal failure, and iatrogenic volume overload as the etiology for pulmonary dysfunction.³² The updated diagnostic criteria, which continue to rely chiefly on BAL studies to exclude infection, are listed in [Box 141-1](#). Adding to the ambiguity of the definition, some authorities include PERDS and DAH in the spectrum of IPS, while others treat them as distinct entities.

The incidence of IPS in the first 120 days following allogeneic HSCT with myeloablative conditioning is in the range of 3% to 15%.³³ Among allogeneic recipients, the incidence appears to be lower after nonmyeloablative versus conventional high-dose conditioning regimens, lending support to the belief that toxicity from intensive chemotherapy and radiation contributes significantly to pathogenesis. Acute GVHD has been identified as a risk factor for IPS, suggesting that alloimmune mechanisms may also come into play. IPS also occurs following autologous HSCT, but the frequency appears to be lower than that among recipients of allogeneic HSCT. It remains unclear whether the source of stem cells (bone marrow vs. peripheral blood vs. umbilical cord blood) impacts the frequency of this complication.

The median time to onset of IPS has been reported to be 19 days, with the majority of cases occurring within the initial 120 days.³³ Patients with IPS present with dyspnea, fever, nonproductive cough, increasing oxygen requirements, and diffuse radiographic infiltrates. When obtained, lung biopsy specimens reveal two main patterns: diffuse alveolar damage and interstitial pneumonitis. The course is typically rapid, with up to two-thirds of patients progressing within several days to respiratory failure requiring mechanical ventilation.³³ Combined mortality in six of the larger published case series was 74%,³⁴ and the mortality rate among those requiring mechanical ventilation may exceed 95%.³³

Beyond supportive care, there is no proven treatment for IPS. High-dose corticosteroid therapy is commonly administered, but substantiation of benefit is lacking.³³ Based on evidence that anti-tumor necrosis factor therapy mitigates acute lung injury in murine models of IPS,³⁵ etanercept, a soluble tumor necrosis factor- α -binding protein, has been administered to patients with IPS. Two case series, encompassing a total of 37 patients treated with a combination of corticosteroids and etanercept, demonstrated high clinical response rates and improved short-term survival, but pending results of prospective randomized trials, it is premature to endorse this approach as standard of care.^{36,37}

OUTCOMES OF ICU ADMISSION

Historically, the prognosis of HSCT patients admitted to ICU has been poor, but more recent studies have suggested that the prognosis has

improved over the past two decades.³⁸⁻⁴⁰ In a series of HSCT patients requiring ICU level of care at Mayo Clinic between 1982 and 1990, overall hospital mortality was 77%.⁴¹ In a subsequent cohort between 1996 and 2000, the ICU, hospital, and 30-day mortality rates were 33%, 46%, and 52%, respectively.⁴⁰ A retrospective analysis of consecutive patients admitted to a center in the Netherlands documented steady improvement in 100-day posttransplant mortality of patients requiring ICU care, declining from 78% in 2004-2005 to 35% in 2008-2009.⁴²

In particular, HSCT patients requiring mechanical ventilation for respiratory failure have experienced the poorest outcomes, leading some authorities to consider this as a futile intervention in the past.⁴³ In one of the largest studies involving 348 mechanically ventilated HSCT recipients at the Fred Hutchinson Cancer Research Center between 1986 and 1990, survival at 6 months was only 3%.⁴⁴ In another study from the same center, investigators found no survivors among ventilated patients with acute lung injury and either hepatic and renal insufficiency or hemodynamic instability necessitating vasopressors.⁴⁵ Notably, however, more recent studies have reported improved outcomes for HSCT recipients who received mechanical ventilation, with survival rates as high as 26%.^{39,46} These reports are encouraging, and despite the fact that survival rates remain disappointingly low, it can be argued that mechanical ventilation in select groups of HSCT recipients should not be considered futile.

In order to inform the appropriate use of the ICU and mechanical ventilation, a number of studies have attempted to identify factors predictive of outcome. Specific pre-ICU characteristics, including age, sex, primary disease, type of transplant, and conditioning regimen, have not proven to be reliable predictors.^{2,39,46} Admission to the ICU within the engraftment period has been associated with a more favorable prognosis compared to later admission, particularly for recipients requiring mechanical ventilation.⁴⁶ Factors during the ICU course that have been associated with unfavorable outcomes are the need for mechanical ventilation, duration of mechanical ventilation exceeding 4 days, presence of multiorgan failure, hyperbilirubinemia, and use of vasopressors.⁴⁵⁻⁴⁸

Well-known instruments used to prognostically stratify patients at the time of admission to the ICU, such as Acute Physiology and Chronic Health Evaluation (APACHE) II and APACHE III, and the Sequential Organ Failure Assessment have limited prognostic value

in the HSCT patient population. As a result, indices specific to the allogeneic HSCT have been developed. One such index, based on factors present at the time of initiation of mechanical ventilation, classifies patients with a creatinine <2 mg/dL and platelet count >20 × 10⁹/L in a favorable category, with an overall survival at 100 days post mechanical ventilation of 29%, compared to only 5% for those not meeting both of these criteria.⁴⁹ The Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI), initially developed to predict outcomes after allogeneic HSCT, also appears to be useful as a predictive instrument for in-hospital mortality among patients admitted to the ICU within 100 days of their transplant; in one study, mortality was 46% for those with an HCT-CI score of 0-1 compared to 69% for those with a score ≥4.⁵⁰

These predictive factors and indices allow for some stratification of risk but fall short of defining patients for whom ICU care and mechanical ventilation would be inappropriate. This is best accomplished through daily assessment of the critically ill patient's status and response to therapy, close communication between the ICU and transplant teams, and awareness of the patient's preferences and goals of care.

KEY POINTS

1. Approximately 15% of HSCT recipients will require ICU care at some point in their course.
2. Pulmonary complications, both infectious and noninfectious, represent the leading cause of ICU admission.
3. Bacterial pneumonia is particularly common during the neutropenic preengraftment phase following both allogeneic and autologous HSCT.
4. Because of the requirement for administration of immunosuppressive agents, allogeneic HSCT recipients are particularly predisposed to opportunistic infections, including CMV and invasive aspergillosis.
5. Noninfectious pulmonary complications leading to respiratory failure include PERDS, DAH, and IPS.

■ References for this chapter can be found at expertconsult.com.

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Fundamental to the management of a critically ill pregnant woman is a detailed knowledge of the normal physiologic changes that occur during gestation and immediately after delivery. Some of these physiologic adaptations are from the hormonal changes associated with pregnancy, and others are to support the mother and the growing fetus.¹ Clinicians must have a good understanding of the extent of these changes, which occur in all pregnant women, to appropriately diagnose and treat critically ill patients whose additional pathology complicates the distinct metabolic homeostasis and hemodynamics of the normal pregnant state. It is important to recognize that these physiologic changes add a level of complexity to diagnosis and management in the critically ill pregnant woman. The normal baseline physiologic changes of pregnancy often alter the presentation of a disease process or illness that presents during pregnancy, and they can unmask a previously silent disease process of the woman. The normal physiologic maternal adaptations will change the interpretation of clinical and diagnostic examination findings in the pregnant woman. Subsequently, the endpoints of treatment can be significantly different from those for nonpregnant patients.

Some of the physiologic changes associated with pregnancy occur early in the normal course of gestation, whereas others occur during the middle or later stages. To render the most effective care of critically ill pregnant patients, the clinician must be aware of the timing of important physiologic changes. They affect almost all organ systems to varying degrees, depending in part on the gestational age of the fetus. Hemodynamic, metabolic, hormonal, and structural changes all occur during pregnancy and allow for the natural growth and development of the fetus. The healthy pregnant woman adapts remarkably well to these changes, as does the fetus, allowing the two to coexist symbiotically without harm to the other. However, if the pregnant woman is ill, either from a preexisting underlying disease process or from a new pathologic process that occurs during the pregnancy, the normal physiologic adaptive mechanisms of pregnancy are often insufficient to maintain the normal healthy union between mother and fetus. Depending on the severity of the underlying process or new illness, the hemodynamic ramifications to the pregnant woman and her fetus can be devastating and life threatening.

CARDIOVASCULAR CHANGES IN PREGNANCY

Cardiovascular and blood volume changes are among some of the more significant changes that occur in pregnancy (Table 142-1). These changes are primarily adaptive mechanisms, allowing the pregnant woman to accommodate her additional metabolic needs as well as those of the fetus during gestation and immediately after delivery. Cardiac output is significantly increased during pregnancy by as much as 50% compared with nonpregnant values. Cardiac output is increased by 15% in twin pregnancies as well as in multiple gestations.^{2,3} The dramatic rise in cardiac output is seen as early as the first 6 to 8 weeks of pregnancy. After the 10th week, cardiac output is increased by 1 to 1.5 L/min, increases by 75% by the end of the third trimester, and reaches a maximum value by approximately the 20th to 24th week of gestation. The early increase in cardiac output is primarily due to a significant increase in stroke volume. However, stroke volume decreases as the pregnancy advances because of aortocaval compression by the

uterus and the pressure of the fetal presenting part on the common iliac vein. Caval compression occurs because the large, gravid uterus rests on the vena cava, decreasing venous return to the heart and therefore effectively decreasing ventricular preload. In the latter half of pregnancy, a progressive increase in the maternal heart rate by 15 to 20 beats/min is primarily responsible for maintaining the elevated cardiac output. The additional increase in cardiac output before labor and delivery is caused by a further increase in heart rate. Resting cardiac output either is maintained or decreases slightly as term approaches.⁴

Influence of Body Position

Venous return is further compromised with changes in body position, particularly if the pregnant patient is supine. As a result, cardiac output can be diminished by as much as 25% to 30%. The effects of changes in body position are most obvious in the latter half of pregnancy when the fetal size and gravid uterus can effectively tamponade the vena cava, the abdominal aorta, and the iliac arteries. This phenomenon is exaggerated in women with poorly developed venous collaterals. With compression of the vena cava in the supine position, these women exhibit signs of severe hypoperfusion (hypotension and bradycardia), a phenomenon described as the *supine hypotensive syndrome of pregnancy*. Symptoms quickly resolve after the patient is repositioned to the left lateral recumbent position.⁵ Cardiac output can decrease by 30% to 40% in patients with this syndrome. This vasovagal phenomenon underscores the influence of maternal body position on the hemodynamic alterations occurring in pregnancy.

Hemodynamic changes associated with decreases in preload and cardiac output are less pronounced when the gravid uterus is minimally compressing the vena cava, which is optimally achieved by maintaining the pregnant woman, at greater than 20 weeks' gestation, in the left lateral position when recumbent. Alternatives to this position, less optimal than the left lateral position but preferable to the supine position, are a left lateral tilt to 15 degrees or manual displacement of the gravid uterus. The latter maneuver of left uterine displacement can be performed by manually moving the uterus away from the midline to the left side when the patient is supine. This maneuver is particularly useful when performing cardiac compressions in a pregnant patient. In the supine position, the gravid uterus, which accounts for as much as 10% of the cardiac output, hinders successful resuscitation because of its adverse effects on intrathoracic pressure and venous return. Although hemodynamics are best in the left lateral position, it is difficult to achieve optimal chest compressions with the patient in the left lateral decubitus position. Acceptable alternatives are to perform cardiac compressions with the patient supine but with concurrent manual displacement of the uterus to the other side; it is also satisfactory to place a firm wedge under the right hip of the patient.^{6,7}

Oxygen Consumption and Ventricular Performance

As cardiac output progressively increases, maternal oxygen consumption also increases. However, the increase in cardiac output is seen earlier than the rise in maternal oxygen consumption. Accordingly, the arteriovenous oxygen difference actually narrows early in pregnancy.

TABLE 142-1 Normal Hemodynamic Changes During Pregnancy

| PHYSIOLOGIC PARAMETER | TERM PREGNANCY | LABOR AND DELIVERY | POSTPARTUM |
|------------------------------|---|---|------------------------------------|
| Cardiac output | Increases 30%-50% | Increases 50% | Increases 60%-80% within 15-20 min |
| Blood volume | Increases 30%-50% | Additional 300-500 mL with each contraction | Decreases to baseline |
| Heart rate | Increases by 15-20 beats/min | Increase depends on stress and pain relief | Decreases to baseline |
| Blood pressure | Decreases by 5-10 mm Hg in midpregnancy | Increase depends on stress and pain relief | Decreases to baseline |
| Systemic vascular resistance | Decreases | Increases | Decreases to baseline |
| Oxygen consumption | Increases by 20% | Increases with stress of labor and delivery | Decreases to baseline |
| Red blood cell mass | Increases by 15-20% | — | — |

The arteriovenous oxygen difference widens at the end of gestation. By term, there is a 20% increase in maternal oxygen consumption, mostly as a result of the increase in metabolic needs of the fetus. The increase in oxygen consumption is also a result of maternal increased work of ventilation during pregnancy, maternal increase in myocardial oxygen demand, and maternal increase in renal oxygen consumption. Oxygen extraction also gradually increases throughout gestation. The increase in cardiac output is probably the result of a combination of factors including increased uterine blood flow, increased maternal circulating blood volume (and hence ventricular preload), and possibly estrogen- and prolactin-induced augmentation of myocardial contractility. Ventricular dynamics are improved during pregnancy as a direct result of the action of steroid hormones on the pregnant myocardium. In animal models, estrogens have been shown to increase cardiac output and decrease peripheral vascular resistance.⁸ Echocardiographic studies performed in healthy pregnant women have demonstrated a decrease in the prejection period of left ventricular systole but an increase in the left ventricular end-diastolic dimension.⁹⁻¹¹ It may be that a combination of improved myocardial contractility and increased ventricular diastolic area may be responsible for increases in cardiac output during normal pregnancy.¹²

Hemodynamic Changes During Labor and Delivery

Although cardiac output remains relatively constant in the latter half of pregnancy, there is a significant increase during active labor and immediately after delivery. With each uterine contraction, cardiac output dramatically increases as an additional 300 to 500 mL of maternal blood volume from the uterus is returned to the heart. Cardiac output can rise to 50% greater than normal when the pregnant woman is pushing in the second stage of labor. The amount of blood returned to the heart is accentuated in the supine position. When the pregnant patient is supine, uterine contractions can cause a 25% increase in

cardiac output, a 15% decrease in maternal heart rate, and a 30% to 35% increase in stroke volume. In the lateral recumbent position, the hemodynamic changes associated with uterine contractions are less pronounced; cardiac output and stroke volume may rise by only 6% to 7%, and there may be only a small change in maternal heart rate. Cardiac output may be preferentially diverted to the heart if there is partial obstruction of the abdominal aorta by the uterus during contraction.

The hemodynamic changes seen during labor and delivery are influenced by anesthetic and analgesic techniques. The increase in cardiac output is less if caudal anesthesia is used.^{13,14} Within the immediate 20 to 30 minutes after delivery of the fetus and placenta, there is an even greater increase in cardiac output, because blood is no longer diverted to the uteroplacental vascular bed. Approximately 500 mL is redirected to the maternal circulation in the so-called autotransfusion effect of pregnancy. This effect can increase cardiac output by 60% to 80% after aortocaval compression is removed and blood volume is increased. Many of the physiologic changes of pregnancy resolve and revert to normal within several days after delivery. Cardiac output returns to normal within 2 weeks to 3 months after delivery as sodium and water balances normalize.

Blood Volume Changes

The changes in maternal blood volume during pregnancy are significant. Plasma volume increases by 30% to 50% by the end of gestation. This value is increased in the multigravida patient compared with primigravidas, but the exact mechanism responsible for this effect is unclear. The increase in blood volume can be as high as 70% with twin pregnancies. An increase of 10% to 15% in blood volume is seen as early as the sixth week of gestation. Blood volume is maximal at 30 to 34 weeks, after which the value plateaus until term.¹⁵ Others have suggested that blood volume continues to increase until term.¹⁶ Ventricular filling pressures do not increase despite the large increases in plasma volume.¹⁷ This is most likely the result of vasodilatation with concurrent decreases in systemic and pulmonary vascular resistance as well as a normal heart adapting to chronic volume overload.

The increase in blood volume is a striking adaptive mechanism that permits additional blood flow to the uterus and other maternal organs, in particular the kidneys. Uterine blood flow increases to 100 mL/min by the end of the first trimester and reaches 1200 mL/min at term. Both sodium and water retention contribute to the increase in plasma volume. Total body water increases by approximately 6.5 to 8 L. Most of this increase is seen in the extracellular space and is preferentially distributed in the lower extremities. The total increase in body water includes approximately 3.5 L of amniotic fluid, placental fluid, and water in the fetus. The relative hypervolemia leads to a mild reduction in the serum sodium concentration (135-138 mEq/L) and in serum osmolality (approximately 280 mOsm/L). The maternal blood volume increases by 1 to 2 L. Red blood cell (RBC) mass accounts for only 300 to 400 mL of the increase in total blood volume.

Plasma renin and aldosterone levels are elevated during pregnancy despite expansion of the maternal blood volume. Activation of the renin-angiotensin-aldosterone system may result from the concomitant decrease in peripheral vascular resistance and the increase in vascular capacitance seen as early as the first 6 weeks of pregnancy.³ Both estrogens and progesterone increase aldosterone levels, increasing sodium and water retention.¹⁸ At 12 weeks of gestation, atrial natriuretic peptide levels also increase, most likely in response to the increase in plasma volume.

The increase in blood volume is an adaptive mechanism that provides some level of protection for the inevitable blood loss that accompanies delivery of the fetus and placenta.^{19,20} Average blood loss during vaginal delivery is 500 mL; average blood loss during cesarean delivery is approximately 1000 mL. Although providing some degree of protection from peripartum blood loss, the increased plasma volume associated with pregnancy also can lull the clinician into a false sense of security. A pregnant woman can lose up to 35% of her blood volume

before the usual signs of hypovolemia and acute hemorrhage are obvious. Although the pregnant woman may appear to have stable vital signs up to this point, the fetus may be severely compromised and deprived of adequate maternal blood flow. Tachycardia, hypotension, and other signs of hemodynamic instability are late manifestations of a significant deficit in maternal blood volume.

Physiologic Anemia of Pregnancy

Accompanying the increase in blood volume is an increase in RBC mass stimulated by increased circulating levels of erythropoietin. The RBC mass increases during the second trimester and continues to increase progressively throughout the pregnancy. However, the increase of 15% to 20% in RBC mass is disproportionate to the 30% to 50% increase in blood volume. As a result, the hematocrit decreases, resulting in the “physiologic hemodilutional anemia” of pregnancy. Hemodilution is most notable during the 30th to 34th gestational weeks. The hemoglobin concentration can decrease by as much as 9%. In the second trimester, the hemoglobin level can decrease to 11 to 12 g/100 mL, compared with the normal nonpregnant value of 13 to 14 g/100 mL. The decrease in blood viscosity associated with the anemia of pregnancy allows for a decrease in resistance to blood flow that improves placental perfusion. The hematocrit decreases until the end of the second trimester but increases later in the pregnancy, when the increase in RBC mass is proportionate to the increase in plasma volume. The hematocrit stabilizes at that point or even increases slightly as term approaches.

The degree of change in RBC mass during pregnancy depends in part on whether iron is supplemented. With the increase in RBC mass, there is a need for additional iron to prevent the development of iron-deficiency anemia. Maternal requirements for iron can increase to 5 to 6 mg/d. The fetus uses iron from maternal stores to prevent fetal anemia, but the presence of significant maternal iron-deficiency anemia has been shown to result in a higher incidence of fetal complications, including preterm labor and late spontaneous abortions.²¹

Renal Blood Flow During Pregnancy

Under the influence of circulating hormones, there is a preferential redistribution of blood flow to the uterus, breast, and kidneys during pregnancy. Each kidney increases in length and weight, and the renal pelvis and ureters dilate, leading to urinary stasis that predisposes pregnant women to frequent urinary tract infections.²² The glomerular filtration rate (GFR) increases by 50%, and renal blood flow increases by 60% to 80% above prepregnancy levels.²³ Changes in GFR and renal blood flow occur by the sixth week of gestation. The increase in renal blood flow plateaus early in pregnancy and remains unchanged or decreases slightly as term is approached. Urine flow and sodium excretion are increased and are influenced by position, especially in late pregnancy. Flow rates and the sodium excretion rate are significantly higher in the lateral recumbent position compared with the supine position. Concentrations of serum creatinine and blood urea nitrogen are reduced proportionately to the increase in GFR. Glycosuria may also occur during pregnancy as a result of the increase in GFR and impaired tubular reabsorption of glucose.

Changes in Blood Pressure and Vascular System

Systolic and diastolic blood pressures usually decrease by 5 to 10 mm Hg below the patient's baseline blood pressures in the second trimester and may normalize to nonpregnant values by term.²⁴ Arterial blood pressure decreases as early as the sixth week of pregnancy; the lowest diastolic pressures are recorded during the second trimester. By the eighth week of gestation, diastolic blood pressure decreases by approximately 10%. Diastolic pressure reaches a nadir at 16 to 24 weeks and is typically 5 to 10 mm Hg less than normal. After the 16th to 24th gestational weeks, blood pressure progressively increases and is back

to baseline by term. With the increase in venous return associated with uterine contractions and the additional factors of pain, anxiety, and stress during labor and delivery, an increase in blood pressure usually occurs during this time. Although earlier studies showed that blood pressure decreases during pregnancy, recent studies have demonstrated progressive increases in blood pressure during pregnancy, particularly in obese and overweight women.^{25,26} The decrease in blood pressure during pregnancy is associated with a significant decrease in peripheral vascular resistance. Decreased systemic vascular resistance begins as early as the 5th week of gestation and plateaus between the 20th and 32nd weeks, after which it slowly increases to prepregnancy values by term.²⁷ The decrease in arteriolar tone is influenced by several factors, including hormonal changes that induce vasodilatation and lack of responsiveness to the pressor effect of angiotensin II.²⁸ There is evidence for blood vessel remodeling in pregnancy, leading to increased venous compliance.^{29,30} During pregnancy, circulating levels of numerous endogenous procoagulant and anticoagulant proteins change, leading to a hypercoagulable state. As a consequence, the risk of venous thrombosis increases during pregnancy. The reported incidence is 0.7 cases per 1000 women, and this rate increases threefold to fourfold in the postpartum period.³¹

The treatment of choice for severe hypotension resulting from acute hemorrhage, sepsis, or other critical illness during pregnancy is aggressive fluid resuscitation. When hypotension is refractory and unresponsive to fluids, vasopressors should be used to prevent detrimental consequences of the hypotension to both the mother and fetus as a result of inadequate uterine blood flow. Most vasopressors increase maternal blood pressure at the expense of fetal blood flow, inducing vasoconstriction of the uterine vessels. There are few human studies of these agents in pregnant women. However, animal studies have indicated that epinephrine and dopamine increase uterine blood flow to the uteroplacental circulation while at the same time increasing maternal blood pressure.³²

Structural Remodeling of the Heart

The heart is dramatically remodeled during the first few weeks of pregnancy. There is enlargement of all four chambers. The valvular annular diameters increase, as do the thickness and volume of the left ventricular wall. End-diastolic volume increases, although end-diastolic pressure remains unchanged.^{11,30} Chamber enlargement, particularly of the left atrium, may be a predisposing factor for supraventricular and atrial arrhythmias. Nonspecific ST-T wave changes may also be found in asymptomatic pregnant woman.

As the uterus enlarges and the diaphragm elevates, the heart is rotated upward and to the left. The apical impulse on physical examination is heard best over the fourth intercostal space, lateral to the midclavicular line. Left axis deviation is seen on the electrocardiogram as a result of the rotation of the heart. Because of the displacement of the heart, pregnant women may appear to have cardiomegaly on the chest radiograph. In addition, lung markings may be more prominent, suggesting vascular congestion. These changes can be similar to those seen in patients with heart disease. Even in women with no underlying cardiac pathology, the normal physiologic changes of pregnancy can result in signs and symptoms that are difficult to differentiate from those associated with cardiac disease. Symptoms such as fatigue, decreased exercise tolerance, peripheral edema, palpitations, chest pain, dyspnea, and orthopnea are common complaints as pregnancy advances.

New murmurs often appear during pregnancy. Systolic flow murmurs and a third heart sound are common but are soft. Mild pulmonic and tricuspid regurgitation occurs in more than 90% of healthy pregnant women.^{33,34} One-third of pregnant women have evidence of clinically insignificant mitral regurgitation. Diastolic, pansystolic, and late systolic murmurs are rare in normal pregnancy and may indicate underlying heart disease. As a result of the mild 4-chamber dilatation, clinically insignificant mitral, tricuspid, and mitral regurgitation is seen. Bruits originating from the internal mammary artery

and venous hums with diastolic components are common during pregnancy. These findings can initially confuse the diagnosis of a more serious underlying cardiac illness.

Cardiac Disease and Pregnancy

In women with significant cardiac pathology, the hemodynamic aberrations associated with pregnancy can be life threatening. The incidence of significant cardiac disease in pregnancy is less than 2% but is increasing.^{35,36} Advances in medical therapy and in cardiac surgery including transplantation have allowed female cardiac patients to survive to childbearing age and to have successful term pregnancies.³⁷ For women with severe cardiac problems such as pulmonary hypertension, Eisenmenger's syndrome, severe mitral stenosis, or Marfan's syndrome (in which the risk of aortic dissection is high during pregnancy), the physiologic changes of pregnancy can increase both maternal and fetal morbidity and mortality by transiently or permanently worsening the underlying heart disease.³⁸ Increases in blood volume, stroke volume, cardiac output, and heart rate and the decrease in systemic vascular resistance are poorly tolerated by pregnant women with severe underlying cardiac disease. Maternal mortality is less than 1% for patients with less severe cardiac problems, but it increases to 50% if pregnancy is associated with the presence of underlying primary pulmonary hypertension or cyanotic disorders such as Eisenmenger's syndrome.^{39,40}

Approximately 90% of pregnant women with cardiac disease are rated as New York Heart Association (NYHA) functional class I or class II. These patients tolerate the hemodynamic changes of pregnancy and can be managed well with medical therapy, although the incidence of heart failure and arrhythmias tends to be higher in this group of patients.⁴¹ The 10% of pregnant patients with NYHA functional class III or IV heart disease account for 85% of cardiac deaths.⁴² Fetal morbidity and mortality are increased in these patients, and there is a higher incidence of prematurity, miscarriage, and intrauterine growth retardation.⁴³ Cardiac telemetry, fetal monitoring, and hemodynamic monitoring are usually necessary for these high-risk patients during labor and delivery and, because of the large changes in intravascular volume after delivery, during the first few postpartum days.

ENDOCRINE AND METABOLIC CHANGES IN PREGNANCY

There are numerous endocrine and metabolic alterations during pregnancy, many of which are directly attributable to hormonal signals originating from the fetoplacental unit. Maternal adaptations to hormonal changes that occur during pregnancy directly influence the growth and development of the fetus and placenta. In pregnancy, there is also a change in the normal hormonal feedback mechanisms that control the synthesis and release of hormones. As with cardiac disease, the presentation of endocrine and metabolic disorders may be difficult to differentiate from the normal hypermetabolic state of pregnancy.

Hypothalamic and Pituitary Alterations

As in the nonpregnant state, the hypothalamic-pituitary axis is responsible for regulating many aspects of metabolism. Circulating levels of most of the releasing hormones of the hypothalamus increase during pregnancy because of increased production by the placenta rather than increased production and release by the hypothalamus. The target organ of the hypothalamus, the pituitary gland, undergoes remarkable structural and metabolic changes in pregnancy. Its size increases almost threefold secondary to estrogen stimulation. Gonadotropin and growth hormone production decrease during pregnancy. However, synthesis of ACTH, prolactin, and thyroid-stimulating hormone (TSH) increases.

Free and bound cortisol levels are increased in pregnancy, even though circulating ACTH concentrations are elevated. These changes suggest that the normal negative feedback loop between ACTH and

cortisol concentrations is altered in the pregnant state.⁴⁴ Free plasma cortisol concentrations may be two to three times higher than normal at term. Diurnal variation of cortisol is blunted but maintained throughout pregnancy. The clinical signs of weakness, peripheral edema, glucose intolerance, and weight gain associated with Cushing's disease are sometimes difficult to differentiate from the clinical features of normal gestation. The symptoms of Cushing's disease are exacerbated by pregnancy but often resolve after delivery. Improved outcomes are seen with surgical therapy in partum, if pituitary or adrenal tumors are discovered during the course of the pregnancy.^{38,45} In normal pregnancy, cortisol release may not be suppressed with a low intravenous dose (1 mg) of dexamethasone. An 8-mg dose of dexamethasone is usually needed to suppress cortisol secretion if a tumor is present. In patients with occult adrenal insufficiency, a life-threatening adrenal crisis may be precipitated by the stress of labor and delivery. During pregnancy, the signs and symptoms may be vague and nonspecific, but with the stress of labor, these symptoms are exaggerated. The clinical diagnosis is made in conjunction with laboratory evidence of a low cortisol level or even a low-normal level and no increase in the plasma cortisol concentration with an ACTH stimulation test. Immediate treatment with stress doses of hydrocortisone is indicated in these patients.

In preparation for lactation, circulating prolactin levels progressively increase to about 10 times normal during the course of pregnancy, secondary to stimulation of the anterior pituitary by placental estrogens and progesterone. The dramatic increase in plasma prolactin concentration may lead to an increase in size of preexisting pituitary adenomas larger than 1 cm.⁴⁶ Symptoms resulting from an increase in prolactin secretion usually subside within 6 weeks after delivery if the patient is not breastfeeding.

The thyroid gland increases the production of thyroid hormones during pregnancy. TSH secretion is transiently decreased in the first trimester, but circulating TSH concentrations are usually increased by term. Circulating levels of thyroxine (T_4) and triiodothyronine (T_3) increase as a result of a twofold estrogen-stimulated increase in the synthesis of thyroxine-binding globulin. Levels of free (dialyzable) T_4 and free T_3 are unchanged. In 15% of women, the thyroid gland increases in size and volume. Pregnant women who obtain sufficient dietary iodine (more than 200 μ g daily) have no untoward complications from the changes in thyroid function.^{47,48} Patients with preexisting hypothyroidism should increase their levothyroxine daily dose by 30% early in pregnancy.⁴⁹

Posterior pituitary hormones are altered in pregnancy. Circulating oxytocin levels increase, but the vasopressin concentration remains essentially unchanged. Plasma osmolality decreases by 5 to 10 mOsm/kg, suggesting that the threshold for secretion of vasopressin decreases during gestation. Although vasopressin levels remain unchanged, some women develop transient diabetes insipidus during pregnancy.⁵⁰

Changes in Glucose Metabolism

Early in pregnancy, increased levels of estrogens and progesterone influence glucose metabolism primarily by inducing pancreatic β -cell hyperplasia and increased insulin secretion. Placental hormones control glucose metabolism later in the pregnancy in response to the increased nutritional and metabolic demands of the fetus. Circulating glucose and insulin levels fluctuate widely depending on the nutritional state of the mother. Morning fasting levels of glucose can decrease to less than 55 mg/dL. Fasting blood glucose levels decrease by 10% to 20% because of increased peripheral glucose utilization, decreased hepatic glucose production, and increased consumption of glucose by the fetus.

Pregnant women with diabetes mellitus experience more hypoglycemic episodes in the first trimester, because hepatic gluconeogenesis is decreased during this period. Insulin secretion increases during pregnancy. There is a relative state of insulin resistance, as evidenced by postprandial maternal hyperglycemia.⁵¹ Normally, women adapt to the state of relative insulin resistance during pregnancy. However,

those women with marginal pancreatic reserve or preexisting insulin resistance due to obesity may not produce sufficient insulin, leading to the development of gestational diabetes mellitus. Pregnant women with preexisting diabetes mellitus require as much as 30% more insulin than before pregnancy. There is a close correlation between maternal blood glucose levels and glucose uptake and utilization by the fetus, because glucose crosses the placental barrier. Poor maternal glucose control worsens fetal morbidity. For patients with preexisting insulin-dependent diabetes mellitus, fetal and neonatal mortality rates have

decreased significantly, from 65% to between 2% and 5%, as a result of implementing strict metabolic glucose control with insulin.⁵²

Lipid metabolism is accelerated in pregnancy, and the circulating concentrations of triglycerides and cholesterol increase. Increased production of triglycerides allows for maternal consumption while sparing glucose for use by the fetus.⁵³ Lipolysis is stimulated in adipose tissue, and there is a release of glycerol and fatty acids that decreases maternal glucose utilization, additionally sparing glucose for the fetus.

KEY POINTS

1. Normal pregnancy is associated with numerous physiologic changes that affect almost all maternal organ systems.
2. Hemodynamic, metabolic, hormonal, and structural changes that occur during pregnancy are adaptive mechanisms for maintaining a healthy homeostasis between the mother and the fetus.
3. Maternal hemodynamic alterations and poor fetal outcome can occur if the physiologic adaptive mechanisms are insufficient to maintain the normal homeostasis between the mother and the fetus.
4. The physiologic changes occur at different stages throughout the pregnancy.
5. The normal physiologic changes of pregnancy may alter the presentation of a maternal disease process, confound the diagnosis, or alter the endpoints of treatment.
6. Cardiac output is increased significantly, up to 50% above prepartum values, by the 24th week of gestation. The value then plateaus until term. During labor and delivery, cardiac output is further increased with uterine contractions and the "auto-transfusion" effect of increased preload after delivery of the fetus and placenta.
7. The increase in cardiac output early in pregnancy is primarily caused by an increase in blood volume. Later in pregnancy, an increase in the heart rate by 15 to 20 beats/min is mainly responsible for the increase in cardiac output. Improved myocardial contractility may account in part for an improvement in cardiac output in pregnancy.
8. Maternal body position directly affects cardiac output and stroke volume. In the supine position, the gravid uterus causes aortocaval compression and decreased preload. An extreme manifestation of this effect is the "supine hypotensive syndrome" of pregnancy.
9. After the 20th week of gestation, pregnant women should not be placed supine but rather in the left lateral recumbent position, which maximizes maternal hemodynamics. During cardiac resuscitation, the pregnant patient should be placed in this position, or manually displace the uterus to the left.
10. Left ventricular end-diastolic volume is increased during pregnancy, but filling pressures are relatively unchanged; this may reflect the decrease in afterload caused by a decrease in systemic and pulmonary vascular resistance.
11. Blood volume increases by 30% to 50% by the end of gestation. However, red blood cell mass increases by only 15% to 20%, creating the "physiologic anemia" of pregnancy.
12. A pregnant woman can lose up to 35% of her blood volume before tachycardia and hypotension occur as a result of acute hemorrhage or severe hypovolemia.
13. Blood flow is increased to many organs during pregnancy, especially to the breasts, uterus, and kidneys. Renal blood flow increases by 25% to 50%, and the glomerular filtration rate increases by up to 50%, with a decrease in the plasma creatinine and blood urea nitrogen concentrations.
14. A decrease in the diastolic blood pressure by 10% is seen in the second trimester, secondary to the decrease in systemic vascular resistance. By the end of pregnancy, blood pressure levels should increase to prepartum values.
15. Blood vessel remodeling and changes in the coagulation system during pregnancy, including an increase in most clotting factors, makes the pregnant woman hypercoagulable and more susceptible to venous thromboembolism throughout pregnancy and in the postpartum period.
16. Remodeling of the heart causes enlargement of all four chambers. The pregnant woman may be more susceptible to supra-ventricular and atrial arrhythmias because of left atrial enlargement.
17. Systolic ejection murmurs and a third heart sound can commonly be heard during pregnancy. Diastolic, pansystolic, and late systolic murmurs should prompt the clinician to look for an underlying cardiac problem.
18. Pregnant patients with mild to moderate cardiac disease usually tolerate the hemodynamic changes of pregnancy. Those patients with pulmonary hypertension and right-to-left shunts have mortality rates as high as 50%.
19. There are numerous endocrine and metabolic alterations during pregnancy that primarily affect the hypothalamus, pituitary, and adrenal glands. As with cardiac disease, the presentation of a patient with endocrine and metabolic disorders may be difficult to differentiate from the normal hypermetabolic state of pregnancy.
20. Both corticotropin (ACTH) and cortisol levels are elevated in pregnancy. Cushing's syndrome can be exacerbated by pregnancy. Acute adrenal crisis may be precipitated by the stress of labor and delivery. The treatment is immediate glucocorticoid administration.
21. In preparation for lactation, prolactin levels are increased 10-fold throughout the pregnancy as a result of estrogen and progesterone stimulation. This increase in prolactin may

KEY POINTS—cont'd

- increase the size of pituitary adenomas and precipitate symptoms during the pregnancy.
- 22. Thyroid hormones are increased during pregnancy as a result of increased synthesis of thyroxine-binding globulin. Free levels are unchanged. Despite the complex thyroidal changes that occur during pregnancy, pregnant women have no untoward complications if their daily iodine intake is sufficient.
- 23. Transient diabetes insipidus can develop during pregnancy, secondary to a state of vasopressin resistance.
- 24. Large fluctuations in glucose and insulin levels are seen in pregnancy, depending on the nutritional state of the mother. Fasting glucose levels can decrease by 10% to 20%.
- 25. During pregnancy, there is increased insulin secretion, with a relative state of insulin resistance.
- 26. Obese women with insulin resistance and women with marginal pancreatic reserve can develop gestational diabetes mellitus.
- 27. Fetal and neonatal mortality rates are low if strict metabolic glucose control with insulin therapy is maintained.
- 28. Maternal lipid metabolism is increased during pregnancy, allowing for increased glucose utilization by the fetus.

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Hypertensive disorders associated with pregnancy are the most common medical diagnoses in pregnancy, occurring in approximately 6% to 8% of pregnancies.¹ Guidelines from the Society of Obstetricians and Gynecologists have classified hypertension of pregnancy into two categories: (1) preexisting or (2) gestational with preeclampsia superimposed on either gestational or preexisting chronic hypertension.² The National High Blood Pressure Education Working Group on High Blood Pressure in Pregnancy classified hypertension as (1) chronic hypertension, (2) preeclampsia-eclampsia, (3) preeclampsia superimposed on chronic hypertension, and (4) gestational hypertension, which is transient during pregnancy, or chronic hypertension identified in the latter half of pregnancy.¹ In 2015, the American College of Obstetricians and Gynecologists Committee on Obstetrics defined a hypertensive obstetric emergency as acute-onset, severe hypertension persistent for 15 minutes or longer.⁴

Gestational hypertension, including preeclampsia, occurs de novo after 20 weeks of gestation. Chronic hypertension is defined as blood pressure $>140/90$ mm Hg either preexisting before the pregnancy or manifesting before the 20th week of gestation. Chronic hypertension is present in up to 22% of women of childbearing age and occurs more commonly in women older than 35 years of age. Approximately 1% of pregnancies are complicated by chronic hypertension, 5% to 6% by gestational hypertension, and 1% to 2% of all pregnancies are associated with preeclampsia. Preeclampsia occurs in 20% to 25% of women with preexisting chronic hypertension.

Preeclampsia, which is usually seen after 20 weeks' gestation, is seen more frequently, although not exclusively, in the older parturient. Preeclampsia is most often observed in younger women (<18 years) and in the older parturient (>35 years). Predisposing factors for the development of hypertension and/or preeclampsia during pregnancy include a family history of hypertension or preeclampsia, preexisting diabetes mellitus, black race, obesity (BMI ≥ 30), vascular or renal disorders, primigravid state, preeclampsia with a previous pregnancy, migraine history, and multiple gestational pregnancies.⁵ Smoking during pregnancy may actually decrease the incidence of hypertension and preeclampsia during pregnancy, although this is controversial.⁶ Hypertensive disorders in pregnancy are a significant leading cause of maternal mortality and morbidity, particularly when preeclampsia is superimposed on preexisting chronic hypertension. A pregnancy-related mortality of 7.6% was reported as a result of hypertensive disorders in the United States from 2006 to 2012.⁷ The risk of recurrent preeclampsia during subsequent pregnancies is approximately 18%. Those who develop preeclampsia earlier during pregnancy have been shown to be at risk for cardiovascular disease later in life.⁷ Women with hypertensive pregnancy disorders are at both immediate and long-term risk for cardiovascular complications.⁸

BLOOD PRESSURE MEASUREMENTS IN PREGNANCY

The definition of hypertension during pregnancy has been controversial in the past. *Hypertension* is now most commonly defined as a blood pressure (BP) greater than 140/90 mm Hg. Recently, there has been a consensus that the degree of increase in systolic (SBPs) and diastolic blood pressures (DBPs) may actually be more important than the baseline values. Many authors now agree that significant hypertension

in pregnancy is defined by an increase of at least 30 mm Hg in the SBP and an increase in the DBP of at least 15 mm Hg. Treatment of a DBP greater than 110 mm Hg or an SBP greater than 160 mm Hg is advocated because of the increase in maternal complications with this degree of hypertension.⁹

Sustained (rather than transient) increases in BP are the key risk factors; accordingly, BP should be measured on at least two separate occasions. BP measurements should be made in a standardized fashion (e.g., with the patient sitting in the same position) at each evaluation. Measurements in the upper arm in the recumbent position may yield false-low values because of aortal and caval compression by the gravid uterus. BP is best recorded with the patient in the sitting position or in the inferior arm in the lateral recumbent position. Many automated blood pressure cuffs are accurate during pregnancy but may underestimate blood pressure measurements in preeclamptic women. Manual BP readings are best suited for this group.

PHYSIOLOGIC CHANGES IN PREGNANCY

Essential to the management of hypertension in pregnancy is an understanding of the normal physiologic changes in cardiac output, vasomotor tone, and systemic BP that occur. During pregnancy, cardiac output increases by 30% to 40% in the second trimester, peaking at about the 24th week of gestation. The increase in cardiac output during the first two trimesters of pregnancy is primarily caused by increased maternal blood volume. Cardiac output plateaus for the remainder of the pregnancy until labor. An increase in cardiac output is seen with each uterine contraction. Cardiac output increases again during the immediate postpartum period after delivery of the fetus and the placenta. It is during this period that cardiac output is highest due to the *autotransfusion effect* (see Chapter 154).

Systemic vascular resistance, and consequently BP, decreases during the second trimester. Increased synthesis of vasodilating prostaglandins may play a role in the regulation of BP and uterine blood flow in pregnancy. In a normal pregnancy, vascular resistance is determined by a proper balance of the effects of vasoconstricting and vasodilating factors, including prostaglandins. This balance may be disturbed in hypertensive states, owing to inadequate prostaglandin synthesis. In pregnancy-related hypertensive states, there is a paradoxical increase in the systemic vascular resistance, compared with pregnancy without hypertension. It is noteworthy that all patients with newly acquired or preexisting hypertension in pregnancy have a relative decrease in DBP during the second trimester, reflecting a relative decrease in systemic vascular resistance. Indeed, BP normalizes during the second trimester in some patients with preexisting hypertension.

CAUSES OF HYPERTENSION IN PREGNANCY

There are multiple causes of hypertension during pregnancy (Box 143-1). The most common hypertensive states are gestational hypertension without the presence of proteinuria, essential chronic hypertension, and preeclampsia (i.e., gestational hypertension with significant proteinuria). This classification is clinically useful to the practitioner, but the risk from systemic hypertension is significant for all three conditions, regardless of the specific cause of high BP. Hypertension

BOX 143-1 Causes of Hypertension in Pregnancy

Pregnancy-induced hypertension (gestational hypertension without proteinuria)
 Essential hypertension
 Preeclampsia (gestational hypertension with proteinuria)
 Primary aldosteronism (Conn's syndrome)
 Renal artery stenosis
 Coarctation of the aorta
 Pheochromocytoma
 Cushing's syndrome

during pregnancy is associated with an increased risk of death for both the mother and fetus. Severe maternal hypertension during pregnancy is associated with placental abruption and intrauterine growth retardation.¹⁰

Preeclampsia is defined as primarily diastolic hypertension that occurs transiently during the pregnancy, usually manifesting after the 20th gestational week, and resolves within 1 to 2 months after delivery. Women who develop preeclampsia have a high rate of recurrence of hypertension with subsequent pregnancies and often develop chronic hypertension at a later time.

Essential chronic hypertension (i.e., hypertension that was present before the pregnancy, whether diagnosed or undiagnosed) persists in the postpartum period and accounts for approximately one-third of all cases of hypertension during pregnancy. Essential chronic hypertension may manifest during the first 20 weeks of pregnancy. Women who develop hypertension without proteinuria in the last trimester of pregnancy may have essential hypertension, either unmasked or precipitated by the pregnancy. In these cases of *de novo* presentation of hypertension, care must be exercised to rule out other nonpregnancy-related causes of hypertension, such as renal artery stenosis, polycystic kidneys, glomerular or interstitial renal disease, pheochromocytoma, coarctation of the aorta, primary aldosteronism, Cushing's syndrome, hyperthyroidism, and hyperparathyroidism. Previously undiagnosed essential chronic hypertension is a consideration, particularly in older multiparous women. As the age of parturients has increased, the incidence of essential hypertension in pregnant women has also increased. For some patients, the initial diagnosis of hypertension may be made during a routine prenatal visit with an obstetrician. For some patients, this prenatal visit is their first encounter with a physician as an adult. Essential hypertension should be suspected if there is a family history of hypertension, diabetes, or obesity. If there is a suspicion of preexisting essential hypertension, cardiac echocardiography should be performed to evaluate for left ventricular hypertrophy, which would suggest that hypertension has been a problem for an extended period. If BP extremes are avoided with treatment, there is no significant worsening of maternal and perinatal outcomes for pregnant patients with essential hypertension. Complications related to intrapartum hypertension (e.g., placenta previa, placental abruption, and preeclampsia) are less likely with judicious treatment of elevated BP. Patients with essential hypertension have not been shown to have a higher incidence of preeclampsia, particularly if the BP is well controlled. In general, mortality and morbidity are not increased in patients with uncomplicated mild chronic hypertension. However, morbidity and mortality are both increased in those patients with severe uncontrolled hypertension, and this is further complicated by superimposed preeclampsia.¹¹

■ PATHOLOGY OF PREECLAMPSIA

Preeclampsia is a pregnancy-related multisystem disease process that usually occurs after the 32nd week of gestation. Systemic hypertension and significant proteinuria (i.e., 0.3 g or greater in a 24-hour urine collection) are invariably present. Clinical onset is usually characterized by rapid weight gain associated with generalized edema, followed by onset of hypertension or proteinuria or both. The incidence of

preeclampsia in the United States ranges from 5% to 7%. The highest frequency occurs in young primigravidas, and the second highest incidence is in older multiparous women, a group that has a higher maternal mortality rate than the young primigravidas. The incidence is higher in patients with preexisting hypertension or renal vascular disease, and the symptoms may present earlier than the 32nd gestational week in these patients. Diastolic hypertension is most often seen in association with preeclampsia. It is less common to record SBP values greater than 160 mm Hg. If the SBP is greater than 200 mm Hg, the clinician should consider the possibility of underlying essential hypertension, which may be superimposed on the preeclamptic state. Since preeclampsia is a multisystem disease process, it may imitate or mask other pathologic conditions, and a thorough investigation to rule out other coexisting pathologies should be carried out.¹² Familial prevalence of preeclampsia has been reported.^{13,14} In some cases, preeclampsia manifests 1 to 7 days after delivery.^{15,16} Most commonly, if preeclampsia is present during the postpartum period, it manifests as the HELLP syndrome, a severe variant of the preeclamptic spectrum of diseases.¹⁷ This syndrome always includes some, if not all, of the following features: microangiopathic hemolytic anemia (H), elevated liver enzymes (EL), and low platelets (LP). The syndrome can develop without substantial BP changes or with no significant changes compared with BP readings taken during the pregnancy.

A significant elevation of BP in the second trimester is associated with an increased risk of preeclampsia later in the pregnancy.¹⁸ One-third of pregnant women with mean arterial pressures greater than 90 mm Hg in the second trimester develop preeclampsia later during pregnancy. Only 2% of women with mean arterial pressures less than 90 mm Hg develop preeclampsia. Relatively mild hypertension early in pregnancy, which might be ignored in nonpregnant patients, should not be overlooked or dismissed in the parturient. As many as 25% of all pregnant women have slightly elevated BPs in the last month of pregnancy, but the incidence of preeclampsia is also highest during this period. Accordingly, clinicians must remain vigilant when faced with new-onset hypertension and look for other signs and symptoms that might suggest the presence of the preeclamptic syndrome.

The exact pathogenesis of preeclampsia is still unknown, although it is believed to be related to endothelial cell injury and dysfunction that occurs in most maternal organs as a result of toxic substances released from a poorly perfused placenta. Genetic and immunologic factors also have been implicated in the pathogenesis of preeclampsia.^{19,20} The generalized vasospasm that occurs in preeclampsia is responsible for many of the organ-specific signs and symptoms apparent in this multisystem disease. Widespread vasospasm is associated with increased circulating levels of vasoconstrictors, increased sensitivity to angiotensin II, and decreased levels of vasodilators. An imbalance in circulating angiogenic factors is emerging as a prominent mechanism that mediates endothelial dysfunction and the clinical signs and symptoms of preeclampsia.²¹ There is an imbalance in the ratio of prostacyclin to thromboxane production that contributes to the pathogenesis of preeclampsia, although preeclampsia is not simply a state of prostacyclin deficiency. This idea has prompted studies of low-dose aspirin to prevent development of preeclampsia. Duley et al. reviewed 59 trials involving 37,560 women that examined the use of antiplatelet agents in preeclampsia. Antiplatelet agents, including low-dose aspirin showed moderate benefits when used for the prevention of preeclampsia and its consequences, decreasing preterm births, fetal and neonatal deaths, and small-for-gestational age babies. However, they recommended that further information would be required to assess which women are most likely to benefit, when treatment is best started, and at what dose.²² The maternal organs most affected in preeclampsia are the kidneys, brain, liver, and hematologic system. Despite a lack of understanding of the exact pathogenesis of preeclampsia, significant improvements in the identification of the disease, monitoring, and management of these complex cases has improved perinatal and maternal morbidity and mortality. If vasospasm affects the uteroplacental bed, the incidence of intrauterine growth retardation, stillbirths, and neonatal deaths increases.²³

Peripheral edema is a common symptom and complaint of pregnant women that cannot be ignored, because it may herald the onset of preeclampsia. The majority of women with preeclampsia presents with generalized edema, and significant weight gain is the first symptom. However, since peripheral edema is a ubiquitous symptom during pregnancy, it is no longer considered a hallmark trait of preeclampsia. Preeclampsia is often manifested initially by peripheral edema that is usually accompanied by a gradual increase in BP. Sodium retention is partly responsible for edema formation and hypertension. In normal pregnancy, the glomerular filtration rate increases by as much as 50%. There is a concomitant increase in sodium reabsorption by the renal tubules and a 60% to 80% increase in renal blood flow. Renal blood flow increases because of the increase in cardiac output and a decrease in renal vascular resistance. In preeclampsia, sodium retention is caused by a decrease in the glomerular filtration rate, possibly resulting from a vasospasm of the renal vasculature, commonly seen in preeclampsia. Renin and aldosterone secretion decrease in patients with preeclampsia, probably as a result of extracellular volume expansion and associated edema. The exact cause of the decreased activity of these factors is unknown, but it may be related to decreased renal prostaglandin synthesis, increased systemic BP, or the expansion of extracellular volume. In spite of the decreased levels of renin and aldosterone, sensitivity to angiotensin II is increased, a factor that may play a role in the pathogenesis of hypertension in preeclampsia.²⁴ Vascular maladaptation with increased vasomotor tone, endothelial dysfunction, and increased sensitivity to angiotensin II and norepinephrine in preeclampsia may be explained on the basis of angiotensin II-mediated mechanisms. Although sodium retention occurs in preeclampsia, blood volume actually can be diminished compared with that in normotensive pregnant patients.²⁵ Plasma volume contracts as extracellular fluid is preferentially shifted from the vascular space to the interstitium. However, the decrease in plasma volume does not indicate volume depletion in patients with preeclampsia. In contrast to hypovolemic patients, cardiac output is increased and central venous and pulmonary capillary wedge pressures are normal to high in patients with preeclampsia.²⁶ These data guide the management of preeclampsia, because efforts should be directed to control BP rather than injudicious volume resuscitation.

Hyperuricemia in preeclampsia occurs at least in part because of decreased renal excretion of uric acid. However, the development of hyperuricemia frequently predates increases in serum blood urea nitrogen and creatinine, suggesting that other mechanisms are involved as well. Hyperuricemia has been used as a marker of severity of preeclampsia, and it is a risk factor for fetal mortality.²⁷

CLINICAL PRESENTATION OF PREECLAMPSIA

The severity of illness is defined as mild, moderate, or severe depending on the presenting signs and symptoms and associated comorbidities. Since the nature of the process is a multisystem, preeclampsia may manifest with a wide spectrum of organ-specific abnormalities in addition to the general findings of edema, hypertension, and proteinuria. The pathologic abnormalities associated with preeclampsia are not necessarily secondary to hypertension, and thus, the severity of preeclampsia does not always correlate with the degree of BP elevation.¹⁸ BP elevations are classified as mild, moderate, or severe. Hypertension in preeclampsia may result from increases in systemic vascular resistance and cardiac output.

In mild preeclampsia, SBP is 130 to 140 mm Hg and DBP is 80 to 95 mm Hg. Peripheral edema is minimal, and there is a lack of associated visual or cerebral symptoms. In moderately severe preeclampsia, the SBP may increase to as high as 150 to 160 mm Hg, and the DBP can be as high as 110 mm Hg. An increase in SBP of 25 mm Hg or more and an increase in DBP of 15 mm Hg or more suggests the presence of moderate to severe preeclampsia. Peripheral edema, hyperreflexia, and visual symptoms are present with moderately severe preeclampsia. In severe forms of preeclampsia, the SBP is greater than

160 mm Hg, and the DBP is 110 mm Hg or greater. In severe preeclampsia, there are signs of multiple organ system involvement. Pulmonary, cardiac, renal, and neurologic disturbances may be present. Severe renal involvement in preeclampsia leads to glomeruloendotheliosis, which manifests as marked proteinuria (excretion of greater than 5 g protein daily). Oliguria (urine output less than 500 mL/day) is also common, and the serum creatinine concentration is usually greater than 1.6 mg/dL. Acute renal failure is relatively rare, although clinical evidence of renal involvement in preeclampsia significantly increases perinatal mortality.²⁸ Hepatic involvement is manifested by epigastric or right upper quadrant pain with elevated circulating levels of bilirubin and transaminases. Severe preeclampsia itself is the most common cause of hepatic tenderness and liver dysfunction in pregnancy.²⁹ Severe hepatic pathology can result in subcapsular hematomas and lacerations that may require surgical intervention. Neurologic changes may include persistent headaches, visual disturbances, focal neurologic deficits, and severe hyperreflexia with or without clonus. Computed tomography of the brain may exhibit cerebral edema, especially in the occipital region.

Severe preeclampsia associated with central nervous system irritability, manifesting as generalized tonic-clonic seizures not caused by other cerebral pathology, is defined as *eclampsia*.³⁰ Eclampsia can occur without significant hypertension or proteinuria. Cardiovascular and respiratory changes can manifest as pulmonary edema, resulting from iatrogenic fluid overload; acute systolic left ventricular failure; or diastolic left ventricular dysfunction secondary to chronic essential hypertension. Pulmonary edema may also result from increased capillary permeability or from a decrease in colloid osmotic pressure that occurs to some extent during normal pregnancy but can be accentuated by preeclampsia.³¹ Hematologic disturbances consist of thrombocytopenia, disseminated intravascular coagulation, and hemolysis.

It is unknown whether preeclampsia leads to persistent chronic hypertension after delivery, although it seems that this is unlikely. Nevertheless, an episode of preeclampsia may identify a subgroup of women with an increased risk of the eventual development of essential hypertension at a later time. In a recent study, women with preeclampsia had an increased risk of death due to cardiovascular disease later in life, independent of other measured risk factors.³² These findings reinforced previously reported recommendations that a history of preeclampsia should be used to target women at risk for cardiovascular disease. Debate continues as to whether the presence of preeclampsia or the duration of the disease process may be responsible for influencing factors that later lead to the development of essential hypertension. Women who develop preeclampsia superimposed on previously undiagnosed essential hypertension or underlying renal disease are predisposed to the later development of essential hypertension.

OTHER CAUSES OF HYPERTENSION IN PREGNANCY

Some of the less common causes of hypertension are listed in [Box 143-1](#).

Primary aldosteronism in pregnant women has been reported but is uncommon. The treatment of hypertension in these patients is directed toward medical management during the pregnancy and postpartum operative intervention if an adenoma is present.

Renal artery stenosis can be associated with preeclampsia. Medical therapy with antihypertensive agents is recommended. Although ideal therapy for these patients would include angiotensin-converting enzyme (ACE) inhibitors, these agents are contraindicated during pregnancy, and other alternatives must be employed.³³

Coarctation of the aorta is a rare cause of hypertension. It may be previously undiagnosed and then initially diagnosed during a patient's first pregnancy. It can be associated with preeclampsia. The greatest risk to these patients is aortic rupture due to cystic medial necrosis of the aortic wall. This risk is amplified because the normal physiologic changes of pregnancy place further stress on the abnormal aorta. Increases in BP, cardiac output, and the strain of labor with

contractions can increase this risk. Aggressive medical management with antihypertensive medications, including β -adrenergic blockers, improves the outcome of these high-risk patients.

Pheochromocytoma is a rare cause of hypertension, but patients have a poor outcome if the tumor is not diagnosed and treated. These patients can present with nausea, vomiting, profuse diaphoresis, severe headache, generalized weakness, palpitations, and seizures. The immediate causes of sudden death are secondary to pulmonary edema, cerebral hemorrhage, and cardiovascular collapse. Since there is a risk of significant morbidity and mortality to both mother and fetus, it was previously recommended that immediate surgical intervention be carried out during pregnancy. Currently, most experts advocate medical therapy with α - and β -adrenergic blockade during pregnancy and tumor removal after delivery.

■ GENERAL TREATMENT PRINCIPLES

The benefits of a well-balanced low-salt diet and exercise have been shown to decrease the incidence and severity of hypertension. Bennett conducted a retrospective analysis of women who had prior bariatric surgery before becoming pregnant. These patients had lower rates of hypertensive disorders in subsequent pregnancies.³⁴ Previously, some experts were concerned that aggressive management of hypertension in pregnancy might be detrimental, perhaps because hypertension improved the uterine blood flow. These concerns appear to be unfounded, because later studies showed that uterine blood flow either increases or shows no change after hypertension is controlled. Nevertheless, caution must be exercised to ensure that the treatment of hypertension during pregnancy does not induce hypotension, which adversely affects maternal hemodynamics and compromises fetal well-being. There is a significant correlation between maternal BP control and fetal morbidity, and evidence now suggests that antihypertensive treatment for severe hypertension results in an improved perinatal outcome. The development of mild hypertension or preeclampsia at or near term is associated with minimal maternal and neonatal complications. However, the onset of severe gestational hypertension and/or severe preeclampsia early in gestation is associated with significant maternal and perinatal complications.³⁵ General recommendations for management and monitoring of hypertension in pregnant patients include the stabilization and treatment of acute changes in BP. Specific goal-directed therapy is indicated for various organ system abnormalities that may be present, particularly in those patients with moderate to severe preeclampsia. If proteinuria is not present and there is no suspicion of preeclampsia, conservative management on an outpatient basis is usually adequate. Immediate hospitalization with bed rest is recommended for patients presenting with proteinuria if there is a high index of suspicion for the diagnosis of preeclampsia.

■ ANTIHYPERTENSIVE DRUG THERAPY

There is now an extensive pharmaceutical armamentarium available for the treatment of hypertension in pregnancy. In 1979, the U.S. Food and Drug Administration (FDA) established categories for all drugs with potential and actual adverse effects on the fetus.³⁶ Although helpful to the clinician, these categories most often do not reflect current scientific knowledge regarding specific teratogenic effects of the drugs.³⁷

The FDA categories are listed in Table 143-1. Most antihypertensive drugs used during pregnancy are classified as category C. Thiazide diuretics, prazosin, and α -methyl dopa are designated as category A, and metoprolol is a category B agent. Since most antihypertensive drugs are used later in pregnancy, the potential teratogenic effects of these drugs are not usually a major concern. However, if treatment is initiated for patients with preexisting essential hypertension or early-onset gestational hypertension, teratogenic effects must be considered when choosing antihypertensive drugs. It may be necessary to change the antihypertensive therapy early in pregnancy, if the patient is taking drugs that could increase the risk of fetal abnormalities.

TABLE 143-1

FDA Categories of Fetal Drug Toxicities

| CATEGORY | DESCRIPTION |
|----------|--|
| A | Controlled studies in pregnant women have not demonstrated any risk to the fetus in the first trimester. These drugs are considered to be relatively safe for use during pregnancy. |
| B | No known specific risks are associated with use of the drug in pregnancy, but controlled human studies are lacking. If adverse effects were shown in animal reproduction studies, these were not confirmed in controlled human trials. |
| C | Studies in women and animals are not available, or studies in animals have revealed adverse effects on the fetus. Most new drugs fall into this category. These drugs should be given only if the potential benefit justifies the potential risk to the fetus. |
| D | These drugs have shown a definite fetal risk in controlled human trials. However, their use may be necessary during pregnancy, and a risk-benefit assessment needs to be considered for the use of these agents. |
| X | These drugs have shown a definite risk to the fetus, and their use is contraindicated because the potential risks to the fetus outweigh the potential benefits. |

FDA, U.S. Food and Drug Administration.

The goal of hypertensive therapy in pregnancy is the prevention of maternal complications such as intracerebral hemorrhage, stroke, and decompensated heart failure. There are no convincing data to determine the optimal BP goal with drug therapy. There is also disagreement concerning the proper normal values for BP during pregnancy, but most agree that acute treatment is mandated if (1) the SBP is greater than 160 mm Hg or the DBP is 105 mm Hg or greater or (2) if the SBP is more than 30 mm Hg greater than the baseline value or the DBP is more than 15 mm Hg greater than the baseline. For women with preexisting chronic hypertension, a blood pressure of more than 160/100 should be targeted. If acute and urgent drug therapy management is required, some patients may need to be hospitalized, depending on their compliance with drug therapy and the urgency of lowering the BP based on concomitant organ system involvement. For patients presenting with SBP 140 mm Hg or higher and DBP 90 mm Hg or higher, urgent drug therapy should be implemented if there is concurrent evidence of symptoms, underlying essential hypertension, or end-organ involvement. If the patient presents after the 24th gestational week and fetal viability is ascertained, both cardiac and fetal telemetry may be required. For patients presenting with SBP less than 140 mm Hg and DBP less than 90 mm Hg and no evidence of significant proteinuria, management and treatment can be provided on an outpatient basis, with frequent office visits and close maternal and fetal assessments. If the hypertension is refractory to standard therapy, hypertension worsens despite adequate drug therapy, or the suspicion of preeclampsia arises, then immediate hospitalization is recommended.

Conservative drug therapy is advocated for moderately severe preeclampsia, but the treatment of choice for severe preeclampsia and associated end-organ involvement is the immediate delivery of the fetus. Delay in delivery for patients with severe preeclampsia and end-organ involvement can result in serious maternal and fetal complications. If the fetus is of mature gestational age, factors influencing the decision to deliver are dependent on the progression of the disease process, assessment of fetal lung maturity, and the status of the cervix. The conservative management of preeclamptic patients at a gestational age less than 24 weeks is associated with serious maternal complications, and termination of the pregnancy should be considered. For patients at 28 to 32 weeks of gestation, conservative management with

vigilant monitoring and assessment should be performed in a hospital setting. There is a lack of evidence from the limited trials performed to recommend either early delivery or expectant care for women with severe preeclampsia before 34 weeks of pregnancy.³⁸

Updated guidelines from 2015 from the American College of Obstetricians and Gynecologists Committee on Obstetric Practice⁴ recommend that:

- In addition to parenteral hydralazine and labetalol, oral nifedipine and/or oral labetalol (200 mg) may be considered as a first-line therapy, particularly if there is no IV access.
- Parenteral labetalol should be avoided in women with asthma, heart disease, or congestive heart failure.
- Magnesium sulfate is not recommended as an antihypertensive agent but is the drug of choice for seizure prophylaxis in severe preeclampsia and for controlling seizures in eclampsia.
- Although sodium nitroprusside can be used for treatment in emergent situations, there is a risk of cyanide and thiocyanate toxicity in the mother and fetus and increased intracranial pressure with potential worsening of cerebral edema in the mother.

During pregnancy, the clinician must decide when to use antihypertensive medications and what level of BP to target. The choice of antihypertensive agents is more limited in pregnancy, since not all available antihypertensive drugs have been adequately evaluated in pregnant women, and some agents are contraindicated.³⁹ A first-line drug still used today in pregnant patients, although less commonly in the general populace, is oral α -methyl dopa, a central α_2 -adrenergic agonist. Historically this has been a first-line drug of choice for many obstetricians in the past, and there has been little evidence to convince them otherwise. The starting dose is 250 mg orally 2 to 3 times a day for the first 48 hours of treatment. Dosing can be increased every 2 days until the desired BP level is achieved. The maximum daily dose is 4 g. β -Adrenergic blocker therapy with oral labetalol, a combined α - and β -adrenergic antagonist, has become popular as a single-agent antihypertensive. The recommended initial dose is 100 mg orally twice daily. The dose can be increased as indicated, either semiweekly or weekly, and the maintenance dose is usually 200 to 400 mg administered twice daily. The benefits of the β -adrenergic blockade make this an attractive drug for parturients with underlying chronic essential hypertension and possible cardiac and vascular involvement. Diuretics also may be used, although care must be exercised to prevent excessive fluid loss, which can exacerbate the decrease in blood volume associated with preeclampsia. As mentioned previously, ACE inhibitors and angiotensin II receptor antagonists should be avoided intrapartum because these agents can increase perinatal morbidity and mortality.

For acute and emergent drug therapy for severe hypertension, intravenous (IV) antihypertensive drugs should be used; IV infusions are particularly attractive because they provide rapid control of BP and can be titrated easily. Intravenous hydralazine, a direct arteriolar vasodilator, remains the standard for many obstetricians, although other drugs may be preferable since hydralazine may decrease BP precipitously.⁴⁰ Excessive lowering of BP is a particular problem when hydralazine is administered to preeclamptic patients with contracted blood volume. If hydralazine is used, it should be given as 5- to 10-mg IV boluses every 15 to 30 minutes until BP is controlled. Onset of the hypotensive effect is 10 to 20 minutes, and duration of action is about 8 hours. Infusions of hydralazine are difficult to titrate and may be associated with increased incidence of fetal distress.

Intravenous labetalol, a nonselective β - and α -adrenergic receptor blocker, is also commonly used for the acute management of hypertension. Labetalol rapidly decreases the BP but not at the expense of uteroplacental blood flow. Labetalol crosses the placenta but rarely causes significant neonatal bradycardia. An initial IV bolus of 10 or 20 mg should be given, followed by boluses of 40 to 80 mg at 10- to 15-minute intervals as needed to control hypertension. Labetalol also can be given by continuous IV infusion; the usual dose is 1 to 4 mg/min. Contraindications to the use of labetalol are the same as those for other β -adrenergic antagonists, notably heart block and acute asthma.

TABLE 143-2

Antihypertensive Drugs Commonly Used in Pregnancy

| TYPE | AGENTS |
|----------------------|-----------------------|
| Oral | α -Methyl dopa |
| Labetalol | |
| Clonidine | |
| Diuretics | |
| Parenteral | Labetalol |
| Hydralazine | |
| Sodium nitroprusside | |
| Nitroglycerin | |

Sodium nitroprusside is a potent arterial and venous vasodilator that quickly decreases the BP. Rapid titration with a continuous IV infusion can be instituted starting at a dose of 0.25 to 0.5 μ g/kg/min and adjusted every few minutes and titrated to effect. Invasive arterial monitoring is often recommended in conjunction with its use. As with all potent vasodilators, care must be taken when using sodium nitroprusside, because patients with volume depletion may be particularly sensitive to its effects. Despite a paucity of data, concern regarding the risks of fetal cyanide toxicity prompts some practitioners to avoid using this drug in pregnant patients. Careful attention to dosing and duration of use should minimize the risk of toxicity.

Other less frequently used agents include IV nitroglycerin, oral clonidine, and β -adrenergic blockers other than labetalol. Intravenous nitroglycerin is easily titrated and is especially attractive for the management of patients with pulmonary edema. However, its antihypertensive potency is somewhat limited. Oral clonidine, a centrally acting α_2 -adrenergic agonist, is an effective antihypertensive drug, but concerns about the risk of rebound hypertension after cessation limit its use.

There remains considerable debate concerning the use of β -adrenergic blockers in pregnancy because of the potential risks of fetal bradycardia and a decrease in perfusion to the uteroplacental bed. Beta-blockers have been used during pregnancy without evidence of teratogenic effects. Although there is limited experience, they are considered as indicated in pregnant women with hypertension, mitral stenosis with pulmonary hypertension, coarctation of the aorta, ischemic heart disease, supraventricular and ventricular arrhythmias, and can be continued during delivery.^{1,41,42} Esmolol has been used widely for heart rate control in pregnancy, but its efficacy is limited as an antihypertensive agent.

Antihypertensive drugs commonly used during pregnancy are listed in Table 143-2.

MANAGEMENT OF HYPERTENSION DURING LABOR AND DELIVERY

Management of hypertension during labor and delivery is directed toward avoiding acute and maternal complications. Antihypertensive drug therapy with a judicious use of IV fluids is of paramount importance to avoid unnecessary complications. Postpartum monitoring is advocated for high-risk, chronically hypertensive patients. Hypertension associated with preeclampsia usually resolves spontaneously within a few weeks after delivery. These patients are at risk for the development of acute complications, such as hypertensive encephalopathy, pulmonary edema, and acute renal failure. The choice of antihypertensive medications or the doses used may have to be adjusted after delivery, and minute amounts of all antihypertensive agents are found in breast milk. Although limited data are available, adverse perinatal effects have not been observed with the more commonly used drugs, such as α -methyl dopa, hydralazine, and the various α -adrenergic blockers.

KEY POINTS

1. Hypertensive disorders associated with pregnancy are not uncommon and can either predate the pregnancy or be precipitated or unmasked by the pregnancy.
2. Women with a prenatal history of diabetes mellitus, renal disease, vascular disease, or a family history of hypertension are predisposed to developing hypertension during pregnancy.
3. Treatment is recommended if the systolic blood pressures (SBPs) are 160 mm Hg or higher, or the diastolic blood pressures (DBPs) are 110 mm Hg or higher, or with lower BPs if the patient is symptomatic.
4. BP measurements should be consistently taken in either the sitting position or in the inferior arm in the lateral recumbent position with each evaluation.
5. Cardiac output and blood volume are dramatically increased during pregnancy, and there is a decrease in systemic vascular resistance, particularly during the second trimester. DBP is lowest during the second trimester.
6. Elevated BPs caused by essential hypertension may transiently improve during the second trimester of pregnancy.
7. Consistently elevated SBPs greater than 200 mm Hg should prompt the practitioner to consider undiagnosed chronic hypertension or some of the less common causes of hypertension such as primary aldosteronism, renal artery stenosis, or pheochromocytoma.
8. Preeclampsia most often appears after the 32nd week of gestation and resolves with the delivery of the fetus.
9. Preeclampsia can be superimposed on chronic hypertension.
10. Preeclampsia may initially present after delivery as the HELLP syndrome (*hemolysis, elevated liver enzymes, and low platelets*).
11. Hypertension with BP elevation of 140/90 mm Hg or higher and proteinuria are the principal characteristics of preeclampsia. Edema is no longer a criterion for preeclampsia.
12. Preeclampsia is a multisystem disease. Severe preeclampsia manifests with signs and symptoms of end-organ involvement.
13. The antihypertensive drugs most frequently used in pregnancy have not been associated with significant fetal abnormalities.
14. First-line antihypertensive drugs for moderate hypertension are oral α -methyldopa and oral labetalol.
15. Parenteral antihypertensive agents are used for more severe elevations of BP. The agents most commonly employed are labetalol, hydralazine, and sodium nitroprusside.
16. Caution should be exercised with the administration of hydralazine, particularly in patients with decreased plasma volume.
17. Most forms of gestational hypertension resolve in the postpartum period.

ANNOTATED REFERENCES

AACE Hypertension Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of hypertension. *Endocr Pract* 2006;12:193.

In 2006, the American Association of Clinical Endocrinologists (AACE) proposed guidelines for the diagnosis and treatment of hypertension, focusing on identifying and managing hypertension relating to or coinciding with endocrinopathies. These guidelines are based on positive data from randomized clinical trials. They recommended diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) for treating hypertension in patients, particularly those with diabetes mellitus.

Magee L, Cham C, Waterman EJ, et al. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. *BMJ* 2003;327:955.

A meta-analysis was performed to review the outcomes in randomized controlled trials published between 1966 and 2002 that compared hydralazine with other antihypertensive agents for severe hypertension in pregnancy. In 13 trials comparing hydralazine with either nifedipine or labetalol, hydralazine was an effective antihypertensive drug for severe hypertension but was associated with an increased incidence of maternal hypotension, cesarean section, placental abruption, oliguria, adverse effects on fetal heart rate, and lower Apgar scores.

Magee LA, Helewa M, Moutquin J-M, et al. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *J Obstet Gynaecol Can* 2008;30:S1.

These guidelines from the Society of Obstetricians and Gynecologists are a comprehensive review of the different manifestations of hypertension during pregnancy. The guidelines focus on the classification, pathophysiologic features, and management of the hypertensive disorders of pregnancy. The authors classified hypertension of pregnancy into two categories, preexisting or gestational with preeclampsia superimposed on either gestational or preexisting chronic hypertension. Through a combination of evidence-based medicine and consensus, this report updates contemporary approaches to hypertension control during pregnancy.

Seely EW, Maxwell C. Chronic hypertension in pregnancy. *Circulation* 2007;115:e188–e190.

This review describes chronic hypertension during pregnancy. It further describes the complications of chronic hypertension during pregnancy and how chronic hypertension affects both maternal and fetal outcomes.

Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet* 2005;359:785.

This is a comprehensive review of preeclampsia with information on epidemiology, pathogenesis, and different treatment modalities. Maternal and perinatal outcomes are also discussed. The authors reviewed findings on the diagnosis and risk factors of preeclampsia and the present status of its prediction, prevention, and management.

References for this chapter can be found at expertconsult.com.

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During pregnancy, the respiratory system undergoes a number of changes and is subject to functional and anatomic stresses. The critical care provider must remember these changes to appropriately care for the maternal-fetal unit. Although the need for ventilatory support is rare in pregnancy, respiratory insufficiency is still the most common indication in pregnancy for admission to a critical care unit. In this chapter, the unique physiologic changes that occur during pregnancy are addressed, and guidance is provided to critical care specialists who may encounter pregnancies that are complicated by acute pulmonary complications.

PULMONARY PHYSIOLOGY IN PREGNANCY

A number of physiologic changes affect respiration during pregnancy. Normal pregnancy is associated with a 20% increase in oxygen consumption and a 15% increase in metabolic rate. During the first trimester, minute ventilation is increased, while the respiratory rate remains the same. Although one might assume that the lung volume during pregnancy would decrease owing to a rise in the maternal diaphragm, the tidal volume (V_T) is actually increased by 40% over baseline values. The increase in V_T is thought to be due to the increase in circulating progesterone that affects the respiratory center.¹ Arterial blood gas measurements reflect respiratory alkalosis compensated by metabolic acidosis that results in a relatively normal pH. P_{aCO_2} usually ranges from 28 to 32 mm Hg. Functional residual capacity (FRC), residual volume, and total lung volume are decreased near term. Because of this decrease, respiratory distress occurs more rapidly in the gravid than in the nongravid state. The function of the large airways as measured by forced expiratory volume at 1 second (FEV_1), and peak expiratory flow rate (PEFR) is essentially unchanged throughout pregnancy.²

Colloid osmotic pressure is decreased by 20%. This change in hydrostatic pressure results in a propensity for pregnant patients to develop cardiogenic and noncardiogenic pulmonary edema.

Dyspnea on exertion is common, especially in the third trimester of pregnancy, making the diagnosis of respiratory problems more difficult than that in the nongravid state.

Figure 144-1 illustrates the graphic relationship of pulmonary changes.

ASTHMA

Epidemiology

Asthma is one of the most common pulmonary problems in pregnant women; recent studies have reported that approximately 8% are affected.³ The disease is characterized by hyperactive airways leading to episodic bronchoconstriction. The role of inflammatory mediators in the pathogenesis of asthma has become apparent in recent years, leading to the early use of antiinflammatory medications in the treatment of exacerbations.

The cause of asthma is unknown; however, it has been observed that its prevalence in the general population is increasing.

Effects of Asthma on Pregnancy

Asthma may be triggered by environmental allergens, medications, especially aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), or stress.⁴ Most exacerbations are marked by cough, wheezing, and dyspnea. Rapid therapeutic intervention at the time of an exacerbation is imperative to prevent impaired maternal and fetal oxygenation because uncontrolled asthma can increase maternal morbidity. In several studies, even after controlling for confounding variables, adverse pregnancy outcomes are more pronounced in patients with asthma. These include low birth weight, preeclampsia, preterm birth, and stillbirth.^{5,6}

Although historical data have shown an increase in perinatal death and low birth weight,⁷ Fitzsimmons and colleagues observed low birth weight in only those patients treated for status asthmaticus.⁸ In addition, Schatz and colleagues noted that intrauterine growth restriction was directly related to lung function as measured by FEV_1 .⁹

Effect of Pregnancy on Asthma

Numerous studies have observed that the course of asthma may be affected by pregnancy. Gluck et al. found that, on average, asthma improved in 36% of women during pregnancy, remained unchanged in 41%, and worsened in 23%.¹⁰ Schatz et al., in an analysis of 366 pregnancies in which patient status was followed by objective criteria, found that asthma improved in 28% of women, remained unchanged in 33%, and worsened in 35%. Fifty-nine percent of the patients had similar asthma control in successive pregnancies.¹¹

Fetal sex may influence asthma in pregnancy. In one study, mothers who gave birth to boys were more likely to report improved asthma symptoms.¹² Dodds and colleagues found that the use of medications to treat asthma was less common in mothers of boys.¹³ While a number of hypotheses have been proposed, including alterations in progesterone levels and the role of leukotrienes, changes in not one of these mediators can explain the varied course of pregnant asthmatics.¹⁴

Management

The National Asthma Education and Prevention Program issued specific guidelines regarding asthma treatment. In 1993, the Working Group on Asthma and Pregnancy established criteria for diagnosis and treatment among the gravid population (Fig. 144-2).¹⁵

The goals of treatment during pregnancy are to control exacerbation and prevent status asthmaticus, thereby reducing maternal and fetal hypoxemia. The initial step in treatment involves monitoring pulmonary function, and FEV_1 is the single best measure. A physical examination and chest radiography are poor measures of disease severity. A portable hand-held peak flow meter gives a quick, accurate assessment by measuring the PEFR. Most authorities believe that airways remain essentially unchanged throughout pregnancy; therefore, every patient with asthma should be given a peak flow meter and be educated in its use. The patient should obtain a baseline PEFR during a quiescent period. The severity of disease is determined by the occurrences of exacerbations and changes in FEV_1 and

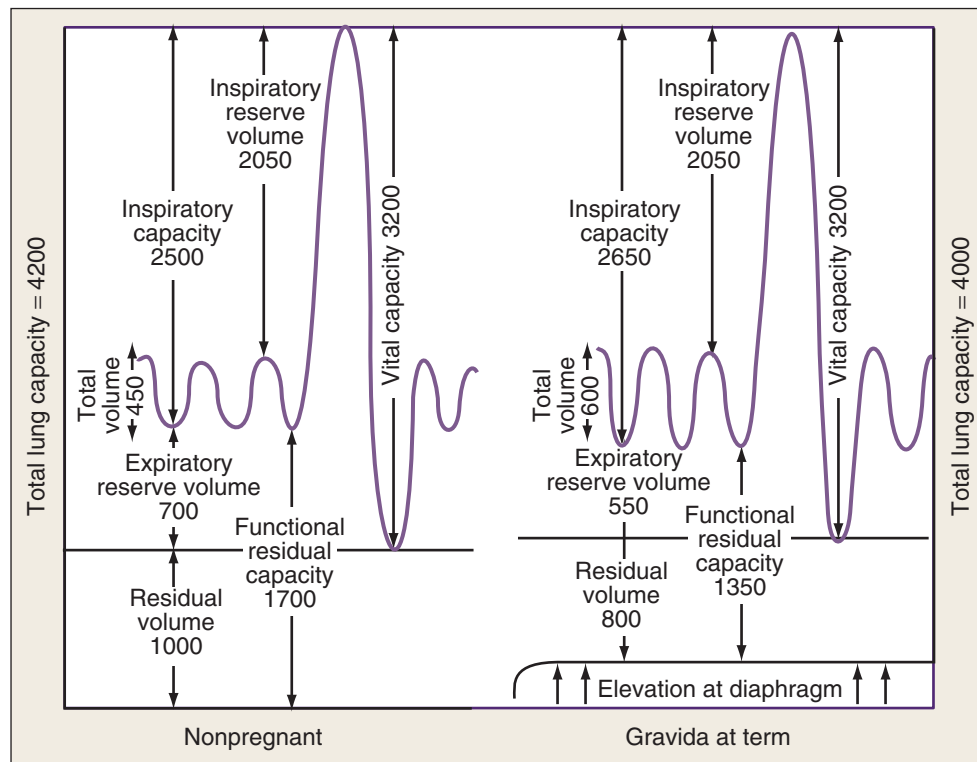


FIGURE 144-1 ■ Respiratory changes in pregnancy.

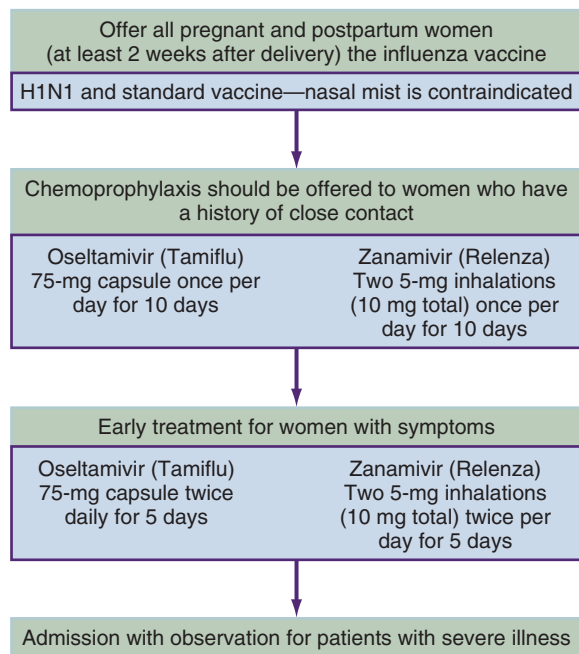


FIGURE 144-2 ■ Treatment during pregnancy.

PEFR. The PEFR can be used as a guide to refer the patient for emergency care.

Pharmacologic therapy is the mainstay of asthma treatment. Most drugs used in the treatment of asthma are thought to be safe in pregnancy. Inhaled β -agonists are the most frequently used in asthma treatment. A prospective study of inhaled β -agonists in 259

pregnancies showed no change in the rate of congenital malformation, perinatal mortality, low birth weight, or complications of pregnancy.¹⁶ There is little role for the use of oral β -agonists, which may cause more adverse systemic symptoms and are not more effective than inhaled drugs.

Inhaled corticosteroid therapy remains the mainstay of antiinflammatory treatment of asthma. Corticosteroids have also been advocated as first-line therapy in patients with mild asthma.¹⁷ Studies have demonstrated that with asthma, those taking an inhaled corticosteroid were four times less likely than their nontreated counterparts to suffer an exacerbation.¹⁸ Another randomized study noted that there was a 55% reduction in readmission rates due to acute asthma in patients using inhaled beclomethasone.¹⁹ Inhaled corticosteroids can increase the effectiveness of β -adrenergic agents by inducing the formation of new β receptors. Because beclomethasone is the most studied of the inhaled corticosteroids in pregnancy, it is recommended as first-line therapy.¹⁵ However, if patients are well controlled on other corticosteroid preparations, it is suggested they be continued on their current medication because all inhaled corticosteroids are labeled by the U.S. Food and Drug Administration (FDA) as pregnancy class C. Other antiinflammatory medications used in the treatment of asthma (e.g., cromolyn sodium and nedocromil sodium) appear to be less effective than inhaled corticosteroids in reducing asthma symptoms.

Systemic corticosteroids should be reserved for the periodic treatment of acute asthma exacerbations. Chronic oral corticosteroid therapy may increase the risks of gestational diabetes mellitus, preterm labor, low-birthweight infants, and preeclampsia; however, it is evident that the benefits of controlled severe asthma outweigh the potential risks to the mother and fetus.

Intravenous corticosteroids have no increased benefits over oral corticosteroids in the treatment of acute exacerbations.²⁰ Methylprednisolone, hydrocortisone, and prednisone are safe for use in pregnancy, unlike betamethasone or dexamethasone, because very little active drug crosses the placenta.

BOX 144-1 Treatment of Asthma in Pregnancy**MILD ASTHMA**

Characterized by FEV_1 or $PEFR \geq 80\%$

Brief (<1 hour) exacerbations

Treatment: inhaled β_2 -agonist

MODERATE ASTHMA

Characterized by FEV_1 or $PEFR$ range from 60% to 80%

Exacerbations more than twice per week; exacerbations may last for several days, and occasional emergency care needed

Treatment: inhaled corticosteroids and inhaled β_2 -agonist

SEVERE ASTHMA

Characterized by FEV_1 or $PEFR < 60\%$ of baseline

Continuous symptoms, limited activity, frequent exacerbations and nocturnal symptoms, occasional hospitalization and emergency treatment needed

Treatment: inhaled corticosteroids, inhaled β_2 -agonist, sustained-release theophylline; oral corticosteroid taper for active symptoms

Leukotriene pathway moderators have been shown to improve pulmonary function, as measured by FEV_1 .²¹ Zafirlukast and montelukast are rated as FDA category B; however, these drugs have not been frequently used in pregnancy, and their role is undetermined.

The treatment of asthma requires providing patient education in the preconceptional period and during the pregnancy for optimum outcome. Box 144-1 shows a suggested schematic for the treatment of asthma in pregnancy.

STATUS ASTHMATICUS

Status asthmaticus is a rare complication in pregnancy. Diagnosis is established by a Pao_2 of less than 70 mm Hg, a $Paco_2$ of greater than or equal to 35 mm Hg, or a measured expiratory flow of less than 25% of expected. Because of impending respiratory failure, these patients should be managed in a critical care unit. Aggressive treatment of status asthmaticus is mandatory to protect the mother and fetus. Maternal mortality may be as high as 7% and fetal mortality as high as 11% despite adequate treatment. Epinephrine is not contraindicated in pregnancy during a respiratory emergency. Criteria for intubation in gravida with status asthmaticus include (1) inability to maintain a Pao_2 of greater than 60 mm Hg despite supplemental oxygen; (2) inability to maintain a Pco_2 of less than 40 mm Hg; (3) evidence of maternal exhaustion, with worsening acidosis ($pH < 7.2$) despite intensive bronchodilator therapy; and (4) altered maternal consciousness.¹⁵

When traditional treatment proves to be ineffective, a number of therapies have been reported to be beneficial. The use of a helium-oxygen mixture that has been reported to be effective in studies in nonpregnant women has been used safely in pregnancy.²²

PULMONARY EDEMA

Pulmonary edema can be divided into two categories during pregnancy. *Cardiogenic pulmonary edema* is the result of high intravascular pressures creating a hydrostatic pressure gradient that results in extravasation of fluid into lung tissues despite the integrity of normal lung microcirculation. *Noncardiogenic pulmonary edema* is the result of a leaky pulmonary capillary bed despite normal intravascular pressures. During pregnancy, the distinction between these two types of edema may be blurred owing to disease states that exacerbate the hypooncotic state of pregnancy.

Etiology

There are a number of causes of pulmonary edema in pregnancy. Some are pathologic in their process; others are due to idiopathic causes. One

BOX 144-2 Treatment in Patients with Pulmonary Edema

1. Determine the etiology, stop fluids, tocolysis, etc.
2. Treat with a diuretic (the author prefers furosemide in increments of 10- to 20-mg IV push).
3. Consider the use of morphine sulfate for patient comfort, 1- to 2-mg IV push q 2-3 h.
4. Proceed with hemodynamic monitoring if the patient does not rapidly respond to the above measures.
5. Consider intubation and mechanical ventilation with positive pressure for those patients with noncardiogenic pulmonary edema and those patients with cardiogenic pulmonary edema who need further support.

of the most common associations with pulmonary edema during pregnancy is hypertensive disease. In patients with hypertensive disease, pulmonary edema may be cardiogenic due to fluid overload or left ventricular dysfunction or noncardiogenic due to decreased oncotic pressure.

Another common cause of pulmonary edema in pregnancy is tocolytic therapy. Most cases described have resulted from the intravenous use of beta sympathomimetics. The use of magnesium sulfate therapy as well as the use of corticosteroids in association with tocolysis for preterm labor have been shown to exacerbate the condition. The incidence of edema is increased in multiple gestations and in patients with subclinical infection.

Other causes of acute pulmonary edema in pregnancy include amniotic fluid embolism, aspiration, and the need for massive transfusion after hemorrhage.²³

Treatment

The treatment of pulmonary edema during pregnancy depends on its etiology. The cause is best determined by the use of pulmonary artery catheterization and measurement of pulmonary capillary wedge pressure. Although all patients may not require this intervention, it is recommended in patients in whom the clinical picture may be unclear (e.g., those with hypertensive disease) and in those who do not respond to standard diuretic therapy.

For patients who do not improve rapidly with diuretic therapy, intubation and ventilation with positive pressure is recommended. In addition to the use of diuretic therapy, reduction of preload and afterload may be achieved by the use of vasodilators such as nitrates, hydralazine, or calcium channel blockers. All are safe for use in pregnancy.

Box 144-2 shows a guide for the treatment of patients with pulmonary edema.

ACUTE RESPIRATORY DISTRESS SYNDROME**Etiology**

The causes of acute respiratory distress syndrome (ARDS)²⁴⁻²⁷ in pregnancy include preeclampsia, sepsis, aspiration, pyelonephritis, intrauterine infections, acute fatty liver of pregnancy, and amniotic fluid embolism.²⁸ In a review of 83 cases of ARDS associated with pregnancy, it was noted that among the causes of ARDS, 35 cases were attributed to uniquely obstetric conditions.²⁹ In addition, it was noted that varicella pneumonia and pyelonephritis were associated with ARDS. These conditions rarely trigger ARDS in immunocompetent adults. De Vaciana et al. pointed out that the development of lung injury in pregnancy correlates with known physiologic changes including increased blood volume, decreased colloid osmotic pressure, and an unchanged critical lung closing volume despite a diminished FRC.³⁰

Management

Management of ARDS includes diagnosis, maternal stabilization, fetal monitoring, investigation and treatment of underlying causes, and in many cases, evaluation for delivery.²⁹

Maternal stabilization includes intubation for mechanical ventilation if necessary. The clinician should consider intubation sooner rather than later in the presence of respiratory deterioration, keeping in mind that a decreased FRC exacerbates respiratory distress.

Contemporary thinking regarding the treatment of ARDS has found that a lung-protective ventilator strategy is the first therapy that has been found to improve outcomes in ARDS. It has been noted in numerous studies that decreasing the V_T from the standard of 12 mL/kg to 6 mL/kg or less and peak inspiratory pressures to less than 30 cm H_2O from 50 cm H_2O have resulted in decreased morbidity and mortality in patients with ARDS.³¹ There has been considerable discussion in the literature concerning permissive hypercapnia and its use in preventing lung injury. However, there have been no controlled studies in pregnancy, and it is the opinion of the author that increasing $Paco_2$ in pregnant patients should be undertaken with caution.

Judicious use of fluids is important in the management of ARDS. Although some authors have advocated the use of fluid restriction, clinicians must consider the volume-dependent status in pregnancy. It is recommended that fluid management be carefully guided by the use of hemodynamic monitoring.

Although oxygenation is important, it should be noted that oxygen should be used at the lowest concentration possible because it is toxic to the lung tissue in high doses. The goal of therapy is to keep the Sao_2 higher than or equal to 95%.

A number of other methods have been discussed in the treatment of ARDS, including inhaled nitric oxide, prostacyclin, surfactant, and inverse ratio ventilation. Currently, these modalities cannot be recommended because they have not been shown to decrease morbidity and mortality. Other trials considering prone ventilation and corticosteroids in late ARDS appear promising but have not been proven in large prospective randomized trials.³²⁻³⁴

Fetal surveillance during ARDS may be more difficult because drugs used to sedate the mother can affect fetal heart rate and variability. Sedatives, anxiolytics, hypnotics, and nondepolarizing agents are not contraindicated in pregnancy. In addition, preterm contractions and labor may present a problem due to maternal hypoxemia. Clinicians are cautioned against starting tocolytic therapy before achieving adequate maternal oxygenation. If tocolysis is needed, β -agonists such as terbutaline should be avoided because of the risk of increased pulmonary capillary permeability and increased demands on cardiac load. Magnesium sulfate is not strictly contraindicated, but it may also increase pulmonary capillary permeability. The use of NSAIDs may be the best choice for tocolysis because they have been proven to improve ARDS in animal models.²⁹ Consultation with a maternal-fetal specialist is recommended to assist intensivists in caring for these complex patients.

The timing of delivery of the patient with ARDS is a question that must be addressed by clinicians. Some authors advocate delivery after maternal stabilization, citing the possible "therapeutic effect" of delivery. Whitty and colleagues failed to demonstrate any significant benefit to delivery.³³ It is this author's opinion that delivery should be considered on a case-by-case basis, carefully weighing the risk/benefit ratio to the mother and fetus.

Box 144-3 shows a reasonable management scheme for a patient with ARDS.

EMBOLISM

Because of the hypercoagulable changes in the coagulation cascade associated with pregnancy, there is an increased risk of venous thromboembolism. It has been estimated that clinically symptomatic pregnancy-related venous thromboembolism occurs in 1 to 2 per 1000 pregnancies. Maternal age (>40 years) and ethnic and genetic

BOX 144-3

Management of the Patient with ARDS

1. Evaluate the patient in respiratory distress; calculate PaO_2/FiO_2 ratio; consider intubation if ≤ 200 mm Hg. The PEEP or CPAP mask is not recommended in pregnancy, owing to the high risk of aspiration.
2. Set tidal volume at 8 to 9 mL/kg to prevent increased peak pressures. Given recent evidence, aim to keep peak pressures less than 40 cm H_2O .
3. Use PEEP starting at 5 to 8 cm H_2O to assist in recruiting alveoli.
4. Aim to keep FiO_2 less than 60%; keep SaO_2 greater than or equal to 95%.
5. Use a pulmonary artery catheter to assist in fluid management and to guide hemodynamic parameters.
6. Consider the use of tocolysis only after the patient has been adequately hydrated and oxygenated.
7. Consider delivery if indicated for obstetric conditions or if continuing the pregnancy has no clear benefit.

ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; PEEP, positive end-expiratory pressure.

BOX 144-4

Treatment of Pulmonary Embolism in Pregnancy

1. Begin therapy immediately based on strong clinical suspicion while awaiting complete diagnostic workup.
2. Establish the diagnosis with appropriate diagnostic imaging test.
3. Maintain maternal and fetal oxygenation.
4. Administer intravenous heparin and maintain full anticoagulation for 7 to 10 days prior to changing to subcutaneous injections (antepartum) or warfarin (postpartum). Oral anticoagulation should be continued 6 to 8 weeks after delivery.
5. Keep international normalized ratio, activated partial thromboplastin time, or factor Xa level in therapeutic range.

factors may increase this risk. Postpartum thromboembolism is 3 to 5 times more common than antepartum thromboembolic events. A cesarean section confers a risk of 3 to 16 times that of a vaginal delivery.

Clinical signs of a pulmonary embolism include unexplained tachycardia, dyspnea, and diaphoresis and a nonproductive cough. The workup for a suspected pulmonary embolism should include normal laboratory studies (arterial blood gases) and an electrocardiogram in conjunction with radiographic testing.³⁵ Pregnancy should not prevent obtaining appropriate radiographic studies. In patients with a high clinical index of suspicion for thromboembolic phenomena, a definitive diagnosis is imperative (Box 144-4). Ventilation-perfusion scans are recommended as the first diagnostic test. Spiral computed tomography has replaced ventilation-perfusion scanning in many centers as an initial test. Pulmonary angiography is still the gold standard for offering a definitive diagnosis. All of the aforementioned tests use less than the 5 rads of radiation exposure that has been associated with fetal teratogenesis. The use of an abdominal shield further decreases fetal exposure.

D-dimer levels may not be useful for the diagnosis of a thromboembolism during pregnancy because it may be elevated in the absence of a thrombus. Low-molecular-weight heparin (weight-based dosing bid) is the anticoagulant of choice in antepartum patients. Warfarin should be avoided during pregnancy, if possible. Unfractionated heparin can also be used. Neither of these drugs crosses the placenta, owing to the size of the drug molecule. Patients on low-molecular-weight heparin should be monitored with factor Xa levels to ensure a therapeutic level.

Warfarin may be used in the second and third trimesters in patients in whom heparin therapy may be contraindicated. Coumarins may be difficult to reverse and are not routinely recommended during pregnancy. All anticoagulants can be used the postpartum period and are compatible with breastfeeding.³⁶

The goals for therapy during the antepartum and postpartum periods (6-8 weeks post delivery) should be an activated partial thromboplastin time of 2.0 to 2.5, a factor Xa level of 0.6 to 1.1, or an international normalized ratio (INR) of 2.5 to 3.0.

An amniotic fluid embolism is a rare phenomenon that may initially present as severe respiratory distress. Risk factors include rapid labor, multiple gestation, polyhydramnios, and uterine rupture. Patients with an amniotic fluid embolism usually have symptoms of acute respiratory distress, cardiovascular collapse, and profound disseminated intravascular coagulation. Treatment is supportive; however, maternal mortality may be as high as 80%.

■ PNEUMONIA

Concern over the H1N1 virus has reinforced the seriousness of influenza infection in pregnant patients. Historical data have shown that during an influenza pandemic, mortality rates among pregnant women are unusually high. Neuzil et al. noted that even during a normal season, compared to their postpartum counterparts, pregnant women were more likely to be hospitalized.³⁷ The risk of hospitalization was highest in the third trimester, with women nearly five times more likely to be hospitalized than the postpartum control group. Influenza-related morbidity occurs in 10.5 of 10,000 pregnant women, compared to 1.91 of 10,000 in nonpregnant controls. Influenza pneumonia mortality in pregnancy has been noted to range from 12.5% to 42.1%.³⁸

Contemporary management of influenza infection in pregnancy includes the use of antiviral medications for preventing and treating the disease. Amantadine and rimantadine have been shown to be effective in shortening the course and duration of disease in influenza A and influenza B. Recently, oseltamivir (Tamiflu) and zanamivir (Relenza) have been recommended for the prevention of influenza infection. Current Centers for Disease Control and Prevention (CDC) guidelines recommend that treatment be initiated for pregnant women

(including patients until 2 weeks postpartum) with documented exposure to influenza virus and those patients who present with symptoms in the first 48 hours of illness, regardless of their gestational age. Medication should be started at the first sign of symptoms; awaiting confirmation of the diagnosis and delaying therapy could result in rapid progression of the disease. In the 2009 flu season, 6% of deaths were in pregnant women, even though only 1% of the population is pregnant at any given time. Data suggest that the use of antiviral medications significantly reduces perinatal morbidity and mortality. Since 1995, the CDC has recommended that all pregnant women receive influenza immunizations. There has been some discussion regarding the use of thimerosal, which is used in the standard influenza vaccine; most authorities feel that the thimerosal-free vaccine, when available, is preferable. It is the opinion of the author that all pregnant patients who present with respiratory symptoms after exposure to viral illness should be hospitalized for observation.³⁸⁻⁴⁰ Changes in maternal respiratory physiology during pregnancy can make progression from mild respiratory distress to respiratory distress rapid and unpredictable³⁷ (see Fig. 144-1).

■ CONCLUSION

Because of the rare need for mechanical ventilation, there are no randomized controlled trials to determine the treatment modalities that are most effective in pregnancy. A retrospective study noted a maternal mortality rate of 14% and a fetal mortality of 11% in patients who required mechanical ventilation during pregnancy. The critical care specialist, perinatologist, anesthesiologist, and other members of the healthcare team should work closely to provide coordinated care. Understanding the physiologic changes during pregnancy, combined with aggressive treatment of early pathologic changes, will assist in providing improved management in gravid patients with potentially lethal pulmonary complications.

KEY POINTS

Pregnancy

1. Tidal volume is increased during pregnancy; however, functional residual capacity is decreased.
2. A normal arterial blood gas determination in pregnancy reflects compensated respiratory alkalosis.
3. Respiratory distress occurs more rapidly in gravid patients, owing to changes in pulmonary physiology.

Asthma in Pregnancy

1. The treatment of asthma in pregnancy does not differ significantly from that in the nonpregnant state.
2. Because FEV₁ does not change during pregnancy, a peak flow meter is a useful tool in monitoring patients with asthma.
3. A PaCO₂ of greater than 35 mm Hg in the setting of severe asthma represents respiratory distress in the gravid patient.

Acute Respiratory Distress Syndrome in Pregnancy

1. Caution should be used when considering treatment for preterm labor in patients requiring respiratory support. Correction of oxygenation is usually more effective than pharmacologic therapy.
2. The need for mechanical ventilatory support does not mandate delivery of the fetus. Most studies do not report significant maternal improvement after delivery.

3. Sedatives, hypnotic drugs, anxiolytic agents, and nondepolarizing neuromuscular blockade agents are not contraindicated in pregnancy.

Embolism in Pregnancy

1. Pregnancy is a hypercoagulable state that increases the risk of thromboembolic phenomena.
2. Radiographic studies should not be avoided in gravid patients with respiratory compromise.
3. Anticoagulation therapy is not contraindicated in pregnancy; however, warfarin is contraindicated for use in the first trimester.
4. Amniotic fluid embolism occurs in about 1 in 80,000 pregnancies. It is associated with significant maternal morbidity and mortality.

Pneumonia in Pregnancy

1. Pneumonia during pregnancy is the third most common cause of indirect obstetric death.
2. Misdiagnosis may occur in up to 20% of pregnant patients.
3. Care should be taken to carefully evaluate pregnant patients with influenza for acute respiratory symptoms.
4. Prompt pharmacologic treatment for influenza is safe during pregnancy and is recommended by the CDC.

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DEFINITION

The commonly accepted definition of *postpartum hemorrhage* (PPH) is excessive and life-threatening bleeding after 20 weeks of gestation, which occurs at the time of delivery of the fetus or placenta. Primary PPH is excessive blood loss within 24 hours of delivery. Secondary PPH is any abnormal or excessive bleeding that occurs between 24 hours and 12 weeks after delivery. Most commonly, bleeding occurs in the third stage of labor, which refers to the time between delivery of the fetus and delivery of the placenta after its separation and expulsion from the uterus. Defining excessive bleeding is somewhat problematic because it can be difficult to determine the exact amount of blood loss, and clinicians tend to underestimate blood loss. With a normal vaginal delivery, blood loss is typically 500 mL or less; after a normal cesarean section, it is usually 800 to 1000 mL. Blood loss greater than these amounts has been used to define PPH. However, uncomplicated vaginal and cesarean deliveries can occasionally occur with greater amounts of blood loss but without hemodynamic compromise. Therefore, a more comprehensive definition of PPH is bleeding (regardless of the volume of shed blood) that is severe enough to cause hemodynamic compromise.

A decrease in hematocrit greater than 10% as a diagnostic criterion has also been widely accepted as a definition of postpartum hemorrhage. The hematocrit level initially may be in the low-normal to normal range despite excessive bleeding, because hematocrit does not change quickly in response to rapid hemorrhage. The hematocrit is also determined in part by the volume of infused resuscitation fluid. Because the parturient's blood volume is increased by 30% to 50%, she may not manifest signs of tachycardia and hypotension until blood loss exceeds 1500 mL. If the patient is hemodynamically unstable but the amount of blood visualized externally is relatively insignificant, occult sites of internal bleeding should be suspected immediately.

INCIDENCE AND MORTALITY

Maternal mortality has significantly decreased over the past 50 years in developed countries, in part because of improvements in obstetric care. However, in the United States maternal mortality rose to a high of 17.8 per 100,000 in 2011. Much of this increase was associated with rising rates of hemorrhage. This increase was the highest among developed countries.¹ Mortality rates are significantly higher for African American and Asian or Pacific Island women compared with Caucasian women.^{2,3} According to a study by the CDC of pregnancy-related mortality in the United States between 2011 and 2012, hemorrhage accounted for 11% of maternal deaths.²

Obstetric hemorrhage is the world's leading cause of maternal mortality, causing 24% of maternal deaths or an estimated 127,000 maternal deaths annually. Postpartum hemorrhage is the most common type of obstetric hemorrhage and accounts for the majority of the 14 million cases of obstetric hemorrhage that occur each year.² In developed countries, PPH may cause up to 40% of all maternal deaths.⁴

PATHOPHYSIOLOGY

At term, blood flow to the uterus and placenta increases to 600 to 1200 mL/min, accounting for 10% of the maternal cardiac output. To

stem the flow of blood and provide immediate hemostasis after delivery of the fetus, the uterus begins to contract. Myometrial contraction is the primary mechanism for both placental separation and hemostasis. The myometrial muscle fibers of the uterus contract and simultaneously retract, causing compression and occlusion of the blood vessels. Uterine atony results when this adaptive mechanism fails and the myometrial fibers are unable to contract and retract normally. Excessive bleeding from the uterus and lower genital tract from many causes, including lacerations, placental anomalies, and trauma, is directly related to the increase in blood flow to the uterus and placenta. At term, there is a physiologic increase in the circulating concentrations of various clotting factors. This adaptive response also helps control the bleeding that is a normal consequence of delivery. However, these factors are overwhelmed by the excessive bleeding of PPH.

PRESENTATION

PPH often manifests as brisk and excessive flow of blood from the vagina. This finding is easily observed on physical examination. If the placenta has been delivered, blood can be seen at the vaginal entrance. Maternal hemodynamics may be unaltered initially. If the bleeding is left untreated, typical presenting signs of hypovolemic shock (i.e., tachycardia, tachypnea, and hypotension) become apparent. Bonnar described the symptoms related to PPH in relation to the amount of blood loss ([Table 145-1](#)).⁵ However, the signs and symptoms of hemorrhagic shock may not occur immediately and may extend over a longer period of time if shed blood is sequestered in the uterus. Occult bleeding occurs most frequently with retained placental fragments, uterine atony, and concealed hematomas in the pelvis, perineum, or retroperitoneal space. Occult hemorrhage in the uterus or hematomas should be suspected in patients who are in the third stage of labor with hemodynamic instability but little or no evidence of external bleeding. Signs and symptoms of excessive bleeding also may be delayed because of the relative hypervolemic state of the patient and by the position of the patient after delivery with the legs elevated in stirrups.

CAUSES

Obtaining a detailed antenatal history is important in helping to determine a possible cause of PPH. A history of prior bleeding episodes associated with heavy menses or with dental or surgical procedures should raise the possibility of an underlying coagulation or bleeding disorder. Significant predisposing risk factors for the development of PPH include previous episodes of PPH, multiparity, and multiple fetuses. Women with a prior history of PPH can have up to a 15% risk of recurrence with subsequent pregnancies.⁶ Risk factors associated with the development of PPH are listed in [Box 145-1](#). Early recognition of these risk factors may aid in the diagnosis and subsequently in the management of PPH. A randomized, controlled trial (RCT) comparing oxytocin administration before and after delivery of the placenta found that birth weight, labor induction with augmentation, chorioamnionitis, use of magnesium sulfate infusions, and previous episodes of PPH increased the risk of developing PPH.⁷ However, a significant number of patients with PPH have no obvious predisposing factors.

Potential causes of PPH are listed in [Box 145-2](#). Risk factors for obstetric causes at the time of admission should be identified and

TABLE 145-1 Presentation of Symptoms in Postpartum Hemorrhage

| % BLOOD LOSS (mL) | SYSTOLIC BLOOD PRESSURE (mm Hg) | SIGNS AND SYMPTOMS |
|------------------------------------|---------------------------------|--------------------------------------|
| Stage I 10-15 (500-1000) | Normal | Tachycardia, palpitations, dizziness |
| Stage II 15-25 (1000-1500) | Low-normal | Tachycardia, weakness, diaphoresis |
| Stage III 25-35 (1500-2000) | 70-80 | Restlessness, pallor, oliguria |
| Stage IV 35-45 (2000-3000) | 50-70 | Collapse, air hunger, anuria |

BOX 145-1 Predisposing Risk Factors for Obstetric Hemorrhage**LOW RISK**

No previous uterine incision
 Singleton pregnancy
 <4 previous vaginal births
 No known bleeding disorder
 No history of PPH

MODERATE RISK

Prior cesarean section or uterine surgery
 Multiple gestation
 >4 previous vaginal births
 Chorioamnionitis
 History of previous PPH
 Polyhydramnios
 Large uterine fibroids

HIGH RISK

Placenta previa or low lying
 Suspected accreta or percreta
 HCT < 30 AND other risk factors
 Platelets < 100,000
 Active bleeding on admission
 Known coagulopathy

PPH, postpartum hemorrhage.

BOX 145-2 Causes of Postpartum Hemorrhage

Uterine atony
 Cervical or vaginal lacerations
 Retention of placental fragments
 Placental anomalies
 Traumatic hematomas of the perineum or pelvis
 Coagulation disorders
 Uterine rupture
 Uterine inversion

reassessed during the intrapartum and postpartum process. The most frequent cause of PPH is uterine atony after delivery of either the fetus or placenta. Bleeding is from the uterine vessels or from the placental site of implantation if the placenta has been delivered. The incidence of uterine atony is approximately 1 in 20 deliveries. Uterine atony can lead to rapid and severe PPH. Overdistention of the uterus secondary to multiple gestation, fetal macrosomia, or polyhydramnios is a major predisposing risk factor for the development of uterine atony. Other predisposing factors are retained placenta, chorioamnionitis, uterine structural abnormalities, and muscle fatigue after prolonged or stimu-

lated labor. General anesthesia, particularly with halogenated anesthetics, and magnesium sulfate infusions can inhibit effective uterine contractions and lead to uterine atony. The diagnosis of uterine atony is a clinical diagnosis made by assessing the tone of the uterus and its size by manually palpating the uterus externally. Bimanual examination of the uterus also can be performed to diagnose uterine atony. A boggy uterus associated with heavy vaginal bleeding or with an appreciable increase in the size of the uterus is diagnostic of uterine atony. The size of the uterus may be larger than normal due to accumulated blood within.

Lacerations of the lower genital tract are the second most frequent cause of PPH. Lacerations of the vagina and cervix can result from a number of causes. These lesions occur most commonly as a result of prolonged or tumultuous labor, particularly with uterine hyperstimulation with oxytocic agents. Nevertheless, lacerations can occur spontaneously as well. They are seen in deliveries associated with instrumentation, such as forceps deliveries, or with extrauterine or intrauterine manipulations of the fetus. Attempts to remove the placenta or placental fragments manually or with instrumentation can lead to traumatic lesions or hematomas. Excessive vaginal bleeding or traumatic hematomas can result from these lacerations. Careful examination with palpation of the vagina and cervix may reveal the presence of lacerations.

Retention of placental fragments or the entire placenta can lead to severe and life-threatening hemorrhage, which may be immediate or delayed depending on the extent of accumulated blood in the uterus. The most common definition of retention of the placenta in utero is when part or all of the placenta is retained in the uterus for more than 30 to 60 minutes after delivery of the fetus. Retained placenta is more likely to occur with a preterm gestation of less than 24 weeks.

Placental abnormalities (i.e., placenta accreta, placenta increta, and placenta percreta) have been associated with retained placenta and failure of complete separation of the placenta from the uterus. If the placenta has been delivered, it is imperative to closely examine the placenta to look for missing fragments, a finding that suggests retained placental tissue.

Placenta accreta occurs when a portion or the entire surface of the placenta is abnormally attached to the uterus. Where placenta accreta is present, the failure of the placenta to separate normally from the uterus after delivery is accompanied by severe postpartum hemorrhage. Placenta increta involves actual invasion of the uterus by the placenta. Placenta percreta involves invasion of the placenta into other organs. Multiple uterine surgeries, such as cesarean sections, or other uterine procedures like uterine ablation increase the risk of placental invasion. If placental invasion is anticipated, the patient should be delivered in a center with experience in taking care of these patients.

Another less frequent cause of PPH is uterine rupture. Rupture is more common in patients with prior cesarean incisions and in those with any prior operative procedures of the uterus (e.g., intrauterine device placement, laparoscopy, hysteroscopy). Uterine rupture may manifest with severe and acute abdominal pain and hemodynamic instability, but there may not be significant bleeding initially. Uterine inversion is relatively uncommon but may be associated with blood losses of up to 2 L.

A defect in hemostasis resulting from an underlying coagulopathy should be considered if the uterus is contracting normally and manual exploration has excluded either placental retention or uterine rupture. Disseminated intravascular coagulation (DIC) associated with placental abruption (premature separation of a normally implanted placenta), the HELLP syndrome (*hemolysis, elevated liver enzymes, and low platelets*), intrauterine fetal death, acute fatty liver of pregnancy, sepsis, or amniotic fluid embolism may precipitate PPH. The incidence of severe DIC associated with PPH is estimated at 0.1% of pregnancies.⁸

Amniotic fluid embolism syndrome (AFES) is a catastrophic condition that can occur either during the pregnancy or after the delivery. AFES manifests with acute respiratory failure, cardiogenic shock, and/or DIC.⁹ As many as 80% of these patients develop DIC, and in some, DIC is the major clinical abnormality. Oozing from intravenous (IV)

or skin puncture sites, mucosal surfaces, or surgical sites should raise the suspicion of DIC; confirmation of the diagnosis is made by laboratory coagulation studies. Although the coagulation profile is unlikely to be abnormal with acute postpartum bleeding in the absence of DIC, coagulation parameters are clearly abnormal in the presence of DIC regardless of the cause. In late pregnancy, the circulating fibrinogen level usually is two to three times the normal prenatal value, but fibrinogen concentration is dramatically decreased if DIC is present. Preexisting or pregnancy-acquired disorders of coagulation are relatively infrequent causes of significant PPH.

DIAGNOSTIC STUDIES

Although the diagnosis is obvious with significant and excessive bleeding after delivery, not all patients present with immediate bleeding, because of hematoma formation or accumulations in the interior of the uterus. Bedside ultrasonography can be used for the detection of clots, hematomas, and retained placental products. For patients who are at high risk for development of PPH, periodic ultrasound examinations during pregnancy can offer invaluable information concerning the extent and progression of placental disease. Angiography with selective arterial embolization can be used both diagnostically and therapeutically. Bleeding sites can be visualized and embolized simultaneously. For evaluation of a proven or suspected case of PPH, the following laboratory studies are almost always indicated: complete blood count with platelet count, coagulation studies with prothrombin and activated partial thromboplastin times, fibrinogen, and fibrin split products. D-dimer may be a limited use as it may be elevated in normal pregnancies. With acute hemorrhage, the measurements of hemoglobin concentration and hematocrit may be of limited use.

PREVENTION

There has been much controversy concerning the preferred methods of managing the third stage of labor in terms of decreasing bleeding complications. The debate concerns active versus expectant management. Expectant management consists of waiting for separation and expulsion of the placenta, with minimal intervention except for gentle fundal massage. Active management of the third stage of labor involves three components. The first consists of administering a uterotonic drug, usually oxytocin, immediately after delivery of the fetus to promote contraction of the uterus and subsequent expulsion of the placenta. The second maneuver consists of gentle traction on the umbilical cord after the uterus is well contracted and then using countertraction against the uterine fundus.¹⁰ The third maneuver is uterine massage after delivery of the placenta. The two modalities were compared in five randomized, controlled trials in a Cochrane meta-analysis of studies enrolling more than 6000 women. A 60% decrease in PPH was associated with active management of the third stage of labor.¹¹

GENERAL TREATMENT MEASURES

Many deaths associated with PPH may have resulted because clinicians underestimated the extent of blood loss and failed to provide rapid and aggressive resuscitation with fluids and blood products. Several authors have suggested the use of specific management protocols for the care of patients with PPH.^{5,12,13} These guidelines can expedite rapid diagnosis and management of obstetric hemorrhage. Quantification of blood loss during delivery has been recommended as it gives a better assessment of blood loss. Several current toolkits are available to assist medical personnel in managing the weighing of pads and laps in order to give an accurate assessment. Simulation may also be used to assist the team in responding more quickly to this emergency.

A general assessment of the patient, evaluation of vital signs, a detailed physical examination, and a review of the obstetric delivery details are all necessary for the clinician to formulate a comprehensive evaluation and critique of the situation. The general treatment mea-

BOX 145-3

General Treatment Measures for Postpartum Hemorrhage

Oxygen administration
Gentle massage of the uterine fundus
Placement of large-caliber intravenous catheters for rapid and aggressive fluid resuscitation with isotonic solutions using the "3:1" rule
Blood product administration depending on the extent of bleeding and coagulation abnormalities

TABLE 145-2

Therapeutic Response to Initial Fluid Resuscitation

| RESPONSE | DESCRIPTION | FOLLOW-UP TREATMENT |
|------------------------|---|---|
| Rapid response | <20% of blood volume lost | No additional fluids or blood are needed. |
| Transient response | 20%-40% of blood volume lost; responds to initial fluid bolus but later has worsening vital signs | Continue fluids and consider blood transfusions. |
| Minimal or no response | Ongoing severe hemorrhage with >40% blood volume lost | Continue aggressive fluid and blood product replacements. |

asures for PPH are the same as those for any patient with acute hemorrhage (Box 145-3). Oxygen should be administered routinely. At least two large-caliber IV lines should be placed immediately. Central venous access is usually unnecessary unless peripheral access cannot be obtained quickly. Aggressive volume resuscitation should be instituted immediately, because this intervention can be lifesaving in patients with ongoing bleeding and hemodynamic instability. Either normal saline or lactated Ringer's solution is the preferred fluid for aggressive resuscitation. Isotonic electrolyte solutions provide transient intravascular volume expansion. Monitoring of changes in blood pressure, heart rate, and pulse pressure can help the clinician to determine the amount of blood loss, particularly in cases in which bleeding is internal (Table 145-2).

General guidelines for fluid resuscitation of patients with hemorrhagic shock are based on the "3:1" rule. This recommendation derives from the empiric observation that patients require about 300 mL of crystalloid fluid replacement for every 100 mL of blood loss. This rule must be applied in the context of the clinical scenario. Applied blindly, this guideline can result in either excessive or inadequate volume resuscitation. Patients with expanding hematomas or areas of concealed active bleeding have hypotension out of proportion to the obvious blood loss and require resuscitation in excess of the 3:1 recommendation. In contrast, patients with ongoing blood losses that are being replaced with blood transfusions typically require less electrolyte fluid replacement. Although initial fluid resuscitation is critical, caution should be exercised to prevent abdominal compartment syndrome that may occur when more than 10 L of fluids are administered. Red blood cell transfusions to replace ongoing blood loss remain the mainstay of fluid replacement.

Blood transfusions usually are necessary for patients with severe ongoing PPH. Healthy pregnant patients usually do not require transfusion if blood loss is 2000 mL or less. However, if blood loss is greater than 2 L or there is ongoing hemorrhage and hemodynamic instability, transfusion can be lifesaving. Crossmatched packed red blood cells or type-specific blood can be infused rapidly using a blood-warming device in cases of severe ongoing hemorrhage (Box 145-4). Recombinant activated factor VII (rFVIIa) has been recommended in cases of refractory postpartum hemorrhage that has not responded to medical

BOX 145-4 Blood Product Replacement

Crossmatched blood
 Type-specific or "saline crossmatched" blood
 Compatible ABO and Rh blood types
 Rh-negative blood is preferable.
 Warm the blood, if possible, especially if the rate of infusion is >100 mL/min or if the total volume transfused is high; cold blood is associated with an increased incidence of arrhythmias and paradoxical hypotension.
 Administer calcium if blood is transfused rapidly at >100 mL/min because of binding of calcium by anticoagulants in banked blood.
 Give 6-10 units fresh frozen plasma (FFP) for every 10 units of packed red blood cell (PRBC) transfusions.
 Give 10-12 units of platelets if the platelet count decreases to $<50 \times 10^9$ /L.
 Cryoprecipitate can be given to replace fibrinogen in addition to the FFP.
 Consider 60-120 μ g/kg intravenous bolus injection of recombinant activated factor VII (rFVIIa).

measures including blood product administration.¹⁴ Although supported by few and uncontrolled studies, the available data suggest a potential role of rFVIIa in the management of severe PPH prior to performing a definitive hysterectomy.

Manual external uterine massage should be performed immediately to stimulate uterine contractions and express clots if uterine atony is suspected or confirmed. If the uterus does not respond to vigorous manual external massage and the rapid administration of oxytocin, bimanual massage with one hand on the uterus and the other hand placed anterior to the cervix in the vagina should be performed. Aggressive uterine manipulation can result in uterine inversion. Direct pressure should be maintained over visible perineal, vaginal, or cervical lacerations. These general treatment measures can control excessive bleeding and even stop the hemorrhage in a significant proportion of patients.

SPECIFIC TREATMENT MEASURES

Oxytocic (uterotonic) drugs administered IV, intramuscularly, or intramyometrially are used to stimulate the uterus by producing rhythmic contractions and control the degree of hemorrhage. Dosing regimens for oxytocic drugs are listed in Table 145-3.

Oxytocin (Pitocin) remains first-line therapy for most obstetricians. Prophylactic oxytocin, given either before or after placental delivery, decreases the incidence of PPH up to 40%.¹⁵ It is also used prophylactically after delivery of the fetus but before delivery of the placenta to decrease the duration of the third stage of labor and the amount of blood loss. In an RCT, the incidence of PPH was similar regardless of whether oxytocin was given before or after placental delivery.⁷ Additionally, the incidence of retained placenta was similar for patients treated with oxytocin before or after delivery of the placenta. Oxytocin should be used with caution in patients with hyperactive uterine contractions or hypertension, because the pressor effect of sympathomimetic drugs can increase if they are used with oxytocin.

Methylergonovine (Methergine) is now considered second-line therapy. It is a direct uterotonic agent that reduces uterine bleeding and shortens the third stage of labor. Hypertension is a relative contraindication for the use of Methergine. Carboprost tromethamine (Hemabate), a synthetic prostaglandin similar to prostaglandin $F_{2\alpha}$ but with a longer duration, produces myometrial contractions that induce hemostasis at the placentation site, reducing postpartum bleeding. It is used in some centers as a second-line uterotonic agent. Asthma is a relative contraindication to the use of carboprost. Carboprost has been shown to be as effective in decreasing PPH refractory to oxytocin and ergonovine. Misoprostol, prostaglandin E_1 , causes uterine contractions, and rectal administration of this drug has been shown to be useful in refractory PPH. Although oxytocin is considered the standard of care for treating postpartum hemorrhage, it is not always viable or available, particularly in resource-poor clinical settings, because of

TABLE 145-3**Dosing Regimens for Oxytocic Drugs**

| DRUGS | REGIMENS |
|--------------------------------|---|
| Oxytocin (Pitocin) | 5-unit IV bolus Add 20-40 units oxytocin to 1 L of fluids. 10 units intramyometrially |
| Methylergonovine (Methergine) | 0.2 mg IM every 2-4 h |
| Ergonovine maleate (Ergotrate) | 100-125 μ g IM or intramyometrially every 2-4 h 200-250 μ g IM Total dose 1.25 mg |
| Carboprost (Hemabate) | 250 μ g IM or intramyometrially every 15-90 min Total dose 2 mg |
| Misoprostol | 800 μ g PR or 800 μ g of sublingual misoprostol |

IM, intramuscular; IV, intravenous; PR, per rectum.

refrigeration requirements and the need for IV administration. In a large randomized prospective trial, the efficacy and acceptability of 800 μ g of sublingual misoprostol were compared to 40 international units of IV oxytocin to control postpartum bleeding.¹⁶ The primary endpoints were cessation of active bleeding within 20 minutes and additional blood loss of 300 mL or more after treatment. The findings suggested that sublingual misoprostol is a viable alternative to 40 international units of IV oxytocin for treatment of primary postpartum hemorrhage after oxytocin prophylaxis during the third stage of labor. Misoprostol stopped bleeding as rapidly as oxytocin and with a similar quantity of additional blood loss.

The practice of uterine packing to control bleeding remains somewhat controversial. Although this practice had been abandoned for many years, it has recently resurged as an effective method for tamponade of bleeding from the uterus. Balloon occlusion catheters have been used in the treatment of PPH.¹⁷ Recent data suggest that balloon tamponade is an effective method for controlling hemorrhage, and in 80% of cases hysterectomy was averted. When a specific uterine balloon catheter is not available, placement of a Sengstaken-Blakemore tube or a large Foley catheter can also be used for control of bleeding.¹⁸

If there is a suspicion of retained placenta, examination of the uterus is both diagnostic and therapeutic. The uterus must be explored digitally and retained placental fragments removed either manually or with instruments. Because this procedure can be difficult and quite painful, it may be necessary to use regional or general anesthesia to obtain optimal visualization and manipulation of the uterus. Administration of oxytocic drugs should continue during manual extraction of placental fragments. Administration of broad-spectrum antibiotics has been recommended whenever there is manipulation or instrumentation of the uterus.

Compression of the abdominal aorta against the vertebral column, which can be achieved by pressing a fist on the abdomen cephalad to the umbilicus, can be a lifesaving temporizing maneuver to control hemorrhage before surgery in the presence of fulminant bleeding with severe hemodynamic compromise. If there is persistent and significant bleeding despite the therapeutic measures described, consideration should be given to arteriography with selective arterial embolization. This procedure requires the expertise of an interventional radiologist and may not be readily available in many hospitals. Successful embolization of the bleeding sites can be accomplished, obviating the need for surgical intervention.¹⁹ Fertility can be preserved with this procedure.²⁰ Prophylactic placement of embolization catheters in patients at high risk for PPH to minimize the procedural delay in the presence of active bleeding has also been utilized in some centers. If embolization is unsuccessful, balloon catheter occlusion of the hypogastric and iliac arteries has been successfully performed as a temporizing measure

before surgery.²¹⁻²³ Complications are minimal, and postprocedural fever appears to be the most common complication of the procedure.

SURGICAL THERAPY

Surgical therapy is reserved for cases not amenable to medical therapy. Patients with ongoing hemorrhage despite aggressive medical therapy are candidates for operation. Surgery is the treatment of choice for uterine rupture. Lacerations, if visible, are directly repaired and oversewn. Lacerations high in the vaginal vault or in the cervix may require operative repair, primarily for improved visualization of the lesions. Hematomas of the lower genital tract are incised and drained. Arterial embolization of vaginal and vulvar lesions has been used. Hematomas of the broad ligament and in the retroperitoneal space are often managed conservatively if there is only minimal further expansion of the hematoma, but surgical exploration or embolization is mandated if additional significant bleeding occurs. Radiographic imaging with computed tomography, magnetic resonance imaging, and/or ultrasonography is a useful adjunct to monitor the expansion of these hematomas.

Ligation of the uterine, ovarian, or internal iliac (hypogastric) arteries can be performed. The uterine arteries provide 90% of uterine blood flow. Ligation of these arteries can often control bleeding with success rates of up to 92% and a complication rate of 1%.²⁴ If hemostasis is not achieved with uterine artery ligation, the ovarian and internal iliac arteries can be ligated as well. Ligation of the internal iliac arteries is technically more difficult, and success rates range from 40% to 100%.^{24,25} Ligation of the internal iliac arteries usually is done only if ligation of the uterine and ovarian arteries has proved unsuccessful in halting bleeding.

Uterine compression sutures running through the full thickness of both uterine walls (posterior as well as anterior) have recently been described for surgical management of atonic PPH.²⁶⁻²⁸ The different uterine suture techniques have proved to be valuable and safe alternatives to hysterectomy in the control of massive PPH. In contrast, hys-

terectomy remains the definitive surgical therapy to control bleeding. Hysterectomy is required if bleeding continues despite ligation of the internal iliac arteries. Subtotal or total hysterectomy is curative in PPH. In cases of uterine rupture, it is the only surgical option, and nonsurgical modalities are only temporizing measures until the patient can be brought to the operating room. In developed countries, the incidence of postpartum emergent hysterectomy is approximately 1 in 2000 deliveries. Rossi et al. reviewed 24 articles that included 981 cases of emergency postpartum hysterectomy. They found women at highest risk of emergency hysterectomy are those who are multiparous, had a cesarean delivery in either a previous or the present pregnancy, or had abnormal placentation.²⁹

COMPLICATIONS

Serious morbidity may follow PPH. Complications from postpartum bleeding include hematologic abnormalities such as DIC and dilutional coagulopathy from massive fluid resuscitation and/or massive transfusion (greater than 10 units of packed red blood cells). New protocols suggest that aggressive transfusion with whole blood or packed red blood cells and fresh frozen plasma in a 1:1 ratio may reduce the incidence of DIC in this population.³⁰ Dilutional coagulopathy occurs when more than 80% of the original blood volume has been replaced. Life-threatening complications of hemorrhagic shock, including renal failure and liver failure, acute respiratory distress syndrome (ARDS), and pituitary necrosis (Sheehan's syndrome), can occur. Sheehan's syndrome can result from severe PPH that causes permanent hypopituitarism from avascular necrosis of the pituitary gland.³¹

PROGNOSIS

The prognosis of PPH depends on many factors, some of which are directly related to prompt diagnosis and treatment. The cause of bleeding, the duration of bleeding, and the extent of bleeding all affect the likelihood of a good outcome.

KEY POINTS

1. *Postpartum hemorrhage* (PPH) is defined as excessive bleeding after a vaginal or cesarean delivery that can be associated with hemodynamic instability if the bleeding is severe.
2. The usual signs of tachycardia and hypotension associated with severe bleeding may not manifest early because of the relative hypervolemic state of pregnancy or in cases of concealed hematomas with ongoing blood losses.
3. PPH is the leading cause of maternal death worldwide and one of the major causes of death in the United States, along with embolism, infection, and hypertensive disorders of pregnancy.
4. Massive blood loss can occur from the uterus because of the significant physiologic increase in blood flow to the uterus at term.
5. Occult bleeding occurs most frequently with retained placental fragments, uterine atony, and concealed hematomas in the pelvis, perineum, or retroperitoneal space.
6. Women with a prior history of PPH have a 10% risk of recurrence with a subsequent pregnancy.
7. Many women have predisposing factors leading to the development of PPH. Antenatal identification of potential predisposing factors allows for close monitoring of the high-risk patient.

Women with multiple cesarean sections may pose one of the highest risks for hemorrhage.

8. The most frequent cause of PPH is uterine atony, which occurs in 1 of every 20 deliveries. Risk factors for uterine atony include overdistention of the uterus, retained placenta, uterine muscle fatigue, and use of halogenated anesthetic agents.
9. The diagnosis of uterine atony is made clinically by palpation of a boggy and enlarged uterus.
10. The second most frequent cause of PPH is lacerations of the lower genital tract that occur as a result of traumatic labor or spontaneously.
11. Manual exploration of the uterus confirms the diagnosis of retained placental fragments. Placental retention is most commonly associated with several types of placental anomalies.
12. Disseminated intravascular coagulation (DIC) is associated with placental abruption, the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), acute fatty liver of pregnancy, intrauterine fetal death, sepsis, and amniotic fluid embolism.
13. Amniotic fluid embolism syndrome usually manifests as sudden and acute respiratory failure, cardiogenic shock, and DIC.
14. In the United States, most obstetricians practice expectant management of the third stage of labor, allowing for spontaneous

KEY POINTS—cont'd

- delivery of the placenta. Active management of the third stage of labor involves fundal massage, use of an oxytocic drug, and gentle traction on the umbilical cord, with countertraction of the uterus to facilitate delivery of the placenta.
15. General treatment measures include aggressive and early fluid resuscitation while investigating the potential source of the bleeding. Higher maternal mortality rates are seen when blood losses are underestimated and treatment is delayed.
 16. Patients with ongoing severe bleeding, blood losses greater than 2 L, or hemodynamic compromise require blood transfusions in addition to volume resuscitation.
 17. Specific treatment modalities include administration of oxytocic drugs, uterine packing, tamponade procedures with arterial balloon occlusion, and selective arterial embolization.
 18. Surgical therapy is reserved for cases of uterine atony and after all other modalities have failed. Uterine, ovarian, and iliac artery ligations and uterine compression sutures have been successful in controlling bleeding.
 19. Total or partial hysterectomy is the definitive surgical procedure. Uterine rupture necessitates a hysterectomy.
 20. Complications from PPH are the same as those of hemorrhagic shock, with risk of multiple organ failure, acute respiratory distress syndrome, dilutional coagulopathy, and Sheehan's syndrome.
 21. Sheehan's syndrome results from severe PPH and manifests as severe hypopituitarism.
 22. The prognosis of PPH depends on the cause of the bleeding, its extent and duration, and the speed of diagnosis and treatment.

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■ References for this chapter can be found at expertconsult.com.

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One of the most challenging critical care situations is the care of a pregnant patient who develops critical illness.¹ The complexity of care is increased by constraints imposed by concerns for balancing maternal health with the health of the unborn or, in some cases, recently born child. Although many potential critical illnesses may occur during pregnancy, we focus our discussion on neurocritical illness that may arise, leading to an intensive care admission in this chapter. We further focus on the ongoing developments in this topical area and on the critical care aspects of care, most typical of late-term pregnancy.

The main points to emphasize in this chapter are as follows: (1) Pregnancy creates a condition prone to inflammatory and thrombotic disease in the brain.^{1,2} (2) Treatments of common conditions, such as seizures, are unique in a pregnant woman. (3) Systemic circulatory concerns need to be adjusted for consideration of intracranial hemodynamics. (4) Brain monitoring may be useful to guide therapy and limit toxicity of treatments.

There are three main diagnoses or conditions that complicate pregnancy and lead to neurologic emergencies. These are myasthenic crisis, preeclampsia/eclampsia with seizures, and ischemic or hemorrhagic stroke. We explore the important critical care bedside considerations and treatment approaches to each of these conditions and focus on decision making and integration with general critical care goals.

FUNDAMENTAL PEARLS FOR NEUROCRITICAL CARE

As we begin our discussion, it is important to follow certain fundamentals of neurocritical care in assessing a pregnant patient who presents with neurologic deterioration. The important steps are as follows: (1) Obtain a detailed history of the timing and specifics of the neurologic deterioration. This is in contrast to our routine practice in critical care of assessing a brief synopsis of the presentation. A detailed approach will help discriminate between central and peripheral nervous system diseases, the presence of symptoms of elevated intracranial pressure, seizures, and similar pathophysiology. (2) Perform a detailed neurologic examination that can be compared to future examinations. This is important to assess the clinical treatment and also important to avoid misdiagnosing a peripheral neurologic problem as being a central nervous system problem, and vice versa. (3) Closely evaluate brain imaging for signs of intracranial hypertension. For most pregnant patients, the risks of computerized tomography (CT) are acceptably low so that a brain CT can be obtained. Magnetic resonance imaging (MRI, including MR venography) may be preferred but may not be feasible in critically ill patients. (4) Make use of brain monitoring for seizures in obtunded or encephalopathic pregnant patients. This may include transcranial Doppler ultrasound (TCD) and electroencephalography. As you will read later, seizures are a major problem for pregnant patients. (5) Develop an approach to optimize the intracranial hemodynamics in patients suspected of intracranial hypertension or cerebral ischemia. This may result in blood pressure (BP), mechanical ventilation, or systemic hemodynamic management that is considerably different from what would be optimal for an uncomplicated pregnancy. (6) Discuss fetal-maternal balance issues with an obstetrician, and seek treatment parameters that favor the welfare of the mother without harming the fetus if possible.

MYASTHENIC CRISIS

Myasthenia gravis (MG) during pregnancy usually does not result in critical illness.³ There is a large fraction of patients who will have improvement in MG during pregnancy. For general myasthenic care, consultation with a neurologist should be done, as standard treatments such as steroids may entail an increased risk of birth defects (e.g., cleft palate). For the most part, the routine care of MG will not change during pregnancy, and the typical medications may be used. For the 30% of patients who demonstrate myasthenic crisis, some are in the postpartum period.³ The main clinical questions concern the optimal critical care for pregnant patients with myasthenic crisis and the optimal disease-modifying treatment while in crisis in the intensive care unit (ICU).

Myasthenic crisis can be complicated by acute respiratory failure due to diaphragm fatigability. In the ICU, the clinical examination of facial and eyelid weakness, bulbar weakness, tachypnea with paradoxical respirations, and limb weakness are helpful diagnostic clinical signs of myasthenic crisis. Monitoring of vital capacity and negative inspiratory force is desirable as additional diagnostics. The respiratory mechanics, criteria for intubation, and methods of mechanical ventilation are similar to those of nonpregnant patients. Definitive treatment with the use of plasmapheresis or intravenous (IV) immunoglobulins is considered to be safe and effective for myasthenic crisis during pregnancy. The standard doses and scheduling apply. However, a few special considerations of plasmapheresis during pregnancy include an increased risk of perinatal bleeding because of depletion of coagulation factors.^{3,4} It is recommended that plasmapheresis be withheld 24 hours before childbirth.⁴ The newborn must be monitored for hypogammaglobulinemia and perinatal infections. Positioning of the mother on her left side during apheresis is a specific precaution to avoid compression of the vena cava. Monitoring of circulating blood volume and avoidance of hypovolemia are other unique precautions.

Post birth, about 10% of newborns develop neonatal MG because of the transfer of maternal antiacetylcholine receptor antibodies. This is usually short-lived but requires supportive care for a short duration, usually 12 to 24 hours.

PREECLAMPSIA AND ECLAMPSIA

Preeclampsia/eclampsia (PE/EC) is a mid- to late pregnancy clinical problem that initially manifests as new hypertension in pregnancy.⁵ The underlying pathophysiology may be related to increased cerebral blood flow and loss of cerebral autoregulation.^{6,7} The threshold for systolic BP is more than 140 with repeated elevations over time. The systemic hypertension may be accompanied by other systemic problems including proteinuria, acute kidney injury, acute liver transaminase elevation, or combinations of these findings.⁵ Alteration of mental status may occur as well as mild confusion or visual symptoms. Seizures are typically later stage manifestation, and once seizures occur, the patient is considered eclamptic. The timing of this problem is typically before birth but may occur during delivery or 1 to 4 weeks after childbirth. The highest risk period is during labor.^{5,8} The seizures are most commonly generalized tonic-clonic seizures but may be focal with altered mental status. The seizures may take the form of status epilepticus (SE) and be severe enough to induce coma.

TABLE 146-1 Drugs for PE/EC in a Pregnant Woman

| TRIGGER | DRUG | DOSE | MONITOR |
|---------------------|-------------------|---------------|--------------------------|
| SBP >140 | Magnesium | 4-6 g IV push | BP |
| SBP >140 | Magnesium | 1-3 g/h IV | BP, reflexes, dysarthria |
| Refractory SBP >140 | Hydralazine | 5-10 mg IV | BP response |
| Seizure | Magnesium | 1-3 g/h IV | Clinical or EEG |
| Seizure | Anticonvulsant IV | Loading dose | EEG |

BP, Blood pressure; EEG, electroencephalography; PE/EC, preeclampsia/eclampsia; SBP, systolic blood pressure.

The critical care for the preeclamptic/eclamptic (PE/EC) woman is focused on early reduction in BP and prevention of seizures. In contrast to the standard use of antiseizure medications, the use of intravenous magnesium is the mainstay of treatment.⁸ Table 146-1 outlines the treatment approach in PE/EC.

The patient with PE/EC is typically monitored for changes in BP with the goals of the normal range of BP (130-150/90-100). Hydralazine and labetalol have each been demonstrated to be useful in controlling BP in PE/EC. During the control of BP, cerebral perfusion pressure (CPP) should also be considered. As a reminder, CPP is the mean arterial pressure (MAP) – intracranial pressure (ICP), or CPP = MAP – ICP. The lower limit of the normal CPP is usually 60 mm Hg. In most situations, the ICP is unknown in a PE/EC woman, but this is where the brain imaging can be helpful. If the brain appears normal on CT, the ICP can be considered to be 10 mm Hg, and hence the MAP would need to be more than 70 mm Hg to provide a CPP of more than 60 (CPP = 70-10 mm Hg). If the brain appears to be edematous, then the ICP should be considered to be 20 mm Hg, and the MAP would need to be more than 80. Ideally, if an elevated ICP is suspected, then an ICP monitor should be inserted. One must also caution that CPP may be higher in PE/EC women than in normal women.^{6,7,9} Monitoring of ICP is not commonly done in most PE/EC patients; therefore, these basic guidelines can be followed. To assess ICP, TCD may be useful, and we will explore this concept later. Preliminary studies suggest that TCD can be used to determine CPP and the state of autoregulation in PE/EC and may therefore be useful to guide BP management. While intermittent agents can be effective for lowering BP, at times continuous infusions of antihypertensive agents are also needed.

For patients who remain in SE despite standard dosing of Mg,¹⁰ the transition of standard antiseizure medications may be needed. This can be done in several ways including the use of a loading dose of an anticonvulsant. In the past, phenytoin has been recommended as the initial drug,¹¹ but now, levetiracetam can also be given as an intravenous loading dose. Seizures may become controlled using this approach but may persist and take the form of SE.

Status epilepticus is the state of repeated or continuous seizure activity lasting for over 5 minutes. Status epilepticus is frequently nonconvulsive, so that there are no motor signs that the brain is seizing. The longer the seizures persist, the harder it is to stop them, and the more the damage to the brain. Hence, SE is a true emergency. There have been a number of treatments for SE, but two prospective randomized controlled trials have indicated that the best first drug is lorazepam, given intravenously. The treatment of refractory SE most commonly involves continuous infusions of deeply sedating agents such as midazolam, propofol, or pentobarbital. The continuous electroencephalography (cEEG) is used to monitor the biological effect of the treatment. Patients demonstrating SE may be treated with continuous midazolam infusion 0.5 to 2 mg/kg per hour to induce burst suppression. The treatment is then titrated to the EEG, and long-acting antiseizure

TABLE 146-2 Summary of the Treatment of Status Epilepticus in Eclampsia

| STAGE | MEDICATION | ENDPOINT |
|-------------------------------|---|---------------------------------|
| Brief seizure | Magnesium infusion | Clinical seizure control |
| Status epilepticus | Lorazepam, LEV or DPH, Mg | cEEG for seizure suppression |
| Refractory status epilepticus | IV midazolam or pentobarbital continuous infusion | cEEG for burst suppression coma |

The treatment may entail not only the use of magnesium but also treatments including continuous infusions of anesthetic drugs.

cEEG, continuous electroencephalography; DPH, phenytoin; IV, intravenous; LEV, Levetiracetam; Mg, magnesium.

medications are optimized. Table 146-2 shows the progression of interventions for seizures in PE/EC.

Most PE/EC patients with seizures are maintained on an antiseizure medication for the duration of critical illness. The longer-term treatment and total duration of antiseizure medications may vary and are beyond the scope of our discussion. This will likely need consultation with a neurologist for longer-term care and assessment.

STROKE AND BRAIN HEMORRHAGE IN PREGNANCY

Stroke is a potential complication of the late stages of pregnancy and can present to the ICU with either ischemic stroke or hemorrhagic stroke.^{2,12,13} Stroke frequently occurs in the context of a hypercoagulable state and has been thought to be related to EC. There are three common forms of stroke that can occur in pregnancy and may come to the attention of the intensivist: (1) cerebral sinus thrombosis (CST), (2) posterior reversible encephalopathy syndrome (PRES), and (3) intracerebral hemorrhage (ICH) related to coagulopathy including thrombotic thrombocytopenic purpura (TTP), as can be seen in a rare form of EC.^{2,12,13} These forms of stroke often can elicit severe brain edema, seizures, and coma, and present in extremis.

Cerebral sinus thrombosis, sometimes known as dural sinus thrombosis, is one of the most common forms of stroke in pregnancy.¹² The presentation is commonly subacute with progressive headache, somnolence, and then stroke-like signs. Brain imaging shows ICH with the classic locations of parasagittal white matter (Fig. 146-1). The brain is edematous and ICP is elevated. The treatment is centered on the reduction in ICP and includes systemic anticoagulation, hydration, and osmolar treatment. These patients are among the most critically ill pregnant patients with neurocritical illness. Diagnostic evaluation including MR venography is typically required. Systemic anticoagulation can be safely performed even in the setting of ICH.¹⁴ However, anticoagulation may not be enough, and invasive endovascular venous thrombectomy may be required.¹⁵ In the latter case, shielding of the fetus during angiography can be done. The use of anticoagulation is with intravenous heparin infusion with titration to moderate levels of anticoagulation. This is combined with hydration and osmolar therapy to enhance cerebral circulation. Monitoring for seizures, elevated ICP, and brain edema may be necessary if the brain edema is severe. Systemic hemodynamic management should be optimized for CPP, similar to the discussion for EC.

Posterior reversible encephalopathy syndrome is another potential complication of pregnancy.^{2,13} It may occur in the context of EC or CST, or be isolated. It is distinguished by imaging, typically MRI. The posterior parietal regions have extracellular brain edema noted on T2-weighted images, such as fluid-attenuated inversion recovery sequences. Posterior reversible encephalopathy syndrome can result from exposure to selected drugs or spontaneously during pregnancy.

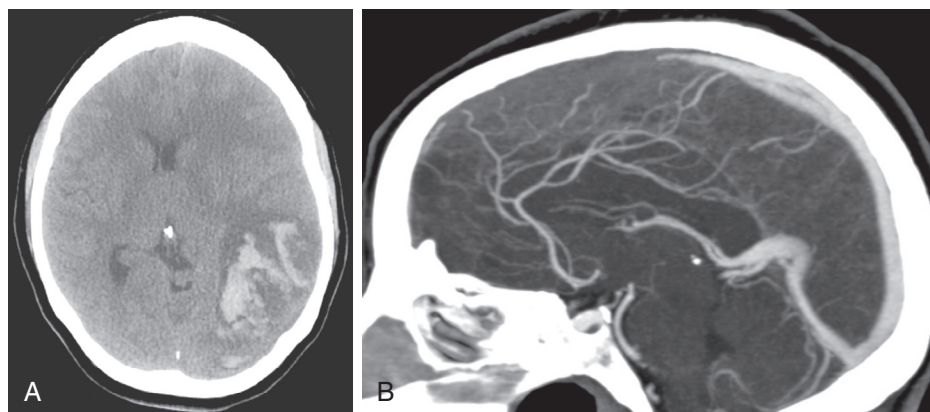


FIGURE 146-1 ■ Case example of superior sagittal sinus thrombosis giving rise to an intracerebral hemorrhage. **A**, CT brain showing a brain hemorrhage and brain edema. **B**, CT venogram showing occlusion of the anterior portion of the superior sagittal sinus. CT, computed tomography.

The overlap with PE/EC is noteworthy. The treatment is strict reduction of BP to the normal range.

Coagulopathy-related ICH may occur during the later stages of pregnancy. This can occur with the HELLP¹⁶ (hemolysis, elevated liver enzymes, low platelets) syndrome, TTP, or as a result of embolism of amniotic fluid. Coagulopathy-related ICH patients are frequently in extremis, with elevated ICP, and are treated similarly to other patients with elevated ICP. Systemic correction of coagulopathy is required.

There are less common cerebrovascular events in pregnancy—namely, subarachnoid hemorrhage and reversible vasoconstriction syndrome. The latter is characterized by an abrupt onset of headache and cerebral vasospasm in the absence of an intracranial aneurysm. This is usually self-limited but may require induced hypertension and treatment of vasospasm, similar to the typical subarachnoid hemorrhage.

MONITORING AND TREATING THE NEUROLOGICALLY IMPAIRED PREGNANT PATIENT

The critically ill pregnant patient will frequently be neurologically impaired. This impairment may range from being delirious to comatose. Use of brain imaging should be encouraged for diagnostic specificity. However, monitoring the patient for seizures, elevated ICP, and cerebral ischemia is very important. Table 146-3 outlines some of the potential means for brain monitoring in the neurologic critically ill patient: (1) cEEG monitoring: cEEG monitoring consists of routine scalp EEG using 16 to 21 electrodes to monitor for seizures. Seizures are frequently nonconvulsive, and hence EEG is necessary to observe them. Monitoring for a minimum of 48 to 72 hours has been advocated by some to diagnose seizures, and monitoring for titration of seizure suppression is necessary for SE. (2) Transcranial Doppler (TCD): TCD detects flow velocity in the brain noninvasively and can be used to determine the relative cerebral blood flow. It can derive a pulsatility index (PI), which is a noninvasive measure of vascular resistance. The PI is directly proportional to ICP and can therefore be used as a noninvasive measure of ICP. A value of PI more than 1.5 is indicative of elevated ICP in the setting of a child-bearing-aged woman (Fig. 146-2). (3) Pupillometer: The pupillometer is an automated light source and high-speed digital video camera that measures the reaction time of the pupil constriction to light.¹⁷ The pupillometer provides a summary reading called the neurologic pupil index (NPI) that has been correlated with ICP. An NPI less than 3 in the setting of brain edema indicates the presence of elevated ICP. Figure 146-3 shows an example

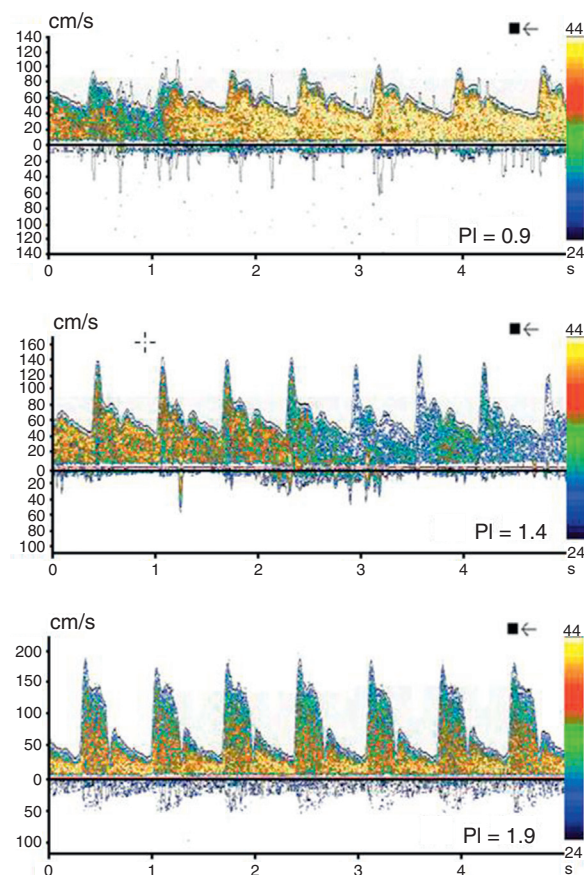


FIGURE 146-2 ■ Sequence of transcranial Doppler ultrasound of the cerebral circulation. The PI values are shown at the bottom right of each panel. The PI value increases from 0.9 to 1.9 across the panels, indicating worsening of brain edema and ICP; PI may be used as a noninvasive measure of ICP. ICP, intracranial pressure; PI, pulsatility index.

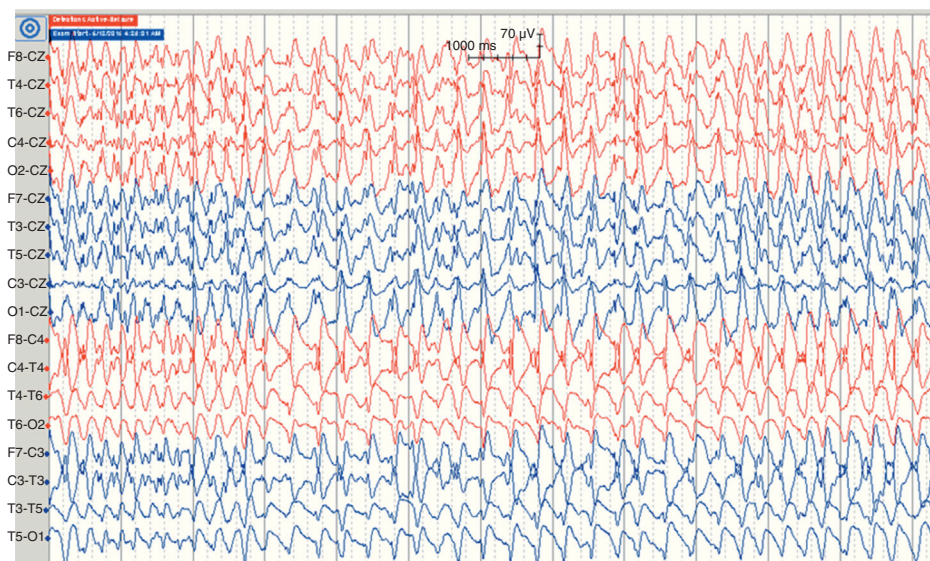


FIGURE 146-3 ■ Example of a nonconvulsive seizure detected on EEG monitoring. The generalized high-amplitude waves are similar to ventricular tachycardia and represent seizures.

TABLE 146-3

Common Tools Used to Monitor the Brain of Pregnant Women with a Central Nervous System Critical Illness

| MONITOR | SETTING | INDICATOR | INTERPRETATION |
|--------------|-------------------------------|---------------|----------------|
| EEG | Altered mental status or coma | Raw EEG | Seizure |
| TCD | PE/EC | Mean velocity | CBF |
| TCD | Coma | PI >1.5 | ICP |
| Pupillometer | Coma | NPi <3 | ICP |

CBF, cerebral blood flow; EEG, electroencephalography; ICP, intracranial pressure; NP_i, neurologic pupillary index; PE/EC, preeclampsia/eclampsia; PI, pulsatility index; TCD, transcranial Doppler ultrasound.

of TCD waveforms with increasing PI indicative of brain edema and elevated ICP.

CONCLUSION

The critical care of a pregnant patient with neurologic critical illness can be challenging. The main treatment considerations should be for

the welfare of the mother, especially in the later stages of pregnancy, when most presentations to the ICU occur. Consideration for the quick diagnosis of seizures, brain ischemia, and intracranial hypertension is most crucial in these patients.

KEY POINTS

1. Always suspect and rule out a venous sinus thrombosis in a pregnant patient presenting with acute neurologic symptoms.
2. Rapid diagnosis and control of seizures is a top priority for the pregnant patient.
3. Control of intracranial pressure and blood pressure is a key parameter in the pregnant patient with malignant hypertension and PRES.

■ References for this chapter can be found at expertconsult.com.

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ALTERED GLUCOSE REGULATION IN STRESS

At the end of the 19th century, Claude Bernard described a link between acute trauma and the development of hyperglycemia, irrespective of underlying diabetes. It was considered to be an adaptive stress response ensuring adequate glucose supply to obligatory glucose-consuming neurons, phagocytes, and reparative cells.^{1,2} Stress-induced hyperglycemia is evoked by integrated hormonal, cytokine, and nervous counterregulatory signals in glucose metabolic pathways. Essentially, hyperglycemia is due to insulin resistance in the liver and skeletal muscle. Hepatic insulin resistance leads to increased hepatic gluconeogenesis and glucose output.³ Decreased glycogen synthesis and a shift from insulin-dependent to non-insulin-dependent glucose uptake characterize skeletal muscle insulin resistance.⁴

In the acute phase of critical illness, increased levels of glucagon, cortisol, and growth hormone may jointly increase hepatic gluconeogenesis. In addition, the catecholamines epinephrine and norepinephrine released in response to acute injury promote hepatic glycogenolysis. The cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) may directly or indirectly enhance both these hyperglycemic responses.⁵

The important exercise-stimulated glucose uptake in skeletal muscle completely disappears in critically ill patients because of immobilization. Insulin-dependent glucose uptake is also hampered through the combined inhibition of glucose transporter-4 (GLUT-4) and glycogen synthase activity.^{6,7} Although some studies have shown decreased glucose oxidation⁸ through pyruvate produced by glycolysis, others have demonstrated an opposite effect during critical illness.⁹ The decrease in insulin-dependent glucose uptake in skeletal muscle is completely offset by a strong increase in total body glucose uptake, of which the mononuclear phagocyte system in the liver, spleen, and ileum are the main receivers.¹⁰ However, in skeletal muscle, non-insulin-dependent glucose uptake is also increased by the increased expression of GLUT-1.^{11,12} The overall increased peripheral glucose uptake¹³ in light of hyperglycemia underscores the pivotal role of increased hepatic glucose production during critical illness, which cannot be suppressed by exogenous glucose.¹⁴

The role of adipose tissue in the regulation of glucose metabolism during critical illness has been neglected. Nevertheless, in diabetes mellitus, adipose tissue strongly modulates insulin resistance as it is regarded to be an insulin-dependent glucose uptake organ. Recent studies have revealed that during critical illness, adipose tissue undergoes major changes.¹⁵ Possibly stimulated by illness-induced macrophage infiltration, adipocytes become more numerous and smaller and have an increased expression of the non-insulin-dependent glucose transporters GLUT-1 and GLUT-3. The levels of GLUT-4 remain unaltered. As such, adipose tissue is reprogrammed during critical illness to facilitate glucose uptake, independent of circulating insulin levels.

HYPERGLYCEMIA IN CRITICALLY ILL PATIENTS

In normal individuals, blood glucose levels are tightly regulated within the narrow range of 60 to 140 mg/dL (3.3-7.7 mmol/L), both in fed and fasted states. The World Health Organization (WHO) defined diabetic hyperglycemia as a fasting blood glucose concentration of

126 mg/dL (7 mmol/L) or higher and fed blood glucose levels higher than 200 mg/dL (11.1 mmol/L). In their 2006 guidelines, the WHO functionally defined *normoglycemia* as glucose levels associated with a low risk of developing diabetes or cardiovascular disease. Unlike the diagnostic criteria for diabetes mellitus, no clear guidelines have been established for defining hyperglycemia in critically ill patients. This explains the variations in the reported prevalence of hyperglycemia in critically ill patients.

However, stress hyperglycemia is also associated with adverse outcome in several critically ill patients. More precisely, a large cohort study of over 66,000 critically ill patients revealed a J-curved relationship between on-admission blood glucose levels and the risk of mortality, with the nadir between 100 and 150 mg/dL (5.6-8.3 mmol/L).¹⁶ In patients with an acute coronary syndrome, a similar association was observed, with the lowest risk of mortality at blood glucose levels between 80 and 100 mg/dL (4.4-5.5 mmol/L).¹⁷⁻²⁰ Importantly, in patients with established diabetes mellitus prior to critical illness or an acute coronary syndrome, the relationship between hyperglycemia and mortality was significantly blunted and somewhat shifted toward higher blood glucose level¹⁷ (Fig. 147-1).

Until recently, it was considered state of the art to tolerate blood glucose levels of up to 220 mg/dL (12 mmol/L) in fed critically ill patients. It was even suggested that this moderate hyperglycemia in critically ill patients was beneficial to organs such as the brain and blood cells, which rely solely on glucose for their energy supply and do not require insulin for glucose uptake. Treatment of blood glucose levels higher than 12 mmol/L was primarily due to the occurrence of hyperglycemia-induced osmotic diuresis and fluid shifts. Further, from the literature on diabetes, it is known that uncontrolled and pronounced hyperglycemia predisposes to infectious complications.²¹ In patients with known diabetes mellitus, more attention was paid to blood glucose levels and consequently was more strictly controlled. This approach contrasts—in hindsight—with the blunting of the J-shaped relationship between glycemia and mortality risk. Observational studies have also revealed that hyperglycemia in patients with established diabetes mellitus has an at least threefold higher risk of mortality than patients with known diabetes.²²

MAINTENANCE OF NORMOGLYCEMIA IN THE INTENSIVE CARE UNIT

The Leuven Studies

In 2001, a large prospective, randomized, controlled trial (RCT) was the first to challenge the classic dogma of beneficial stress hyperglycemia.²³ It examined the effect of tight glycemic control (TGC) with intensive insulin therapy on the mortality and morbidity of critically ill patients. Over a 1-year period, 1548 mechanically ventilated patients who were admitted to the intensive care unit (ICU), predominantly after extensive or complicated surgery or trauma, were randomly allocated to either intensive insulin therapy with blood glucose levels kept tightly between 80 and 110 mg/dL (4.5-6.1 mmol/L) or the conventional approach, which recommended insulin therapy only if blood glucose levels exceeded 12 mmol/L. The intervention of TGC comprised accurate arterial blood glucose measurements by a blood gas analyzer and a reliable continuous infusion of insulin exclusively via a central venous line using an accurate syringe-driven infusion pump. The fine insulin dose adaptations were performed by trained

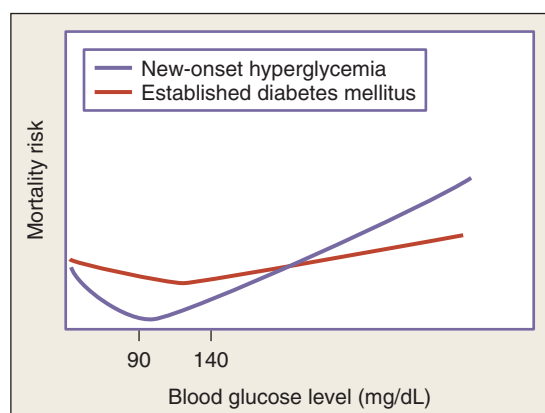


FIGURE 147-1 ■ J-shaped association of blood glucose levels with mortality risk in critically ill patients. In patients without diabetes mellitus, hyperglycemia shows an almost linear relationship with mortality risk. Hypoglycemia is associated with an even steeper increase in mortality risk. Normoglycemia during critical illness conveys the lowest risk of dying. In patients with established diabetes, the J-shaped curve is significantly flattened out.

bedside nurses and based on guidelines that require a high level of intuitive and anticipatory decision making.²³ In this study, patients were kept in a nonfasting state at all times. Dextrose 20% was administered on the first day (192 g glucose over 24 hours, or 768 kcal/d). Thereafter, enteral nutrition was started, with the daily amount progressively increased as tolerated. When enteral nutrition was insufficient, early supplemental parenteral nutrition was given, resulting in administration of 1100 nonprotein kcal/d on average.

Intensive insulin therapy, resulting in the administration of 1100 nonprotein kcal/d on average, lowered ICU mortality from 8% to 4.6% (absolute risk reduction [ARR], 3.4%) and in-hospital mortality from 10.9% to 7.2% (ARR, 3.7%). The effect occurred particularly in the population with prolonged critical illness, among whom mortality was reduced from 20.2% to 10.6%. Even patients in the conventional insulin treatment schedule with only moderate hyperglycemia (110–150 mg/dL) showed higher mortality than those in the strict glycemic control schedule.²⁴ Intensive insulin therapy also had a major effect on morbidity. It decreased the duration of ventilatory support and ICU stay, reduced the need for blood transfusions, and lowered the incidence of bloodstream infections and excessive inflammation. Even more striking, intensive insulin therapy caused a highly significant decrease in the development of critical illness polyneuropathy and acute kidney failure.

Subsequently, the effect of TGC was tested in a medical ICU setting by the same group.²⁵ The difference in in-hospital mortality, 40.0% in the control group and 37.3% in the intervention group, was not statistically significant in an intention-to-treat analysis of the 1200 included patients. However, in patients who stayed in the ICU for 3 or more days, in-hospital mortality was reduced from 52.5% to 43.0% by TGC. Intensive insulin therapy also reduced morbidity (incidence of acute kidney failure, weaning off the ventilator, ICU/hospital stay), but not as strikingly as that in the surgical study. This was, in part, explained by a larger fraction of patients in medical ICUs who were admitted with established organ damage, possibly reducing the opportunity of prevention by glucose lowering.²⁶ The fact that intensive insulin therapy to normal-for-age blood glucose targets in mainly postoperative pediatric critically ill patients reduced mortality by an ARR of 3% may further corroborate this finding.²⁷

The downside of TGC has been the increase in the incidence of hypoglycemia (blood glucose levels <40 mg/dL [<2.2 mmol/L]) despite improving patient outcome. In the Leuven studies, 5.1% (surgical ICU), 18.7% (medical ICU), and 25% (pediatric ICU) of patients

randomized to TGC experienced at least one episode of hypoglycemia. To date, long-term follow-up studies to gauge the impact of brief hypoglycemia on neurocognitive function are lacking. In addition, it is possible that fluctuations in glucose levels, such as those induced by insulin therapy based on inaccurate glycemic monitoring or by over-correction of hypoglycemia, may be more deleterious than those induced by hypoglycemia by itself. Such aspects remain to be investigated in greater detail.

The Initial Repeat Studies

Two European multicenter studies designed to assess whether intensive insulin therapy exerts benefits, with mortality as the primary endpoint, failed to reproduce the Leuven findings. The Volume substitution and Insulin therapy in severe SEpsis (VISEP) (N = 537) trial was designed as a four-arm study to assess the difference between two choices of fluid resuscitation (10% pentastarch versus modified Ringer's lactate) and the efficacy and safety of intensive insulin therapy in patients with severe sepsis and septic shock.²⁸ In this study, blood glucose targets comparable to the Leuven studies were set out for the intervention (80–110 mg/L) and control (180–200 mg/dL) groups. Likewise, insulin administration and blood glucose measurements had been standardized. Nevertheless, the insulin arm of the study was stopped early after 488 patients had been included because the rate of hypoglycemia (12.1%) in the intensive insulin therapy group was considered unacceptably high and may have been associated with higher mortality. Then, at the first planned interim analysis, the fluid resuscitation arm of the study was also suspended because of increased risk of organ failure in the 10% pentastarch arm. The primary endpoint 90-day mortality was 39.7% in the intensive treatment arm and 35.4% in the conventional treatment arm.

The GLUCONTROL multicenter randomized controlled trial (RCT) (N = 1101) investigated whether tight glycemic control (80 and 110 mg/dL) with intensive insulin therapy versus an intermediate target for blood glucose (140–180 mg/dL [7.8–10.0 mmol/L]) improved survival in a mixed population of critically ill patients.²⁹ This study was also stopped early because the target glycemic control was not reached and the incidence of hypoglycemia was 9.8%. ICU mortality did not differ between the intensive insulin therapy group (17.2%) and the control group (15.3%).

Two single-center studies in a mixed medical/surgical ICU population, both smaller than the Leuven studies, followed and were unable to reproduce any significant mortality benefit.^{30,31} In contrast, a number of small RCTs in selected subpopulations, mostly focusing on morbidity as the primary endpoint, as well as several larger implementation studies, revealed improved outcomes as the Leuven studies did.^{32–35}

NICE-SUGAR

All the studies described were in fact statistically underpowered to detect a reasonable mortality difference. To address this issue, the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) included 6100 patients from over 41 participating centers.³⁶ This study compared a blood glucose target of below 108 mg/dL (<6.0 mmol/L) versus “usual care,” which meant an intermediate blood glucose target of 140 to 180 mg/dL (8 to 10 mmol/L). As the result of the Leuven studies, clinicians had become aware of the negative impact of hyperglycemia, so tolerating higher glucose levels was considered unacceptable or even unethical by clinicians and investigators. The aim of NICE-SUGAR, therefore, was to assess whether further lowering blood glucose levels to less than 108 mg/dL (<6.0 mmol/L) in a broad context of clinical practice in ICUs, predominantly located in Australia and New Zealand, and using the normal daily clinical practice tools available would exert additional benefit. Contrary to expectations, NICE-SUGAR revealed that targeting 108 mg/dL with insulin increased 90-day mortality from 24.9% to 27.5% compared to the 140- to 180-mg/dL (8–10 mmol/L) glucose target. Excess deaths were attributed to cardiovascular causes.

COIITSS

Patients with septic shock requiring administration of glucocorticoids are faced with a high mortality risk; the severity of illness and glucocorticoid treatment makes hyperglycemia common. Therefore, this would be an optimal population in which to study whether TGC could reduce mortality. In the Corticosteroids and Intensive Insulin Therapy for Septic Shock (COIITSS) multicenter study, 509 patients were randomized to either intensive insulin therapy aiming for blood glucose levels between 80 and 110 mg/dL or conventional insulin therapy.³⁷ In the latter group, an intermediate target was used as the physicians were recommended to follow the 2004 Surviving Sepsis Campaign Guidelines (blood glucose levels <150 mg/dL [8.3 mmol/L]). Hospital mortality in the intensive insulin therapy group (45.9%) did not differ from that in the conventional group (42.9%). Poor separation of blood glucose levels between the study groups, and the small size of the study may have made it difficult to detect any treatment effect of TGC.

Meta-analyses

Nowadays, practice guidelines are ideally based on systematic reviews and meta-analyses. The two most recent meta-analyses showed that in critically ill adult patients, TGC did not significantly reduce hospital mortality but was associated with an increased risk of hypoglycemia.^{38,39} However, TGC may be beneficial to patients admitted to surgical ICUs.

CRITICAL APPRAISAL OF THE EVIDENCE FOR TIGHT GLYCEMIC CONTROL IN THE ICU

Given that the effect of controlling blood glucose levels during critical illness ranges from beneficial to no effect to potentially harmful, most clinicians are now in agreement that blood glucose levels do, in fact, play a role in patient outcome. The pre-2001 era, where blood glucose levels were rarely measured in critically ill patients, has passed. However, discrepancies in study results have made it difficult to make strong recommendations. Likewise, consensus statements on the glycemic management of hospitalized patients by the American Association of Clinical Endocrinologists and the American Diabetes Association have changed significantly over the past years.⁴⁰ While the 2004 and 2006 statements recommended stricter targets for glycemic management in the ICU, in 2009, it was advised that the starting threshold for intravenous insulin therapy in the ICU be 180 mg/dL (10 mmol/L). Once started, blood glucose levels should be maintained between 140 and 180 mg/dL (7.8–10 mmol/L). Somewhat lower levels may be appropriate in selected patient populations. Targets below 110 mg/dL (<6.1 mmol/L) are not recommended.

Still, more can be learned from the differences between the Leuven proof-of-concept studies and the subsequent repeat trials.⁴¹ First, “normoglycemia” was compared with distinct “control” targets (140–180 mg/dL or 8–10 mmol/L in NICE-SUGAR and GLUCONTROL; 180–215 mg/dL or 10–12 mmol/L in Leuven), making the studies fundamentally different. The control group in the Leuven studies reflected the assumption of hyperglycemia as a potentially beneficial adaptation. Hence, a “do-not-touch” approach unless glucose exceeded the renal threshold of 215 mg/dL was used in this group. In contrast, the NICE-SUGAR trial was executed in the “flatter” part of the observational glycemia-mortality risk curve, with 70% of the patients in the control group receiving insulin treatment to target an intermediate blood glucose level of 140 to 180 mg/dL (8–10 mmol/L) (Fig. 147-2).^{16–19} The control group in the NICE-SUGAR trial, as a result of the changed usual care, already could have benefited from reducing blood glucose level as compared with the control group in the Leuven studies. The lower observed mortality than the carefully documented expected mortality (24.9% vs. 30%, respectively) in the NICE-SUGAR control group suggests that there was already such a benefit in the control group.

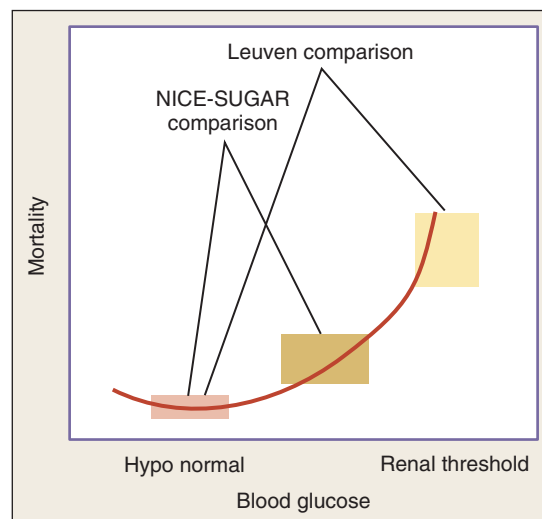


FIGURE 147-2 ■ Relationship of blood glucose levels with mortality in the NICE-SUGAR and Leuven studies. Comparing tight glycemic control with “usual care” strongly depends on mortality risk in the control group. In the Leuven proof-of-concept studies, tight glycemic control was compared with the usual care of tolerating hyperglycemia up to the renal threshold (215 mg/dL). The control group in the NICE-SUGAR trial targeted intermediate blood glucose levels (145–180 mg/dL).

Second, the level of therapy compliance, in this case, the degree of success in reaching and maintaining the preset target range for glucose in the intervention group, as well as the degree of overlap with the control group, varied greatly among the studies. The methodologic aspects of glucose measurement and the level of expertise of the nursing team with blood glucose control in the Leuven studies may have played a key role. In the Leuven studies, 70% of the patients in the intervention group were on average on target,⁴² whereas this was much less than 50% in the NICE-SUGAR trial and in several of the other repeat studies. This could be important as a recent meta-analysis suggested that studies that actually managed to adequately achieve the blood glucose target showed a reduced mortality, whereas those that did not succeed in reaching the target reported no benefit or even increased mortality.^{38,43} Maintaining normoglycemia may be more feasible in patients after surgical critical illness than in those with medical illnesses.

Third, a requirement for safe insulin dose adjusting to reach and maintain normoglycemia should be a standardized, accurate glucose measurement technology. In the NICE-SUGAR trial, a variety of glucose meters were allowed, whereas most of them have recently been shown to be unsuitable for this purpose.⁴⁴ Accuracy of certain glucometers has been shown to be extremely poor in the ICU setting, and the wide error goes in the opposite direction for the low and high glucose ranges, making it impossible to use them for targeting a very narrow glucose range.^{45,46} In addition, varying sampling sites (arterial, venous, and capillary) were accepted in the context of routine clinical practice, and these also have led to erroneous results for blood glucose levels.⁴⁷ Inaccuracy of glucose measurement may have misguided insulin titration and thereby induced (undetected) hypoglycemia and large blood glucose fluctuations. Avoiding highly variable blood glucose levels requires experience and thus has a learning curve, which is inherent with complex interventions.

Fourth, feeding strategies differed in the major studies. The substantially higher amounts of parenteral nutrition in the Leuven studies, although still below normal caloric requirements on average, may have increased the severity of stress-induced hyperglycemia, and thus, the intervention may have been, in part, directed to counteract this side effect of parenteral nutrition. In the NICE-SUGAR trial, feeding relied almost exclusively on the enteral route (80 kcal intravenous glucose on

the first day; on average, a total of 880 kcal/d), whereas in the Leuven studies, early parenteral nutrition (768 kcal on the first day) supplemented insufficient enteral feeding, resulting in an average of 1100 kcal/d for adult patients. Insulin treatment in a nutritionally deprived state early in the disease course, as in the NICE-SUGAR trial as a result of their feeding guidelines, may have been deleterious by evoking a global substrate deficit via insulin-induced counteracting of proteolysis, lipolysis, glycogenolysis, and gluconeogenesis, which could be vital in starvation.

Fifth, in a setting where hyperglycemia is triggered by surgery or trauma, the equivalent of acute ischemia/reperfusion, the delay between the onset of hyperglycemia and the start of glycemic control is short. In contrast, when ICU patients already suffered from chronic illness prior to ICU admission and hyperglycemia was present for a longer time, adaptive changes to protect cells against elevated extracellular glucose levels may have been induced, such that acute lowering of blood glucose levels may be harmful. Alternatively, the time window for prevention of toxicity may have passed and irreversible damage done.⁴⁸ Such a mechanism was suggested by the pooled analyses of the two Leuven studies⁴² and by the different results of RCTs on glucose control in patients with type 2 diabetes.⁴⁹⁻⁵⁴

Finally, insulin therapy induces a shift of potassium from extracellular to the intracellular compartments. This may induce hypokalemia and hypokalemia-induced arrhythmias. By using arterial blood and an accurate point-of-care blood gas analyzer for glucose monitoring with each blood glucose check, potassium levels can be measured and corrected when needed.

All these differences may have contributed to the different outcomes in different studies. It has become clear that results from single-center, proof-of-concept studies cannot simply be repeated in large multi-center effectiveness trials, particularly when studying the effects of a complex intervention, which is regularly incompletely implemented in the repeat studies.⁵⁵ Hence, in reality, such studies did not investigate the same intervention as the proof-of-concept study.

BIOLOGICAL RATIONALE FOR TIGHT GLYCEMIC CONTROL

Research using human material, animal models, and in vitro systems has unraveled potential mechanistic explanations for the beneficial effects of TGC (Table 147-1). As in diabetes mellitus, insulinization to lower blood glucose levels exerts its effects on an array of biological pathways. Striving for metabolic control and inhibiting excess inflammation and mitochondrial damage seem to be of chief importance. Further molecular biology research will not only be essential to fine-tune TGC with other metabolic treatment strategies but also contribute to the quest to explain the potential harm of glucose lowering in critical illness.

Implications for Daily Practice

The failure to repeat the results from well-controlled, meticulously executed, proof-of-concept studies in large pragmatic confirmation trials has indicated that TGC is not yet ready to be broadly implemented in every ICU across the globe (Fig. 147-3). This does not undermine the scientific validity of the benefits of TGC in critically ill patients. Blood glucose levels should be normalized as much as safely

possible without causing a too rapid lowering of blood glucose levels, without an increase in the incidence of hypoglycemia, and without large blood glucose fluctuations. Therefore, it is advisable to gradually tighten glycemic control under diligent monitoring of the safety aspects. Nevertheless, three conditions should always be met:

1. Accurate and frequent blood glucose measurements as a reliable invasive, continuous glucose sensor are not yet available. Capillary blood samples are unreliable in the ICU and should never be used. Blood glucose measurements on on-site blood gas analyzers are the currently preferred devices. However, the use of a single handheld blood glucose meter with an acceptable error range and using arterial blood may be an alternative.
2. Continuous intravenous insulin administration using accurate syringe pumps
3. Thorough training of ICU healthcare providers (i.e., physicians and nurses) in the execution of the complex intervention of TGC. This stimulates intuitive and anticipatory decision making, as computer algorithms to assist in TGC still have to show their benefit on patient outcome.

CONCLUSION

The discrepancy in study quality and results does not permit clear-cut, evidence-based recommendations for one optimal blood glucose target in heterogeneous ICU populations and settings. One could recommend keeping blood glucose levels between 80 and 130 mg/dL (4.4-7.2 mmol/L). A broader target range would partially compensate for the inaccuracies of handheld blood glucose meters and allow more inexperienced ICU teams to implement targeted glycemic control. Trying to steer blood glucose levels within a narrow range without proper measurement devices and experience may cause large blood glucose variations and hypoglycemia. Therefore, frequent and reliable measurements of blood glucose levels remain mandatory.

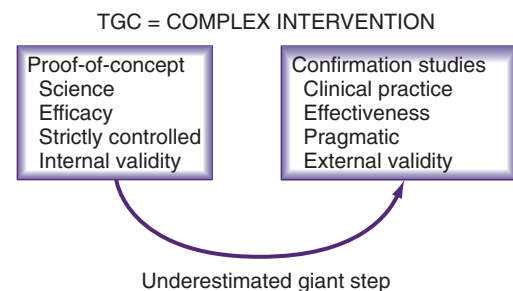


FIGURE 147-3 ■ Difference between proof-of-concept studies and confirmation studies. Proof-of-concept studies are driven by the specific question of whether a certain intervention may work (efficacy). The intervention is tested in a highly controlled setting to minimize confounding factors, resulting in high internal validity. In contrast, confirmation studies wonder whether this intervention would work in clinical practice (effectiveness). Potential confounders are allowed to test the generalizability and pragmatic character of the intervention (external validity). When testing complex interventions, these differences between proof-of-concept and confirmation studies in their aim and setup are often underestimated.

TABLE 147-1 Studies of Biological Effects of Tight Glycemic Control Also Point to Its Potential Benefit

| PATHWAY | CRITICAL ILLNESS | EFFECT IIT | REFERENCES |
|---|---------------------|-------------|------------|
| INSULIN RESISTANCE AND GLUCOSE UPTAKE | | | |
| Circulating insulin | Transient ↑, then ↓ | Transient ↑ | 56,57 |
| Circulating C-peptide | Transient ↑, then ↓ | ↑ | 56 |
| Circulating adiponectin (insulin-sensitizing hormone) | ↓ | ↑ | 56,58 |

Continued

TABLE 147-1 Studies of Biological Effects of Tight Glycemic Control Also Point to Its Potential Benefit—cont'd

| PATHWAY | CRITICAL ILLNESS | EFFECT IIT | REFERENCES |
|---|-------------------------|-------------------|-------------------|
| LIVER | | | |
| Insulin signaling | ↓ | = | 56 |
| Gluconeogenesis (phosphoenolpyruvate carboxykinase mRNA) | ↑ | = | 59 |
| Cytokines, growth hormone, glucagon, cortisol | ↑ in acute phase | ≈, ↑, ?, ↓ | 57,60-62 |
| Glucose uptake and glycogen synthesis (glucokinase mRNA) | ↑ | = | 63 |
| Insulin-like growth factor binding protein-1 mRNA and circulating levels | ↑ | = | 59 |
| SKELETAL MUSCLE | | | |
| Insulin signaling | ↓ | ↑ | 56 |
| Glucose transporter-4 | ↓ | ↑ | 63 |
| Hexokinase-II | ↓ | ↑ | 63 |
| CELLULAR ENERGY PROVISION | | | |
| Microcirculation | ↓ | | |
| Endothelial activation, endothelium-mediated vasorelaxation | ↓, ↓ | ↓, ↑ | 60,64 |
| Perfusion and oxygen supply | ↓ | = | 65,66 |
| Endothelial nitric oxide synthase, inducible nitric oxide synthase | ↓, ↑ | =, ↓ | 60,67 |
| Endogenous nitric oxide synthase inhibitor, asymmetric dimethylarginine | ↑ | ↓ | 67-69 |
| Mitochondrial function | ↑ | ↓ | 65,70,71 |
| Toxic glucose metabolites compromising mitochondrial function (dicarbonyls) | ↑ | ↓ | 70 |
| Oxidative stress | ↑ | ↓ | 70 |
| INFLAMMATION, INNATE IMMUNITY, COAGULATION | | | |
| C-reactive protein | ↑ | ↓ | 27,72,73 |
| Cytokines | ↑ | ≈ | 57,60 |
| Mannose-binding lectin | ↑ | ↓ | 73 |
| Monocyte phagocytosis and oxidative burst | ↓ | ↑ | 64,72 |
| Coagulation | abnormal | = | 57 |
| Fibrinolysis | ↑ | =, ↑ | 57,74 |
| ANABOLISM | | | |
| Skeletal muscle protein content | ↓ | ↑ | 71 |
| Insulin-like growth factor-1 | ↓ | ↓ | 61 |
| MYOCARDIAL FUNCTION | | | |
| Myocardial contractility | ↓ | ↑ | 64 |
| Myocardial damage | ↑ | ↓ | 27 |
| BILE AND LIPID ABNORMALITIES | | | |
| Hypertriglyceridemia | ↑ | ↓ | 63,75 |
| Free fatty acids | ↑ | ↓ | 75 |
| HDL and LDL cholesterol | ↓ | ↑ | 63 |
| Cholestatic liver dysfunction and biliary sludge | ↑ | ↓ | 76 |
| Glucose and triglyceride storage in adipose tissue | ↑ | = | 15 |
| Adipocyte size | ↓ | = | 15 |
| Macrophage infiltration in adipose tissue | ↑ | ↓ | 15 |

KEY POINTS

1. "Stress hyperglycemia" results from the interplay of an increased hepatic glucose output and a decreased insulin-dependent glucose uptake in skeletal muscle. Adipose tissue seems to shift from insulin-dependent to insulin-independent glucose uptake.
2. Stress hyperglycemia was once regarded as a beneficial response. Nevertheless, large observational studies have shown a J-shaped association of blood glucose levels with mortality risk in critically ill patients. In patients with established diabetes mellitus, this relationship is significantly blunted. As such, new-onset hyperglycemia is associated with a higher mortality risk than hyperglycemia in patients with diabetes mellitus.
3. In 2001, a large proof-of-concept study challenged the classic dogma that so-called stress hyperglycemia of up to 12 mmol/L (220 mg/dL) is a beneficial response in nondiabetic patients.

Glycemic control at less than 6.1 mmol/L (110 mg/dL) with exogenous insulin reduced mortality and morbidity among critically ill patients in a surgical ICU.

4. Two other single-center studies from the Leuven investigators showed similar effects of tight glycemic control in medical and pediatric ICU patients. However, several repeat studies could not confirm the beneficial effects of tight glycemic control. The NICE-SUGAR multicenter trial even showed an increased mortality risk by tight glycemic control.
5. Differences in patient populations, blood glucose control in the "usual care" group, nutritional strategies, and methodology of blood glucose measurements may all have contributed to the variability in the treatment effect of tight glycemic control.

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This paper reported the first large (N = 1548) prospective, randomized, controlled single-center study showing that insulin-titrated maintenance of normoglycemia (less than 110 mg/dL) during intensive care improves outcome of (surgical) ICU patients.

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This manuscript compares the increased mortality risk of tight glycemic control (<110 mg/dL) with an intermediate blood glucose target (140–180 mg/dL) during critical illness in a large (N = 6100) multicenter trial.

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This article gives insight on why tight glycemic control could potentially have different treatment effects in repeat studies in contrast to the proof-of-concept studies.

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During the stress response, the central nervous system (CNS) induces activation of both the sympathoadrenergic system (by release of catecholamines) and the hypothalamic-pituitary-adrenal (HPA) axis (by release of steroid hormones, glucocorticoids (GCs), and mineralocorticoids), with the target of maintaining homeostasis by influencing metabolic, cardiovascular, immunologic, and endocrine functions. In this context, the adrenal gland plays a key role, combining the location for synthesis and expression of catecholamines, GCs, androgenic hormones, and factors of the renin-angiotensin-aldosterone (RAA) system. Acute and chronic inflammatory diseases include stimulation of the HPA axis by the immune system, thereby leading to morphologic and functional changes, especially of the adrenal cortex. This phenomenon has been described for acute infectious diseases as well as for sepsis and septic shock.

Over 50 years ago, the seminal observation was made that administering an adrenal cortical steroid extract to a patient with progressive, active rheumatoid arthritis slowed progression of the disease. This soon led to the development of synthetic adrenal cortical steroids, which gained a remarkable reputation in the treatment of a wide range of inflammatory and autoimmune disorders. However, it soon became apparent that this efficacy did not come without a cost in terms of potentially serious adverse effects. In patients with sepsis and septic shock, negative results of trials with high doses of GCs evoked skepticism over the years. Meanwhile, several randomized trials revealed contradictory results with low doses of corticosteroids in patients with septic shock. Hence, there is still controversy about which patients profit best from this therapy and how to define and evaluate adrenal gland disorders.¹⁻⁴

ANATOMY OF THE ADRENAL GLAND

The two paired adrenal glands are located in the retroperitoneal soft tissue near the top of each kidney. In neonates, the adrenal glands are relatively large (approximately one-third of the kidney's size) compared with other organs. In the postnatal period, the cortex portion shrinks, leading not only to a relatively but also an absolutely smaller size of the organ. In adults, each adrenal gland weighs 4 to 5 g, has a flat form with a sagittal diameter of less than 1 cm, a transverse diameter of 3 cm, and a craniocaudal diameter of 4 to 5 cm. The right gland has a triangle/pyramid-like shape, whereas the left gland has a half-moon shape.

Circulatory supply to the adrenals, with a flow rate of about 5 mL per minute, is maintained by up to 50 arterial branches from the aorta, renal arteries, and inferior phrenic arteries for each gland. Blood flow is directed from the capsule into the subcapsular arteriolar plexus through the cortex toward the medulla, where a single vein drains the blood entering the vena cava or the renal vein. Direct blood supply to the medulla is maintained by medullary arteries.

The adrenal cortex receives afferent and efferent innervation. Direct contact of nerve terminals with adrenocortical cells has been suggested, and chemoreceptors and baroreceptors present in the adrenal cortex infer efferent innervation. Diurnal variation in cortisol secretion and compensatory adrenal hypertrophy are influenced by adrenal innervation. Splanchnic nerve innervation has an effect in regulating adrenal steroid release. The adrenal medulla secretes the catecholamines epinephrine and norepinephrine, both of which affect blood

pressure, heart rate, sweating, and other activities regulated by the sympathetic nervous system. The adrenal cortex is divided into three layers: (1) the zona glomerulosa, just under the capsule, (2) the zona fasciculata, the middle layer, and (3) the zona reticularis, the innermost, net-like patterned area with reticular veins draining into medullary capillaries. The zona glomerulosa exclusively produces the mineralocorticoid aldosterone; the zonae fasciculata and reticularis produce GCs and androgens.⁵

PHYSIOLOGY OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The adrenal glands are part of a complex system that produces interacting hormones to maintain physiologic integrity, especially during the stress response.^{6,7} This system, the *HPA axis*, includes the hypothalamic region that produces corticotropin-releasing hormone (CRH), which stimulates the pituitary gland. The pituitary gland is composed of two major structures: the adenohypophysis (anterior pituitary) and neurohypophysis (posterior pituitary). The anterior pituitary is responsible for the secretion of corticotropin (adrenocorticotrophic hormone [ACTH]), thyroid-stimulating hormone (TSH), growth hormone (GH), β -lipotropin, endorphins, prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The posterior pituitary secretes vasopressin (antidiuretic hormone [ADH]) and oxytocin. Corticotropin regulates the production of corticosteroids by the adrenal glands. Hypothalamic neurons receive input from many areas within the CNS; they integrate these inputs and initiate an output to the anterior pituitary via the median eminence. The median eminence secretes releasing hormones into a hypophyseal portal network of capillaries that connect the median eminence with the pituitary hormones.

The anterior pituitary gland secretes corticotropin (ACTH) under stimulation from hypothalamic CRH. ACTH, in turn, stimulates the synthesis and release of GCs, mineralocorticoids, and androgenic steroids from the adrenal gland. In terms of a feedback loop, ACTH release is inhibited by GCs, which act on both the pituitary corticotrophic cells and hypothalamic neurons. ACTH is also released during stress, independent of the circulating serum cortisol level. CRH, vasopressin, and norepinephrine act synergistically to increase ACTH release during stress. Endorphinergic pathways also play a role in ACTH regulation. Acute administration of morphine stimulates release of ACTH, while chronic administration blocks secretion of ACTH. ACTH and cortisol are secreted normally in a diurnal pattern, with lowest concentrations between 10:00 PM and 2:00 AM and highest levels around 8:00 AM. Samples obtained at different times can provide useful dynamic information regarding HPA function. Loss of diurnal rhythm may indicate hypothalamic dysfunction.

The HPA axis is stimulated not only by physical or psychic stress but also by peptides such as ADH and cytokines. Thus, the HPA axis plays an important role during infections and immunologic disorders.^{8,9} Via interaction with the RAA system regulating fluid and salt balance, synthesis of androgens (e.g., dehydroepiandrosterone) with a possible impact on immunomodulation and the sympathoadrenergic system, the HPA axis is probably the most important organ of the stress response. Stimulation of the immune system by infections induces the release of proinflammatory cytokines such as tumor necrosis factor

alpha (TNF- α), interleukin (IL)-1 β , or IL-6. Following a cascade, these cytokines stimulate both the hypothalamus and the anterior pituitary gland, which ultimately leads to the release of GCs. IL-6 is also able to induce a steroid release directly from the adrenal gland. The adequate increase of GC levels during inflammation is a crucial factor for an appropriate stress response. In acute infections, this release maintains metabolic and energy integrity. If the process is chronic, the HPA axis develops an adaptation, which induces typical clinical manifestations such as hypercatabolic states, hyperglycemia, and suppression of androgens, growth, and thyroid hormones. These changes, however, may increase the risk of secondary infections. Increased cortisol levels suppress higher regulatory levels of the HPA axis in terms of a negative feedback loop. Hence, after major surgery or during sepsis and septic shock, high cortisol and low ACTH levels are detectable.^{10,11} Even the infusion of dexamethasone or CRH is not able to suppress increased cortisol levels in these patients.^{12,13} Several investigations have demonstrated that adrenal cortisol synthesis in critically ill patients is not regulated by ACTH but by paracrine pathways via endothelin, atrial natriuretic peptide, or cytokines such as IL-6.¹⁴⁻¹⁶ IL-6 directly induces the adrenal cortex to release cortisol, which, in chronic courses, can worsen the prognosis.¹⁷

CELLULAR RESPONSE TO ADRENOCORTICAL HORMONES AND RELATED DRUGS

Cortisol, the major free circulating adrenocortical hormone, is a hydrophobic hormone and circulates in the bloodstream bound to protein. Cortisol-binding globulin (or transcortin)-protein complexes account for about 95% of circulating cortisol, but only the free form is biologically active with a plasma half-life of 60 to 120 minutes. Cortisol is metabolized by hydroxylation in the liver, and metabolites are excreted in the urine. Steroid hormones enter the cytoplasm of cells where they combine with a receptor protein. Metabolic, immunologic, and hemodynamic responses to adrenocortical steroid hormones are regulated in a very complex manner that includes transactivation, transcription, posttranscriptional/translational regulation, and nongenomic effects. The immediate nongenomic effects of steroid hormones are primarily attributed to mineralocorticoids (aldosterone), with rapid activation of the sodium-proton exchanger, increase in intracellular Ca⁺⁺ levels, and activation of second messenger pathways.^{18,19} A randomized trial in patients during cardiac catheterization revealed that within minutes after aldosterone injection, cardiac index and arterial pressure increased significantly for 10 minutes and returned to baseline thereafter.²⁰ Interestingly, the genomic effects of aldosterone seemed to be mediated by binding to GC receptors (GRs) and not to mineralocorticoid receptors.²¹ There is evidence that GC, like cortisol, also modulates immune functions by rapid, nongenomic effects via nonspecific interactions with cellular membranes and specifically binding to membrane-bound GRs.²² Nonspecific membrane effects have been demonstrated for inhibition of sodium and calcium cycling across plasma membranes by impairing Na⁺/K⁺-ATPase and Ca⁺⁺-ATPase. Moreover, the rapid activation of lipocortin-1 and inhibition of arachidonic acid release after GC were independent of GR translocation. Finally, high-sensitivity immunofluorescence staining revealed membrane-bound GRs on circulating B lymphocytes and monocytes.²²

The multiple mechanisms by which GCs modulate cellular responses include mainly genomic pathways.²³⁻²⁵ Nongenomic effects are thought to account for immediate immune effects of high doses of GC, whereas membrane-bound receptors probably mediate low-dose GC effects. The classic model is that GCs bind to the cytoplasmic ligand-regulated GC receptor alpha (GR α), which is an inactive multiprotein complex consisting of two heat shock proteins (hsp90) acting as molecular chaperones, as well as other proteins (Fig. 148-1). Upon GC binding to GR α , a conformational change causes dissociation of hsp90, with subsequent nuclear translocation of GR α homodimers, binding of

GR α to GC response elements (GREs) of DNA, and transcription of responsive genes (transactivation) such as lipocortin-1 and β_2 -adrenoreceptors. Alternatively, GR α may bind to negative GRE (nGRE) and repress transcription of genes (transrepression) such as pro-opiomelanocortin (POMC). More important, transrepression without direct binding of GR α to GRE by protein-protein interactions of GR α with transcription factors, nuclear factor kappa B (NF- κ B), and AP-1 has been recognized as a key step by which GC suppresses inflammation.²⁶ In turn, synthesis of TNF- α , IL-1 β , IL-2, IL-6, IL-8, inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2, cell adhesion molecules, and growth factors is inhibited, and apoptosis promoted.²⁷ In addition, NF- κ B repression may be mediated by GC-induced upregulation of the cytoplasmic NF- κ B inhibitor, I κ B α (see Fig. 148-1), which prevents translocation of NF- κ B.²⁸ Clinical investigations provide support for the presence of endogenous GC inadequacy in the control of inflammation and peripheral GC resistance.²⁹ With GC treatment, the intracellular relations between the NF- κ B and GR α signaling pathways change from an initial NF- κ B-driven and GR α -resistant state to a GR α -sensitive one. However, data are conflicting and probably do not explain the early (<2 hours) suppressive effects of GC but may account for the longer-term dampening effect of GC on inflammatory processes.²³

Besides transcriptional regulation, posttranscriptional, translational, or posttranslational processes have been described for GC-induced modulation of COX-2, TNF- α , GM-CSF, IL-1 β , IL-6, IL-8, and interferon gamma (IFN- γ).²³ Furthermore, GCs act at multiple levels to regulate iNOS expression via (1) decreased iNOS gene transcription and mRNA stability, (2) reduced translation and increased degradation of the iNOS protein by the cysteine protease, calpain,³⁰ (3) limitation of the availability of the NOS cofactor, tetrahydrobiopterin, (4) reduced transmembranous transport and de novo synthesis of the NOS substrate, L-arginine, and (5) lipocortin-1-induced inhibition of iNOS.^{31,32} Together, these complex mechanisms result in the ability of GC to inhibit inflammation and to stabilize hemodynamics. Finally, GRs have been found in nearly every nucleated cell in the body, and since each cell type has specific responses to GC, it follows that GCs have many effects in the body, equally true of endogenously produced GC hormones or exogenously administered GC medications. Both increase hepatic production of glucose and glycogen and decrease peripheral use of glucose. Steroids also affect fat and protein metabolism. They increase lipolysis both directly and indirectly by elevating free fatty acid levels in the plasma and enhancing any tendency toward ketosis. GCs further stimulate peripheral protein metabolism, using the amino acid products as gluconeogenic precursors.

DEFINITIONS OF ADRENAL INSUFFICIENCY

Adrenal glands may stop functioning when the HPA axis fails to produce sufficient amounts of the appropriate hormones. *Primary adrenal insufficiency* is defined by the inability of the adrenal gland to produce steroid hormones even when the stimulus by the pituitary gland via corticotropin is adequate or increased. Primary adrenal insufficiency affects 4 to 6 out of 100,000 people. The disease can strike at any age, with a peak between 30 and 50 years, and affects males and females about equally. In 70% of cases, the cause is a primary destruction of the adrenal glands by an autoimmune reaction ("classical" Addison's disease or autoimmune adrenalitis), with about 40% of patients having a history of associated endocrinopathies. Most adult patients have antibodies against the steroidogenic enzyme, 21-hydroxylase,³³ but their role in the pathogenesis of autoimmune adrenalitis is uncertain. In the other 30%, the adrenal glands are destroyed by cancer, amyloidosis, antiphospholipid syndrome, adrenomyeloneuropathy, acquired immunodeficiency syndrome (AIDS), infections (e.g., tuberculosis, cytomegaly, fungi), or other identifiable diseases (Box 148-1). In these cases, the typical morphologic changes of the adrenal cortex are atrophy, inflammation, and/or necrosis. In primary adrenal insufficiency, the whole adrenal cortex is involved,

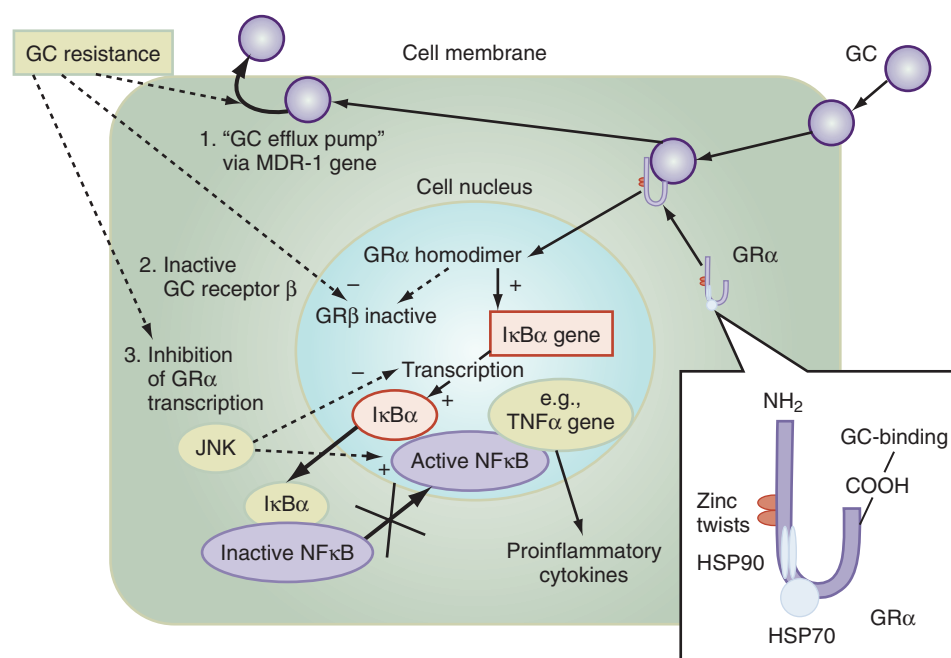


FIGURE 148-1 ■ Cellular mechanisms of glucocorticoid effects (right) and glucocorticoid resistance (left). After passive transport through the cell membrane, glucocorticoids (GC) bind to the intracellular GC receptor alpha (GR α), which is sequestered in the cytoplasm, bound to the heat-shock protein (HSP) complex that comprises chaperone molecules HSP70 and HSP90. Binding of GC to GR α allows formation of a homodimer that is transported into the nucleus. GR-mediated transcription induces inhibitor kappa B alpha (I κ B α), which binds to and inhibits nuclear factor kappa B (NF- κ B). Thus, GC inhibits the NF- κ B-mediated synthesis of proinflammatory cytokines like tumor necrosis factor alpha (TNF- α). Impaired GC sensitivity (GC resistance) includes three major pathways (dotted arrows): (1) decreased cytoplasmatic GC concentrations secondary to increased P-glycoprotein-mediated efflux of GC due to overexpression of the MDR-1 gene; (2) increased expression of a truncated splice variant of the GR that is unable to transactivate GC-sensitive genes (GR β); and (3) activation of proinflammatory mediators via upstream kinases (JNK), which can directly inhibit GR transcription activity. GC, glucocorticoids; GR, glucocorticoid receptor; HSP, heat shock protein; JNK, c-Jun N-terminal kinase; MDR-1, multidrug resistance gene 1.

BOX 148-1 Etiology of Adrenal Insufficiency

PRIMARY ADRENAL INSUFFICIENCY

- Autoimmune adrenalitis (Morbus Addison), often with concomitant endocrinopathies
- Hemorrhage (trauma, anticoagulants)
- Infarction, thrombosis
- Tumors
- Infections (tuberculosis, cytomegaly, fungi, AIDS)
- Amyloidosis, hemochromatosis, sarcoidosis
- Congenital hyper- or hypoplasias
- Congenital ACTH resistance
- Adrenomyeloneuropathy

SECONDARY ADRENAL INSUFFICIENCY (LESIONS OF PITUITARY AND/OR HYPOTHALAMIC REGIONS)

- Tumors
- Hemorrhages, apoplexy
- Infections, inflammations
- Autoimmune lesions
- Trauma, surgery
- Radiation
- Congenital syndromes (e.g., familial CBG deficiency)

resulting in a deficiency of GCs, mineralocorticoids, and adrenal androgens.^{34,35}

Secondary adrenal insufficiency is characterized by adrenal hypofunction due to the lack of pituitary ACTH or hypothalamic CRH. Diseases of the anterior pituitary that can cause secondary adrenal insufficiency include neoplasms (e.g., craniopharyngiomas, adenomas), infarction (e.g., Sheehan's syndrome, trauma), granulomatous disease (e.g., tuberculosis, sarcoidosis), hypophysectomy, and infection.³⁶ Causes also include hypothalamic dysfunction, such as after irradiation or surgical intervention (see Box 148-1). Because aldosterone secretion is more dependent on angiotensin II than on ACTH, aldosterone deficiency is not a problem in secondary adrenal insufficiency. Selective aldosterone deficiency can occur as a result of depressed renin secretion and angiotensin II formation.³⁴ Rarely, patients have an isolated deficiency of CRH,³⁷ and lymphocytic hypophysitis with subsequent adrenal insufficiency has been described in women.³⁸ These disorders may lead to an isolated ACTH deficiency.³⁴

The so-called *tertiary adrenal insufficiency*, which is often summarized together with secondary forms, commonly occurs after withdrawal of exogenous GCs. Many of these patients do well during normal activities but are unable to mount an appropriate GC response to stress. This effect depends on the dose and duration of treatment

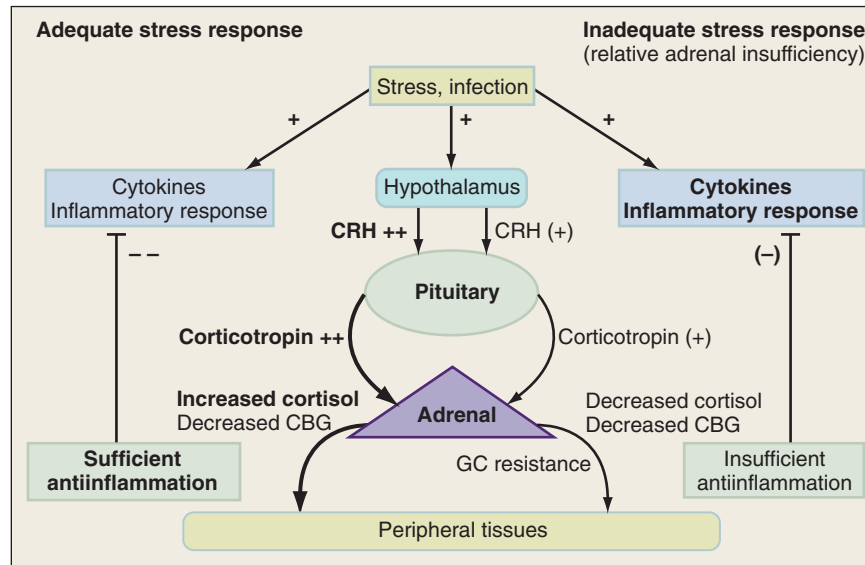


FIGURE 148-2 ■ Concept of relative adrenal insufficiency (RAI). Unlike in an adequate stress response (*left*), RAI may occur when causal or additional factors impair the function of the hypothalamic-pituitary-adrenal (HPA) axis. This may be due to microcirculatory failure, additional drugs like antibiotics, anesthetic drugs, infections, long-term use of steroids, or hemorrhages. Impaired HPA axis function results in an insufficient antiinflammatory response and an increased inflammatory response. Plus (+) denotes activation; minus (–), inhibition. CBG, cortisol-binding globulin; CRH, corticotropin-releasing hormone; GC, glucocorticoids.

and varies greatly from person to person. It should be anticipated in any patient who has been receiving more than 30 mg of hydrocortisone per day (or 7.5 mg of prednisolone or 0.75 mg of dexamethasone per day) for more than 3 weeks.³⁵ If supraphysiologic doses of GCs have been administered to a patient for more than 1 to 2 weeks, the drug should be tapered to allow for adrenal gland recovery. It may take 6 to 12 months for the adrenal glands to recover fully after prolonged use of exogenous GCs.³⁹ Since ACTH is not a major determinant of mineralocorticoid production, the basic deficit in adrenal insufficiency is that of deficient GC production. It is important that neither the dose of applied GCs, nor the time of treatment, nor the basal plasma level of cortisol allows sufficient assessment of the function of the HPA axis. Several drugs have also been described to induce adrenal insufficiency, either by directly affecting adrenocortical steroid release (e.g., fluconazole, etomidate)^{40,41} or by enhanced hepatic metabolism of cortisol (e.g., rifampicin, phenytoin).³⁵

Isolated hypoaldosteronism is very rare and should be suspected in cases of hyperkalemia in the absence of renal insufficiency. The main causes for isolated deficiency of aldosterone secretion are congenital deficiency of aldosterone synthetase, hyporeninemia due to defects in the juxtaglomerular apparatus, or treatment with angiotensin-converting enzyme inhibitors that lead to loss of angiotensin stimulation. Other forms of hypoaldosteronism usually occur in patients with chronic renal disease and/or diabetes mellitus.

■ RELATIVE ADRENAL INSUFFICIENCY

The aforementioned forms of adrenal insufficiency, which lead to an absolute deficiency of steroid production, are rare in critically ill patients (0% to 3%).⁴² To reflect the notion that subnormal adrenal corticosteroid production during acute severe illness can also occur without obvious structural defects in the HPA axis, deficiency syndromes due to a dysregulation have been termed *functional adrenal insufficiency*.⁴³ Functional adrenal insufficiency can develop during the course of critical illness and is usually transient.³⁵ Decreased levels of GCs occur much more often; these levels might be sufficient in normal subjects but are too low for stress situations, owing to higher need, and

are associated with a worse outcome.⁴⁴ This led to the concept of *relative adrenal insufficiency* (RAI). The major cause for RAI is inadequate synthesis of cortisol due to cellular dysfunction. Hence, in contrast to absolute adrenal insufficiency, the morphologic changes in the adrenal glands associated with RAI may be minor, sometimes characterized by cellular hyperplasia within the adrenal cortex. This is often combined with peripheral GC resistance of the target cells, which is caused by inflammatory events and aggravates the clinical course, although the absolute cortisol serum levels might be normal.⁴⁵ In septic shock, RAI may be due to impaired pituitary corticotropin release, attenuated adrenal response to corticotropin, and reduced cortisol synthesis (Fig. 148-2).^{35,46,47} In addition, cortisol transport capacity may be reduced, and response to cortisol may be impaired at the tissue level by cytokines modulating GC receptor affinity to cortisol and/or GREs.^{48,49} In clinical trials, it was demonstrated that prolonged treatment of systemic inflammation in patients with severe acute respiratory distress syndrome (ARDS) with methylprednisolone can improve the decreased GC response by increasing the GC receptor affinity and reducing the NF-κB-mediated DNA binding and transcription of proinflammatory cytokines.²⁹ Thus, if RAI can be identified, treatment with supplemental corticosteroids may be of benefit.³⁵ Prevalence of RAI in the critically ill varies from 0% to 77% with different definitions, cutoff values, study populations, and adrenal function tests^{34,35,46,50,51} and may be as high as 50% to 75% in septic shock.⁵²

■ EVALUATION OF ADRENAL INSUFFICIENCY

In clinical practice, assessment of adrenal function is difficult, especially in critically ill patients, since the diurnal rhythm is disrupted. Values indicating normal adrenocortical function are listed in Box 148-2. Normally, serum cortisol concentrations in the morning (8:00 AM) of less than 3 µg/dL (80 nmol/L) are strongly suggestive of absolute adrenal insufficiency,⁵³ while values below 10 µg/dL (275 nmol/L) make the diagnosis likely. Basal urinary cortisol and 17-hydroxycorticosteroid excretion is low in patients with severe adrenal insufficiency but may be low-normal in patients with partial

BOX 148-2**Values Indicating Normal Adrenocortical Function**

- Plasma cortisol (7:00 to 8:00 AM): 5 to 25 µg/dL (135 to 700 nmol/L)
- Plasma ACTH (7:00 to 8:00 AM): <70 pg/mL
- Urine excretion rate of free cortisol: 20 to 90 µg/d
- Urine excretion rate of 17-hydroxycorticosteroid (17-OHCS): 4 to 10 mg/d

adrenal insufficiency. Generally, baseline urinary measurements are not recommended for the diagnosis of adrenal insufficiency. To differentiate among primary, secondary, and tertiary adrenal insufficiency in cases of low cortisol, it is recommended to measure plasma ACTH concentrations simultaneously. Inappropriately low serum cortisol concentrations in association with increased ACTH concentrations are suggestive of primary adrenal insufficiency, whereas the combination of low cortisol and ACTH concentrations indicates secondary or tertiary disease. This diagnosis, however, should be confirmed by stimulation of the adrenal gland with exogenous ACTH. In secondary or tertiary adrenal insufficiency, the adrenal glands release cortisol, whereas in primary adrenal insufficiency, the adrenal glands are partially or completely destroyed and do not respond to ACTH.

ACTH stimulation tests usually consist of administering 250 µg (40 International Units) of ACTH (so-called high-dose ACTH stimulation test). For long-term stimulation tests, which are preferred for differentiating between secondary and tertiary adrenal insufficiency, 250 µg of ACTH are infused either over 8 hours or over 2 days.⁵⁴ Serum cortisol and 24-hour urinary cortisol and 17-hydroxycorticosteroid (17-OHCS) concentrations are determined before and after the infusion. This test may be helpful in distinguishing primary from secondary/tertiary adrenal insufficiency. In primary adrenal insufficiency, there is a minimal to no response of plasma or urinary cortisol and urinary 17-OHCS. Increases of these values over the 2 to 3 days of the test are indicative of a secondary/tertiary cause of adrenal insufficiency. In normal subjects, the 24-hour urinary 17-OHCS excretion increases 3- to 5-fold above baseline. Serum cortisol concentrations reach 20 µg/dL (550 nmol/L) at 30 to 60 min and exceed 25 µg/dL (690 nmol/L) at 6 to 8 hours post initiation of the infusion. At present, this approach is used frequently because clinical manifestations of adrenal insufficiency combined with basal cortisol levels, short-term ACTH stimulation tests, and CRH tests (see later discussion) usually provide sufficient information.

A short-term stimulation test with 250 µg ACTH, mostly used for patients who are not critically ill, determines basal serum cortisol levels and the induced-response concentration 30 and 60 minutes after intravenous (IV) administration of ACTH. The advantage of the high-dose test is that pharmacologic plasma ACTH concentrations can be achieved by either IV or intramuscular injection.⁵⁵ This dose of ACTH, however, may be too high to identify mild cases of secondary adrenal insufficiency or chronic deficiencies.⁵⁶ Furthermore, it should not be used when acute secondary adrenal insufficiency (e.g., Sheehan's syndrome) is presumed, since it takes several days for the adrenal cortex to atrophy, and it will still be capable of responding to ACTH stimulation normally. In these cases, a low-dose ACTH test or an insulin-induced hypoglycemia may be required to confirm the diagnosis of adrenal insufficiency.^{57,58} A rise in serum cortisol concentration after 30 to 60 minutes to a peak of 18 to 20 µg/dL (500 to 550 nmol/L) or more is considered a normal response to a high-dose ACTH stimulation test and excludes the diagnosis of primary adrenal insufficiency and almost all cases of secondary adrenal insufficiency except those of recent onset.⁵⁹⁻⁶¹

To further differentiate between secondary and tertiary adrenal insufficiency, laboratory investigations may be augmented by a CRH stimulation test. In both conditions, cortisol levels are low at baseline and remain low after CRH. In patients with secondary adrenal insufficiency, there is little or no ACTH response, whereas in patients with

tertiary disease, there is an exaggerated and prolonged response of ACTH to CRH stimulation that is not followed by an appropriate cortisol response.^{62,63} In the past, the HPA axis was also tested by a stimulated hypoglycemia test. After administering 0.1 units of insulin per kilogram body weight, inducing a hypoglycemic state of less than 40 mg/dL serum glucose, an intact HPA axis is associated with a serum cortisol concentration of more than 20 µg/dL. Nowadays, this procedure is considered obsolete because of the high risk of symptomatic hypoglycemia.

In critically ill patients, primary causes of absolute or RAI are multiple and often undetectable if no specific hypothesis exists. Volume-resistant septic shock or any other form of life-threatening hypotension with an increased need for catecholamines indicates the need to evaluate adrenal function. Previously, a serum cortisol value less than 20 µg/dL was suggestive of the diagnosis of adrenal insufficiency.

Several factors complicate investigations of the HPA axis in patients with critical illness. A short-term ACTH stimulation test may be performed in critically ill patients suspected of having adrenal insufficiency. However, in most patients, RAI will be present, especially in patients with sepsis and septic shock. A clear definition of RAI is still missing, and the pathophysiology is rather complex, which makes it difficult to define clear cutoffs for both basal serum cortisol concentrations and incremental increases after short-term ACTH stimulation tests. Proposed cutoff points may depend on different methods used to measure cortisol, with variations when compared to high-performance liquid chromatography (HPLC) as the reference method.⁶⁴ In addition, considering free cortisol or an increase in free cortisol in response to ACTH could increase accuracy of adrenocortical function tests.⁴⁸ Furthermore, extrapolating the diagnosis from reference values obtained from healthy people or patients with HPA disorders may be misleading, since normal or high-normal cortisol concentrations in septic shock may indicate inadequate adrenal response to stress. In a large series of patients, receiver operating characteristic curve (ROC) analysis reached highest sensitivity (68%) and specificity (65%) for a reference value of less than 9 µg/dL (incremental increase) to detect nonresponders.⁵² Basal cortisol of 34 µg/dL and an incremental increase of 9 µg/dL after stimulation were the best cutoff points to discriminate between survivors and nonsurvivors. The higher the basal plasma cortisol and the weaker the cortisol response to corticotropin, the higher was the risk of death. Some investigators have questioned the discriminative power of the incremental increase of cortisol after stimulation in patients with high basal cortisol values, as increases may reflect adrenal reserve more than adrenal function. Hence, RAI was defined based on the hemodynamic response when a randomly measured cortisol was less than 25 µg/dL.⁴⁶

Routine use of the low ACTH stimulation test in critically ill patients cannot be recommended at present, although the low-dose test is preferred in patients with secondary or tertiary adrenal insufficiency.⁶⁵ After stimulation with 250 µg ACTH, circulating corticotropin concentrations are 40 to 200 pg/mL during stress but may be as high as 60,000 pg/mL.³⁵ Stimulation of the adrenal gland with low doses of ACTH (1 µg) was shown to increase sensitivity and specificity to detect adrenal insufficiency in patients with HPA disorders who respond normally to traditional high-dose stimulation.^{35,66-69} The test is performed by measuring serum cortisol concentrations immediately before and 30 minutes after IV injection of ACTH at a dose of 1 µg (160 mIU) per 1.73 m² body surface.³⁴ This dose stimulates maximal adrenocortical secretion up to 30 minutes post injection, and in normal subjects results in a peak plasma ACTH concentration about twice that of insulin-induced hypoglycemia.⁷⁰ A value of 18 µg/dL (500 nmol/L) or more at any time during the test is indicative of normal adrenal function. The advantage of this test is that it can detect partial adrenal insufficiency that may be missed by the standard high-dose test.^{57,58}

Using the 1-µg ACTH stimulation test to identify patients with RAI in septic shock has been proposed, but the 1-µg stimulation test has not been well validated in critically ill patients or patients with septic shock.^{34,35} In addition, studies evaluating low-dose and high-dose

ACTH stimulation tests in septic shock may have been flawed by methodologic problems. At present, using the 1- μ g ACTH stimulation test cannot be recommended routinely until further data from well-designed randomized studies in septic shock patients are available.

The current recommendation is to use a three-level therapeutic guide for evaluating RAI in critically ill patients, especially those with septic shock. Patients with a random basal cortisol below 15 μ g/dL will likely benefit from low-dose corticosteroid therapy, whereas corticosteroid replacement is unlikely to be helpful when basal cortisol is above 34 μ g/dL. When a random basal cortisol value is between 15 and 34 μ g/dL, adrenocortical stimulation with 250 μ g ACTH should discriminate responders (incremental increase ≥ 9 μ g/dL) from nonresponders (< 9 μ g/dL). However, it has been pointed out that no cutoff values are entirely reliable.³⁵

CLINICAL SYMPTOMS

About 25% of patients with adrenal insufficiency present with adrenocortical crisis.³⁴ The symptoms are nonspecific and include sudden dizziness, weakness, dehydration, hypotension, and shock (Box 148-3). In many cases, the clinical picture may be indistinguishable from shock due to loss of intravascular fluid volume. Other features such as anorexia, nausea, vomiting, diarrhea, abdominal pain, and delirium may be present, but they are also common in patients with other acute illness. Hence, these symptoms may not be helpful in establishing the diagnosis of adrenal insufficiency and are often misleading. Hypoglycemia is rare in acute adrenal insufficiency but more common in secondary adrenal insufficiency; it is a common manifestation in children and women with the disorder. For patients in the intensive care unit (ICU), it remains extremely difficult to recognize acute, absolute adrenal insufficiency based on clinical symptoms. However, if the diagnosis is missed, the patient will probably die, so the threshold for laboratory investigations in cases of unexplained catecholamine-resistant hypotension should be low. It is important to be mindful that the onset of an acute adrenocortical crisis is not necessarily the acute beginning of the underlying disease itself. The preceding course is often gradual and may go undetected until an acute illness, stress, trauma, pregnancy, or other conditions precipitate adrenal crisis.^{34,71}

BOX 148-3

Clinical Manifestations of Adrenal Insufficiency

ACUTE ADRENAL INSUFFICIENCY

- Acute apathy
- Nausea, vomiting
- Fever
- Acute dehydration, tachycardia
- Craving for salt
- Hypotension, shock

CHRONIC ADRENAL INSUFFICIENCY

- Weakness, fatigue
- Lack of appetite
- Orthostatic hypotension
- Weight loss, anorexia
- Hyperpigmentation (only in primary Addison's disease due to increased ACTH)
- Vitiligo
- Nonspecific gastrointestinal symptoms (diarrhea, nausea, abdominal pain)
- Nonspecific pain (myalgia, arthralgia, headaches)
- Nonspecific psychological symptoms (depression, lack of concentration, confusion, psychosis)
- Hypoglycemia
- Hyponatremia
- Hyperkalemia
- Acidosis, prerenal azotemia
- Lymphocytosis, eosinophilia

Typical symptoms of primary adrenal insufficiency, such as hyperpigmentation, scanty axillary and pubic hair, hyponatremia, or hyperkalemia may be diagnosed in the acutely ill patient. Adrenal crisis can occur in patients receiving appropriate doses of GCs if their mineralocorticoid requirements are not met.⁷² After spontaneous events leading to primary adrenal insufficiency (e.g., hemorrhage, myocardial infarction, adrenal vein thrombosis), these signs are absent. If an acute adrenal crisis is suspected, a blood sample should be obtained to confirm the diagnosis. The main clinical problem is hypotension and shock due to acute mineralocorticoid deficiency. However, GC deficiency may also contribute to hypotension by decreasing vascular responsiveness to angiotensin II, norepinephrine, and other vasoconstrictive hormones, reducing the synthesis of renin substrate and increasing production and effects of prostacyclin and other vasodilatory hormones.^{73,74} Finally, panhypopituitarism may be associated with symptoms, owing not only to lack of corticotropin but also TSH, gonadotropin, and GH.

In chronic adrenal insufficiency, the major clinical features (see Box 148-3) may be detected but may also be absent if adrenal gland insufficiency develops over a prolonged period of time. There is a stage characterized by normal basal steroid secretion but an inability to respond to stress; hence, the patient may be asymptomatic. In other cases, there may also be signs and symptoms suggestive of other hormone deficiency such as decreased thyroid and gonadal function. Independent of the underlying cause, the most common clinical manifestations are general malaise, fatigue, weakness, anorexia, weight loss, nausea, vomiting, abdominal pain, arthralgia, postural syncope, diarrhea that may alternate with constipation, hypotension, electrolyte abnormalities (hyponatremia, hyperkalemia, metabolic acidosis), decreased axillary and pubic hair, and loss of libido and amenorrhea in women.^{34,71}

In primary adrenal insufficiency, hyperpigmentation and autoimmune manifestations (vitiligo) are typically due to increased ACTH concentrations, whereas these findings are not seen in secondary or tertiary adrenal insufficiency. Another specific symptom of primary adrenal insufficiency is a craving for salt.³⁵ Typical laboratory abnormalities are hyponatremia, hyperkalemia, acidosis, slightly elevated creatinine concentrations, mild normocytic anemia, and, rarely, hypercalcemia.³⁵

In secondary adrenal insufficiency, since production of mineralocorticoids by the zona glomerulosa is generally preserved, dehydration and hyperkalemia are not present, and hypotension is less prominent than in primary disease. Especially in the early stages, the onset of chronic adrenal insufficiency is often insidious, and the diagnosis may be difficult. Some patients initially present with gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal cramps.^{35,75} In other patients, the disease may be misdiagnosed as depression or anorexia nervosa.^{76,77} Hyponatremia and increased intravascular volume may be the result of an "inappropriate" increase in vasopressin secretion. Decreased libido and potency as well as amenorrhea may occur. Hypoglycemia is more common in secondary adrenal insufficiency, possibly due to concomitant GH insufficiency, and in isolated ACTH deficiency. Clinical manifestations of a pituitary or hypothalamic tumor, such as signs and symptoms of deficiency of other anterior pituitary hormones, headache, or visual field defects, may also be present.^{34,71} Finally, in young patients suspected of having adrenal insufficiency, delayed growth and puberty point to the presence of hypothalamic-pituitary disease, as would headaches, visual disturbances, or diabetes insipidus in patients of any age.^{35,36} Laboratory screening in patients with chronic adrenal insufficiency usually reveals hyponatremia, hypoglycemia, lymphocytosis, and eosinophilia.³⁵

THERAPEUTIC APPROACHES

Treatment of adrenal insufficiency involves addressing the precipitating cause (e.g., tumor, infection) and hormone replacement. In acutely ill patients, if the diagnosis of adrenal crisis is suspected but not known, blood should be obtained for measurement of cortisol concentrations,

followed by the administration of 250 µg of ACTH in patients with an unknown history. Replacement therapy should be started immediately while awaiting the results of testing.⁷⁸ Dexamethasone (1 mg every 6 hours) may be given as the initial GC replacement, since it does not cross-react with cortisol in the plasma while adrenal testing is being performed. Patients are usually treated with IV fluids in the form of isotonic saline to restore intravascular volume and replace urinary salt losses. Dextrose infusion may be added to prevent hypoglycemia. Hydrocortisone (100-mg IV bolus or over 30 min, followed by continuous infusion of 10 mg/h, or 50 mg every 4 hours, or 75 to 100 mg every 6 hours, resulting in a total daily dose of 240 to 300 mg hydrocortisone) is frequently given for hormonal replacement.^{34,78} However, equivalent GC doses of methylprednisolone or dexamethasone may also be used. Typically, mineralocorticoid replacement therapy is not required in adrenal crisis as long as the patient is receiving isotonic saline. Prophylactic use of antibiotics is not beneficial, but specific infections should be treated aggressively with appropriate antibiotic therapy.

Once the patient is stable, GCs can be tapered to maintenance doses. Long-term replacement doses consist of hydrocortisone, usually 30 mg/d, with two-thirds (20 mg) given in the morning and one-third (10 mg) given at night, or prednisone, 7.5 mg in a similar regimen (5 and 2.5 mg, respectively). The daily dose may be decreased to 20 or 15 mg of hydrocortisone as long as the patient's well-being and physical strength are not reduced.³⁴ The goal should be to use the lowest dose that relieves the patient's symptoms, in order to prevent weight gain and osteoporosis.^{34,78,79} If the patient continues to experience weakness or other symptoms of GC deficiency, the dose can be increased. Excessive GC therapy should be avoided so as to minimize complications. In addition, mineralocorticoid effect is provided with fludrocortisone (50-100 µg orally daily) to prevent sodium loss, intravascular volume depletion, and hyperkalemia, especially when the dose of hydrocortisone decreases below 100 mg/d. Therapy can be guided by monitoring blood pressure, serum potassium, and plasma renin activity, which should be in the upper normal range.^{34,61} Clinical response, however, is the best indicator of the adequacy of replacement. Excessive mineralocorticoid replacement may cause congestive heart failure, alkalosis, hypokalemia, or hypertension. Patients receiving prednisone or dexamethasone may require higher doses of fludrocortisone to lower their plasma renin activity to the upper normal range, whereas patients receiving hydrocortisone, which has some mineralocorticoid activity, may require lower doses. The mineralocorticoid dose may have to be increased in the summer, particularly if patients are exposed to temperatures above 29°C (85°F). In cases of isolated hypoadosteronism, treatment includes liberal sodium intake and daily administration of fludrocortisone. In patients with secondary adrenal insufficiency due to panhypopituitarism, replacement with other hormones may also be necessary. In women, the adrenal cortex is the primary source of androgen in the form of dehydroepiandrosterone and dehydroepiandrosterone sulfate. Although the physiologic role of these androgens in women has not been fully elucidated, their replacement is being increasingly considered in the treatment of adrenal insufficiency.^{80,81}

Once the patient is stable and on maintenance doses of steroids, ACTH testing can be repeated to document adrenal recovery. Patients with primary adrenal insufficiency require lifelong GC and mineralocorticoid replacement therapy and should carry a card containing information on current therapy, as well as some type of MedicAlert bracelet or necklace with recommendations for treatment in emergency situations. One of the important aspects of the management of chronic primary adrenal insufficiency is patient and family education. Patients should understand the reason for lifelong replacement therapy, the need to increase the dose of GCs during minor or major stress, and how to inject hydrocortisone, methylprednisolone, or dexamethasone in emergencies. Patients should also have supplies of dexamethasone sodium phosphate and should be educated about how and when to administer it. The survival rate for patients with chronic primary adrenal insufficiency has gone from 2 years or less before the availability of steroid replacement to that of the normal population now that GCs are readily available. In acute adrenal insufficiency, prompt

recognition and treatment usually result in a favorable outcome, provided the underlying disease process can be treated.

GLUCOCORTICOID REPLACEMENT IN PATIENTS WITH SEPTIC SHOCK

In patients with sepsis and septic shock, the clinical course is extremely varied. The impact of the primary disease, as well as immunologic factors (including cytokines) associated with sepsis, affect the HPA axis. In contrast to the early phase of septic shock, adrenal cortisol release may recover, thus leading to RAI with absolute steroid levels around or even above normal range.⁸² In refractory septic shock, prevalence of RAI may be as high as 50% to 75%.⁵² Furthermore, dynamic testing is not always available in ICUs, making it difficult for the physician considering hormone replacement therapy, because decisions have to be made within hours in severe forms of septic shock to improve prognosis.

Proposed mechanisms of protection from high-dose GCs include improvement of hemodynamic, metabolic, endocrine, and phagocytic functions, resulting in the maintenance of normal morphologic-functional status of tissues including brain, liver, heart, kidneys, and adrenals.⁸³ In addition, GCs are recognized to inhibit key features of inflammation: endothelial cell activation and damage, capillary leakage, granulocyte activation, adhesion and aggregation, complement activation, and formation and release of eicosanoid metabolites, oxygen radicals, and lysosomal enzymes.⁸⁴⁻⁸⁹

However, in only one long-term, prospective study in humans receiving high doses of methylprednisolone (30 to 60 mg/kg) or dexamethasone (2 to 4 mg/kg), including 179 bacteremic septic shock patients over a period of 8 years, were experimental results confirmed and mortality reduced from 38% to 10%.⁹⁰ Evidence from another study suggested that prolongation of treatment might have been beneficial, since shock reversal and improved survival occurred after a bolus GC application in an early time window but vanished after several days.⁹¹ Two meta-analyses included 9 and 10 randomized trials, respectively, of patients with severe sepsis and septic shock who received up to 42 g of hydrocortisone equivalent or more; both concluded that high doses of corticosteroids were ineffective⁹² or harmful.⁹³ This was confirmed by a large randomized trial in 1987.⁹⁴ High-dose GCs were associated with increased risk of secondary infections, mortality,⁹³ and increased incidence of renal and hepatic dysfunction.⁹⁵ Taken together, these results suggest that high-dose GCs are not effective in septic shock.

Similar to studies of high-dose GC treatment, numerous randomized controlled trials with low-dose corticosteroids in patients with septic shock also confirmed shock reversal and reduction of vasopressor support within a few days after initiation of therapy in most patients.⁹⁶⁻¹⁰¹ In a crossover study, mean arterial pressure and systemic vascular resistance increased during low-dose hydrocortisone treatment, and heart rate, cardiac index, and norepinephrine requirement decreased significantly.¹⁰² All effects were reversible with cessation of hydrocortisone. Some studies indicated that corticosteroid-induced increase of sensitivity to norepinephrine was more pronounced in patients with RAI than in patients without RAI.^{46,101} There are multiple potential mechanisms by which corticosteroids may modulate vascular tone. Considerable evidence confirms that cytokine-induced formation of nitric oxide (NO) plays a central role in vasodilation, catecholamine resistance, maldistribution of blood flow, and mitochondrial and organ dysfunction and that the amount of NO production correlates with shock severity and outcome.^{103,104} In a crossover trial, norepinephrine requirement could be reduced by administering low-dose hydrocortisone in nearly all patients within 1 to 2 days. Hydrocortisone treatment also induced a significant and prolonged decline of nitrite/nitrate levels, which significantly correlated with reduction of norepinephrine requirements during hydrocortisone infusion.¹⁰² Considering the complex genomic and nongenomic actions of corticosteroids described earlier, it is probable that NO is not the only

GCs modulate the stress response in a very complex manner that includes not only antiinflammatory and immunosuppressive actions to protect the host from overwhelming inflammation but also immune-enhancing effects.²⁷ Markers of the inflammatory response, antiinflammatory response, granulocyte, monocyte, endothelial activation, antigen-presenting capacity, and innate immune response were investigated in septic shock patients.¹⁰² Hydrocortisone significantly attenuated inflammatory and antiinflammatory responses as well as granulocyte, monocyte, and endothelial activation. Monocyte HLA-DR expression was depressed, but receptor downregulation was limited and was followed by a rebound increase after drug withdrawal.¹⁰² The immune effects of low-dose hydrocortisone treatment in septic shock may thus be characterized as immunomodulatory rather than immunosuppressive.

Although data on outcomes in septic shock patients after low-dose corticosteroid treatment are limited, up to 300 mg hydrocortisone per day may improve survival. In some trials with low-dose corticosteroids,⁹⁶⁻¹⁰⁰ 28-day all-cause mortality was reduced, whereas in high-dose trials, there was no significant effect. In a multicenter trial in 300 patients with severe volume and catecholamine-refractory septic shock, survival time was significantly increased in patients with RAI but not in responders to ACTH.⁹⁷ Similar results were obtained for ICU and hospital mortality but not for 1-year follow-up. Significant increases of serious adverse events during treatment with low-dose hydrocortisone have not been reported. The incidence of gastrointestinal bleeding, superinfections, or hyperglycemia has not been different in patients treated with corticosteroids or placebo, and wound infections were even less frequent in patients treated with low-dose hydrocortisone.⁹⁷ However, these findings were not confirmed by another large randomized trial, the Corticosteroid Therapy of Septic Shock (CORTICUS) trial,¹⁰⁵ which used different inclusion criteria. Only patients who were successfully resuscitated by volume therapy plus vasopressors were included.¹⁰⁵ These contradictory results led the Surviving Sepsis Campaign to redefine their guidelines in 2012/2013,¹⁰⁶ recommending against the use of low-dose GCs for patients who are responding adequately to volume plus vasopressor therapy—that is, those who are no longer hypotensive. Only in the minority of patients, when a stabilization of blood pressure cannot be obtained by using volume plus vasopressors, continuous, low-dose hydrocortisone might be considered.¹⁰⁶

Treatment with low-dose hydrocortisone may induce an increase of sodium levels within a few days, and hyponatremia with values over 155 mmol/L have been reported during prolonged treatment.¹⁰⁰ Nevertheless, the indication for low-dose corticosteroids should be weighed against possible risks, and treatment should be limited to the duration of volume- and vasopressor-restrictive hypotension.

Dosing of hydrocortisone in septic shock is similar to that in adrenal crisis (100 mg initial bolus, followed by 200–300 mg per day), and the dose should be tapered once the patient stabilizes. Hydrocortisone is the synthetic equivalent to the physiologic final active compound, cortisol, so treatment with hydrocortisone directly replaces cortisol independently from metabolic transformation. In contrast to dexamethasone, hydrocortisone has intrinsic mineralocorticoid activity. A recent randomized trial demonstrated that the addition of oral fludrocortisone to low-dose hydrocortisone has no benefit in septic shock patients.¹⁰⁷ It has not been established whether a weight-adjusted regimen (e.g., 0.18 mg/kg/h)⁵⁶ of continuous hydrocortisone infusion is superior to a fixed regimen; moreover, a comparative study of bolus versus infusion regimens has not been performed so far. Patients should be weaned from low-dose hydrocortisone over several days to avoid hemodynamic and immunologic rebound effects. In patients with septic shock, abrupt cessation of low-dose hydrocortisone was followed by significant reversal of many hemodynamic and immunologic effects observed during corticosteroid therapy, even after a short treatment period of 3 days.¹⁰² Adrenal function tests with 250 µg ACTH can be performed in patients with septic shock; however, at present this approach cannot be recommended to exclude responders or patients with high random cortisol values from low-dose cortico-

steroid therapy.³⁵ When basal serum cortisol concentrations are less than 15 µg/dL in septic shock, low-dose hydrocortisone replacement is recommended; levels of over 34 µg/dL are considered sufficient. Between 15 and 34 µg/dL, an incremental increase of less than 9 µg/dL serum cortisol makes RAI likely, and therapy may be considered according to the clinical state.³⁵ Other recommendations use a randomly assigned cutoff level of below 25 µg/dL serum cortisol.⁴⁶ The routine use of the low ACTH stimulation test (1 µg ACTH) cannot be recommended at present until further data from well-designed randomized studies in septic shock patients are available. Most importantly, it has to be realized that all the aforementioned studies were performed in patients with catecholamine-resistant septic shock. To date, there are no data justifying the use of low-dose steroids in patients with sepsis. Significant effects on outcome have been observed only in patients with systolic blood pressure below 90 mm Hg despite vasopressor therapy.⁹⁷ It is not yet known whether low-dose corticosteroids are also effective in patients with less severe shock. Sufficient data on the dose-response characteristics of GCs in septic patients are still lacking, and the current recommended strategy using 200 to 300 mg hydrocortisone per day is based on empiric recommendations; further investigations are needed.

FURTHER IMPLICATIONS FOR ANESTHESIA AND CRITICAL CARE

Surgical stress increases serum cortisol levels five- to sixfold postoperatively, with return to normal at 24 hours unless stress continues. Patients who have received GCs equivalent to 30 mg/d cortisol for longer than 3 weeks may have impairment in this stress response, and steroid supplementation should be considered. However, short-term treatment of heterogeneous groups of patients with critical illness is controversial, and supraphysiologic doses of GCs are not beneficial and may even be harmful.¹⁰⁸ Hence, outside the situations in which benefit has been proved, supraphysiologic doses of GCs (e.g., 30 mg methylprednisolone per kilogram of body weight per day) in patients with critical illness are not indicated. While early treatment with dexamethasone was suggested to decrease morbidity in bacterial meningitis,^{109,110} a recent meta-analysis was less enthusiastic.¹¹¹ The positive effects of steroid treatment on tissue-specific resistance to GCs have already been described. However, despite the frequent suggestion that unexplained intraoperative hypotension and even death reflect unrecognized hypocortisolism, there is no evidence that primary adrenal insufficiency is a likely explanation for this response.

Patients with known chronic adrenal insufficiency must be advised to double or triple the dose of hydrocortisone temporarily whenever they have any febrile illness or injury.³⁴ In stressful situations or during major surgery, trauma, burns, or medical illness, high doses of GCs up to 10 times the daily production are required to avoid an adrenal crisis, although no data from randomized trials are available. A continuous infusion of 10 mg of hydrocortisone per hour or the equivalent amount of dexamethasone or prednisolone eliminates the possibility of GC deficiency. This dose can be halved on the second postoperative day, and the maintenance dosage can be resumed on the third postoperative day. However, it is important with regard to possible detrimental effects and the possibility of decreased resistance to infections that this treatment should not be used for prolonged periods in the absence of evidence of corticosteroid insufficiency. General perioperative management should include avoidance of etomidate as an anesthetic drug (selection of other drugs and muscle relaxants is not influenced by the presence of treated hypocortisolism); infusion of sodium-containing fluids; minimal doses of any anesthetic drugs to avoid increased sensitivity to drug-induced myocardial depression; invasive monitoring of hemodynamics, glucose, and electrolytes; and decreased initial doses of muscle relaxant while monitoring the effect using a peripheral nerve stimulator. Especially when acute adrenal insufficiency has been detected in a critically ill patient with a previously unknown disorder, thorough diagnostic evaluation is required, even after improvement.

The control of cortisol secretion in response to stress is more complex than originally thought. Interactions between corticotropin-releasing factor (CRF), vasoactive intestinal polypeptide, arginine vasopressin, catecholamines, and other hormones involved in the control of cortisol secretion have been described.¹¹² α_2 -Adrenergic receptor antagonists (e.g., clonidine), which are widely used in ICUs, may suppress the cortisol response to surgical stress. On the other hand, increases in intracranial pressure stimulate cortisol release without increasing ACTH levels, and adrenalectomy, but not adrenal demedullation, increase the permeability of brain tissue to macromolecules.¹¹³ Evidence also suggests that white blood cells may release ACTH-like peptides that can stimulate adrenal gland secretion of cortisol and that primary adrenal insufficiency is associated with increases in serum levels of angiotensin-converting enzyme.¹¹⁴

There are multiple interactions between drugs and the HPA axis that have to be considered if absolute or RAI is suspected. Moreover, in patients with hepatic dysfunction, GC doses should be tapered, especially when using prednisone, since hydroxylation to the active component needs considerable metabolic capacity. Special attention is required in the concomitant use of GCs with other drugs, because of potential interactions and because some drugs may affect the metabolism of steroids, which may lead to a decreased or increased GC effect on their target tissues.^{115,116} GCs decrease blood levels of aspirin, coumarin anticoagulants, isoniazid, insulin, and oral hypoglycemic agents, whereas cyclophosphamide and cyclosporine levels may be increased. Conversely, antacids, carbamazepine, cholestyramine, colestipol, ephedrine, mitotane, phenobarbitone, phenytoin, and rifampicin decrease GC blood concentrations, whereas they are increased by cyclosporine, erythromycin, oral contraceptives, and troleandomycin. Furthermore, the combination of exogenous GC administration and amphotericin B, digitalis glycosides, and potassium-depleting diuretics may induce or worsen hypokalemia, warranting frequent monitoring of potassium levels. Finally, the general risk of immunosuppression by

GCs precludes any use of vaccines from live attenuated viruses to avoid severe generalized infections.^{115,116}

CONCLUSION

Underproduction of adrenal hormones can lead to serious illness. GCs play a critical permissive role in intermediary metabolism, are counter-regulatory in relation to insulin, modulate inflammatory and immune responses, and optimize cardiovascular and CNS function. Therefore, diseases with a primary adrenocortical dysfunction or those leading to secondary adrenal insufficiency may have severe sequelae, which often are life threatening. The concept of RAI in critically ill patients with functional disorders of the HPA axis has gained attention. Especially in patients with sepsis and septic shock, this phenomenon is suspected of having a major impact on the severity of illness and prognosis. Both absolute adrenal insufficiency and RAI should be diagnosed by using adequate laboratory investigations. In most cases, testing the basal level of cortisol, combined with a short-term stimulation test with 250 μ g ACTH, can identify the disease. In patients with critical illnesses, however, it continues to be difficult to diagnose RAI.

In cases of suspected adrenal crisis with severe volume- and catecholamine-resistant shock, immediate replacement therapy is indicated. If the diagnosis is questionable, dexamethasone should be administered to allow an appropriate diagnostic evaluation. Once the diagnosis of adrenal insufficiency is made, hydrocortisone is the preferred therapy, since it provides both gluco- and mineralocorticoid effects. After stabilization, the dose of GCs should be tapered down to a total of 20 to 35 mg hydrocortisone per day or equivalent. Randomized controlled trials of high-dose GCs failed to improve outcome from sepsis and septic shock. However, prolonged treatment of refractory septic shock with low doses of corticosteroids is only considered a therapeutic option if the patient does not respond to volume replacement and vasopressor therapy.

KEY POINTS

1. The definition of adrenal insufficiency is based on the inability of the adrenal gland to produce adrenocortical steroid hormones.
2. Three major regulatory influences affect the hypothalamic-pituitary-adrenal (HPA) axis and lead to secretion of corticotropin (ACTH) as the main stimulatory factor for the adrenal cortex to release its hormonal products: circadian diurnal rhythms, stress, and feedback from free cortisol levels in blood and body fluids.
3. Physical or emotional stress leads to an immediate, significant, and possibly continual increase of ACTH and cortisol excretion. This is typically paralleled by loss of the circadian rhythm. The response to stress is proportional to the intensity of the stimulus.
4. The main cause for *primary adrenal insufficiency* (70% to 80%) is an autoimmune disorder that induces morphologic destruction of more than 90% of the adrenal cortex. The result is a critically decreased synthesis of steroids, with typical clinical manifestations.
5. *Secondary adrenal insufficiency* is characterized by reduced stimulation of the intact adrenal gland due to low ACTH levels (hypothalamic-pituitary insufficiency), which also results in reduced cortisol levels.
6. *Tertiary adrenal insufficiency* is caused by long-term treatment with steroid hormones, which induces feedback inhibition of the HPA axis.
7. The definition of *relative adrenal insufficiency* (RAI) in critically ill patients is based on plasma cortisol levels. The critical threshold is a basal cortisol level of 18 to 25 μ g/mL without preceding stimulation.
8. Clinical manifestations of adrenal insufficiency are usually nonspecific and include weakness, anorexia, orthostatic hypotension, and general gastrointestinal symptoms. Typical signs for primary forms are hyperpigmentation due to increased ACTH levels, vitiligo in cases of autoimmune disorders, and hyperkalemia. Secondary forms cause milder symptoms due to maintained mineralocorticoid effects.
9. Evaluation of adrenal insufficiency generally includes measurement of basal serum cortisol concentrations as well as the incremental increase after stimulation with ACTH. A high-dose test (250 μ g ACTH) is preferred, which uses 30- and 60-minute cortisol levels after stimulation. Long-term tests or low doses (1 μ g ACTH) are only used for special indications. Basal values for serum cortisol of less than 3 μ g/dL indicate severe, absolute hypocortisolism warranting immediate intervention. In critically

KEY POINTS—cont'd

- ill patients, basal cortisol levels of less than 18 to 25 $\mu\text{g/mL}$ have been recommended as an indication for low-dose replacement therapy.
10. Acute adrenal insufficiency (Addisonian crisis) requires immediate intervention. Establishing intravenous access, infusion of saline, monitoring serum glucose, and administering dexamethasone after drawing a blood sample may be lifesaving. ACTH stimulation tests should be used for diagnosis. Once the results after stimulation are known, hydrocortisone therapy is preferred for its mineralocorticoid effects.
 11. Chronic adrenal insufficiency may require long-term replacement therapy with gluco- and mineralocorticoids (for primary forms). Any physical or emotional stress must be considered as possibly harmful, with the need for 3 to 10 times increased doses of glucocorticoids.
 12. In patients with septic shock who are not adequately responding to volume and vasopressor therapy, replacement with low-dose hydrocortisone (200 to 300 mg/d) may be considered, although optimal dosing and timing have yet to be established. A preliminary ACTH test in these patients is no longer recommended.

ANNOTATED REFERENCES

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- The authors performed a randomized trial in patients with septic shock, using a crossover design that demonstrated that (1) hemodynamic stabilization by low-dose steroids is paralleled by reduced synthesis of endogenous nitric oxide, (2) low-dose hydrocortisone modulates rather than suppresses immunologic functions, and (3) rapid withdrawal of steroids induces rebound phenomena with impairment of the clinical course.*
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In contrast to the aforementioned study, this randomized trial did not show any benefit of low-dose hydrocortisone therapy in septic shock; however, these patients were responsive to vasopressor therapy, which underlines the relevance of thorough patient selection.

■ References for this chapter can be found at expertconsult.com.

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Thyroid storm and myxedema coma are life-threatening emergencies that represent the extreme ends of the spectrum of thyroid dysfunction in the decompensated patient. Their presentation is usually dramatic and is often precipitated by a nonthyroidal-related illness or event. Recognition of these disorders requires a high degree of clinical suspicion because thyroid function abnormalities, as well as other biochemical parameters, do not differ significantly from uncomplicated thyrotoxicosis and hypothyroidism. As thyroid storm and myxedema coma are clinical diagnoses, measurement of serum thyroid hormones serve as confirmatory tests in the appropriate setting.

In contrast to these dramatic clinical presentations, critical illness also causes multiple nonspecific alterations in thyroid hormone concentrations in patients without intrinsic thyroid dysfunction that relate to the severity of the illness. Since a wide variety of illnesses tend to result in the same changes in serum thyroid hormones, such alterations in thyroid hormone indices have been termed the *sick euthyroid syndrome* or *nonthyroidal illness*. The differentiation between patients with sick euthyroid syndrome and those with intrinsic thyroid disease is a frequent diagnostic challenge in the intensive care unit (ICU).

This chapter will review normal thyroid physiology, changes in thyroid hormone metabolism seen with critical illness, and the evaluation of thyroid function in critically ill patients. Finally, diagnosis and management of sick euthyroid syndrome, thyroid storm, and myxedema coma will be reviewed.

NORMAL THYROID HORMONE ECONOMY

Regulation

Synthesis and secretion of thyroid hormone is under the control of the anterior pituitary hormone thyrotropin (or thyroid-stimulating hormone [TSH]). Consistent with a classic negative feedback system, TSH secretion increases when serum thyroid hormone levels fall and decreases when they rise (Fig. 149-1). TSH secretion is also under the regulation of the hypothalamic hormone thyrotropin-releasing hormone (TRH). The negative feedback of thyroid hormone is targeted mainly at the pituitary level but also likely affects TRH release from the hypothalamus. In addition, input from higher cortical centers can affect hypothalamic TRH secretion.

Under the influence of TSH, the thyroid gland synthesizes and releases thyroid hormone. Thyroxine (T_4 , 65% iodine by weight) is the principal secretory product of the thyroid gland, comprising about 90% of secreted thyroid hormone under normal conditions.¹ Although T_4 may have direct actions in some tissues, it primarily functions as a hormone precursor that is metabolized in peripheral tissues to the transcriptionally active 3,5,3'-triiodothyronine (T_3 , 59% iodine by weight).

Metabolic Pathways

The major pathway of metabolism of T_4 is by sequential monodeiodination.² At least three deiodinases, each with its unique expression in

different organs, catalyze deiodination reactions involved in the metabolism of T_4 . Removal of the 5', or outer ring, iodine by type I iodothyronine 5'-deiodinase (D1) or type II iodothyronine 5'-deiodinase (D2) is the "activating" metabolic pathway leading to the formation of T_3 . Removal of the 5', or inner ring, iodine by type III iodothyronine deiodinase D3 is the "inactivating" pathway producing the metabolically inactive hormone 3,3',5'-triiodothyronine (reverse T_3 , rT_3). D1 is found most abundantly in the liver, kidneys, and thyroid. It is upregulated in hyperthyroidism and downregulated in hypothyroidism. D2 is found primarily in the brain, pituitary, and skeletal muscle and is downregulated in hyperthyroidism and upregulated in hypothyroidism. D3 is expressed primarily in the brain, skin, and placental and chorionic membranes. The actions of D3 also include inactivation of T_3 to form T_2 , another inactive metabolite. Under normal conditions, about 41% of T_4 is converted to T_3 , about 38% is converted to rT_3 , and about 21% is metabolized via other pathways, such as conjugation in the liver and excretion in the bile.^{3,4}

T_3 is the metabolically active thyroid hormone and exerts its actions via binding to chromatin-bound nuclear receptors and regulating gene transcription in responsive tissues.⁵ Important in understanding the alterations in circulating thyroid hormone levels seen in critical illness is the fact that only around 10% of circulating T_3 is secreted directly by the thyroid gland, while more than 80% of T_3 is derived from the conversion of T_4 in peripheral tissues.^{1,2} Thus, factors that affect peripheral T_4 -to- T_3 conversion will have significant effects on circulating T_3 levels. Serum levels of T_3 are approximately 100-fold less than those of T_4 , and like T_4 , T_3 is metabolized by deiodination to form diiodothyronine (T_2) and by conjugation in the liver. The half-lives of circulating T_4 and T_3 are 5 to 8 days and 1.3 to 3 days, respectively.³

Serum Binding Proteins

Both T_4 and T_3 circulate in the serum as hormones bound to several proteins synthesized by the liver.⁴ Thyroid-binding globulin (TBG) is the predominant transport protein and binds to approximately 80% of the circulating serum thyroid hormones. The affinity of T_4 for TBG is about 10-fold greater than that of T_3 and, in part, accounts for increased circulating T_4 levels, compared to T_3 levels. Other serum binding proteins include transthyretin,⁶ which binds about 15% of T_4 but little, if any, T_3 , and albumin, which has a low affinity, but a very large binding capacity, for T_4 and T_3 . Overall, 99.97% of circulating T_4 and 99.7% of circulating T_3 is bound to plasma proteins.

Role of Free Hormone

Essential to an understanding of the regulation of thyroid function and the alterations of circulating thyroid hormones seen in critical illness is the "free hormone" concept, which is that only the unbound hormone has metabolic activity. Under regulation by the pituitary, overall thyroid function is affected when there is any change in free hormone concentration. Changes in either the concentrations of binding proteins or the binding affinity of thyroid hormone to the serum binding proteins have significant effects on total serum hormone levels, owing to the high degree of binding of T_4 and T_3 to these proteins. Despite these changes, this does not necessarily translate into thyroid dysfunction.

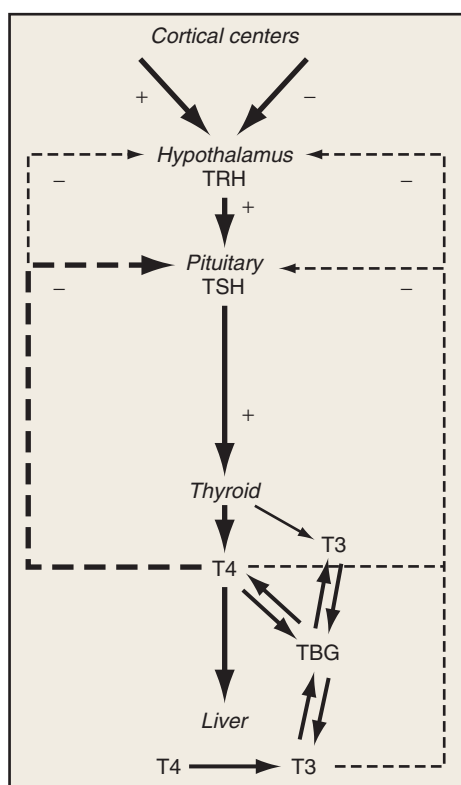


FIGURE 149-1 ■ Diagram of the hypothalamic-pituitary-thyroid axis. Inhibitory effect of T_4 and T_3 on TSH secretion is shown by dashed line and minus sign, and stimulatory effects of TRH on TSH secretion and TSH on thyroid secretion are shown by solid lines and plus signs. T_4 and T_3 may also have an inhibitory effect on TRH secretion.

THYROID HORMONE ECONOMY IN CRITICAL ILLNESS

Widespread changes in thyroid hormone economy in critically ill patients occurs as a result of (1) alterations in peripheral metabolism of thyroid hormones, (2) alterations in TSH regulation, and (3) alterations in the binding of thyroid hormone to TBG.

Peripheral Metabolic Pathways

One of the initial alterations in thyroid hormone metabolism in acute illness is the acute inhibition of D1, resulting in the impairment of T_4 -to- T_3 conversion in peripheral tissues.⁷ D1 is inhibited by a wide variety of factors, including acute illness (Box 149-1),² resulting in the acute decrease in T_3 production in critically ill patients. In contrast, inner ring deiodination by D3 may be increased by acute illness, resulting in increased levels of rT_3 .⁸ Additionally, because rT_3 is subsequently deiodinated by D1, degradation of rT_3 decreases, and levels of this inactive hormone rise in proportion to the fall in T_3 levels. Nondeiodinative pathways may play an important role in critical illness as sulfoconjugation and alanine side chain deamination/decarboxylation is increased, resulting in increased levels of T_3 -sulfate and Triac, respectively. Sulfoconjugation has been postulated as the reason why T_3 levels fall rapidly during coronary bypass surgery as T_3 levels rise.⁹ Triac, which binds to the thyroid hormone receptor and has weak thyromimetic activity, increases locally during illness and fasting. An increase in Triac production in the pituitary may be a factor in decreasing TSH levels during illness. Finally, in the critical illness setting, there is impaired transport of T_4 to peripheral tissues, such as the liver and kidney, where much of the circulating T_3 is produced, further

BOX 149-1

Factors That Inhibit Type 1 5'-Deiodinase Activity

Acute and chronic illness
Caloric deprivation
Malnutrition
Glucocorticoids
 β -Adrenergic blocking drugs (e.g., propranolol)
Oral cholecystographic agents (e.g., iopanoic acid, sodium ipodate)
Amiodarone
Propylthiouracil
Fatty acids
Fetal/neonatal period
Selenium deficiency
Hepatic disease

BOX 149-2

Factors That Decrease Thyrotropin Secretion

Acute and chronic illness
Adrenergic agonists
Caloric restriction
Carbamazepine
Clofibrate
Cyproheptadine
Dopamine and dopamine agonists
Endogenous depression
Glucocorticoids
IGF-1
Metergoline
Methysergide
Opiates
Phenytoin
Phentolamine
Pimozide
Somatostatin
Serotonin
Surgical stress
Thyroid hormone metabolites

IGF, insulin-like growth factor.

contributing to the decrease in the production of T_3 .^{10,11} Interestingly, increased expression of the thyroid hormone transporters OATP1C1 and MCT8 in animal models¹² and increased expression of MCT8 and MCT1 in the liver and muscle in human studies involving critical illness has been observed.¹³ Thus, the mechanism underlying the decrease in tissue transport in this clinical setting has yet to be elucidated.

Thyrotropin Regulation

Serum TSH levels are usually normal early in acute illness.¹⁴ Decreased TRH secretion due to inhibitory signals from higher cortical centers, impaired TRH metabolism,¹⁵ alteration of pulsatile TSH,¹⁶ and the decrease or absence of a nocturnal TSH surge^{16,17} may all further lower TSH levels. Serum levels of leptin, the ob gene product that has been shown to vary directly with thyroid hormone levels,¹⁸ also falls as illness progresses¹⁹ and hypothalamic TRH secretion falls, which in turn lead to lowered TSH levels.²⁰

The decrease of hypothalamic TRH gene expression in animal models is, however, not associated with increased serum T_4 and T_3 levels.¹² Finally, certain thyroid hormone metabolites that are increased during acute nonthyroidal illness may play a role in the inhibition of TSH and TRH secretion.²¹

Common medications used in the treatment of critically ill patients may also have inhibitory effects on serum TSH levels (Box 149-2). Van

TABLE 149-1 Factors That Alter Binding of T_4 to Thyroid-Binding Globulin

| | INCREASE BINDING | DECREASE BINDING |
|-------------------------|------------------|---|
| DRUGS | Estrogens | Glucocorticoids |
| | Methadone | Androgens |
| | Clofibrate | L-Asparaginase |
| | 5-Fluorouracil | Salicylates |
| | Heroin | Mefenamic acid |
| | Tamoxifen | Antiseizure medications (phenytoin, Tegretol) |
| | Raloxifene | Furosemide |
| SYSTEMIC FACTORS | | Heparin |
| | | Anabolic steroids |
| | Liver disease | Inherited |
| | Porphyria | Acute illness |
| | HIV infection | Nonesterified free fatty acids (NEFAs) |
| | Inherited | |

den Berghe et al.²² reported that intravenous (IV) administration of dopamine for as short a time as 15 to 21 hours can acutely decrease TSH levels, and its withdrawal results in a 10-fold increase in serum TSH levels. In one study, children who received dopamine infusions during a pediatric ICU admission for meningococcal sepsis had lower TSH levels than those who did not.^{23,24} Increased levels of glucocorticoids, whether from endogenous or exogenous sources, also have direct inhibitory effects on TSH secretion.

Serum Binding Proteins

The affinity of thyroid hormones binding to transport proteins and the concentration of serum binding proteins are altered with acute illness (Table 149-1). Serum levels of transthyretin and albumin decrease, especially during prolonged illness, malnutrition, and in high catabolic states. TBG levels may be increased, as seen with liver dysfunction and human immunodeficiency virus (HIV) infection,²⁵ or decreased, as seen with severe or prolonged illness.⁴ TBG may also be rapidly degraded by protease cleavage during cardiac bypass, thereby partially explaining the rapid fall of serum T_3 levels in patients undergoing cardiac surgery.²⁶

An acquired binding defect of T_4 to TBG is commonly seen in patients with critical illness. This is thought to result from the release of some as yet unidentified factor from injured tissues that has the characteristics of unsaturated nonesterified fatty acids (NEFA),²⁷ which also inhibit T_4 -to- T_3 conversion.²⁸ In systemically ill patients, NEFA levels rise in parallel with the severity of the illness,²⁹ and drugs such as heparin stimulate the generation of NEFA.³⁰ Many drugs including high-dose furosemide, antiseizure medications, and salicylates also alter the binding of T_4 to TBG. The alteration in serum binding proteins in critical illness makes estimating free hormone concentrations difficult (see later).

EVALUATION OF THYROID FUNCTION IN CRITICALLY ILL PATIENTS

Diagnostic Tests

Thyrotropin Assays

Abnormal thyroid function tests have been reported in 20% to 40% of acutely ill patients, more than 80% of whom have no intrinsic thyroid dysfunction after resolution of the illness.³¹⁻³³ In a study of 1580 hospitalized patients, only 24% of patients with suppressed TSH values (TSH < assay limit of detection) and 50% of patients with TSH values over 20 mU/L were found to have thyroid disease.^{31,32} More

important, none of the patients with subnormal but detectable TSH values and only 14% of patients with elevated TSH values less than 20 mU/L were subsequently diagnosed with intrinsic thyroid dysfunction. A review by Kaptein and colleagues suggested that patients with isolated increased TSH concentrations in the setting of chronic cardiac, hepatic, or renal disease usually do not persist or progress to overt hypothyroidism.³⁴

The development of sensitive third-generation TSH assays has led to small improvements in discerning between overt hyperthyroidism and nonthyroidal illness.³¹ Overall, however, while a normal TSH level has a high predictive value of normal thyroid function, an abnormal TSH value alone is not helpful in evaluating thyroid function in critically ill patients.

Serum T_4 and T_3 Concentrations

Measurement of free thyroid hormone concentrations in patients with nonthyroidal illness is fraught with difficulty.³⁵ The gold standard for determination of free hormone levels is equilibrium dialysis. However, this technique is labor intensive and time consuming and is thus rarely used. The most commonly available laboratory tests for thyroid hormone concentrations, free T_4 index, free T_4 , and free T_3 , are measured by analog methods; these methods are estimates of free hormone concentrations and are thus subject to inaccuracies.^{36,37}

The free T_4 index (FT4I) is determined by multiplying the total T_4 concentration by the T_3 or T_4 resin uptake, which is an inverse estimate of serum TBG concentrations.³⁷ Free T_4 levels can also be measured by the analog method, a less expensive alternative to the free T_4 index³⁸; the two tests are likely comparably accurate,³⁹ and in a healthy population, there is a close correlation between the free T_4 index and free T_4 levels. However, in critically ill patients, this association is no longer seen, mainly because of difficulties in estimating TBG binding with resin uptake tests. Despite this, the sensitivity of the free T_4 index in a large study of hospitalized patients was 92.3%, compared to 90.7% for the sensitive TSH test.³¹

Of the serum thyroid function tests, serum T_3 concentrations are affected to the greatest degree by alteration in thyroid hormone economy resulting from acute illness. Therefore, there is no indication for routine measurement of serum T_3 levels in the initial evaluation of thyroid function in critically ill patients. This test should be obtained only if thyrotoxicosis is clinically suspected in the presence of a suppressed sensitive TSH and elevated (or high normal) free T_4 index or free T_4 values. The total T_3 assay is preferable to the free T_3 (analog) assay, owing to the variability among laboratories with the latter test.³⁷

Although some investigators have reported that serum rT_3 levels are a significant prognostic indicator of mortality in the ICU,^{11,40} rT_3 levels are generally unreliable and should not be used to distinguish between intrinsic thyroid dysfunction and nonthyroidal illness.⁴¹

Serum Thyroid Autoantibodies

Autoantibodies to thyroglobulin and thyroid peroxidase (TPO), two intrinsic thyroid proteins, are commonly ordered tests.³⁷ Increased serum titers of either or both of these antibodies indicate the presence of autoimmune thyroid disease, but the presence of thyroid autoantibodies alone does not necessarily indicate thyroid dysfunction, as they are present in up to 26% of the general population.^{42,43} Thyroid autoantibodies do, however, add to the sensitivity of abnormal thyroid-stimulating hormone (TSH) and FT4I values in diagnosing known intrinsic thyroid disease.^{31,32}

Imaging Studies

Imaging studies are rarely essential for the diagnosis of thyroid disorders in critically ill patients. Occasionally, functional analysis of thyroid glands using the radioisotope iodine-123 (¹²³I) may be useful in patients with suspected thyrotoxicosis and equivocal laboratory tests. However, these studies are labor intensive, and managing the underlying acute illness often overshadows the benefits of obtaining these studies. Anatomic studies such as ultrasound, isotopic imaging,

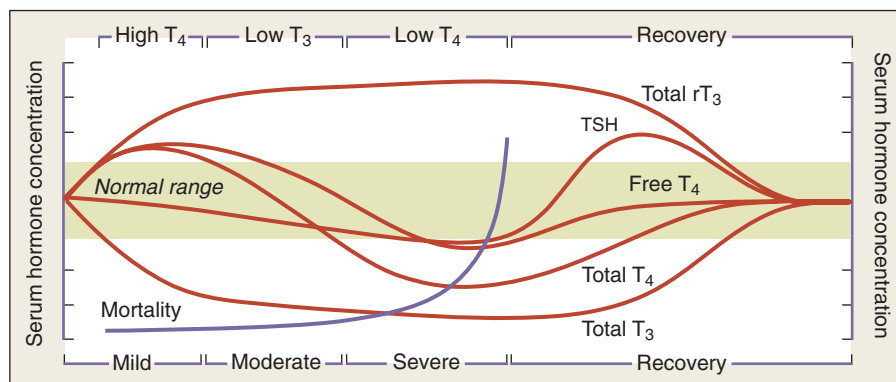


FIGURE 149-2 ■ Alterations in thyroid hormone concentrations with critical illness. Schematic representation of the continuum of changes in serum thyroid hormone concentrations in patients with nonthyroidal illness. Alterations become more pronounced with increasing severity of illness and return to normal range as illness subsides and patient recovers. A rapidly rising mortality accompanies the fall in total and free T_4 concentrations. rT_3 , reverse triiodothyronine (3,3',5'-triiodothyronine); T_3 , 3,5,3'-triiodothyronine; TSH, thyroid-stimulating hormone (thyrotropin). (From Farwell AF. Sick euthyroid syndrome in the intensive care unit. In: Irwin RS, Rippe JM, editors. Intensive care medicine. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2003.)

computed tomography (CT), and magnetic resonance imaging (MRI) are useful in the evaluation of thyroid nodules and goiter, but these conditions are rarely the cause of acute illness; as such, these studies are not usually helpful in critically ill patients.

Diagnosis

Routine screening of an ICU population for the presence of thyroid dysfunction is not recommended because of the high prevalence of abnormal thyroid function tests and low prevalence of true thyroid dysfunction. When thyroid function tests are ordered in hospitalized patients, they should only be done if there is a high clinical index of suspicion for thyroid dysfunction. Whenever possible, it is best to defer evaluation of the thyroid-pituitary axis until the patients have recovered from the acute illness.⁴⁴ Because every test of thyroid hormone function can be altered in critically ill patients, no single test can definitively rule in or rule out the presence of intrinsic thyroid dysfunction.

If there is a high clinical suspicion for intrinsic thyroid dysfunction in critically ill patients, reasonable initial tests should include either free T_4 index or free T_4 and TSH measurements. Assessment of these values in the context of the duration, severity, and stage of illness will allow the correct diagnosis in most patients. For example, a mildly elevated TSH coupled with a low free T_4 index or free T_4 is more likely to indicate primary hypothyroidism early in an acute illness, as opposed to the same values obtained during the recovery phase of the illness. Similarly, the combination of an elevated TSH and low-normal free T_4 index or free T_4 is more likely to indicate thyroid dysfunction in hypothermic, bradycardic patients than the tachycardic, normothermic individuals. If both the free T_4 index or free T_4 and TSH are normal, thyroid dysfunction is effectively eliminated as a significant contributing factor. If the diagnosis is still unclear, measurement of thyroid antibodies is helpful as a marker of intrinsic thyroid disease and increases the sensitivity of both the free T_4 index or free T_4 and the TSH. Only in the case of a suppressed TSH and a mid- to high-normal free T_4 index or free T_4 are measurements of serum T_3 levels indicated.

■ SICK EUTHYROID SYNDROME

As discussed earlier, critical illness causes multiple nonspecific alterations in thyroid hormone concentrations in patients without intrinsic thyroid dysfunction that relate to the severity of the illness.^{21,45,46}

One theory postulates that sick euthyroid syndrome may be a compensatory mechanism in response to the oxidative stress of acute illness.⁴⁷ Whatever the underlying cause, these alterations in thyroid hormone parameters represent a continuum of changes that depends on the severity of the illness and can be categorized into several distinct stages (Fig. 149-2).²¹ The wide spectrum of changes observed often results from the differing points in the course of the illness when the thyroid function tests were obtained. Importantly, these changes are rarely isolated and are often associated with alterations of other endocrine systems, such as decreases in serum gonadotropin and sex hormone concentrations⁴⁸ and increases in serum ACTH and cortisol levels.⁴⁹ Thus, the sick euthyroid syndrome should not be viewed as an isolated pathologic event but as part of a coordinated systemic reaction to illness involving both the immune and endocrine systems.

The effect of nonthyroidal illness has been studied in several acute and chronic diseases. Some investigators have postulated an association between hypothyroidism and chronic kidney disease, although the thyroid function abnormalities in this patient population with a chronic illness may represent a component of nonthyroidal illness.⁵⁰ Others have reported that the presence of nonthyroidal illness portends worsened overall prognosis in patients with coexisting end stage renal disease,⁵¹ cardiorenal syndrome,⁵² and enterocutaneous fistulas⁵³ and in burn patients.⁴⁰ There is limited literature regarding nonthyroidal illness in children hospitalized in the ICU.⁵⁴

Low T_3 State

Common to all of the abnormalities in thyroid hormone concentrations seen in critically ill patients is a substantial depression of serum T_3 levels, which can occur as early as 24 hours after the onset of illness. Over half of patients admitted to the medical service will demonstrate depressed serum T_3 concentrations.^{31,32} As noted above, there are multiple pathways that contribute to the development of the low T_3 state in critical illness, including decrease in peripheral T_4 -to- T_3 conversion through inhibition of type 1 deiodinase, increase in T_3 -to- T_2 conversion through increased type 3 deiodinase expression,⁵⁵ increase in T_3 sulfation, and increase in Triac formation. This results in marked reduction of T_3 production and rT_3 degradation,⁵⁶ thereby leading to reciprocal changes in serum T_3 and serum rT_3 concentrations. The low T_3 state has been described as a predictor of both all-cause and cardiac mortalities in critical care patients with

acute decompensated heart failure.⁵⁷ Low T_3 levels are also found in peripheral tissues.¹¹ Thyroid hormone receptor expression is also decreased in acute nonthyroidal illness,⁵⁸ possibly in response to the decrease in tissue T_3 levels.

High T_4 State

Serum T_4 levels may be elevated early in acute illness due to either the acute inhibition of type 1 deiodinase or increased TBG levels. This is seen most often in the elderly and in patients with psychiatric disorders. As the duration of illness increases, nondeiodinative pathways of T_4 degradation increase serum T_4 levels to the normal range.³²

Low T_4 State

As the severity and duration of the illness increase, serum total T_4 levels decrease into the subnormal range. Contributors to this decrease in serum T_4 levels are (1) a decrease in the binding of T_4 to serum carrier proteins, (2) a decrease in serum TSH levels, leading to decreased thyroidal production of T_4 , and (3) an increase in nondeiodinative pathways of T_4 metabolism. The decline in serum T_4 levels correlates with prognosis in the ICU, with mortality increasing as serum T_4 levels drop below 4 $\mu\text{g}/\text{dL}$ and approaching 80% in patients with serum T_4 levels below 2 $\mu\text{g}/\text{dL}$.⁵⁹⁻⁶¹ Despite marked decreases in serum total T_4 and T_3 levels in critically ill patients, free hormone levels have been reported to be normal or even elevated,^{35,36} providing a possible explanation for why most patients appear eumetabolic despite thyroid hormone levels in the hypothyroid range. Thus, the low T_4 state is unlikely to be a result of a hormone-deficient state and is probably more of a marker of multisystem failure in these critically ill patients.

Recovery State

As acute illness resolves, so do the alterations in thyroid hormone concentrations.⁶² This stage may be prolonged and is characterized by modest increases in serum TSH levels.⁶³ Full recovery with restoration of thyroid hormone levels to the normal range may require several weeks⁶⁴ or months after hospital discharge.³¹ One study reported that 35 of 40 patients with nonthyroidal illness after coronary artery bypass grafting were able to regain normal thyroid function 6 months after surgery.⁶⁵

Treatment of Sick Euthyroid Syndrome

The question of whether the sick euthyroid syndrome in critically ill patients represents pathologic alterations in thyroid function that negatively impact these patients or simply reflects multisystem failure (i.e., respiratory, cardiac, renal, hepatic failure) that occurs in critically ill patients is still debatable.^{52,53,66-69} However, in most studies, thyroid hormone replacement therapy has been shown to not be beneficial (Box 149-3),^{68,69} including in pediatric patients.⁷⁰

Initial evidence suggested a beneficial effect of liothyronine ($L-T_3$) on increasing organs available for harvest from brain-dead patients,⁷¹ such that $L-T_3$ was included in hormonal preservation of organs prior to transplant.⁷² However, a subsequent meta-analysis, including prospective studies, failed to confirm any beneficial effect.⁷³ While $L-T_3$ appears to slightly improve hemodynamic and neurohumoral parameters in patients with dilated cardiomyopathy⁷⁴ and impaired myocardial function,⁷⁵ these benefits may represent a pharmacologic effect of T_3 rather than a physiologic replacement hormonal effect. Further, the studies involving patients with congestive heart failure are more remarkable for a lack of deleterious effect of $L-T_3$ treatment than for any sustained clinical benefit; future studies are warranted in this patient population.

Therapies other than thyroid hormone replacement have been shown to be beneficial in treating the sick euthyroid syndrome. One randomized multicenter clinical trial reported that the use of

BOX 149-3

Summary of Clinical Trials on the Effects of Treatment of Sick Euthyroid Syndrome with Thyroid Hormone*

STARVATION/UNDERNUTRITION

- $L-T_3$ treatment results in increased protein breakdown and increased nitrogen excretion in fasting normal and obese patients.

GENERAL ICU PATIENTS

- No benefit of $L-T_4$ on general medical patients, patients with acute renal failure, or renal transplant
- No benefit of $L-T_3$ on burn patients

PREMATURE INFANTS

- No benefit of $L-T_4$ on developmental indices of premature infants at 26-28 weeks' gestation
- Possible beneficial effect of $L-T_4$ on infants of at 25-26 weeks' gestation but possible deleterious effects on infants of 27-30 weeks' gestation
- No benefit of $L-T_3$
- Meta-analysis shows no significant effects of thyroid hormone treatment on premature infants.

CARDIAC SURGERY PATIENTS

- Small studies suggest improved hemodynamic parameters with $L-T_3$.
- Large trials show no benefit of $L-T_3$ noted in patients undergoing cardiac bypass.
- Possible improvement in hemodynamic parameters and hospital stay with $L-T_3$ in children undergoing cardiac surgery

CARDIAC DONORS

- Variable results (helpful to no benefit) on the effects of $L-T_3$ in preserving function of normal hearts in brain-dead cardiac donors prior to transplantation
- Possible benefits of $L-T_3$ in improving function of impaired hearts prior to transplant, potentially increasing the pool of organs available for transplantation
- Consensus conferences recommend the use of $L-T_3$ as part of the hormonal resuscitation in donors whose cardiac ejection fraction is <45%.

CONGESTIVE HEART FAILURE

- Small uncontrolled study suggested short-term $L-T_4$ therapy increased cardiac output and functional capacity and decreased systemic vascular resistance.
- Improved hemodynamic parameters and neurohumoral profiles with short-term intravenous $L-T_3$ infusion, possibly requiring supraphysiologic concentrations

*Refer to Reference 69 for detailed citations.

N -acetylcysteine (NAC) was able to prevent serum thyroid function derangements, consistent with nonthyroidal illness among patients following an acute myocardial infarction.⁷⁶ The findings suggest that NAC, a potent intracellular antioxidant, is able to reduce oxidative stress, presumed as a causative factor of nonthyroidal illness.⁷⁷ Changes in thyroid hormone parameters occurring postoperatively have been prevented by early institution of nutritional support.⁷⁸ Finally, some investigators have suggested that patients with prolonged critical illness may represent a different disease entity than those with acute disease,^{79,80} and treatment with hypothalamic releasing factors should be tested in future trials.⁷⁹ In summary, in the absence of any clinical evidence of hypothyroidism, there does not appear to be any compelling evidence for the use of thyroid hormone therapy in patients with decreased thyroid hormone parameters due to the sick euthyroid syndrome.⁸¹

THYROID STORM

Thyroid storm is an acute, life-threatening complication of hyperthyroidism and represents the extreme manifestation of the disease.⁸²⁻⁸⁴ Historically, thyroid storm was associated with surgery for hyperthyroidism and approached an incidence of 10% in some series, depending upon the diagnostic criteria employed. Currently, because of better

recognition of the disease and improved perioperative management, thyroid storm is rare, accounting for less than 2% of all hospital admissions related to thyrotoxicosis.⁸⁵ Most often, thyroid storm is precipitated by an intercurrent medical problem in untreated or partially treated hyperthyroid patients.⁸²⁻⁸⁴ The diagnosis of thyroid storm is a clinical one; there are no distinctive laboratory features, and thyroid hormone concentrations are similar to those observed in uncomplicated thyrotoxicosis. Although the cause of rapid clinical decompensation is unknown, a sudden inhibition of thyroid hormone binding to plasma proteins by the precipitating factor, causing a rise in free hormone concentrations in the already elevated free hormone pool, may play a role in the pathogenesis of thyroid storm.⁸⁶

Clinical Manifestations

Thyroid storm is primarily a clinical diagnosis; as such, the varying incidence of this disorder in patient series likely results from the strictness of the diagnostic criteria. Clinical features are similar to those of thyrotoxicosis but more exaggerated (Box 149-4). Cardinal features of thyroid storm include fever (temperature usually $>38.5^{\circ}\text{C}$), tachycardia out of proportion to the fever, and mental status changes.⁸⁷ Tachyarrhythmias, especially atrial fibrillation in the elderly, are common. Nausea, vomiting, diarrhea, agitation, and delirium are frequent presentations. Vascular collapse and shock due to dehydration and cardiac decompensation are poor prognostic signs, as is the presence of jaundice.⁸⁸ Multiorgan failure has been reported.⁸⁹ Coma and death may ensue in up to 20% of patients, frequently due to cardiac arrhythmias, congestive heart failure, hyperthermia, or the precipitating illness.⁹⁰ Involvement of the central nervous system may portend a worsened prognosis.^{91,92}

Most patients display the classic signs of Graves' disease, the most common cause of thyrotoxicosis, with ophthalmopathy and a diffusely enlarged goiter as the usual manifestations.⁸³ Thyroid storm has also been associated with toxic nodular goiters. In the elderly, atypical signs and symptoms may include severe myopathy, profound weight loss, apathy, and a minimally enlarged goiter.⁹³

Precipitating Factors

In the past, thyroid storm was frequently associated with surgery for hyperthyroidism (Box 149-5), with symptoms beginning a few hours after thyroidectomy in patients prepared for surgery with potassium iodide alone. Most of these cases occurred in patients who were not appropriately prepared for surgery by current standards. Certain clinical and socioeconomic factors have also been suggested to be associated with complicated hyperthyroidism, including lack of insurance, age younger than 30 or older than 50, and serum T_4 concentrations greater than twice the upper limit of normal.⁹⁴ Because of better recognition of the disease, preoperative treatment with thionamides to deplete the gland of thyroid hormone prior to surgery, and improved perioperative management with β -blockade, thyroid storm now is rarely a postoperative complication of thyroid surgery.

Currently, thyroid storm appears most commonly following infection, causing the thyrotoxic state to decompensate.⁸³ Pneumonia, upper respiratory tract infections, and enteric infections are common precipitating infections. Other precipitating factors include stress, trauma, nonthyroidal surgery, diabetic ketoacidosis, labor, heart disease, and iodinated contrast studies in unrecognized or partially treated hyperthyroid patients.⁹⁵⁻⁹⁹ Iatrogenic thyroid storm has been reported due to thyroid hormone overdose.^{100,101} Thyroid storm associated with gestational trophoblastic disease and TSH-secreting pituitary adenoma are uncommon.^{102,103} Thyroid storm occurring after ^{131}I therapy is extremely rare.¹⁰⁴⁻¹⁰⁷ When reported, radioiodine-induced thyroid storm usually occurs if there was no pretreatment with antithyroid drugs.¹⁰⁴ Sorafenib, a tyrosine kinase inhibitor used for the treatment of renal cell carcinoma, is known to be associated with thyroid dysfunction and has been described to precipitate thyroid storm.¹⁰⁸

BOX 149-4 Clinical Features of Thyroid Storm

- Fever (as high as 105.8°F)
- Tachycardia/tachyarrhythmias
- Mental status changes
- Delirium/agitation
- Congestive heart failure
- Tremor
- Nausea and vomiting
- Diarrhea
- Sweating
- Vasodilatation
- Dehydration
- Hepatomegaly
- Splenomegaly
- Jaundice

BOX 149-5 Precipitating Factors for Thyroid Storm

- Surgery
 - Thyroidal
 - Nonthyroidal
- Infections
 - Pneumonia
 - Upper respiratory
 - Enteric
 - Other
- Stress
- Trauma
- Diabetic ketoacidosis
- Labor
- Cardiac disease
- Iodinated intravenous contrast agents
- Radioactive iodine (^{131}I) therapy

Diagnosis

As mentioned earlier, the diagnosis of thyroid storm is a clinical one. The Burch-Wartofsky⁸² and Akamizu¹⁰⁹ scoring systems may be helpful in distinguishing the likelihood of thyroid storm in patients presenting with hyperthyroid symptoms. These scoring systems utilize criteria that include temperature, central nervous system effects, gastrointestinal effects, cardiovascular effects, and precipitant history to assist in the diagnosis.

There are no distinct laboratory abnormalities apart from elevated thyroid hormone concentrations, which are similar to those found in uncomplicated thyrotoxicosis. Serum T_3 concentrations are often elevated to a greater degree than serum T_4 concentrations, owing to the preferential secretion of T_3 in the hyperthyroid gland.⁸³ There is little correlation between the degree of elevation of thyroid hormones and the presentation of thyroid storm. Serum TSH concentrations are typically undetectable; however, because of the influence of nonthyroidal illness on TSH secretion (see earlier), a low TSH by itself is insufficient to make a diagnosis of thyroid storm. Serum T_4 and T_3 concentrations in the normal range, regardless of the TSH concentration, effectively eliminate thyroid storm as a tenable diagnosis.

Abnormal liver function tests are common. Hypocalcemia may be observed secondary to increased osteoclast-mediated bone resorption in the hyperthyroid patient. Hematocrit concentrations may be elevated due to volume contraction, and leukocytosis is common even in the absence of infection.

The differential diagnosis of thyroid storm includes sepsis, neuroleptic malignant syndrome, malignant hyperthermia, and acute mania with lethal catatonia, all of which can precipitate thyroid storm in the appropriate setting. Clues to the diagnosis of thyroid storm are a

history of thyroid disease, history of iodine ingestion, and the presence of a goiter or stigmata of Graves' disease. The physician must have a high clinical index of suspicion for thyroid storm, as therapy must be instituted before the availability of thyroid function test results in most cases.

Treatment

It should be emphasized that a thyroid storm is an important medical emergency that must be treated in an ICU.⁸²⁻⁸⁴ Therapy can be divided into two major categories (Box 149-6): (1) *thyroid-directed treatment* aimed at decreasing thyroid hormone production, conversion, and secretion and blocking the peripheral manifestations of thyroid hormone and (2) *supportive treatment* aimed at controlling the fever, stabilizing the cardiovascular system, and managing the precipitating cause.

Thyroid-Directed Treatment

Prompt inhibition of thyroid hormone synthesis and secretion is essential. Antithyroid drugs are given in large doses to both inhibit

synthesis of thyroid hormones and block the uptake of iodine. Propylthiouracil (PTU) is preferred over methimazole, given its greater efficacy when used in large doses, in reducing T_3 levels during severe hyperthyroidism (by inhibition of type 1 deiodinase), and impairing peripheral conversion of T_4 to T_3 .¹¹⁰ However, since other more powerful inhibitors of type 1 deiodinase are usually part of the therapeutic regimen in thyroid storm, the main beneficial effects of PTU are its inhibition of iodide uptake and hormone synthesis. PTU and methimazole can be administered by nasogastric tube or rectally, if necessary.¹¹¹ Neither of these preparations is available for parenteral administration, although a protocol has been reported for the reconstitution of methimazole to be given IV.¹¹²

Iodides, the most effective drugs to block release of thyroid hormone from the thyroid gland, should be used only after antithyroid drugs have been administered. Monotherapy with iodides will actually increase the synthesis of new thyroid hormones and markedly worsen the hyperthyroidism when the gland escapes from the initial iodide-induced blockade of hormone secretion (the acute Wolff-Chaikoff effect).¹¹³ Previously, the iodide preparation of choice was the radiographic contrast dye, iopanoic acid (Telepaque), because of its high iodine content (0.6 mg iodine/g dose) and the ability for the drug to directly inhibit type 1 deiodinase and thus block T_4 -to- T_3 conversion.² However, this drug is largely unavailable worldwide. Lugol's solution and saturated solution of potassium iodide (SSKI) are currently the main sources of therapeutic iodides.^{114,115} It is important to realize that use of iodides precludes the use of radioactive iodine as a definitive therapy for hyperthyroidism for several months. Lithium has also been reported to be effective in inhibiting thyroid hormone release to a similar degree as iodides.¹¹⁶

High-dose dexamethasone is recommended as supportive therapy, both as an inhibitor of T_4 -to- T_3 conversion and as management of possible coexistent adrenal insufficiency. β -adrenergic blockers, specifically propranolol, are also weak inhibitors of T_4 -to- T_3 conversion, although their main beneficial effect is on heart rate control.¹¹⁷ Orally administered ion-exchange resin (colestipol or cholestyramine) can trap hormone in the intestine and prevent recirculation.^{118,119} Plasmapheresis, peritoneal dialysis, and charcoal hemoperfusion have also been used in severe cases.¹²⁰

Supportive Treatment

Simultaneously with antithyroid-directed therapy, treatments aimed at cooling the patient down to a reasonable temperature and providing hemodynamic support should be instituted. IV fluids, antipyretics, and cooling blankets are all effective. β -adrenergic blockers such as propranolol (oral or IV) and esmolol (IV) are given for heart rate control. Calcium channel blockers may be used to control tachyarrhythmias. Anxiolytics are frequently helpful once the patient's mental status improves. Finally, treatment of the underlying precipitating illness is essential to survival in thyroid storm.

Long-Term Therapy

Once the acute phase of thyroid storm is controlled, antithyroid drug therapy should be continued until euthyroidism is achieved, while the adjunctive therapy can be discontinued. Definitive therapeutic options for hyperthyroidism include radioactive iodine (after a few months to allow excretion of the excess iodides used during acute management of thyroid storm) and surgery.¹²¹⁻¹²³ Long-term (1 to 2 years) treatment with antithyroid drugs in the hopes of achieving a remission is an option for patients with Graves' disease,¹²⁴ although this is best achieved using methimazole because of the concern about rare complications of severe liver injury with PTU.¹²⁵

MYXEDEMA COMA

Myxedema coma is a rare syndrome that represents the extreme expression of severe long-standing hypothyroidism.^{84,126,127} It is a medical emergency, and even with early diagnosis and treatment, the

BOX 149-6 Treatment of Thyroid Storm

THYROID-DIRECTED THERAPY

Direct

Inhibition of Thyroid Hormone Synthesis

Propylthiouracil: 800 mg PO/PR first dose, then 200 to 300 mg PO/PR q 8 h, *or*
Methimazole: 80 mg PO/PR first dose, then 40 to 80 mg PO/PR q 12 h

Block Release of Thyroid Hormones from the Gland

Telepaque (iopanoic acid): 1 g PO once daily (if available), *or*
SSKI: 5 drops PO q 8 h, *or*
Lugol's solution: 10 drops PO q 8 h, *or*
Lithium: 800-1200 mg PO once daily; achieve serum lithium levels 0.5 to 1.5 mEq/L

Adjunctive

Block T_4 -to- T_3 Conversion

Telepaque (iopanoic acid)
Corticosteroids: dexamethasone, 1 to 2 mg PO/IV q 6 h
Propylthiouracil
Most β -blockers: propranolol, 40 to 80 mg PO q 6 h

Remove Thyroid Hormones from Circulation

Cholestyramine: 4 g PO q 6 h, *or*
Colestipol: 20 to 30 mg PO once daily, *or*
Plasmapheresis, *or*
Peritoneal dialysis

SUPPORTIVE THERAPY

Hyperthermia

IV fluids
Antipyretics
Cooling blanket

Hemodynamic

β -Adrenergic blocking drugs:
Propranolol: 1 mg IV/min to a total dose of 10 mg, then 40 to 80 mg PO q 6 h, *or*
Esmolol: 500 mg/kg/min IV, then 50 to 100 mg/kg/min, *or*
Metoprolol: 100 to 400 mg PO q 12 h, *or*
Atenolol: 50 to 100 mg PO daily

Other

Vasopressors
Digoxin

Etiologic

Treatment of underlying illness(es)

Other

Anxiolytics (once mental status clears)

IV, intravenous; PO, orally; PR, rectally.

BOX 149-7 Clinical Features of Myxedema Coma

Mental obtundation
Hypothermia
Bradycardia
Hypotension
Coarse, dry skin
Myxedema facies
Hypoglycemia
Atonic gastrointestinal tract
Atonic bladder
Pleural, pericardial, and peritoneal effusions

mortality can be as high as 40%.¹⁰¹ The name is somewhat of a misnomer, as actual coma is rare.¹²⁶ The syndrome includes decompensated hypothyroidism, central nervous system impairment, and cardiovascular compromise. Myxedema coma occurs most often in the elderly and during the cold months; in one series in India, 15 of 23 cases of myxedema coma were admitted in the winter.¹²⁸ As with thyroid storm, myxedema coma is usually caused by a precipitating event in untreated or partially treated hypothyroid patients.

Clinical Manifestations

The cardinal features of myxedema coma are (1) hypothermia, which can be profound, (2) altered mental status, (3) cardiovascular depression, and (4) a precipitating cause(s) (Box 149-7). Severely hypothyroid patients essentially become poikilothermic due to disordered thermoregulation. This is the reason many cases occur in the winter months. Body temperatures as low as 23.3°C have been reported; thus, rectal temperatures are essential in making the diagnosis. Excessive lethargy and sleepiness may have been present for weeks to months, often interfering with meals, and patients may even present obtunded.¹²⁹ Decreased consciousness has been found to be an important adverse prognostic indicator for mortality.¹³⁰ Rarely, psychosis and delirium have been reported. Bradycardia and hypotension may be profound, and the respiratory rate is often depressed. Since intrinsic hypothyroidism by itself is insufficient to produce the clinical syndrome of myxedema coma, a precipitating cause must be assumed to be present.¹²⁶

In addition to the noted features, most patients have the physical features of severe hypothyroidism,¹²⁷ including macroglossia, delayed reflexes, dry, rough skin and myxedematous facies, which results from periorbital edema, pallor, hypercarotinemias, and patchy hair loss. Hypotonia of the gastrointestinal tract is common and often so severe as to suggest an obstructive lesion.¹³¹ Urinary retention due to a hypotonic bladder is related but less frequent. Pleural, pericardial, and peritoneal effusions; cardiac tamponade¹³²; and heart failure¹³³ may be present. Severe airway obstruction has been reported.¹³⁴

Precipitating Factors

As mentioned, cold stress is a common precipitant to myxedema coma (Box 149-8). Other common precipitating factors include pulmonary and urinary tract infections, cerebrovascular accidents, trauma, surgery, congestive heart failure, and intravascular volume loss from acute or chronic gastrointestinal bleeding or overuse of diuretics.^{84,126,127} The clinical course of lethargy proceeding to stupor and then coma is often hastened by drugs, especially sedatives, narcotics, antidepressants, and tranquilizers.¹³⁵ Amiodarone, due to its high iodine content, has been reported to induce both thyroid storm¹³⁶ and myxedema coma.¹³⁷ Similar to the association of tyrosine kinase inhibitors and thyroid storm, agents such as sunitinib have also been reported to induce severe hypothyroidism.¹³⁸ Many cases of myxedema coma have occurred in undiagnosed hypothyroid patients who present for other medical problems.¹³⁹

BOX 149-8 Precipitating Factors of Myxedema Coma

Cold stress
Infection
 Pneumonia
 Urinary tract
 Other
Stroke
Congestive heart failure
Trauma
Burns
Surgery
Intravascular volume contraction
 Gastrointestinal blood loss
 Diuretic use
CNS-active drugs
 Analgesics/narcotics
 Sedatives/hypnotics
 Tranquilizers
 Anesthetic agents

CNS, central nervous system.

Diagnosis

Like the diagnosis of thyroid storm, myxedema coma is a clinical diagnosis and, similar to thyroid storm, a scoring system by Wartofsky and colleagues has been proposed.¹⁴⁰ Elderly patients may present with particularly subtle findings.¹⁴¹ Even though rare, the diagnosis of myxedema coma should be considered in hypothermic, obtunded patients. Medical histories of these patients, including a prior history of hypothyroidism, may only be able to be confirmed from other sources. Friends, relatives, and acquaintances might have noted increasing lethargy, complaints of cold intolerance, and changes in voice. Clues to the diagnosis include an outdated container of L-T₄ (levothyroxine) discovered with the patient's belongings, which suggests that the patient has been noncompliant in taking thyroid hormone replacement medication. The medical record may also indicate prescribed thyroid hormone use, previous referral to treatment with radioactive iodine, or a history of thyroidectomy. Finally, the physical exam finding of a thyroidectomy scar should raise suspicion as to the diagnosis.

Because more than 95% of cases of myxedema coma are due to primary hypothyroidism,^{84,126,127} the laboratory findings include an elevated serum TSH and low or undetectable total and free serum T₄ concentrations. These thyroid hormone abnormalities are similar to those in uncomplicated overt hypothyroidism. In patients with central hypothyroidism, the diagnosis of myxedema coma may be very difficult, as serum TSH concentrations will be normal or low. However, other symptoms of pituitary dysfunction are usually present in these rare patients.

Dilutional hyponatremia is common and may be severe. Elevated creatine kinase concentrations, sometimes markedly so, are encountered frequently and may misdirect the clinical picture toward cardiac ischemia.^{142,143} However, the MB fraction in most of these cases is normal, and an electrocardiogram (ECG) often demonstrates low voltage and loss of T waves that is characteristic of severe hypothyroidism. Elevated lactate dehydrogenase (LDH) concentrations, acidosis, and anemia are common findings. Lumbar puncture reveals increased opening pressure and high protein content in the cerebrospinal fluid.

Few of the signs and symptoms discussed are unique to myxedema coma. Protein-calorie malnutrition, sepsis, hypoglycemia, and exposure to certain drugs and toxins, as well as cold exposure can cause severe hypothermia. Hypotension and hypoventilation, other cardinal features of myxedema coma, occur in other disease states. Furthermore, low thyroid hormone concentrations may be seen in critically ill patients with nonthyroidal illness (see earlier). As with thyroid storm,

BOX 149-9 Treatment of Myxedema Coma**SUPPORTIVE**

Assisted ventilation
 Hemodynamic support
 Passive rewarming for hypothermia
 Intravenous glucose for hypoglycemia
 Water restriction or hypertonic saline for severe hyponatremia
 Hydrocortisone IV (100 mg q 8 h)
 Treatment of precipitating factor(s)
 Avoidance of all CNS-acting medications

THYROID HORMONE REPLACEMENT

L-T₄: 200- to 300-μg loading dose IV, up to 500 μg IV in the first 24 h and/or
 L-T₃: 12.5 μg IV q 6 h

CNS, central nervous system; IV, intravenous.

the physician must have a high clinical index of suspicion for myxedema coma, as therapy must be instituted before the availability of thyroid function test results, in most cases.

Treatment

Treatment of myxedema coma is a medical emergency and should be managed in an ICU setting. The mainstays of therapy are supportive care with ventilatory and hemodynamic support, rewarming, correction of hyponatremia and hypoglycemia, treatment of the precipitating incident, and administration of thyroid hormone (Box 149-9).^{84,126,127} Sedatives, hypnotics, narcotics, and anesthetics must be minimized or avoided altogether because of their extended duration of action and exacerbation of obtundation in hypothyroid patients.

Hypothermia is one of the hallmarks of myxedema coma, and its severity may be underestimated if the thermometer used does not register below 30°C. At core temperatures below 28°C, ventricular fibrillation is a significant life-threatening risk. Despite its gravity, the management of the hypothermia of myxedema coma differs from the treatment of exposure-induced hypothermia in euthyroid subjects. In myxedema coma, patients should be kept in a warm room and covered with blankets. Active heating should be avoided, since it increases oxygen consumption and promotes peripheral vasodilation and circulatory collapse. Active heating is recommended only for situations of severe hypothermia where ventricular fibrillation is an immediate threat. In these cases, the rate of rewarming should not

exceed 0.5°C per hour, and the core temperature should be raised to approximately 31°C.^{84,126,127}

Because of a 5% to 10% incidence of coexisting adrenal insufficiency in patients with myxedema coma,¹⁴⁴ IV steroids (i.e., hydrocortisone 100 mg IV every 8 hours) are indicated before initiating L-T₄ therapy. Parenteral administration of thyroid hormone is necessary due to uncertain absorption through the gut.¹⁴⁵⁻¹⁴⁷ A reasonable approach is an initial IV loading dose of 200 to 300 μg of L-T₄. If there is inadequate improvement in the state of consciousness, blood pressure, or core temperature during the first 6 to 12 hours after administration, another dose of L-T₄ should be given to bring the total dose during the first 24 hours to 0.5 mg. This should be followed by 50 to 100 μg IV every 24 hours until the patient is stabilized. Alternatively, in the most severe cases, some clinicians recommend using L-T₃ at a dosage of 12.5 to 25 μg IV every 6 hours until the patient is stable and conscious. Caution must be used to avoid overstimulation of the cardiovascular system. Once stable, the patient should be switched to L-T₄. The dose of thyroid hormone should be adjusted on the basis of hemodynamic stability, the presence of coexisting cardiac disease, and the degree of electrolyte imbalance.¹⁴⁸

Although myxedema coma is associated with a high mortality, which may be as high as 40%,¹⁴⁹ survival can be maximized by correcting the secondary metabolic disturbances and reversing the hypothyroid state in a sustained but gradual fashion, since an effort to correct hypothyroidism too rapidly may completely negate the beneficial effects of the initial treatment.

Long-Term Therapy

Once the patient with myxedema coma is clinically stable, thyroid hormone replacement can be switched to oral L-T₄. The dose of L-T₄ should be adjusted over the ensuing weeks and months to achieve serum T₄ and TSH concentrations in the normal range.

CONCLUSION

In summary, thyroid storm and myxedema coma are medical emergencies, diagnosed by their clinical presentation and confirmed by serum thyroid function tests.¹⁵⁰ The interpretation of thyroid function tests in the ICU patient outside of these dramatic presentations is often fraught with difficulty. Identifying those patients with intrinsic thyroid dysfunction must take into consideration both the clinical assessment of the patient and the duration and severity of the illness. Whenever possible, it is best to defer evaluation of thyroid function until the patient has recovered from the critical illness.

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Diabetes insipidus is a disorder of water metabolism associated with polyuria, urine hypotonicity, and hypernatremia.¹⁻³ The criteria for this diagnosis include urine output greater than 200 mL/h or 3 mL/kg/h, urine osmolality less than 150 mOsm/kg, and plasma sodium greater than 145 mEq/L. If urine osmolality measurement is not available, hypotonicity can be assessed from a urine specific gravity less than 1.005.

CENTRAL DIABETES INSIPIDUS

Neurogenic or central diabetes insipidus is characterized by a lack of antidiuretic hormone (ADH) that may result from any injury to the anterior hypothalamus, pituitary stalk, or posterior pituitary gland. In acute critically ill patients, the most common causes of diabetes insipidus are surgery for pituitary tumors, cerebral trauma, intracranial hypertension, and brain death (Box 150-1). Diabetes insipidus also may occur as a complication of bacterial meningitis or encephalitis, vascular aneurysm or thrombosis, drug administration, or alcohol intoxication. Injuries to the hypothalamus most often yield permanent diabetes insipidus because ADH is synthesized in the hypothalamus itself. Injuries to the pituitary stalk and neurohypophysis more commonly cause transient diabetes insipidus because hypothalamic ADH secretion can be effective even in the absence of anatomic pathways to the normal site of release. Chronic diabetes insipidus in critically ill patients generally results from tumors of the pituitary region and from the sequelae of cerebral trauma.

Clinical Picture

In complete hypothalamic or pituitary injuries, diabetes insipidus generally develops 6 to 24 hours after the injury because previously released ADH remains circulating for several hours. Patients with untreated diabetes insipidus usually develop urine output of 10 to 15 L/day. When the thirst mechanism is preserved, it is activated as soon as osmolality or volemia decreases. If the patient remains conscious and is given free access to water, he or she may be able to drink large amounts and compensate for the urine losses. In other cases, the large amounts of dilute urine rapidly result in dehydration with hypovolemia and hypotension as well as hypernatremia with neurologic deterioration. It is important that diabetes insipidus be recognized and treated rapidly, especially in comatose or noncommunicative patients. In patients with partial diabetes insipidus, the onset of polyuria may be delayed, and the volume of urine may be lower. Nevertheless, if urine is hypoosmolar and diabetes insipidus is not treated, dehydration and hypernatremia eventually occur and cause symptoms.

Clinical signs of hypernatremia usually appear only when the plasma sodium concentration increases to greater than 155 to 160 mEq/L or plasma osmolality increases to greater than 330 mOsm/kg.⁴ Signs may appear sooner if hypernatremia is associated with other metabolic disorders, particularly with disorders that also increase plasma osmolality. Symptoms mainly include confusion and lethargy. Severe hypernatremia results in coma and sometimes in seizures. Acute and severe dehydration and hypernatremia may lead to cerebral shrinkage, sometimes associated with subdural or intraparenchymal hemorrhage.

Clinical signs of dehydration include blood volume depletion and hypotension in the most severe cases. Biologic markers of dehydration

are usually absent in ICU patients with central diabetes insipidus because the urine loss begins abruptly and commonly reaches more than 1 L/h. The free water deficit can be estimated by the following formula:

$$\text{Deficit (L)} = \text{body weight (kg)} \times 0.6 \times (\text{Na}^+ - 140) / \text{Na}^+$$

This formula assumes that only free water has been lost and that sodium stores are normal. Most often, some sodium has been lost together with additional water, and the total water deficit is even higher than that estimated from the formula. A moderate level of hypernatremia (e.g., 155 mEq) is associated with a free water deficit of more than 4 L and total water deficit that may be much higher if sodium has been lost.

Differential Diagnosis

The differential diagnosis of polyuria includes the intake of diuretic drugs, hyperglycemia, fluid overload, and fluid mobilization. The search for diuretic administration should include not only conventional diuretics but also mannitol and iodinated contrast agents. The administration of diuretics may not be evident when these substances have been given before admission to the ICU (e.g., in another hospital before patient transfer; in an ambulance during transfer; or in the operating room during neurosurgery, trauma surgery, or vascular surgery). Preventive administration of furosemide and mannitol is given routinely in some neurosurgical procedures and may result in marked polyuria during and after the operation. Hyperglycemia-induced osmotic diuresis is common, can be suspected from polyuria or from hyperglycemia, and is confirmed or ruled out by the presence or absence of glucosuria. Hypervolemia, resulting from fluid overload or unmasked by discontinuation of sustained positive-pressure ventilation, may increase urine output to greater than 5 L/day for several days in patients with normal renal function. Mobilization of edema, at the time of recovery from disease or from surgery, also can result in sustained polyuria. In all these conditions, however, urine remains close to isotonic (osmolality ~300 mOsm/kg). Abundant intake of hypotonic fluid can cause polyuria and urine hypotonicity but does not result in hypernatremia if renal function is normal. The observation of decreased urine output after ADH administration is not diagnostic of diabetes insipidus because ADH is able to reduce urine output and to increase urine osmolality in all conditions except nephrogenic diabetes insipidus.

Treatment

The management of diabetes insipidus includes two components (Box 150-2): (1) reduction of excessive urine output and (2) correction of water deficit. The polyuria of central diabetes insipidus is treated effectively by vasopressin (ADH) or by its synthetic analog desmopressin acetate (DDAVP [1-deamino-8-D-arginine vasopressin]).^{5,6} As indicated by its multiple names, vasopressin not only has antidiuretic but also vasoconstrictive and oxytocic effects, whereas desmopressin essentially retains the antidiuretic action. The effects of aqueous vasopressin (4 to 10 U subcutaneously or intramuscularly) on diuresis begin rapidly but last for only a few hours. Dosing of vasopressin must therefore be repeated every 4 to 6 hours and has been recommended only for diagnostic purposes or in acute conditions (e.g., trauma) in

BOX 150-1 Causes of Diabetes Insipidus**CENTRAL**

Congenital anomalies: corpus callosum agenesis, cleft palate
 Granulomatous disease: sarcoidosis, tuberculosis, Wegener's disease
 Histiocytosis
 Sickle cell disease
 Idiopathic—autoimmune
 Tumors: suprasellar, infrasellar, aneurysms
 Infection: meningitis, encephalitis
 Head trauma, neurosurgery, brain death

NEPHROGENIC

Congenital disease
 Renal disease: obstructive uropathy, reflux nephropathy, cystic disease, electrolyte disorders
 Renal involvement in systemic disease: sarcoidosis, amyloidosis, sickle cell disease
 Drugs: phenytoin, aminoglycosides, amphotericin, antivirals, demeclocycline, lithium

BOX 150-2 Management of Diabetes Insipidus

Control polyuria with DDAVP or vasopressin.
 Calculate and replace free water loss.
 Monitor and replace urine losses hourly.
 Monitor plasma electrolytes and adapt therapy every 4 h.

DDAVP, 1-deamino-8-D-arginine vasopressin.

which the diabetes insipidus might be transient. The effects of vasopressin tannate in oil emulsion (2 to 5 U intramuscularly) last 48 to 96 hours, but the preparation requires close attention to warming and mixing the suspension before injection. Vasopressin tannate previously used to be the standard therapy in patients with central diabetes insipidus but now has been abandoned in favor of desmopressin. Vasopressin tannate, where available, still may be used in patients who are refractory to desmopressin or who experience significant side effects. Desmopressin has prolonged effects (8 to 20 hours) and is appropriate for intravenous, subcutaneous, and intranasal routes. Lypressin is another ADH analog that is appropriate for intranasal use, but its effectiveness is limited by its duration of action of only 4 to 6 hours. Desmopressin is known to increase factor VIII and von Willebrand factor levels and is sometimes used for this reason in patients with coagulation disorders or in the setting of surgical procedures associated with significant bleeding.

In critically ill patients with acute central diabetes insipidus, desmopressin is initially given as 10 to 20 µg intranasally and repeated every 30 to 60 minutes until urine output is reduced to less than 100 mL/h. The initial dose required to maintain a normal urine volume ranges from 10 to 60 µg in most patients. This dose is given again when the urine output increases to greater than 200 mL/h (i.e., after 8 to 24 hours). Dosage must be reduced if urine output is excessively decreased. The subcutaneous route is seldom used because absorption may be erratic in vasoconstricted patients and because an intravenous line is virtually always available in ICU patients. Desmopressin is injected intravenously when the intranasal route is not available (i.e., in cases of rhinorrhea and facial trauma). The required initial dose ranges from 2 to 20 µg and is given as repeated 2- to 4-µg boluses.

Vasopressin therapy can be associated with arterial hypertension, myocardial infarction, mesenteric infarction, peripheral ischemia, and uterine cramps. Vasopressin tannate may cause allergic reactions, ranging from urticaria to anaphylaxis, and sterile abscesses at sites of injection. Desmopressin may interfere with anticoagulant drugs and cause hypercoagulability. When given in excess, all these antidiuretic

agents can result in oliguria, hyponatremia, and water intoxication. The severity of diabetes insipidus may vary over time, even in patients with chronic diabetes insipidus, and some patients with chronic diabetes insipidus who are used to drinking large amounts of water may continue to do so even if urine output is limited by a diuretic drug.

Patients with acute diabetes insipidus should receive a sufficient amount of water to match urine output until the polyuria is controlled and to correct the deficit of free water that already exists at the time of diagnosis. If the gastrointestinal system is functional, water can be infused at rates of 1 to 2 L/h through a gastric tube. Otherwise, isotonic dextrose should be infused intravenously in appropriate amounts (hypotonic dextrose administration can be obtained by infusing equal amounts of water and isotonic dextrose in a central vein, but this procedure has been associated with vascular injuries). The gastric or intravenous infusion rate is adjusted at least hourly to match urine output of the last equivalent period. Plasma electrolytes should be monitored every 4 hours until normal sodium levels are restored and stabilized. Blood glucose must be monitored closely and hyperglycemia treated aggressively using intravenous insulin. Failure to control hyperglycemia may be associated with osmotic diuresis due to glucosuria and superimpose an equivalent of diabetes mellitus on the already present diabetes insipidus.

NEPHROGENIC DIABETES INSIPIDUS

Nephrogenic diabetes insipidus is characterized by the inability of the renal parenchyma to concentrate urine in response to ADH.^{7,8,9} The disorder is seldom diagnosed in the ICU and is usually more severe when it is congenital. Hereditary forms generally result from mutations to the AVP-2 receptors or AQP-2 water channels. Acquired forms are due to vasopressin resistance of the distal tubule and collecting duct or to markedly reduced renal concentrating capacity. Most acquired forms are attributed to electrolyte disturbances and to lithium therapy, but many other drugs have been implicated. Nephrogenic diabetes insipidus may be treated with a low-sodium low-protein regimen that reduces the solute load, with thiazide diuretics that induce a mild volume depletion and help reduce the urine volume to acceptable values, and with nonsteroidal antiinflammatory drugs, such as indomethacin, that inhibit prostaglandin synthesis.

KEY POINTS

1. Diabetes insipidus is characterized by polyuria, urine hypotonicity, and hypernatremia.
2. Central diabetes insipidus results from a lack of antidiuretic hormone (ADH); nephrogenic diabetes insipidus results from renal insensitivity to ADH.
3. In the ICU, diabetes insipidus is caused mainly by pituitary surgery, trauma, and brain death.
4. Clinical signs are related to dehydration and hypernatremia.
5. ICU patients generally are unable to compensate for excessive urine losses by drinking.
6. Differential diagnosis includes administration of diuretics, mannitol, and iodinated agents.
7. Polyuria is controlled with desmopressin, 10 to 20 µg intranasally or 2 to 4 µg intravenously.
8. Water deficit is corrected with enteral water or intravenous 5% dextrose in water.
9. Diuresis should be monitored hourly, and ongoing urinary losses should be compensated.

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■ References for this chapter can be found at expertconsult.com.

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Increasing numbers of metabolic and endocrine conditions are being recognized, and the number of children in treatment programs for these conditions is increasing. Although improved screening programs and therapy may decrease the number of children requiring critical care for these conditions, it is likely that these conditions will be recognized with larger numbers of critically ill children in the future. There is growing awareness of the significance of metabolic changes such as hypo- and hyperglycemia in the pediatric intensive care unit (PICU),¹ of the endocrine associations with medications such as etomidate² and conditions such as traumatic brain injury,^{3,4} and of the importance of vitamins such as vitamin D (which functions as a steroid hormone) in critical illness.⁵

General principles of PICU management apply to patients with endocrine and metabolic crises (Table 151-1).^{6,7} Crises may cause damage with long-term sequelae for the child and family; however, they also present unique diagnostic opportunities. Intensivists have a responsibility to

- Be aware of metabolic and endocrine problems
- Consider these problems in the differential diagnosis of particular clinical syndromes
- Perform appropriate clinical and biochemical investigations (this may include investigations necessary to make a diagnosis despite a poor outcome for a child)
- Seek advice from specialists in the clinical and laboratory diagnosis and management of the conditions
- Consider the implications of metabolic and endocrine problems for the family of the affected child⁸
- Support the development of protocols for the comprehensive management of metabolic problems from infancy to adulthood⁹

Abnormalities of glucose control are common in the PICU, but with the possible exception of diabetes mellitus, endocrine and metabolic crises are uncommon, and most intensivists do not see sufficient case numbers to become experts at managing these disorders. It is thus crucial to manage children with suspected or proven endocrine or metabolic crises in conjunction with specialist teams. The laboratory investigation of inborn errors of metabolism (IEM) may be complex, and there are few laboratories worldwide that have the capacity to fully elucidate most of the IEM. Close cooperation with specialty laboratory centers is essential for accurate diagnosis and management. A specific challenge of endocrine and metabolic crises is that laboratory investigation of specific conditions may take time, while patients require urgent treatment. Because it may not always be possible to closely follow algorithms of investigation, a reasonable laboratory approach is to collect relevant specimens immediately,¹⁰ store them appropriately, and liaise with laboratory services to use the specimens in a logical and cost-effective manner to confirm the diagnosis.

■ ENDOCRINE CRISES

Endocrine crises present in a limited number of ways that include abnormalities in glucose control, fluid and electrolyte balance, and blood pressure control. Management consists of identifying the problem, investigating the cause, and correcting the abnormality directly or via managing the underlying problem. This chapter provides an overview of pediatric endocrine crises.

Abnormalities of Glucose Control

Abnormalities of glucose control, including diabetic ketoacidosis (DKA), are the most common endocrine crises encountered in the PICU. Hypoglycemia¹¹⁻¹³ and hyperglycemia^{1,14} are associated with increased mortality and morbidity in sick children and may be part of a wide variety of disease processes. Measurement of blood glucose level is part of the initial biochemical evaluation of any sick child, particularly if a depressed level of consciousness or shock is present. When an abnormal glucose level is identified, it must be addressed and reassessed at appropriate intervals until the problem is resolved. The situation is complicated by technical issues in the measurement of blood glucose levels,¹⁵⁻¹⁷ with differences between blood and plasma glucose levels and between arterial, venous, and capillary glucose levels (which may also vary depending on clinical context) and potentially significant differences among different measurement techniques.¹⁵ In general, a specific concern is that inaccuracies tend to increase at lower glucose levels.¹⁵ Central laboratory measurements are generally taken as the standard, although there is increasing utilization (and convenience) of point-of-care devices.

Hypoglycemia

Hypoglycemia may be associated with devastating damage to the brain and requires immediate attention. A diagnosis of hypoglycemia depends on the presence of (1) symptoms consistent with hypoglycemia, (2) a low blood glucose level, and (3) resolution of symptoms with correction of the low glucose level. Unfortunately, symptoms of hypoglycemia are non-specific (ranging from lethargy, poor feeding, hypotonia, and "jitteriness" to convulsions, apneic episodes, cardiovascular collapse, and sudden infant death syndrome [SIDS]) and may be hidden in the complexity of critical illness, particularly if patients are deeply sedated and/or paralyzed. Some diabetic patients have reduced awareness of hypoglycemia.¹⁸ Thus, regular monitoring of blood glucose levels is an important part of the management of any critically ill child, although the implications of a particular level may also be related to the availability of other energy sources such as ketones.¹⁹ Although the exact definition of hypoglycemia in children is controversial, a minimal level of 2.6 mmol/L or greater should be maintained to ensure normal neural function.^{20,21} It probably is safer to maintain a level higher than 3.5 mmol/L. Because there are multiple causes for hypoglycemia and symptoms may not be due to the hypoglycemia alone, it is essential to identify the cause of hypoglycemia.

In childhood, hypoglycemia may result from inadequate glucose intake (prolonged starvation, malabsorption), defects in glycogenolysis (glycogen storage disorders) or gluconeogenesis (fructose-1,6-diphosphatase deficiency, ethanol intoxication, Jamaican vomiting sickness, etc.), fatty acid oxidation disorders and defects in ketogenesis, a deficiency of gluconeogenic hormones (such as adrenaline, corticosteroids, glucagons, growth hormone, and thyroid hormone), excessive insulin secretion (hyperinsulinism), or a variety of specific disorders including abnormalities of amino acid metabolism.²²

The amount of glucose required to achieve normoglycemia and the duration of fast that can be endured without the development of hypoglycemia may assist in identifying a likely cause. Transient hypoglycemia that can be reversed with normal infusion rates of glucose (4 to 6 mg/kg/min) and does not recur is unlikely to be associated with

TABLE 151-1 Principles of Management of Metabolic and Endocrine Crises

| PRINCIPLE | SPECIFICS OF CONDITIONS |
|---|--|
| Airway management | Many patients have depressed level of consciousness, and airway management is essential to prevent complications. |
| Breathing support | Acidotic patients may make huge respiratory effort; ventilatory support may help to decrease the metabolic demands on these patients. Although administration of sodium bicarbonate may help to settle some of the acidosis-related symptoms, such as hyperventilation, bicarbonate may aggravate some problems seen in conjunction with urea cycle defects. Give bicarbonate only if the plasma bicarbonate is <10 mmol/L and then only correct deficits by half. |
| Circulatory support | Ensure that there is adequate circulating volume; this may be a particular issue if there has been excessive fluid loss from vomiting or diarrhea. |
| Disability | Control seizures using anticonvulsant agents. Administer pyridoxine if there is a possibility of pyridoxine dependency. |
| Dialysis to remove toxins where necessary | Hemodialysis is the most efficient means of removing toxins such as ammonia and leucine. Hemofiltration is less efficient but may be more applicable in critically ill children. Peritoneal dialysis is slower but has the advantage of ease of initiation. ²²³ In some conditions, it may be possible to remove toxins by stimulating alternative pathways of metabolism. |
| Ensure that glucose is maintained in the normal range | A normal glucose level should be maintained at all times. Excessive administration of glucose in the mitochondrial energy chain problem may exacerbate lactic acidosis. Also, attempt to provide an adequate energy supply (may use medium-chain fatty acids where appropriate). Minimize energy demands on patient. |
| Fluids | In general, provide 1.5× the normal fluid maintenance requirements to accelerate excretion of water-soluble toxins. In the context of encephalopathy (MSUD or urea cycle defects), be careful to avoid overhydration, which may exacerbate cerebral edema. |
| Feeds | If there is accumulation of a product, this needs to be eliminated from the diet (e.g., fructose, galactose). Start with a protein-free diet, but do not continue that beyond 2 days because the catabolic state also creates problems. If a diagnosis not identified, gradually reintroduce feeds and nutrition. If there is a deficiency of any nutrient (e.g., carnitine, which may have a primary or a secondary deficiency), supplement that nutrient. Ensure that there is an adequate energy source along a metabolic route that is functional. Provide specific vitamin therapy where indicated. |
| Family support and information | The diagnosis of an inborn error of metabolism (IEM) has major implications for families, and considerable support is required. ² |
| Treat infection | Infections are an important component of pediatric ICU presentation of inborn errors of metabolism. Some conditions, such as galactosemia, are related to specific infections, such as <i>Escherichia coli</i> . Other conditions are related to pyogenic infections because of neutropenia. Children who are in a poor nutritional or metabolic state are more susceptible to infection. Concomitant infections may be the precipitating factor for metabolic decompensation. |
| Investigations | A wide variety of investigations are relevant to IEMs. Biochemical testing on a range of body fluids and on tissues is fundamental to the accurate diagnosis of the problem; tests may range from screening to more complex tests on tissue culture. Imaging, such as CT, MRI, magnetic resonance spectroscopy, and echocardiography, may be relevant. Functional tests, such as EEG, ECG, and EMG, may be useful in establishing a diagnosis. Increasingly, genetic diagnosis is available, if children have recognized genetic mutations. |
| Monitor response to therapy | Clinical monitoring is essential. Biochemical monitoring of the appropriate metabolites is essential to ensure that metabolic control is established. |

CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram; ICU, intensive care unit; MRI, magnetic resonance imaging; IEM, inborn error of metabolism.

an endocrine problem. Hyperinsulinemia is associated with the rapid development of hypoglycemia and high glucose requirements (>6 to 8 mg/kg/min to >15 to 20 mg/kg/min). Hypoglycemia associated with adrenal insufficiency, growth hormone deficiency, and hypothyroidism tends to occur several hours after fasting, is associated with ketosis, and can be reversed with normal infusion rates of glucose. Fatty acid oxidation defects are associated with hypoglycemia after a fast of several hours. Alternatively, hypoglycemia within 1 to 3 hours of a meal is usually related to hyperinsulinemia, within 4 to 5 hours of a meal signifies problems of glycogenolysis, and after 12 or more hours of fasting signifies problems in gluconeogenesis.²³

As soon as hypoglycemia is noted (and confirmed), specimens should be collected immediately for appropriate testing (Table 151-2). Treatment of hypoglycemia with intravenous glucose should be initiated promptly. An initial bolus dose of 0.5 g/kg of glucose (neonates may require 0.5 to 2 g/kg) should be given as a 10% or 25% (25% in older children) dextrose solution, followed by an ongoing infusion of glucose at a rate of 4 to 8 mg/kg/min. The concentration of the ongoing infusion depends on the fluid requirements of the child and the availability of central venous access (for higher concentrations). Glucagon may be given at a dose of 0.1 to 0.3 mg/kg (intravenously or intramuscularly) but is unlikely to be effective in patients with low glycogen stores, glycogen storage disorders, or hepatic dysfunction.²³ Hydrocortisone at a dose of 5 mg/kg every 12 hours may be useful in some patients. Diazoxide and intravenous octreotide decrease insulin release and may be useful in the management of hyperinsulinemia.

If non-glucose-reducing substances are present in the urine, galactosemia, hereditary fructose intolerance, or tyrosinemia should be considered. In the absence of reducing substances, low urinary ketones with hypoglycemia suggest hyperinsulinism or defects of fatty acid oxidation. The latter can be distinguished from hyperinsulinemia by the presence of high levels of serum free fatty acids. Assays of insulin levels can confirm the diagnosis of hyperinsulinism.

Abnormalities in growth hormone, cortisol, or thyroid hormone typically are associated with high levels of urinary ketones, the absence of hepatomegaly, and increased levels of lactate. Hypoglycemia may also occur as a complication of insulin therapy for diabetes mellitus. Patients with diabetes mellitus may have inadequate responses to hypoglycemia.

Neonates. Hypoglycemia immediately after birth may be common, but there are controversies in its definition.²⁴⁻³¹ The current recommendation for the definition of hypoglycemia in the period after birth includes a single measurement of blood glucose level less than 1 mmol/L (18 mg/dL), blood glucose level less than 2 mmol/L (36 mg/dL) that remains below the same value at the next measurement, or a single measurement of less than 2.5 mmol/L (45 mg/dL) in a newborn with abnormal clinical signs.³¹

In the immediate newborn period, glucose is not the only energy source from oxidative metabolism in the brain, and alternative energy sources such as ketones may be used.³² Breastfed babies routinely have lower glucose levels and higher ketone levels than formula-fed infants. However, there is evidence that hypoglycemic injury is more likely to occur at very low levels of glucose (20 to 25 mg/dL, 1.1 to

TABLE 151-2 Investigation of Hypoglycemia

| TEST | COMMENT |
|---|--|
| Blood glucose | Measurement of glucose using blood from capillary specimens and using test strips may be unreliable (particularly in poorly perfused patients or patients with high hematocrit); where possible, low glucose levels should be confirmed using laboratory assays on venous or arterial blood. |
| Calculation of actual glucose intake | Hypoglycemia in the presence of normal glucose intake or after brief fast suggests hyperinsulinism. Hypoglycemia after hours of fasting is associated with fatty acid oxidation defects and endocrine insufficiency. |
| Non-glucose-reducing substances in the urine | Particularly in neonates and probably not relevant in older children. If present in the urine, consider galactosemia, hereditary fructose intolerance, or tyrosinemia. |
| Serum and urinary ketones | Low ketones suggest hyperinsulinism or fatty acid oxidation problems. |
| Serum free fatty acids | Free fatty acids are low in hyperinsulinism but high in fatty acid oxidation defects. |
| Serum insulin (and C peptide), cortisol, glucagon, growth hormone, and thyroid levels | Normal serum insulin in the presence of hypoglycemia is evidence of hyperinsulinism. C peptide may be necessary to ascertain whether exogenous insulin was administered. Release of C peptide may not be as pulsatile as that of insulin. |
| Serum ammonia | Used to recognize hyperinsulinism/hyperammonemia syndrome. |
| Urinary organic acids and serum amino acids | Used to diagnose fatty acid oxidation defects (urinary organic acids). Aminoacidopathies such as MSUD, propionic acidemia, isovaleric acidemia, methylmalonic acidemia, and tyrosinemia may also present with hypoglycemia. |
| Total and free carnitine with acylcarnitine profile | To recognize primary and secondary deficiency of carnitine and fatty acid oxidation defects. |

1.4 mmol/L), if hypoglycemia is prolonged, if hypoglycemia is the consequence of hyperinsulinemia (when alternative energy sources for the brain may be very limited), and in the presence of other potential injuries.^{28,33}

Infants at particular risk include those with poor hepatic glycogen stores (e.g., preterm or small for gestational age infants), poor glucose intake (e.g., preterm or ill infants), and hyperinsulinism, either primary or secondary to high intrauterine glucose levels (e.g., infants of diabetic mothers).³⁴ Hypoglycemia may also be a feature of perinatal illness, including asphyxia, polycythemia, hypothermia, septicemia, and respiratory distress syndrome. Much less common causes include growth hormone³⁵ or adrenal insufficiency,³⁶ IEM, and glucagon insufficiency. Drugs administered to the mother during pregnancy, including oral hypoglycemic agents, must also be considered. Although the threshold for treatment in an asymptomatic neonate is 25 to 30 mg/dL (0.1 to 1.4 mmol/L), the recommended levels during treatment are higher than 45 mg/dL (2.5 mmol/L).

Hypoglycemia is associated with severe illness. A variety of illnesses, including infections,³⁷ cyanotic and acyanotic congenital heart disease, and cardiomyopathy/myocarditis, are associated with hypoglycemia. Hepatic failure from infection, toxin ingestion, or drug reactions may be associated with severe hypoglycemia, and individuals with Reye syndrome classically present with hypoglycemia. Toxins, such as salicylates and ethanol, may also cause hypoglycemia. Hypoglycemia has been linked with increased mortality from malaria,³⁸⁻⁴⁰ gastroenteritis,⁴¹ and acute bacterial meningitis,⁴² among other conditions. Hypoglycemia has also been described as a complication of

therapy for leukemia with mercaptopurine and methotrexate.^{43,44} Although severe illness or sepsis may be an adequate explanation for hypoglycemia, a diagnosis of sepsis should not exclude the possibility of an endocrine or metabolic crisis.

Hyperinsulinemic Hypoglycemia

Hyperinsulinism is the most common cause of persistent or recurrent hypoglycemia in infancy. It may be secondary to risk factors in the perinatal period (associated with high maternal glucose levels,⁴⁵ rhesus incompatibility, intrauterine growth retardation,⁴⁶ and perinatal asphyxia)⁴⁷ but may also be congenital⁴⁸ or associated with syndromes such as Beckwith-Wiedemann, Sotos, Kabuki, Costello, or Turner (mosaic), with congenital deficiency of glycosylation, among others.⁴⁹ Although most patients with hyperinsulinemic hypoglycemia present in the neonatal period, the first presentation may be during infancy and occasionally during childhood⁵⁰ when it may be more likely to respond to medical therapy. Neonates with hypoglycemia may have macrosomia typical of infants of diabetic mothers, but hyperinsulinemic hypoglycemia may occur in apparently normal infants of normal or low birth weight. Hypertrophic cardiomyopathy and hepatomegaly may be seen⁵¹ in affected infants. The characteristic features of hyperinsulinism include hypoglycemia with onset soon after feeds, glucose requirements of greater than 6 to 8 mg/kg/min to maintain normoglycemia, absence of ketonemia and ketonuria, low levels of plasma free fatty acids and branched-chain amino acids, detectable insulin levels at the time of hypoglycemia (there are a range of reported insulin levels during hypoglycemia in these patients),²³ and a positive response to glucagon therapy.⁵¹ The combination of hypoglycemia with low levels of free fatty acids and the absence of ketonemia is responsible for the potentially devastating effects of this condition on the brain as it is deprived of both normal and alternate substrates.⁵²

Transient hyperinsulinemic hypoglycemia is relatively common in small for gestational age infants and those with perinatal stress²³—this may relate to the inhibition of islet cell function in utero by hypoxia-inducible factor 1 α ,⁵³ with subsequent disinhibition once normal oxygenation occurs after birth. Transient hyperinsulinemic hypoglycemia may also be related to HNF4A mutations. These patients have a higher incidence of macrosomia⁵⁴ and may go on to develop maturity-onset diabetes of the young.⁵⁵ Congenital hyperinsulinemic hypoglycemia is caused by abnormalities in genes controlling the secretion of insulin by beta cells of the pancreas, with abnormalities described in nine genes,⁵⁶ although up to 21% of patients with ongoing congenital hyperinsulinemic hypoglycemia have no identifiable gene abnormalities.⁵⁷ Although the relative frequency of mutations is related to specific populations, the most common group has inactivating mutations in one of the K_{ATP} channel genes. Hyperinsulinemic hypoglycemia with hyperammonemia (previously called leucine-sensitive hypoglycemia) is well described^{58,59} and is attributed to mutations in the gene for glutamate dehydrogenase. Patients generally respond well to therapy with diazoxide, and consumption of extra carbohydrate before protein meals may help ameliorate symptoms. Special low-leucine milks are available. There is, however, also an association with seizure activity in affected children.⁵⁸

Initial stabilization consists of glucose infusions to achieve normoglycemia. Because there may be extremely high glucose requirements, and any cessation of infusion may be associated with severe hypoglycemia, it is essential to ensure that secure vascular access is *always* available; central venous access may be required in these cases. Glucagon (0.5 to 1 mg/kg as an emergency intramuscular [IM] or subcutaneous [SQ] dose,⁶⁰ intravenous [IV] bolus, or as an IV infusion 1 to 20 μ g/kg/h) must always be available and can be used as short-term, emergency therapy to maintain normoglycemia if there are problems with vascular access. Administration of glucagon may be associated with rebound hypoglycemia, and frequent glucose monitoring must be continued. Octreotide (5 to 30 μ g/kg/day SQ or as an IV infusion) may also be given together with glucagon but may be associated with an increased risk of enterocolitis as well as other complications such as

hepatitis^{61,62} or long QT syndrome.⁶³ As soon as normoglycemia has been achieved, the child should be transported to a center with expertise in management of hyperinsulinemia. Care must be taken to ensure that hypoglycemia does not occur during transport. The aim of further management is to confirm the diagnosis and ensure normoglycemia (keep glucose levels >3.5 mmol/L in view of low alternative sources of energy) without the ongoing use of glucose infusions. Glucose polymers can be added to the diet to provide an enteral source of glucose, but care must be taken to limit the osmolar load on the gut, particularly in premature infants.

Clinically, hyperinsulinemic hypoglycemic patients may be categorized by their response to diazoxide (5 to 20 mg/kg/day orally in two to three divided doses) with most responding—exceptions include those with congenital hyperinsulinemia related to focal hyperinsulinemia and those with diffuse hyperinsulinemia related to inactivating mutations in *ABCC8* and *KCNJ11*. Unfortunately, diazoxide may predispose to fluid retention, and its use must be carefully monitored. Chlorothiazide (7 to 10 mg/kg/day in 2 divided doses) may be added (particularly in neonates).⁵² There are also reports of paradoxical hypoglycemia related to high-dose diazoxide therapy.⁶⁴ Nifedipine (0.25 to 2.5 mg/kg/day in three divided doses) may be useful in this case.^{65,66}

An approach to ongoing diagnosis and management is outlined in Figure 151-1. In patients who are responsive, diazoxide will remain the

basis of therapy. In those with no response to diazoxide, genetic testing (for homozygous or compound heterozygous mutations in *ABCC8* and *KCNJ11*), followed by ^{18}F -DOPA positron emission tomography (PET) scanning for those with potentially focal pancreatic lesions will enable identification of those who may benefit from resection of the pancreas. Pancreatic islet cells take up L-3,4-dihydroxyphenylalanine (L-DOPA), where it is converted to dopamine by DOPA decarboxylase. Uptake of the positron-emitting tracer ^{18}F -DOPA PET is increased in beta cells with a high rate of insulin synthesis, and secretion provides visualization of the focal lesion.^{67,68} Patients with focal lesions should respond to partial pancreatectomy (although identification of the focal areas may be difficult at the time of surgery), which may be done laparoscopically.^{69,70} Diffuse disease that is unresponsive to diazoxide therapy will require a near-total pancreatectomy⁷¹ and may be associated with a high incidence of endocrine and exocrine problems. Close long-term follow-up is required in all of these patients, and there may be neurologic and psychologic problems that require management.

Ketotic Hypoglycemia

Although ketotic hypoglycemia (“accelerated starvation”) is probably the most common cause of hypoglycemia in previously healthy children,⁷² it is unlikely to present in the PICU. It usually affects children aged 6 months to 8 years, and features include ketosis, severe nausea,

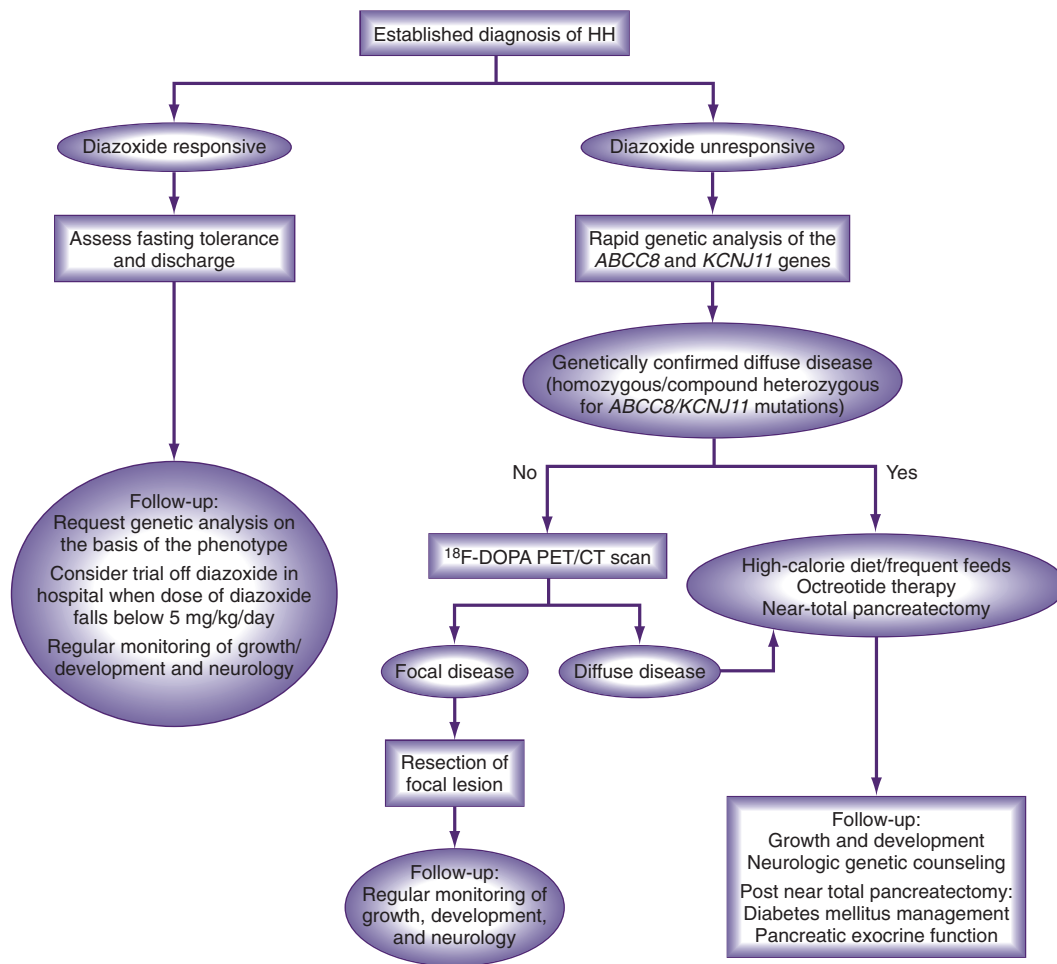


FIGURE 151-1 ■ Flow chart outlining the management cascade of neonates with hyperinsulinemic hypoglycemia (HH). Clinically, HH can be classified into diazoxide-responsive and diazoxide-unresponsive disease. A fluorine-18 L-3, 4-dihydroxyphenylalanine positron emission tomography (^{18}F -dopa PET) scan is currently only indicated in neonates who are unresponsive to diazoxide and do not have genetically confirmed diffuse disease. (From Kapoor RR, Flanagan SE, James C, et al. Hyperinsulinaemic hypoglycaemia. Arch Dis Child 2009;94:450–457.)

and hypoglycemia, usually occurring in the morning after a moderate fast. Treatment consists of ensuring that there is an adequate and regular intake of glucose, particularly during concomitant infection. Ketosis usually precedes the onset of hypoglycemia by several hours.

Adrenal Insufficiency

Adrenal insufficiency after high-dose inhaled corticosteroid therapy has presented with hypoglycemia⁷³ and should be considered if there is a history of inhaled steroid use. Similarly, adrenal insufficiency may follow treatment for childhood malignancy such as leukemia.⁷⁴ Adrenal insufficiency may also occur after adrenal bleeds (e.g., after meningococcal septicemia or difficult delivery), as part of adrenal disease (e.g., congenital adrenal hyperplasia or hypoplasia) in which ambiguous genitalia may (or may not) be a finding in females, or as part of hypopituitarism (e.g., congenital, after craniopharyngioma resection, or after cranial irradiation).⁷⁵ Some patients with primary adrenal insufficiency may also present with hypoglycemia, particularly during acute illnesses.^{36,76} Adrenoleukodystrophy should be considered as part of the etiology in a male patient with Addison's disease (pigmentation may be a clue) and should be tested for by measurement of very long-chain fatty acids.⁷⁷

There has been great interest in adrenocorticoid deficiency in children with critical illness and particularly in acute, severe sepsis (see Chapter 122).⁷⁸ Currently, supplementary steroids are recommended for children with acute, severe sepsis and suspected or proven adrenal insufficiency,⁷⁹ but there are not clear definitions for adrenal insufficiency or catecholamine resistance, nor are there definitive recommendations for the dose of adrenal replacement therapy.⁸⁰

Adrenocorticoid deficiency (both relative and absolute) has also been seen in preterm infants,^{81,82} but there is no consensus on definitions and the need for steroid therapy.⁸³ There is evidence that hypotensive preterm infants improve blood pressure with hydrocortisone therapy but the impact on long-term outcome is not known.⁸⁴

Congenital adrenal hyperplasia is rarely associated with hypoglycemia. Female patients are usually diagnosed early in life as a result of virilization, whereas male patients tend to present later. Patients with the salt-losing form of congenital adrenal hyperplasia present with hyponatremic dehydration and shock, usually associated with hyperkalemia. Because patients with salt-wasting 21-hydroxylase deficiency may also have catecholamine deficiency, shock may be seen. Diagnosis is based on the clinical presentation, typical electrolyte pattern, hypoaldosteronism, and hyperreninemia.⁸⁵ Long-term treatment consists of hydrocortisone (to suppress excess secretion of corticotropin-releasing hormone and corticotropin), together with mineralocorticoid replacement and sodium chloride supplementation.⁸⁶ Little is known about the dose of hydrocortisone required during critical illness, although Charmandari et al.⁸⁷ showed that when 6-hourly bolus doses of 15 mg/m² of hydrocortisone are given, high immediate serum levels are achieved, followed by a rapid decline to undetectable levels by 4 hours after administration. They postulated that continuous infusion of hydrocortisone might be more appropriate in critical illness.

Growth Hormone Deficiency

In the neonatal period, growth hormone deficiency presents with hypoglycemia (possibly with seizures),⁸⁸ prolonged jaundice, and micropenis and undescended testes in boys. Growth failure becomes apparent only toward the end of the first year of life. In later childhood, growth failure is a more common presentation, and hypoglycemia rarely occurs unless associated with adrenocorticotrophic hormone deficiency.

Hyperglycemia Other Than Diabetes Mellitus

Hyperglycemia is relatively common in the PICU⁸⁹ in a variety of conditions including bronchiolitis,⁹⁰ sepsis, hemolytic uremic syndrome,⁹¹ tetanus,⁹² and toxin ingestion (e.g., theophylline poisoning),⁹³ and a number of studies have shown an association between

hyperglycemia and increased mortality in critically ill children⁹⁴⁻⁹⁷; however, this has not been confirmed in all studies.^{95,98} Glucose variability has also been associated with increased mortality, length of hospital stay, and infection in critically ill children.⁹⁹

Iatrogenic causes of hyperglycemia in the PICU include resuscitation using glucose-containing fluids, parenteral nutrition or a high load of administered glucose, and high-dose corticosteroid therapy. Persistent hyperglycemia may also be an indication of ongoing stress or undiagnosed type 1 diabetes and should prompt the clinician to investigate further.

An initial report from an adult surgical unit (predominantly cardiac)¹⁰⁰ suggested that "tight" control of glucose levels was associated with a significant improvement in patient outcomes. Subsequently, glucose control using insulin therapy was instituted in many ICUs across the world, with several studies supporting the initial findings. Unfortunately, there have been increased reports of iatrogenic hypoglycemia, and meta-analyses of studies in adults^{101,102} concluded that tight glucose control was not associated with an improvement in hospital mortality and was associated with an increased incidence of hypoglycemia. Subsequently, a large randomized controlled trial (RCT) of adult patients¹⁰³ compared "tight" (81 to 108 mg/dL or 4.5 to 6.0 mmol/L) with "conventional" glucose control (target of ≤ 180 mg/dL or ≤ 10.0 mmol/L). The 90-day mortality was higher in the group on tight glucose control, and subgroup analysis showed that outcomes favored conventional control in all groups except trauma patients and patients on steroids. A meta-analysis¹⁰⁴ subsequently concluded that intensive insulin therapy in critically ill patients increased the risks of hypoglycemia and provided no reduction in mortality for critically ill patients with the possible exception of patients in a surgical ICU.

There have been a number of RCTs of intensive insulin therapy to maintain tight glucose control in pediatric critical care¹⁰⁵⁻¹⁰⁸ (including children post cardiac surgery, post burn injury, and those admitted to the PICU for a variety of other reasons) with varying results. These have been reviewed in a meta-analysis,¹⁰⁹ and the authors concluded that there is no evidence that tight glucose control using insulin therapy is associated with an improvement in 30-day mortality in critically ill children; however, there may be a reduction in the rate of acquired infection. There was an increase in hypoglycemic events in patients treated with insulin therapy to maintain tight glucose control except in the trial that used continuous glucose monitoring,¹¹⁰ and in one study hypoglycemia was associated with increased mortality.¹⁰⁸ An intriguing finding in one study¹¹¹ was that in patients who were not admitted to the PICU following cardiac surgery, there was a \$13,000 reduction in healthcare costs over a 12-month period in those who had received intensive insulin therapy.

These studies highlight the technical problems associated with reliable monitoring of blood glucose levels in the ICU environment.¹¹² A recent review¹¹³ concluded, "Hence, efficacy and safety of intensive insulin therapy may be affected by patient-related and ICU setting-related variables. Thus, no single optimal blood glucose target range for ICU patients can be advocated. It appears safe not to embark on targeting 'age-normal' levels in PICUs that are not equipped to accurately and frequently measure blood glucose, and have not acquired extensive experience with IV insulin administration using a customized guideline. A simple fallback position could be to control blood glucose levels as close to normal as possible without evoking unacceptable blood glucose fluctuations, hypoglycemia, and hypokalemia."

A review of hyperglycemia in the preterm infant¹¹⁴ suggested the following pragmatic approach to management: confirm hyperglycemia with laboratory testing; treat any underlying problem such as sepsis, stress, etc.; calculate glucose infusion rates, and if greater than 12 mg/kg/min, then reduce infusion rate; treat with insulin if glucose level is more than 10 mmol/L (or other symptoms such as polyuria exist), but start cautiously with very low doses; and, finally, if hyperglycemia persists, consider other diagnoses such as diabetes. A similar approach in older children may still be appropriate, particularly if there are

limited facilities for frequent and accurate monitoring of glucose levels.

Diabetes Mellitus

The incidence of insulin-dependent diabetes mellitus has been increasing across the world,¹¹⁵ and even in countries with highly developed healthcare services, children with diabetes mellitus have a higher mortality than those without^{116,117}; standardized mortality ratios of 2.15¹¹⁸ to 4.2 have been reported,¹¹⁹ although some deaths are not directly related to diabetes. The highest mortality is in children aged 1 to 4 years, in whom the standardized mortality ratios may be much higher. Most deaths attributable to diabetes mellitus occur as a consequence of DKA or hyperglycemia, with the remainder attributable to hypoglycemia.¹²⁰ DKA is relatively common at the time of first presentation and particularly in younger children¹²¹ where the diagnosis may be delayed. The recent mortality rates in the developed world for DKA have ranged from 0.15% to 0.31%¹²² but may be far higher in other settings.^{123,124} The most common cause of death among patients with DKA is cerebral edema. Other causes of death in DKA include electrolyte disturbances, hypoglycemia, pulmonary edema, rhabdomyolysis, infections (including mucormycosis), and thrombosis.¹¹⁵ The management of DKA in childhood has been reviewed elsewhere.¹²⁵

There has also been a marked increase in the incidence of type 2 (or non-insulin-dependent) diabetes mellitus,^{126,127} particularly in association with obesity. Patients with this condition may also present to the PICU with life-threatening hyperglycemic hyperosmolar syndrome.

Cerebral Edema in Diabetic Ketoacidosis

In affluent countries, overt symptomatic cerebral edema occurs in 0.5% to 1% of pediatric DKA episodes¹²⁵ with risks being higher in young children and previously undiagnosed diabetics. Mortality is high (21 to 24%), and 15 to 26% of survivors will have permanent morbidity (including pituitary insufficiency).¹²⁵ However, a much higher proportion of children with DKA will have an altered level of consciousness on presentation, often with features of cerebral edema evident on magnetic resonance imaging (MRI).¹²⁸

The exact mechanisms of cerebral edema in DKA are not clear,¹²⁹ although some studies suggest that it may be related to vasogenic factors rather than osmotic factors.¹³⁰ Cerebral ischemia and reperfusion injury have also been considered.¹³¹

Cerebral hyperemia has also been demonstrated soon after initiation of therapy for DKA.¹³² At the time of presentation, the following features have been associated with increased risk of cerebral edema: younger age, relatively low PCO_2 , high serum urea, and more severe acidosis.^{125,133} Aspects of treatment that have been associated with increased risk include higher volumes of fluid administration during the first 4 hours of resuscitation, administration of insulin during the first hour of therapy, the administration of bicarbonate, and either a slow increase in serum sodium or a fall in glucose-corrected sodium during therapy.^{133,134} Most of these data are epidemiologic, and there are no randomized controlled studies showing that different treatment strategies addressing these issues have reduced cerebral edema.¹³⁵ Such studies are currently planned.¹³⁶

Cerebral edema may be present before therapy for DKA in 5% of cases, although most cases develop 4 to 12 hours after the initiation of therapy.¹³⁷ The clinical signs of cerebral edema in DKA are variable and include headache, deterioration in level of consciousness, inappropriate slowing of pulse rate, and increased blood pressure. However, children with no clinical signs of cerebral edema can have brain swelling,¹²⁸ and a significant proportion of children have disrupted memory function following episodes of DKA.¹³⁸ Adverse outcomes following cerebral edema have been associated with greater neurologic depression at the time of diagnosis, high initial serum urea nitrogen,^{137,139} and intubation with hyperventilation to a PCO_2 of less than 22 mm Hg.¹³⁹

Although the biochemical derangements of hyperglycemia, metabolic acidosis with ketosis, and electrolyte abnormalities are the most obvious problems in DKA, significant derangements in other systems have been seen, including plasma tryptophan levels,¹⁴⁰ thiamine levels,¹⁴¹ cytokine¹⁴² and lymphocyte responses,¹⁴² and coagulation abnormalities. There is little doubt that DKA is associated with a thrombotic state¹⁴³ and an increased incidence of cerebrovascular accidents. Care should be taken in the use of femoral central venous access as this may have a higher than usual complication rate in these patients.¹⁴⁴ A reported case of myocardial infarction related to DKA¹⁴⁵ may be a complication of the thrombotic state. Although myocardial function is generally normal in DKA, myocarditis¹⁴⁶ has been noted in occasional case reports, and pulmonary edema may be more common than previously recognized.¹⁴⁷ Prolongation of the QTc interval may be common in DKA (it correlates with ketosis), and careful cardiac monitoring is essential.¹⁴⁸

Principles of Management. Management of DKA should be coordinated by an experienced diabetes team using guidelines such as the recently published consensus statement,¹²⁵ which is shown in Figure 151-2.

The biochemical criteria for the diagnosis of DKA include a serum glucose concentration higher than 11 mmol/L (approximately 200 mg/dL), ketonemia and ketonuria, and acidosis with venous pH less than 7.3, or serum bicarbonate level less than 15 mEq/L.¹²⁵ The severity of DKA is defined by the level of acidosis, with mild having venous pH less than 7.3 (or bicarbonate level <15 mmol/L), moderate pH less than 7.2 (or bicarbonate level <10 mmol/L), and severe pH less than 7.1 (or bicarbonate level <5 mmol/L).¹²⁵ Children with severe DKA should be managed in a specialized diabetic unit or in the PICU.

Baseline Assessment. An admission weight should be obtained if at all possible, and future therapy should be based on this weight. Blood samples should be taken for the following: serum or plasma glucose, electrolytes (including bicarbonate or total carbon dioxide), blood urea nitrogen, creatinine, osmolality, venous (or arterial in critically ill patients) pH, PCO_2 , calcium, phosphorus, and magnesium concentrations (if possible), HbA1c, and hemoglobin and hematocrit or complete blood count. Measurement of blood β -hydroxybutyrate concentration, if available, is useful to confirm ketoacidosis and may be used to monitor the response to treatment.¹⁴⁹⁻¹⁵³ Urine specimens should be analyzed for ketones, although these may be poorly reflective of serum ketones. Electrocardiograms may be useful if delays are expected in getting potassium results.

Fluid Management. The objectives of fluid and electrolyte replacement therapy are restoration of circulating volume, replacement of sodium and body fluid deficit, improved renal function with enhanced clearance of glucose and ketones from the blood, and minimization of the risk of cerebral edema. There is a wide range in the amount and rate of fluid and electrolyte loss in patients presenting with DKA (depending on the rate of onset and duration of symptoms, the severity of vomiting or diarrhea or both, and the fluid ingested by the patient). There is similarly a wide range of intravascular status ranging from normovolemia to severe hypovolemia (uncommon). Clinical assessment of dehydration is inaccurate,^{154,155} and there is an unpredictable rate of ongoing fluid loss related to the osmotic diuresis. In the (unusual) presence of hypovolemic shock, it may be reasonable to infuse 0.9% saline using aliquots of 5 to 10 mL/kg until an acceptable blood pressure is obtained. Typically, 10 to 20 mL/kg needs to be infused over 1 to 2 hours. Ringer's lactate may be a reasonable alternative because administration of large volumes of 0.9% saline has been associated with the development of hyperchloremic acidosis. There is no evidence to support the use of colloid solutions.

Thereafter, the acceptable principles are that hypovolemia, rapid changes in plasma osmolality, and large volumes of sodium uptake should be avoided. Fluid therapy should be calculated to achieve rehydration over 48 hours. Careful monitoring of fluid balance is essential to ensure that patients are neither losing excessive fluid (via osmotic diuresis) nor gaining excessive fluid. Fluid with a tonicity less than that of 0.45% saline should not be used.

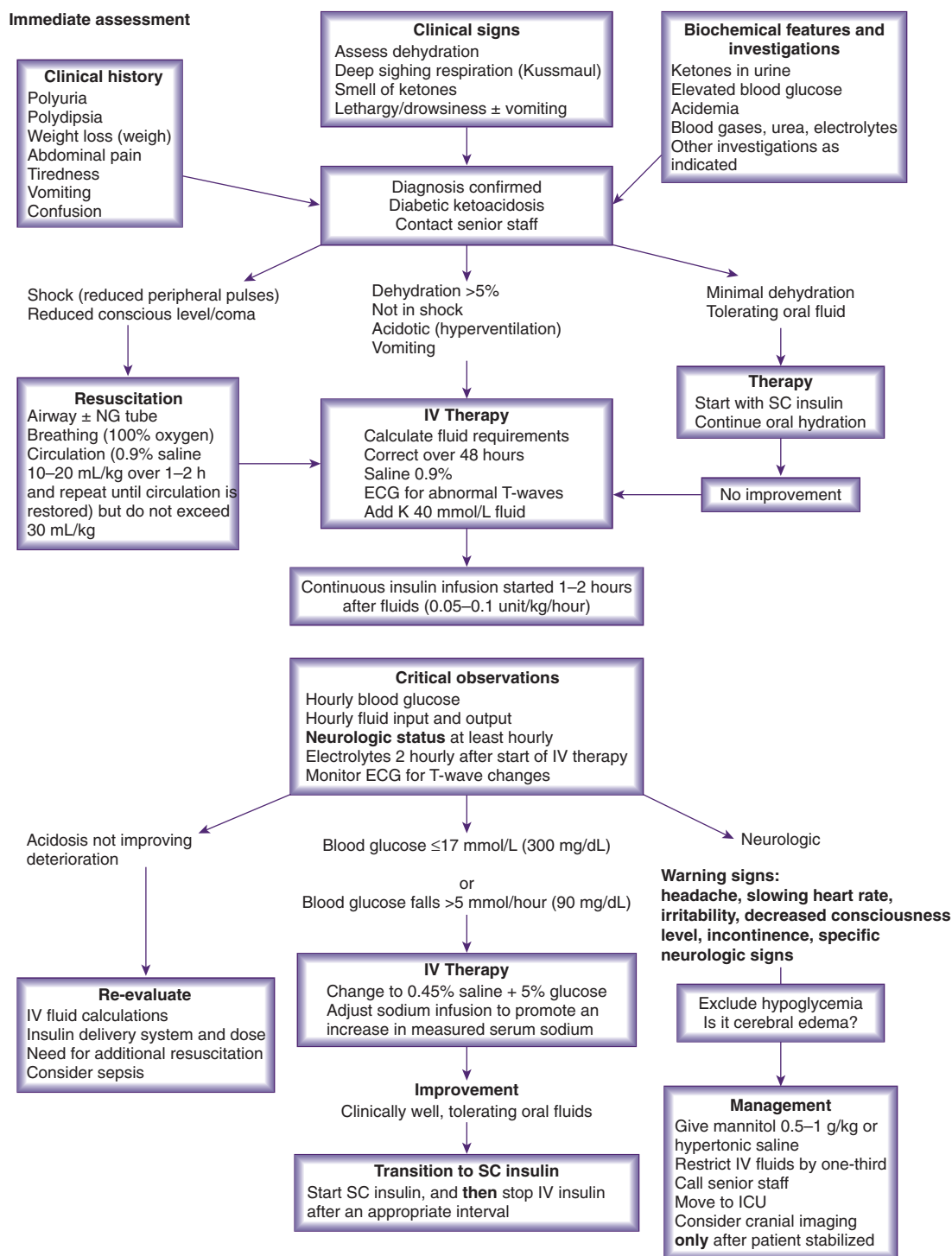


FIGURE 151-2 ■ ISPAD clinical practice guidelines management algorithm for the treatment of diabetic ketoacidosis. (From Wolfsdorf JI, Allgrove J, Craig ME, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatr Diabetes* 2014;15:154–179.)

Despite the fact that almost all patients with DKA are potassium depleted, serum potassium levels frequently are increased at presentation. With initiation of insulin therapy and correction of acidosis, there is rapid intracellular movement of potassium, and careful monitoring of potassium levels is essential. As soon as potassium levels are less than 5.5 mEq/L, 30 to 40 mEq/L of potassium should be added to the

fluid infusions, and 0.5 to 1 mEq/kg/h of potassium may be required to correct potassium deficits. Potassium may be given as chloride or phosphate. Although severe hypophosphatemia is common,¹⁵⁶ and symptomatic hypophosphatemia has been reported,¹⁵⁷ there is no evidence that phosphate administration is routinely necessary in the management of DKA, and the clinical effects of severe hypophosphatemia

are rare in DKA. Theoretically, phosphate administration may reduce insulin resistance and depletion of adenosine triphosphate and have positive effects on 2,3-diphosphoglycerate. Administration of potassium phosphate helps to decrease the chloride load given to patients with DKA and may be used safely, provided that calcium levels are monitored carefully.¹⁵⁸ Glucose must be added to the infusion of fluids when the glucose levels are 14 to 17 mmol/L to avoid hypoglycemia.

Bicarbonate. There is lack of evidence for benefit from the administration of bicarbonate to patients with DKA, and significant complications are documented (particularly in children).¹⁵⁹ Bicarbonate should not be given routinely, not in bolus form, and possibly only in patients who have a pH less than 6.9 despite appropriate correction of intravascular volume and adequate insulin therapy.

Insulin Therapy. Current guidelines recommend that insulin should be provided as a continuous low-dose infusion starting at 0.1 U/kg/h, approximately 1 to 2 hours after starting fluid replacement. However, there is recent evidence that ultra-low-dose insulin at 0.05 U/kg/h may be at least equivalent to the higher dose.¹⁶⁰ If there is no response to insulin therapy, the infusion should be reviewed for technical problems (incorrect preparation, adhesion of insulin to infusion tubing), and the patient should be reviewed for ongoing hypovolemia or uncontrolled sepsis. There is no place for a bolus of IV insulin or an initial loading dose, other than in the management of life-threatening hyperkalemia. The insulin infusion should be continued until ketoacidosis is resolved and the patient is fully conscious and retaining solid food.

Treat Underlying Cause. In previously undiagnosed patients, the cause of DKA is insulin deficiency. Even in previously diagnosed patients, most episodes of DKA probably are related to insulin omission or treatment error, although children 3 years old or younger are more likely to have a bacterial infection.¹⁶¹ If infection is suspected as the precipitating cause of DKA, aggressive therapy with antibiotics and drainage of any abscess should be instituted. Routine prophylactic antibiotic therapy is not indicated in DKA.

Monitoring. Although some patients are hypovolemic on presentation, there is little evidence that invasive hemodynamic monitoring is necessary. Careful monitoring of sodium levels is essential because smaller changes in serum sodium with therapy are associated with the development of cerebral edema.¹³⁷ Hyperlipidemia may decrease the aqueous phase of serum and artificially reduce sodium levels; this can be corrected using the following formula¹⁶²:

$$\text{True sodium (mEq/L)} = \text{reported sodium (mEq/L)} \\ \times (0.021 \times \text{triglycerides [mg/dL]} + 0.994)$$

The osmotic load of glucose also decreases serum sodium levels, with a decrease in sodium level of approximately 1.6 to 1.8 mEq/L per 100 mg/dL increase in glucose¹⁶³ (alternatively, Corrected sodium = measured Na + 2([plasma glucose – 5.6]/5.6) (mmol/L). The expectation is that with decreasing levels of hyperglycemia and hyperlipidemia, sodium levels should increase. This may be offset, however, by urinary losses of sodium secondary to osmotic diuresis. Careful and frequent monitoring of potassium and glucose levels is essential. If phosphate is being given, calcium levels should be monitored. Regular acid-base monitoring is required.

Monitoring of end-tidal PCO₂¹⁶⁴ or transcutaneous PCO₂¹⁶⁵ could be used as a noninvasive method for continuous monitoring of response to therapy for DKA. The only proviso¹⁶⁶ is that any changes in respiratory drive or efficiency of the respiratory system may mask changes in acid-base that otherwise might be reflected by capnometry.

Investigations for Possible Cerebral Edema in DKA. Although cerebral edema is the most common cause of depressed level of consciousness in DKA, there are other causes that are amenable to therapy, including cerebral venous thrombosis¹⁶⁷ and acute hydrocephalus.¹⁶⁸ Other abnormalities, such as brain infarction¹⁶⁹ and extrapontine myelinolysis,¹⁷⁰ have been seen. Computed tomography

(CT) of patients with a depressed level of consciousness may be recommended to exclude other treatable pathology. Because the risks are relatively low, however, excluding other pathology must be balanced against the risks associated with moving ill patients to the radiology suite.

Mannitol has been used for the management of cerebral edema¹⁷¹ (0.25 to 1 g/kg over 20 minutes), although there are no controlled studies. Hypertonic saline (5 to 10 mL/kg of 3% saline) may be an alternative¹⁷²; however, a recent retrospective review suggested that outcomes were worse after hypertonic saline than after mannitol¹⁷³ despite a general increase in the use of hypertonic saline in the United States for this indication. It is possible that cerebral edema in DKA is vasogenic in origin, in which case there may be different roles for mannitol and hypertonic saline.¹³⁰ Hyperventilation after intubation for cerebral edema may be associated with worse outcomes.¹³⁹

Summary. Despite improvements in the management of DKA, it remains a serious illness with significant morbidity and mortality. In addition to improving management of the condition, strong focus must be brought to ensure that the condition is avoided when possible and diagnosed and treated promptly when it occurs.

Thyroid Insufficiency

Neonates¹⁷⁴ and particularly preterm infants^{175,176} exposed to large amounts of iodine in iodine-containing antiseptics or via iodinated contrast media¹⁷⁷ may develop transient hypothyroidism (also called the *Wolff-Chaikoff effect*) as a result of absorption of iodine. This has also been shown in infants undergoing cardiac catheterization and cardiac surgery,¹⁷⁸ particularly following wound irrigation with povidone iodine solutions.¹⁷⁹ Care should be taken to limit the exposure of infants to iodine-containing agents. Triiodothyronine supplementation may be considered in children who have been exposed to significant amounts of iodine before or during a critical illness.

The sick euthyroid syndrome is well documented in the PICU,¹⁸⁰ particularly in patients undergoing cardiac surgery.¹⁸¹ Although there may be benefit to some children, there is no established role for triiodothyronine supplementation after cardiac surgery.¹⁸¹ Additionally, children with Down syndrome have a high incidence of hypothyroidism, both congenital and acquired.¹⁸² Attention should be paid to the possible need for triiodothyronine supplementation in critically ill children with Down syndrome.

METABOLIC CRISES

Epidemiology

IEM are a heterogeneous group of conditions that are characterized by defects in metabolic pathways that result in abnormal metabolism and/or the accumulation of toxic metabolites.¹⁸³ There is a vast range of IEM, with an ever increasing list of conditions. Population data on IEM suggest a minimal incidence of 35 to 40 per 100,000 live births.¹⁸⁴⁻¹⁸⁶ IEM have a diverse presentation and are part of the differential diagnosis of many children admitted to the PICU with acute illness. In the 1960s, newborn screening programs using dried blood spots to identify conditions such as phenylketonuria were initiated in parts of the United States.¹⁸⁷ The advent of techniques such as tandem mass spectrometry has made it possible to screen for a wide range of conditions (including fatty acid oxidation defects, organic acidemias, and amino acidopathies), and this has become the norm for screening programs in many parts of the world. More recently, the American College of Genetics provided guidelines on suitability of a condition to be included in newborn screening programs, including concerns such as whether the condition can be detected within 24 to 48 hours of birth, whether the screening test is specific and sensitive, and whether the condition is amenable to treatment if detected early.¹⁸⁸ A consequence of these screening programs is that in many parts of the world there are less likely to be PICU admissions with undiagnosed IEM, but there may be increased numbers of admissions of children with known IEM.

Although there are a bewildering number of IEM, many are amenable to therapy. Patients with incurable conditions may derive considerable relief of suffering from diagnosis and appropriate therapy. Even when a condition is not amenable to therapy, it is important to make a diagnosis to facilitate counseling for the family involved and prevent unnecessary suffering in future children. Long-term management of most IEM requires a team approach, including metabolic experts, dietitians, geneticists, biochemists, and social workers, to elucidate the exact nature of the problem, provide appropriate therapy and therapeutic plans, and give genetic and family counseling. Although screening tests for IEM can be done in most diagnostic laboratories, the specialized tests required to identify the exact nature of an IEM can be done at relatively few laboratories. Despite the complexity of IEM, there are principles that apply to the management of all children who are admitted to a PICU (see [Table 151-1](#)).

When to Consider an Inborn Error of Metabolism in the Pediatric Intensive Care Unit

IEM may be classified into four diagnostically useful groups: (1) disorders that give rise to intoxication (e.g., organic acidemias and urea cycle defects), (2) disorders involving energy metabolism (e.g., fatty acid oxidation defects and respiratory chain defects), (3) disorders involving complex molecules in which symptoms are permanent, progressive, and independent of intercurrent events (e.g., peroxisomal disorders, lysosomal disorders, and congenital defects of glycosylation), and (4) those disorders that present with seizures (particularly in the neonatal period). The conditions most likely to present acutely in the PICU are conditions involving intoxication and energy metabolism. There is overlap, however, between these groups in terms of presentation. There may also be variation in the presentation of conditions that have the same underlying genetic abnormality.

Although the clinical features of an IEM may be related primarily to the accumulation of a toxic metabolite, the condition may be complicated by the relative deficiency of another compound or increased stress put on other metabolic pathways by the primary problem. Management may involve limiting the intake of potentially toxic substances, increasing the removal of toxic substances, supplementation of deficient substances, and supplementation of other metabolic pathways that are being stressed.

IEM should be considered as part of the differential diagnosis of any child or infant who presents with a severe illness, particularly during the neonatal period.¹⁸⁹ Acute symptoms that are associated with IEM include encephalopathy (acute or acute on chronic), intractable seizures, hepatic failure, cardiomyopathy, metabolic acidosis, and hypoglycemia ([Table 151-3](#)). Family history of SIDS or prior childhood deaths may suggest IEM. Particular attention should be paid to the identification of particular risk factors for the differential diagnoses, including drug exposure, prolonged rupture of membranes, and perinatal asphyxia.

Specific Clinical Presentations

Intractable Seizures

Seizures (in isolation) are an uncommon presentation of IEM and, with the exception of the pyridoxine-dependent seizures, tend to be associated with other clinical and metabolic abnormalities. In neonates or some infants presenting with intractable seizures, pyridoxine-dependent seizures (PDS),¹⁹⁰ pyridoxine phosphate oxidase deficiency (PNPO), hypophosphatasia, and folinic acid-responsive seizures¹⁹¹ should be considered. The clinical diagnosis of PDS and PNPO depends on demonstration that seizure control is dependent on continuous pharmacologic doses of pyridoxine or pyridoxal-5'-phosphate, respectively. There is a range in clinical presentation, and PDS should be considered in any infant up to age 18 months presenting with seizures.

Patients with defects in the transport of glucose across the blood-brain barrier associated with mutations in the *GLUT1* gene may

TABLE 151-3

Factors That Should Alert the Intensivist to the Possibility of an Inborn Error of Metabolism

HISTORY

General

Population group with high incidence of inborn errors of metabolism (IEM)
 Consanguinity of parents
 Previous history of apparent SIDS or childhood deaths in the family
 Presence of dysmorphic features associated with inborn error of metabolism
 Previous history multiple spontaneous abortions
 Hyperemesis may be associated with fat oxidation disorders,²⁴⁰ as may frank hepatic symptoms such as acute fatty liver of pregnancy or the more severe HELLP syndrome (hemolysis, liver enzymes, low platelets).
 Deterioration after apparently being normal at birth, particularly if Apgar scores and early neonatal period were normal
 Earliest signs of IEM in the neonatal period may include lethargy and poor feeding, which may progress rapidly to obvious depressed level of consciousness.
 Depressed level of consciousness without obvious explanation
 Vomiting is an unusual clinical feature of illness in neonates and is strongly associated with IEM.
 Strange odors
 Previous history of being "sickly" with episodes of intermittent vomiting
 Previous hospital admissions (even for apparent respiratory symptoms as this may be acidosis)
 Unusual dietary preferences by the child
 Onset of virtually any organ dysfunction (liver, heart, renal, etc.) may be related to inborn error.

In childhood

EXAMINATION

General

In neonatal period

Dysmorphic features that may be associated with IEM
 Strange odors
 Neurologic signs in IEM tend to include increased tone and abnormal movements, in contrast to the features of sepsis, which usually is associated with decreased tone.
 Acute or intermittent ataxia is a common feature of IEM.

In childhood

IEM, inborn errors of metabolism; SIDS, sudden infant death syndrome.

present with seizures. Often the only clue is the presence of low cerebrospinal fluid (CSF) glucose in the presence of normal blood glucose. Patients may improve on a ketogenic diet.¹⁹²

IEM that may present with seizures associated with lactic acidosis include biotinidase deficiency, disorders of mitochondrial energy metabolism (including pyruvate dehydrogenase deficiency and mitochondrial electron transport chain defects), and peroxisomal and storage disorders.

Biotinidase deficiency (an autosomal recessively inherited disorder of biotin recycling) can be ameliorated or prevented by administering pharmacologic doses of the vitamin biotin.¹⁹³ A large proportion of cases present with seizures and hypotonia, associated with failure to thrive and skin rash or alopecia. Some 50% of cases have ataxia, developmental delay, and eye problems (conjunctivitis and optic atrophy), with more than 75% developing hearing loss. There is a considerable variation in presentation,¹⁹⁴ with features ranging from mild episodes of seizure and ataxia to severe metabolic failure and death. Onset of symptoms may occur at any time from the neonatal period through to adulthood. Untreated individuals may have

ketoacidosis, lactic acidosis, and/or hyperammonemia with a range of other metabolic anomalies.¹⁹⁴ Diagnosis can be made from analysis of organic acids in urine, whereas an enzyme assay can be done on blood. Guidelines for testing have recently been published.¹⁹⁴

Intractable tonic-clonic seizures may also be a feature of molybdenum cofactor deficiency.¹⁹⁵ This presents in early infancy with seizures, encephalopathy in the absence of metabolic acidosis, hypoglycemia or hyperammonemia, and failure to thrive. Clinical features, CT findings, and neuropathology may be similar to that seen in severe hypoxic-ischemic brain injury with initial cerebral edema progressing to atrophy. However, there may be typical imaging findings.¹⁹⁶ Intraocular lens dislocation may be a clinical feature.¹⁹⁷ Uric acid levels are low, whereas urinary amino acid analysis shows increased S-sulfocysteine. Sulfite may be demonstrated on fresh urine specimens. Electrospray tandem mass spectrometry of urine or urine-soaked filter paper may facilitate rapid diagnosis.

Seizures may be part of the clinical presentation of many other disorders, including seizures with lactic acidosis (Leigh disease, mitochondrial encephalopathy lactic acidosis, and stroke-like episodes [MELAS]), mitochondrial encephalopathy with ragged red fibers [MERRF]), GM₂ gangliosidosis, and peroxisomal disorders. Other clinical features predominate in these conditions and should direct investigation.

Investigation and Management. In infants presenting primarily with intractable seizures, investigations should include measurement of blood glucose, blood acid-base status, blood lactic acid (in association with pyruvate levels), CSF glucose, lactic acid and pyruvic acid levels, urinary organic acids, and sulfite. CT and MRI help to diagnose disorders of abnormal accumulation of metabolites and exclude structural brain problems that are responsible for symptoms. Treatment focuses on control of the airway and respiration together with control of seizures. Pyridoxine or biotin should be administered early in appropriate doses if indicated.

Encephalopathy

The onset of acute encephalopathy always constitutes a medical emergency, and the cause must be elucidated as rapidly as possible. The differential diagnosis includes trauma, infection, intracranial space-occupying lesions, toxin ingestion, acute hepatic failure or Reye syndrome, intracranial vascular problems (thrombosis, hemorrhage, or embolic phenomena), and seizure disorders. There is often a strong tendency to attribute neurologic symptoms to hypoglycemia or hypocalcemia, but because these may be associated with IEM, it is vital that IEM be considered as part of the cause of the hypoglycemia. The IEM that present with acute encephalopathy vary with age. In the neonatal period, the common IEM include urea cycle defects (with hyperammonemia), maple syrup urine disease, nonketotic hyperglycinemia, and organic acidopathies.¹⁹⁸ All of these, with the exception of nonketotic hyperglycinemia, may also present during childhood. During childhood, the common IEM presenting with acute encephalopathy include fatty acid oxidation defects and maple syrup urine disease.

Investigation. The specimens collected for diagnosis of sepsis should be collected, including blood culture, hemoglobin, white blood cell count (with differential), and platelets. Serum electrolytes should be checked, including sodium, potassium, calcium, phosphate, and magnesium. Liver function tests are essential because acute hepatic failure may cause acute encephalopathy, and the liver may be affected by IEM. Specimens for testing for IEM must be collected at the time of presentation because this may provide the best opportunity for diagnosis (Table 151-4).

Blood Glucose Levels. The reader is referred to the earlier discussion of the approach to hypoglycemia. Hypoglycemia may be a particular feature of fatty acid oxidation defects and organic acidurias. Immediate correction of hypoglycemia is essential.

Plasma Ammonia Levels. Plasma ammonia levels should be checked in all children, particularly neonates, with unexplained depressed level of consciousness, particularly if there is hypotonia and

apnea (see section on hyperammonemia for management and investigation). Treatment of severe hyperammonemia is an emergency.

Liver Function Tests. Reye syndrome is part of the differential diagnosis of acute encephalopathy, but fatty acid oxidation defects, such as medium-chain acyl-CoA dehydrogenase deficiency, carnitine deficiency (usually with associated myopathy), and, far less frequently, long-chain acyl-CoA dehydrogenase deficiency and short-chain acyl-CoA dehydrogenase deficiency, may present with encephalopathy (usually in the neonatal period).

Blood Gas Analysis. Arterial blood gas analysis should be performed with particular attention to the presence of metabolic acidosis and calculation of the anion gap.¹⁹⁹

Blood Lactate Levels. Blood lactate levels may be increased in many situations but typically are very elevated in mitochondrial electron transport chain defects.

Plasma Carnitine. Carnitine levels may be substantially decreased in organic acidurias and fatty acid oxidation defects. Analysis of acyl carnitine and amino acid profile may help make the diagnosis of isovaleric aciduria, methylmalonic aciduria, and propionic acidemia.

Quantitative Amino Acid Analysis. Quantitative amino acid analysis is necessary to identify the aminoacidopathies. Screening tests on the urine may point in the direction of certain conditions.

Urinary and Blood Ketones. Ketones are unusual in the neonatal period but tend to be a feature of maple syrup urine disease and propionic, isovaleric, and methylmalonic acidemia. Quantitative determination of blood ketones (acetoacetate using urine ketone strips or β -hydroxybutyrate by specific blood strip) may be a useful bedside screen.

Urinary Organic Acids. Urinary organic acids are abnormal in maple syrup urine disease, organic aciduria, and fatty acid oxidation defects.

Management. The principles of therapy are as follows:

1. Maintain airway control and breathing.
2. Maintain circulation.
3. Treat underlying or associated sepsis.
4. Remove toxic compounds.
5. Ensure an appropriate energy source.
6. Provide any specific therapy that is available.

The toxic compounds that potentially can be removed include ammonia and leucine (see below).

Specific Conditions

Maple Syrup Urine Disease (MSUD). If there is no acidosis and the ammonia is not increased, MSUD should be considered. Patients typically are not dehydrated, are not acidotic, have no hyperammonemia, and have no hematologic abnormalities. Cerebral edema is a feature of MSUD within the neonatal period and during later presentations. The urine may smell like maple syrup, but the smell is also similar to that of burned sugar.¹⁹⁸ The urine smell may be difficult to detect in the first few days of life and then may be detected on diapers that have been allowed to dry.²⁰⁰ Urine tests for ketones are usually strongly positive, and dinitrophenylhydrazine is usually positive, although both tests may be negative before 3 days of age.²⁰⁰ Tandem mass spectrometry is the most efficient screening test in neonates. Leucine levels can be checked rapidly on whole-blood filter paper specimens, or quantitative amino acid analysis should be done on plasma or serum. Principles of management have been to remove leucine using dialysis and to reduce the production of leucine by dietary manipulation. Hemodialysis decreases leucine levels rapidly,²⁰¹ particularly if used with dietary therapy, but peritoneal dialysis may be effective if hemodialysis is not available.²⁰² Previously, exchange transfusion, peritoneal dialysis, and hemofiltration were reported to decrease leucine levels. Morton and colleagues²⁰⁰ have used a protocol consisting of total caloric intake of 120 to 140 kcal/kg/day with lipid forming 40% to 50% of calories, 3 to 4 g/kg/day of protein as essential and nonessential amino acids with 80 to 120 mg/kg/day each of isoleucine and valine, and 250 mg/kg/day each of glutamine and alanine, with tyrosine, histidine, and threonine supplemented to normalize plasma amino acid ratios; careful attention should be paid to sodium

TABLE 151-4 Specimen Collection for Inborn Errors of Metabolism

| SUBSTANCE | TESTS | COMMENTS ON TECHNIQUE | CONDITIONS IDENTIFIED |
|---|--|--|--|
| Urine | Detecting odors | Urine odors are best identified from urine drying on filter papers or from urine that has been kept in a closed container at room temperature for a while. | MSUD (smell of maple syrup; some describe this as burned sugar ¹³³) Isovaleric acidemia (sweaty feet odor) 3-methylcrotonyl glycinuria (catlike) |
| Urine screening tests | Ketones | | Urinary ketones are rare in neonates and are almost diagnostic of an inborn error of metabolism in a neonate. |
| | Dinitrophenylhydrazine | | Strongly positive with MSUD, PKU, or in ketoacidosis |
| | Ferric chloride | | Green color with PKU; other colors may occur with other conditions |
| | Merckoquant 10013 Sulfite test | Urine specimen must be fresh because sulfite oxidizes rapidly at room temperature | Molybdenum cofactor deficiency |
| | Reducing substances | | Galactosemia |
| Urine | Measurement of organic acids and amino acids | Specimen collected and frozen at -20°C acidurias | All aminoacidemias and organic acidurias |
| | Measurement of acyl carnitines and acyl glycines | Can increase the sensitivity of these tests by the use of loading dose of levocarnitine, 100 mg/kg orally | Many fatty acid oxidation defects |
| Blood | Anion gap | Correct for hypoalbuminemia | Screen to identify generally unmeasured anions. |
| | Tandem mass spectrometry | Collected as blood on filter paper | All fatty acid oxidation defects, many of the aminoacidemias |
| | Galactose-1-phosphate uridylyltransferase | Collected as blood on filter paper | Abnormalities of the carnitine pathways |
| | Estimation of ammonia, lactate, pyruvate, and ketoacids | All of these substances may be unstable; must collect on ice and transport immediately to laboratory. | Galactosemia |
| | Genetic studies | Before blood transfusion | Aminoacidopathies, urea cycle defects |
| Skin, liver, muscle, and endocardial biopsy | Fibroblast culture, enzyme identification, identification of abnormal collections and organelles | | All problems with identified genetic abnormalities Enzyme defects, organelle defects |

MSUD, maple syrup urine disease; PKU, phenylketonuria.

balance to ensure that serum sodium is kept at greater than 140 mEq/L. Hyperosmolar therapy is initiated if cerebral edema develops. This protocol produces decreases in leucine equal to that seen after dialysis. Recent studies suggest that norleucine may have a role in reducing brain injury in patients with MSUD.²⁰³

Isovaleric Aciduria, Methylmalonic Aciduria, and Propionic Acidemia. Isovaleric aciduria, methylmalonic aciduria (MMA), and propionic acidemia may present in the neonatal period with encephalopathy hyperammonemia, ketoacidosis (occasionally hyperammonemia may induce a respiratory alkalosis), moderate lactic acidosis, and hypocalcemia. The smell associated with isovaleric aciduria may be distinctive (commonly described as resembling “sweaty feet”). Blood glucose levels may be variable from hypoglycemia to hyperglycemia. Dehydration is a feature of the clinical presentation, partly related to vomiting and poor intake and partly related to poor renal concentrating ability. One-third of patients may present later in life. Stroke-like episodes are a feature of isovaleric aciduria, MMA, and propionic acidemia in later life, although there may be a range of neurologic presentations, including hypotonia and developmental delay. Extrapyramidal signs related to infarction of the basal ganglia may be a feature of MMA and propionic acidemia. Neutropenia, thrombocytopenia, and anemia are common in the neonatal presentation, whereas neutropenia may also be a feature of a later presentation. Sepsis may be a significant component of clinical exacerbations, particularly in propionic acidemia. Pancreatitis has been reported to be associated with these disorders. Cardiomyopathy may also develop, particularly during decompensation. Isovaleric aciduria, propionic acidemia, and

MMA aciduria are diagnosed by the organic acid profiles, and tandem mass spectroscopy may be useful by looking at the acyl carnitine profiles.

Patients presenting in the neonatal period with encephalopathy require treatment with limitation of protein intake (this requires varied adjustment to a diet with appropriate amino acid profile), removal of toxins (exchange transfusion may be useful; MMA can be cleared renally if adequate fluid volumes are given), ensuring normal glucose levels, promoting anabolism, and management of sepsis. Some patients with MMA may respond to therapy with hydroxycobalamin, and this should be given for several days to assess response. Supplemental glycine should be given to patients with isovaleric aciduria, and carnitine supplementation is useful for all. Some patients with propionic acidemia may benefit from metronidazole to decrease propionate metabolites from the bowel.

Nonketotic Hyperglycinemia. Nonketotic hyperglycinemia presents in early infancy with severe encephalopathy in the absence of acidosis, ketosis, hypoglycemia, hyperammonemia, or any other clinical abnormalities. Although the outcome is almost invariably poor, there have been more recent descriptions of transient neonatal hyperglycinemia.²⁰⁴ There is an association of abnormality of the corpus callosum with nonketotic hyperglycinemia.²⁰⁵ The outcomes of patients with nonketotic hyperglycinemia have been recently reviewed.²⁰⁶

Hypoglycemia

The reader is referred to the section on endocrine crises for an approach to hypoglycemia. In hyperinsulinemia, the hypoglycemia

typically develops soon after a feed, whereas patients with defects in fatty acid oxidation tend to be able to tolerate fasts of 4 to 8 hours. In hyperinsulinemia, it often is difficult to provide adequate amounts of glucose to correct the hypoglycemia (may require >12 mg/kg/min together with glucagon). In defects of gluconeogenesis, the hypoglycemia is relatively easy to control but usually does not respond to glucagon administration. In hereditary fructose intolerance, the onset of hypoglycemia is concurrent with the introduction of sucrose (source of fructose) into the diet. Although hypoglycemia may occur in association with sepsis, many IEM are associated with sepsis (e.g., direct association with *Escherichia coli* and galactosemia, sepsis as a precipitant of crisis, or ill health from IEM causing increased risk of sepsis) and should be considered diagnostically even if sepsis is proven.

Investigation and Management. If the glucose level is low, a venous specimen of blood should be collected immediately for laboratory glucose estimation. The clinician should give 0.5 g/kg of 10% to 25% dextrose in water (diluted with water for injection) promptly as an IV bolus followed by administration of 4 to 8 mg/kg/min of glucose. The glucose level should be reviewed within 30 minutes. The rate of glucose infusion may need to be increased, and high requirements suggest hyperinsulinemia.

Urine for Reducing Substances. If this test is positive, glucose should be excluded, but in the setting of hypoglycemia this is unlikely unless there have been substantial doses of glucose given. If reducing substances are positive, this suggests galactosemia, hereditary fructosemia, or tyrosinemia.

Urinary Ketones. If urinary ketones are positive, the clinician should assess for urinary and plasma organic acids and quantitative amino acids. High urinary ketones in the presence of hepatomegaly suggest glycogen storage disease type 1, fructose-1,6-diphosphatase (FDPase) deficiency, or β -ketothiolase deficiency.²⁰⁷ In β -ketothiolase deficiency, lactate levels are normal, whereas they are increased in glycogen storage disease type 1 and FDPase deficiency. In the absence of hepatomegaly, high ketones suggest ketotic hypoglycemia or deficiencies of growth hormone or glucocorticoids.

Plasma Free Fatty Acids. If plasma free fatty acids are elevated, the patient is likely to have a fatty acid oxidation defect, but if they are low, hyperinsulinemia is more likely.

Lactate Levels. Lactic acidosis in association with hypoglycemia is characteristic of defects of gluconeogenesis, such as glycogen storage diseases.

Urinary Organic Acids, Plasma Amino Acids, and Ammonia Levels. Urinary organic acids, plasma amino acids, and ammonia levels should be measured as hypoglycemia may be a feature of abnormalities of all these compounds.

Specific Conditions

Galactosemia. Please see the section on hepatitis. Hypoglycemia may be a prominent feature of galactosemia, whereas hepatitis may be a more common presentation.

Hereditary Fructose Intolerance. Hereditary fructose intolerance is characterized by the onset of severe vomiting and hypoglycemia after the ingestion of fructose or sucrose.

Glycogen Storage Disease Type 1. Glycogen storage disease type 1 may present in the neonatal period with hypoglycemia that may be mild or easily controlled. However, patients present later with hepatomegaly and lactic acidosis. The hypoglycemia does not respond to therapy with glucagon.

Fatty Acid Oxidation Defects. Defects in the mitochondrial oxidation of free fatty acids result in the accumulation of fatty acid oxidation products, which may produce encephalopathy, hepatocellular dysfunction, and cardiac arrhythmias, which are a potentially fatal complication of fatty acid oxidation defects. Defects in fatty acid oxidation may also result in failure to meet the energy requirements of tissues such as skeletal muscles or cardiac muscles, resulting in myopathy or cardiomyopathy. Many studies have suggested that fatty acid oxidation defects may be an important cause of SIDS and are an important cause of cardiomyopathy.²⁰⁸

Medium-chain acyl-CoA deficiency is the most common of the fatty acid oxidation defects and most frequently presents with a Reye disease–like episode, with vomiting, encephalopathy, hypoglycemia, and hyperammonemia. Cardiomyopathy never occurs in medium-chain acyl-CoA deficiency. Cardiomyopathy is a more common presentation of carnitine deficiency and long-chain acyl-CoA dehydrogenase deficiency. Diagnosis is based on the clinical features described earlier: tolerance of 8 to 24 hours of fasting, high plasma free fatty acid levels, normal to low ketone levels, increased urinary organic acids and low plasma carnitine levels. The abnormal findings may not be present between acute exacerbations, and it is crucial to collect specimens during the acute illness. Urine specimens must be collected; blood can be collected on filter paper for tandem mass spectrometry. Treatment consists of supplying adequate glucose, supplementing carnitine, and providing symptomatic support.

Hyperammonemia

Transient hyperammonemia may occur in preterm infants in so-called transient hyperammonemia of the newborn, which is not associated with IEM. Ammonia has significant toxic effects on the brain with associated edema development; however, aggressive therapy may yield completely normal outcomes. Hyperammonemia results in a marked encephalopathy, although patients typically are more hypotonic than in other metabolic encephalopathies; patients may also develop a respiratory alkalosis, which is uncommon in other encephalopathies.

Primary hyperammonemia occurs in the urea cycle defects, but a secondary hyperammonemia may occur in defects of fatty acid oxidation or organic acidemia. Hyperammonemia may also be a consequence of acute hepatic failure (e.g., with acute viral infection, toxin ingestion, and drug reactions, particularly antituberculosis drugs and sodium valproate).

Investigation. Ammonia is very toxic, and therapy must be instituted urgently to remove ammonia.²⁰⁹ It is crucial to collect appropriate diagnostic specimens at the time of presentation because it may be difficult to establish a diagnosis when dialysis and other therapies have been instituted. The following tests enable an approach to diagnosis.

Plasma Ammonia Levels. Hyperammonemia with levels greater than 250 μ mol/L typically are associated with urea cycle defects or transient hyperammonemia of the newborn.

Arterial Blood Gas Analysis. Hyperammonemia with urea cycle defects and transient hyperammonemia of the newborn are not associated with acidosis. Patients often may have a respiratory alkalosis. A metabolic acidosis is more likely to be associated with organic acidopathies.

Tests of the Urea Cycle. Tests of the urea cycle include plasma citrulline, urinary argininosuccinic acid synthetase, and urinary orotic acid.

Amino Acids. Quantitative amino acids may be difficult to interpret but help with diagnosis of conditions such as MMA, isovaleric acidurias, and propionic acidemia.

Carnitine Levels and Acyl Carnitine Analysis. Carnitine and the acyl carnitines may be affected as part of the aminoacidemias.

Management. Principles of management for hyperammonemia consist of the following:

1. Provide intravenous glucose and lipid to decrease ammonia production from endogenous protein breakdown.
2. Administer arginine (L-arginine hydrochloride, 600 mg/kg IV over 1 hour, followed by 2 to 4 mmol/kg/24 h in four divided doses).
3. Administer sodium benzoate (250 mg/kg IV followed by 250 mg/kg/day in four divided doses) and sodium phenylacetate (250 mg/kg IV immediately followed by 250 mg/kg/24 h in four divided doses).
4. Dialyze to remove excessive ammonia. Hemodialysis is the most efficient means to remove ammonia, hemofiltration is the next option (and may be particularly useful in neonates who are too unstable to tolerate hemodialysis), and finally, peritoneal dialysis

may be used. Exchange transfusion has been performed but is relatively inefficient at removal of ammonia.

Metabolic Acidosis

The acid-base environment of the body is very tightly regulated. Overall, the pH is related to the following independent variables: PCO_2 , acids in the body (mostly weak acids such as albumin and phosphates), and the relationships between strong ions (ions that exist almost exclusively in the dissociated ionic form).²¹⁰ While respiratory acidosis is primarily related to the carbonic acid system, specifically with CO_2 retention, metabolic acidosis may be related to a variety of issues including changes in ratio of sodium and chloride (as a consequence of IV infusions of 0.9% saline, or as a consequence of renal tubular dysfunction), or the accumulation of abnormal acids, which may be reflected by an increased anion gap.

A variety of IEM may be associated with proximal renal tubular acidosis (with low anion gap), particularly cystinosis and Lowe syndrome. The most common acids related to an increased anion gap are lactic acid and ketoacids, such as acetoacetate and 3-butyrobutyrate. All of the organic acidopathies and aminoacidopathies may be associated with an increased anion gap. One cause of an increased anion gap acidosis is pyroglutamic aciduria (5-oxoprolinuria) which may be related to glutathione synthetase deficiency²¹¹ or to the combination of malnutrition and exposure to agents such as paracetamol.²¹²

Acid may also be produced by bacterial overgrowth in the bowel and absorbed as occurs in D-lactic acidosis.²¹³ D-Lactic acid is not detected by routine blood tests for lactic acid, which employs a lactic dehydrogenase, but is detected by urinary assays for organic acids. These patients present with acidosis with an increased anion gap.

Patients with organic acidemias rarely present with metabolic acidosis as a primary feature of the illness, and the rest of the clinical presentation frequently provides clues as to the appropriate line of investigation. Investigation of organic acids, however, remains an important component of the investigation of any patient with unexplained metabolic acidosis.

Lactic Acidosis

Lactic acidosis is associated with inadequate oxygenation of tissues, as occurs in hypoxemia or in shock. In this situation, treatment consists of ensuring adequate oxygen content of blood and appropriate cardiac output.

So-called primary lactic acidosis occurs in the absence of hypoxemia and shock. Lactate accumulates either as a consequence of increased production of lactate or because of inadequate clearance and metabolism of lactate (primarily in the liver). Accumulation of lactate may occur without the development of acidosis, depending on the compensatory mechanisms. Many patients with congenital lactic acidosis have increased lactate levels with no acidosis between episodes of exacerbation, although episodes of exacerbation usually are associated with severe lactic acidosis.

Congenital lactic acidoses are variable in presentation, ranging from severe neonatal lactic acidosis with generally poor prognosis to children with milder defects and other children with syndromes such as the MELAS and MERRF syndromes and Leigh disease. In many of these conditions, the lactic acidosis is completely or partially overshadowed by the other clinical features of the conditions. Not all children with defects of mitochondrial energy metabolism have elevated levels.

Lactate production may be caused by increased glycolysis (e.g., glycogen storage disease type I, hereditary fructose intolerance) or by decreased oxidation of pyruvate. Oxidation of pyruvate can be limited by many conditions, including (1) pyruvate dehydrogenase complex deficiency, (2) primary pyruvate carboxylase or holocarboxylase deficiency, and (3) electron transport chain defects (associated with increased lactate pyruvate ratios in blood and CSF). The clinical course of pyruvate dehydrogenase (PDH) deficiency may be extremely variable, and diagnosis is confirmed by studies of enzyme activity in cultured fibroblasts. The lactic acidosis in PDH deficiency can be

ameliorated by a ketogenic diet,²¹⁴ although many factors must be considered before embarking on a ketogenic diet, including the protein content of the diet, particularly if there is associated renal failure, and the long-term problems of ketogenic diets.²¹⁵ Dichloroacetic acid may be helpful in some cases.²¹⁶ Many cases have been reported in which thiamine was associated with clinical improvement,²¹⁷ although high levels may be required.

Lactic acidosis occurs in all of the conditions affecting the metabolism of pyruvate through the tricarboxylic acid cycle. Abnormalities include PDH deficiency and mitochondrial energy cycle defects. The mitochondrial energy cycle problems are frequently associated with persistent lactic acidosis, myopathy, failure to thrive, psychomotor retardation, and seizures. Other symptoms that may be present in mitochondrial energy conditions in children include antenatal problems, cardiomyopathy and cardiac arrhythmias, sensorineural hearing loss, stroke and abnormalities of central respiratory drive, and diabetes mellitus.

Acquired defects in mitochondrial function have been associated with severe lactic acidosis in adults and children on antiretroviral therapy.²¹⁸ Lactic acidosis may also be a secondary phenomenon of defects of organic acid metabolism, including 3-hydroxy-3-methylglutaryl-CoA lyase deficiency, propionic acidemia, and methylmalonic acidemia.

Ketoacidosis

Primary defects in ketone use are rare but include β -ketothiolase deficiency, which may respond rapidly to administration of intravenous glucose. Ketoacidosis is a common feature of many of the organic acidemias, including MSUD, MMA, propionic acidemia, and isovaleric aciduria. Investigation should include measurement of urinary organic acids.

Cardiomyopathy

A wide variety of IEM may present with cardiomyopathy or cardiac arrhythmias. In most of these conditions, other clinical problems and symptoms predominate (such as in glycogen storage disease and organic acidopathies), and the cardiomyopathy is just part of the overall clinical presentation. In these situations, the associations assist in making the diagnosis.

A few conditions may present with cardiac problems apparently in isolation. In the differential diagnosis of myocarditis/cardiomyopathy, many conditions need to be considered, including carnitine deficiency, trifunctional protein defects, or isolated long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. In the latter two conditions, urinary organic acid analysis *at the time of the acute illness* shows the presence of medium-chain and long-chain dicarboxylic acids. At least one form of very-long-chain acyl-CoA dehydrogenase deficiency can present as an acute cardiomyopathy. For all of these conditions, measurement of acyl carnitines using tandem mass spectrometry allows diagnosis. Diagnosis is confirmed using enzyme activity in cultured fibroblasts. At least one case report²¹⁹ shows that substantial clinical improvement can be achieved by elimination of long-chain fatty acids from the diet (replacing with medium-chain fatty acids). Many disorders of the mitochondrial energy chain have poor myocardial function as one of multiple symptoms, but echocardiography may be needed to show more subtle abnormalities of contractility.

Hepatopathology

IEM can affect the liver in a variety of ways. Patients may present with symptoms ranging from acute hepatic failure to hepatomegaly to chronic hepatitis and cirrhosis. The hepatic dysfunction may present in apparent isolation or in association with cardiac, cerebral, muscle, and renal disease. The presentations of "hepatitis" may be virtually indistinguishable from the presentation of acute viral hepatitis or toxin ingestion. In one study of infants presenting to a transplant service in acute hepatic failure, IEM were responsible for the hepatic failure in 42.5% of the patients. Of these patients, 35% had hepatorenal tyrosinemia, whereas 50% had mitochondrial abnormalities. Hereditary

fructose intolerance and galactosemia together were present in less than 9% of patients.²²⁰

Hepatorenal tyrosinemia may present in the neonatal period as acute hepatic failure. It is difficult to distinguish from acute viral hepatitis because plasma amino acid levels may be similar in both situations. Alpha-fetoprotein levels may be substantially elevated in hepatorenal tyrosinemia and may be a distinguishing feature. The coagulopathy tends to be relatively severe in hepatorenal tyrosinemia, and coagulopathy may be the only presenting feature.²²¹ Patients tend to have moderate to severe anemia. The response to treatment with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexandion (NTBC) may be dramatic.

Galactosemia is characterized by the development of hypoglycemia in the neonatal period in association with jaundice (initially unconjugated, but subsequently conjugated), marked increase in transaminase levels, some abnormality of coagulation, and moderate hypoalbuminemia. Severe cerebral edema occasionally may be a dominant feature. Management has been reviewed elsewhere.²²² There is a close association with *Escherichia coli* septicemia, and any infant presenting with *E. coli* septicemia should be investigated for galactosemia. Galactosuria clears rapidly if feeds are stopped. A screening test is available on blood collected on filter paper (semiquantitative measure of galactose-1-phosphate uridylyltransferase). The diagnosis can be confirmed by a quantitative measurement of galactose-1-phosphate uridylyltransferase. Wilson's disease may present as acute hepatitis but rarely before age 5 years.

KEY POINTS

1. Although endocrine and metabolic conditions are individually rare, collectively they constitute a significant cause of pathology in the pediatric intensive care unit (PICU).
2. PICU admission is a crucial opportunity to identify endocrine problems and inborn errors of metabolism.
3. Hyper- and hypoglycemia are important metabolic abnormalities and require both an etiologic diagnosis and management. A cause for hypoglycemia or hyperglycemia must always be identified.
4. Inborn errors of metabolism must always be considered as part of the differential diagnosis of critical illness, particularly in infants.
5. Appropriate specimens should be collected at the time of the acute illness, and thereafter the clinician should consult with a specialist laboratory for diagnostic routes.
6. Specialist teams should be consulted early in the course of the illness as few intensivists develop expertise in the management of inborn errors of metabolism.
7. A multidisciplinary team approach is essential for the successful care of affected children.

ANNOTATED REFERENCES

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Marcin JP, Glaser N, Barnett P, et al: Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. *J Pediatr* 2002;141:793-797.

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■ References for this chapter can be found at expertconsult.com.

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Critically ill patients suffer from a variety of physiologic insults that result in a rapidly changing physiologic status, thus making appropriate drug dosing a challenging problem. Understanding how these changes impact pharmacokinetics and pharmacodynamics can result in improved dosing decisions. This chapter reviews the basic principles of pharmacokinetics and pharmacodynamics and how they may be affected by critical illness.

The terms *pharmacokinetics* and *pharmacodynamics* describe the amount of drug in the body at a given time and the pharmacologic effects caused by the drug.¹ Pharmacokinetics describes the movement of a drug into, within, and out of the body over time, whereas pharmacodynamics explains the effects the drug has on the body. Understanding the pharmacokinetic parameters of clearance, volume of distribution, half-life, steady state, and absorption, along with pharmacodynamic principles, such as receptor theory, potency, affinity, tolerance, and minimum effective concentration, can enhance the treatment of critically ill patients.

GENERAL PRINCIPLES OF PHARMACOKINETICS

Clearance, volume of distribution, half-life, and bioavailability are four pharmacokinetic parameters that allow the clinician to better estimate dosing requirements. If the concentration of a drug in a sampled fluid (e.g., plasma, urine, saliva) correlates well with its pharmacologic response (therapeutic or toxic), then the application of pharmacokinetics is likely to be beneficial (Fig. 152-1).

Measurement of the relationship between drug concentration and therapeutic or toxic response in a large number of patients enables the development of a therapeutic range or target concentration for that drug (Fig. 152-2).^{2,3} A multitude of host factors (e.g., hemodynamic status, decreased organ function, nutritional status, concurrent disease states) increase the likelihood that drug dosing based on individualized pharmacokinetic assessment will be beneficial.^{4,5} Gender-related differences can occur in both pharmacokinetic and pharmacodynamic responses.⁶ Individual chapters in this text are devoted to many of these agents and their adjustments for dosage in patients with renal or hepatic failure.

PHARMACOKINETIC MODELS

The pharmacokinetic concepts of clearance, volume of distribution, half-life, and bioavailability are based on enormously complex physiologic principles and use mathematical models that make many assumptions. Most clinically useful pharmacokinetic equations assume one- or two-compartment models (see Fig. 152-2).

When the drug enters the one-compartment model, it is assumed to be instantaneously and completely mixed in a given volume of distribution, resulting in a uniform concentration throughout the compartment. The rate constant K reflects the usual situation of elimination by a first-order, linear process. The drug is assumed to enter the compartment instantaneously in the case of an intravenous bolus dose. If the dosage is administered through oral or intramuscular routes, entry into the compartment is assumed to occur at a rate defined by a

first-order absorption rate constant (K_a), whereas entry into the compartment is assumed to occur at a constant rate described by a zero-order rate constant (R_0) if the drug is administered by intravenous infusion. *Bioavailability* (F) is defined as the fraction of the administered dose that reaches the systemic circulation.

Clearance (CL) is a primary parameter that can be physiologically associated with a particular organ in the body such as the liver or kidney. Clearance is often expressed by the equation $CL = K \times V$, leading to the impression that CL is a function of the parameters K and V . However, this arrangement of the equation is not correct from a physiologic point of view. CL and V are both primary parameters, and K is a secondary parameter. The first-order rate is determined by changes in either CL or V , and the equation is correctly written as $K = CL/V$.

Half-life ($t_{1/2}$) is a useful measure of how quickly a drug is eliminated from the body and is related to the first-order elimination rate constant:

$$t_{1/2} = \frac{\ln(2)}{K} = \frac{0.693}{K} \quad (\text{Equation 1})$$

Specifically, $t_{1/2}$ defines the time taken for the drug concentration to decrease by one-half. In a linear pharmacokinetic system with first-order elimination, $t_{1/2}$ is constant, and it takes the same amount of time for the concentration to fall from 100 to 50 (arbitrary units) as it does to decline from 50 to 25 (Fig. 152-3).

The one-compartment model allows concentrations at any point in time to be calculated:

$$C_2 = C_1 \times \exp^{-K \times \Delta t} \quad (\text{Equation 2})$$

where Δt is the time between measurements C_1 and C_2 . The mono-exponentially decreasing concentration–time curve appears linear when plotted on semi-log coordinates.

Sometimes a drug does not instantly equilibrate with all tissues in the body. This can often be adequately described by a two-compartment model, which is characterized by a rapidly distributing central compartment and a more slowly equilibrating peripheral compartment (Fig. 152-4). The equation describing the concentration–time profile for the two-compartment model is:

$$C = A \times \exp^{-\alpha \times t} + B \times \exp^{-\beta \times t} \quad (\text{Equation 3})$$

The distinguishing feature of this biexponential equation is that when plotted on semi-log coordinates, the concentrations are the sum of two distinct straight lines representing two half-lives. One is the *terminal* or β half-life, and the other is the *rapid distribution* or α half-life. As the rapid distribution exponential becomes negligible in the equation, the slower exponential term dominates, and the concentration–time profile resembles that of a single-compartment drug. Consequently, the equation:

$$C_2 = C_1 \times \exp^{-\beta \times \Delta t} \quad (\text{Equation 4})$$

in which β replaces K , can still be used to predict concentrations, as long as both C_1 and C_2 are in the postdistributive phase. This sum-of-exponentials approach can be extended to three-compartment or even more complex models, but it is difficult to obtain all the concentrations needed to characterize each exponent.

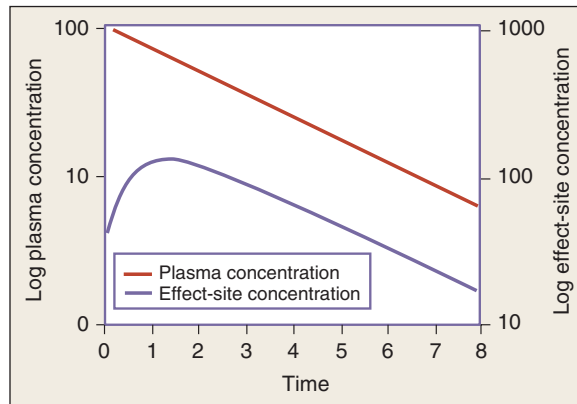


FIGURE 152-1 ■ For concentration monitoring to be useful, there must be a strong relationship between concentration of the drug measured in an easily accessible fluid and concentration at the effect site.

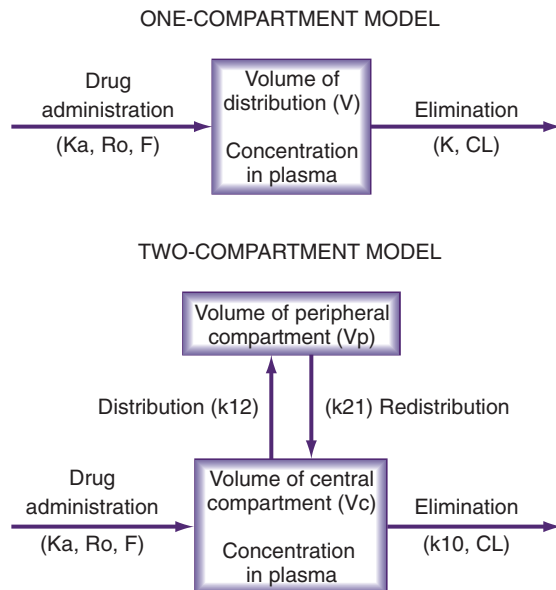


FIGURE 152-2 ■ Pharmacokinetic models simplify complex physiologic process. Concentrations may behave as if the body were a single rapidly equilibrating compartment or follow a more complicated two-compartment model in which a slower distribution phase into tissues is observed. See text for explanation of terms.

Clearance

CL is a primary pharmacokinetic parameter that measures the ability of the body to eliminate a drug. It is often stated that clearance is the volume of blood (plasma) that is completely cleared of drug per unit time. Although this is one way to define clearance, it does not capture the relationship between drug clearance (mL/min) and the rate of drug elimination (mg/h). In pharmacokinetics, the general concept of clearance is also the rate of elimination relative to the concentration. In a first-order pharmacokinetic system, the rate of elimination is proportional to the drug concentration; clearance is this proportionality constant:

$$\text{Rate of elimination} = \text{CL} \times \text{concentration} \quad (\text{Equation 5})$$

Clearance is clinically useful because it can be directly related to the organ of elimination. We can talk about renal clearance, hepatic clearance, or biliary clearance, and the sum of each of the individual

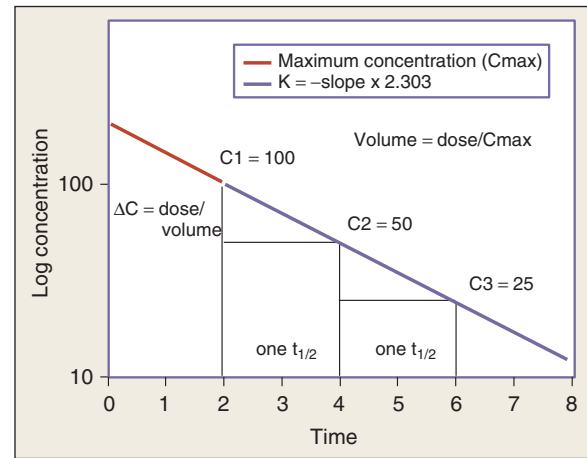


FIGURE 152-3 ■ Log concentration–time curve for a one-compartment model after intravenous administration, illustrating volume of distribution, elimination rate constant, and half-life.

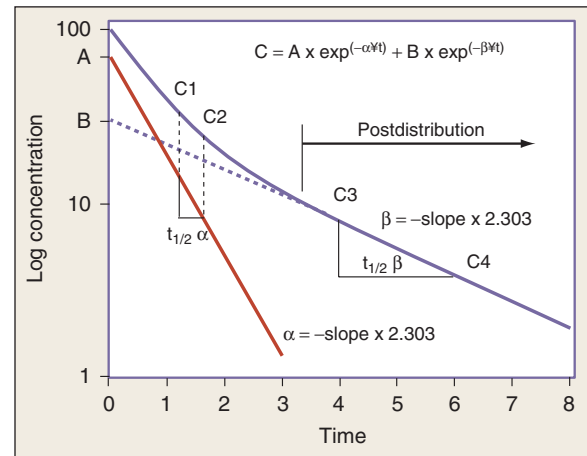


FIGURE 152-4 ■ Log concentration–time curve for a two-compartment model after intravenous administration, illustrating a distribution period (α) and postdistribution period (β). Concentrations C1 and C2 reflect both distribution and elimination processes, whereas concentrations C3 and C4 reflect postdistribution elimination processes.

clearances is the total body clearance. This allows us to adjust doses in response to changes in organ function. A patient with developing renal failure is likely to require a reduction of the dose of a drug that is eliminated by the kidney but not necessarily a dose reduction of a drug that is eliminated by the liver. For example, if the clearance of a drug is known to be 50% renal and 50% hepatic and renal function is decreased by 50%, it is necessary to reduce the dose by only 25% to maintain the same concentration.

The area-under-the-curve (AUC) is a useful measure of drug exposure and results from dose and CL:

$$\text{AUC} = \frac{\text{Dose}}{\text{CL}} \quad (\text{Equation 6})$$

This concept is similar to a steady-state concentration (C_{ss}) being considered as the measure of drug exposure during a continuous intravenous infusion. The C_{ss} is solely a function of the infusion rate (R_o) and CL:

$$C_{ss} = \frac{R_o}{\text{CL}} \quad (\text{Equation 7})$$

Notice that C_{ss} is not a function of the volume of distribution. Though counterintuitive, doubling the volume of distribution will not result in a halving of C_{ss} . The important point is that the equation is predicting the concentration at a steady state. During a constant infusion, rapidly doubling the volume of distribution will only transiently halve the concentration. If clearance remains unchanged, the concentration will return to the same C_{ss} .

With intermittent dosing, drug concentrations go up and come down during each dosing interval. The average C_{ss} ($C_{ss,avg}$) is a time-averaged concentration (i.e., the mean of all concentrations during the dosing interval); it is also a function of clearance and the dosing rate. In the case of oral administration, the dosing rate is a function of the dose administered (D), dosing interval (τ), and F :

$$C_{ss, avg} = \frac{F \times D / \tau}{CL} \quad (\text{Equation 8})$$

As before, the overall drug exposure is not influenced by the volume of distribution, but it does change in proportion to changes in clearance or the dosing rate through changes in F , D , or τ .

Volume of Distribution

The volume of distribution (V) is another primary pharmacokinetic parameter and is useful for determining the change in drug concentration for a given dose. After an intravenous bolus dose in a one-compartment pharmacokinetic model, the change in concentration (ΔC) between the maximum concentration (C_{max}) and the concentration immediately before the dose is administered is a function of the dose (D) and the V :

$$\Delta C = \frac{D}{V} \quad (\text{Equation 9})$$

This equation is useful for predicting both the concentration after a first bolus dose and the increase in concentration at any point in time after a bolus dose. If a concentration before a bolus dose is known, the equation can be used to predict the increase in concentration after the dose is administered (see Fig. 152-3). This equation is also useful for estimating the dose needed to reach a given concentration. If it is known that the volume of distribution is 0.45 L/kg and a C_{max} of 10 mg/L is desired after the loading dose, the dose is estimated to be $10 \text{ mg/L} \times 0.45 \text{ L/kg} = 4.5 \text{ mg/kg}$. This equation only predicts loading doses and not maintenance doses. A steady-state condition is not necessary, which is common in critical care.

The value for the volume of distribution does not necessarily coincide with any particular physiologic space. The veracity of this statement becomes readily apparent when one considers a drug such as digoxin which has a volume of distribution of approximately 440 L. Clearly, a volume of distribution of that magnitude cannot have a relationship to any physiologic space in an average-sized human. Therefore, the term *apparent volume of distribution* is often used.

The concept of the volume of distribution gets more complex when more than one compartment is needed to describe the pharmacokinetics of a drug. Mathematically, the volume of distribution is a hypothetical volume that is needed to relate the amount of drug in the body to a measured concentration in a fluid (plasma). Unlike the one-compartment model, wherein the entire drug in the body is regarded as being in a single compartment until it is eliminated, drug also circulates through additional compartments in a multicompartment model. In this situation, the volume of distribution must increase as drug distributes to other compartments until distribution equilibrium among all compartments is reached. Technically, an infinite number of volumes of distribution are observed as this equilibration process occurs, but only three are commonly defined. The *volume of distribution of the central compartment* (V_c) is the volume of the usual sampling compartment; it is always the smallest volume term. Immediately after the administration of an intravenous bolus, all added drug is in the

central compartment, and V_c can be used to calculate a change in concentration.

The volume of distribution increases over time until a *distribution equilibrium* is reached among all compartments. This is the largest value for the volume of distribution. The fact that the distribution equilibrium has occurred can be discerned from a log concentration versus time plot (see Fig. 152-4). The curve becomes log linear when the rate of drug entry into each peripheral compartment equals the rate of return from each compartment. Because it is often calculated using the clearance and β or terminal elimination half-life, this volume is often called V_β :

$$V_\beta = \frac{CL}{\beta} \quad (\text{Equation 10})$$

The *steady-state volume of distribution* (V_{ss}) is the sum of the volumes of all the compartments in the model. If a drug were infused to steady state, V_{ss} would be the proportionality constant relating C_{ss} to the total amount of drug in the body.

Half-Life

Half-life ($t_{1/2}$) is defined as the time taken to reduce the drug concentration by half (see Fig. 152-3). Half-life is referred to as a *secondary parameter* because it is a function of two primary parameters, clearance and volume of distribution:

$$t_{1/2} = \frac{\ln(2) \times V}{CL} = \frac{0.693 \times V}{CL} \quad (\text{Equation 11})$$

A change in either clearance or volume of distribution results in a proportional change in half-life.

Because the half-life characterizes how rapidly concentrations decrease over time, it is used to determine how frequently a drug needs to be dosed. Drugs with rapid half-lives need to be dosed more frequently than drugs with longer half-lives. The half-life for an aminoglycoside is relatively short in patients with good renal function, and the drug may require dosing every 6 hours. In patients with poor renal function, the half-life is longer, and dosing may be prolonged to 24-hour intervals to maintain appropriate peak and trough concentrations. In the critical care patient, the development of renal failure can significantly change aminoglycoside clearance, and the accompanying change in drug half-life will necessitate a change in dosing interval.

In a one-compartment system with constant clearance and volume of distribution, drug half-life is also constant. However, in a multicompartment model, the volume of distribution increases over time as drug equilibrates into tissue compartments until V_β is reached. According to the previous equation, the half-life also increases over time and eventually reaches a maximum at $t_{1/2}\beta$ (see Fig. 152-4).

In multicompartment models, there is usually one half-life of interest for each compartment. These half-lives are derived from the hybrid time constants associated with each compartment. In a two-compartment model, these two exponentials are typically called α and β and are arbitrarily termed the *rapid* and *slow exponents*, respectively. These time constants give rise to the distribution $t_{1/2}\alpha$ and the slower or terminal $t_{1/2}\beta$. One useful way to think about distribution half-lives is analogous to the standard way of thinking about any half-life. In the one-compartment model, it takes five half-lives for 97% of the drug to be eliminated from the body. The situation is similar for each exponent, but the interpretation is that it takes five distribution half-lives for that exponent to become negligible in the sum of exponentials equation—that is, for the rapid distribution phase to reach equilibrium.

Most drugs have a rapid distribution phase that could be detected if concentrations were measured frequently enough. Aminoglycosides are an illustrative example of this concept because they have a rapid, although not instantaneous, distribution phase (Fig. 152-5). With a distribution phase half-life of 5 to 10 minutes, it would take

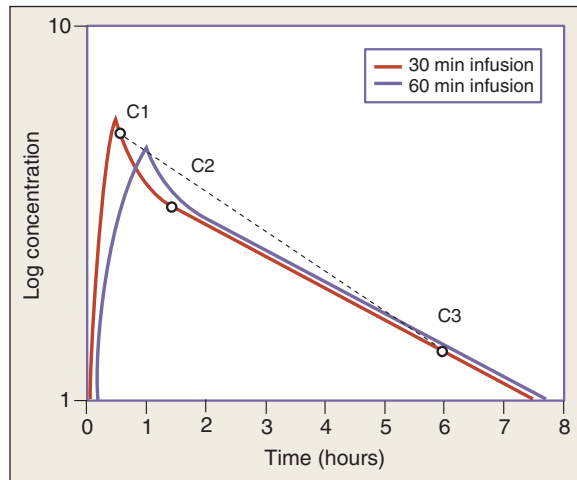


FIGURE 152-5 ■ If an aminoglycoside (tobramycin) is administered by intravenous infusion over 30 minutes, the peak concentration will be higher than with infusion over 60 minutes, but the total area under the curve will be the same. In therapeutic drug monitoring, if sample C1 is obtained during the distribution phase and paired with C3, the calculated half-life will be shorter than if two postdistribution concentrations (C2 and C3) are paired together.

approximately 25 to 50 minutes before the log-linear elimination phase could be observed. This results in the recommendation to wait approximately 1 hour after the end of an infusion before sampling blood to measure an aminoglycoside concentration. If a blood sample is obtained before this time, the drug will still be in the distribution phase, and the concentration measured will lead to underestimation of the drug half-life. In addition, slowly equilibrating compartments have been demonstrated when aminoglycoside concentrations are measured during washout.⁷ Aminoglycosides are usually dosed frequently enough so that the slowly equilibrating compartment is not detected.

Bioavailability

The extent of drug absorption, termed *bioavailability* (F), is generally referenced to the exposure when the drug is intravenously administered. This parameter is determined by comparing the AUC of the drug intravenously administered to that of the same drug administered via another route. The bioavailability of a drug intravenously administered is regarded as being 100% (i.e., F = 1.0), and other routes of administration (e.g., oral dosing, intramuscular injection) often have a reduced bioavailability (e.g., F = 0.8, or 80% bioavailability). Bioavailability is a function of the extent of absorption and the amount of drug metabolized before entering the systemic circulation (first-pass effect). Drugs with low bioavailability either cannot be administered by any route other than the intravenous one (e.g., sodium nitroprusside, dobutamine) or require higher doses when administered via the oral route compared with the intravenous route (e.g., furosemide, morphine, propranolol). Alternative routes of administration (e.g., rectal, topical, subcutaneous injection, intramuscular injection) are occasionally used in critically ill patients, owing to poor oral bioavailability. These routes all suffer from problems with delayed or poorly predictable serum concentrations. Vasoconstriction, hypoperfusion, edema, gastric suctioning, ileus, diarrhea, and enhanced gastrointestinal motility are all common problems in critically ill patients that can adversely affect bioavailability.

The *first-pass effect* limits drug absorption in three ways. As some drugs enter the gut wall, they are susceptible to transport proteins (primarily P-glycoprotein) that actively pump the molecules back into the lumen of the gastrointestinal tract.⁸ Molecules that escape this

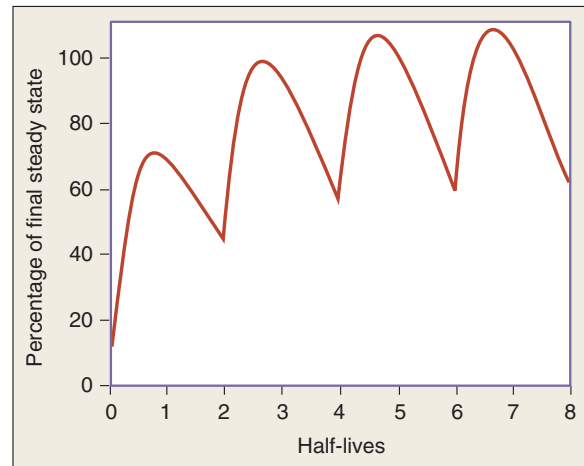


FIGURE 152-6 ■ With intermittent dosing, concentration profiles also approach steady state wherein peak and trough concentrations during one cycle are reproducible in the next cycle.

process are then subjected to metabolism by enzymes in the gut wall. Those that escape gut metabolism enter the hepatic circulation and are subjected to metabolism in the liver before their first opportunity to be presented to the systemic circulation.⁹ Drugs that have a high hepatic extraction ratio (i.e., are very efficiently removed by the liver) are most likely to show decreased bioavailability due to this first-pass effect; conversely, the bioavailability of these drugs increases if liver dysfunction decreases the hepatic extraction ratio.

Steady State

After an infusion is started, drug concentrations increase and eventually reach a concentration that does not change over time. At this point, the amount of drug entering the body is equal to the amount leaving it, and steady-state conditions apply. During intermittent dosing, drug concentrations accumulate over time, and eventually a steady state is attained when the concentration profile over each interval resembles all other steady-state profiles (Fig. 152-6). In the clinical setting, the measurement of drug concentration is often delayed for a period equal to five half-lives because at that point the concentration will reflect 97% of the final C_{ss}.

PHARMACODYNAMICS

Pharmacodynamics is the study of the relationship between the concentration of a drug and its pharmacologic effect. Complex pharmacodynamic models with many linked submodels are routinely employed during drug development to determine drug-dosing regimens. In clinical practice the relatively simple E_{max} model is often adequate¹⁰:

$$\text{Effect} = \frac{E_{\text{max}} \times \text{concentration}}{EC_{50} + \text{concentration}} \quad (\text{Equation 12})$$

Graphically, this equation has a hyperbolic shape (Fig. 152-7) with parameters E_{max} and EC₅₀. E_{max} represents the maximal effect attainable due to the drug. The EC₅₀ is the concentration at which half the maximal effect is observed; it is thus a measure of drug potency. The model dictates that increasing doses of the drug do not proportionately increase its effect; eventually, the effect of the drug begins to reach a plateau. If the drug concentration is expected to be less than EC₅₀, increasing the dose will produce a nearly proportional increase in effect. However, as concentrations exceed the EC₅₀, an increase in dose may not be warranted. The increased concentrations will produce

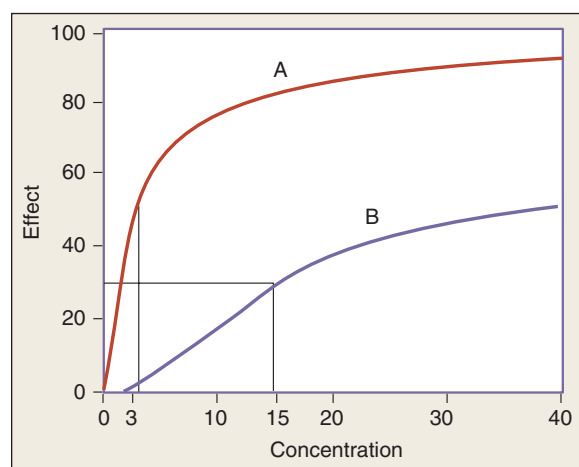


FIGURE 152-7 ■ The Emax pharmacodynamic model illustrates that as drug concentrations continue to increase, the increases in drug effect become progressively smaller. Drug A has a lower EC₅₀ (3) than drug B (15) and is said to be more potent than drug B.

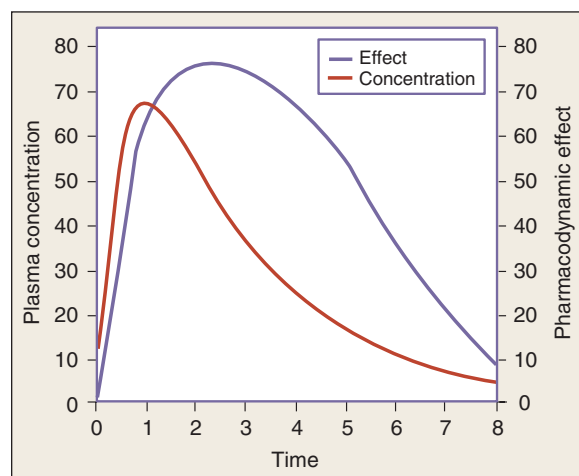


FIGURE 152-8 ■ Pharmacodynamic effects often lag behind the matching pharmacokinetic model. In this instance, maximum concentration in blood occurs at 1 hour, whereas maximal drug effect occurs between 2 and 3 hours.

a lesser increase in desired effect and may place the patient at risk for development of adverse drug-related effects.

Time does not appear in the Emax model, and concentrations are explicitly defined as C_{ss} so that the effect resulting from a given concentration is considered to be a steady-state effect. This model applies when drug in the plasma rapidly equilibrates with drug at the site of action, and there is no indirect mechanism between the concentration at the site of effect and the effect itself. The more common situation is that the effect lags somewhat behind the concentration (Fig. 152-8). If concentrations are going up and coming down over time, as would be expected with an intermittent intravenous or oral dosing schedule, the effect is also expected to go up and down over time, but the time frames may not coincide exactly. For example, the plasma concentration might peak at 1 hour and the effect might peak several hours later. There is a mismatch or disequilibrium between concentration and effect, and a plot of effect versus concentration, with the points connected in time order, yields a hysteresis loop. For any given concentration, there are two effects, one on the upswing of the concentration–time curve and another on the downswing.

The pharmacodynamic effects noted with a given drug result from the drug's interaction with receptors and the resultant activation or inhibition of effects mediated by that receptor. These effects may be either the desired therapeutic action or an unwanted toxic effect. Generally, it is assumed that the intensity of effect produced by the drug is a function of the quantity of drug at the receptor site, whereas relative potency results from varying degrees of selectivity for the receptor and the receptor's affinity for binding the drug. More potent drugs elicit a given effect at lower concentrations than less potent drugs.

Drugs that stimulate a response from the receptor are *agonists*, and those that inhibit a response from the receptor are *antagonists*. Because antagonists have no effect of their own at the receptor, the net effect depends on both the concentration of the antagonist and the agonist being blocked. The relative concentration of the agonist compared with the antagonist primarily determines the effect observed when an antagonist is competing for the same binding site as the molecule or drug that stimulates the receptor. Irreversible antagonists, however, either bind with very strong affinity to the receptor so they cannot be displaced or bind to another site on the substrate that interferes with binding at the receptor. The effect of irreversible antagonists is independent of the agonist's concentration and results in a decrease in the maximal effect of the agonist. The duration of effect for irreversible antagonists is determined by the rate of turnover for the receptor.

Tolerance to a drug is seen when the response at a given dose decreases. This may be a result of receptor downregulation (decreased number or sensitivity of receptors) or enzyme induction (increased metabolism). Cross-tolerance, as is commonly seen with opioids, occurs when similar drugs act on the same receptor.

PROTEIN BINDING

Many drugs are bound to plasma proteins, and the terms *bound drug concentration* (C_b), *unbound (or free) drug concentration* (C_u), *total (bound plus unbound) drug concentration* (C_{tot}), and *unbound (or free) fraction* (f_u) are frequently used:

$$\begin{aligned} C_{tot} &= C_u + C_b \\ f_u &= \frac{C_u}{C_{tot}} \end{aligned} \quad (\text{Equation 13})$$

The pharmacokinetic concepts concerning the implications of protein binding were reviewed in 2002 by Benet and Hoener.¹¹ They demonstrated that changes in plasma protein binding have little clinical relevance as they rarely result in changes to the steady-state unbound concentration. To better understand this concept, the relationships among unbound drug exposure, total drug exposure, and pharmacodynamic effect must be considered. One of the more useful measures of exposure is the AUC, and the unbound AUC (AUC_u) determines drug effect:

$$AUC_u = f_u \times AUC = f_u \times F \times \frac{\text{Dose}}{CL} \quad (\text{Equation 14})$$

where f_u is the fraction unbound, F is the bioavailability, and CL is the clearance.

After standard, well-stirred model assumptions are made regarding high- and low-clearance drugs, something interesting occurs when the equations for clearance and bioavailability are substituted into the equation for AUC_u. For all drugs administered orally and eliminated hepatically, the f_u term cancels out of the equation. Unbound drug exposure is not a function of f_u at steady state, and there should be no changes in pharmacologic effect with changes in protein binding. Similarly, it can be shown that AUC_u for all drugs with low extraction ratios—whether administered orally or by the intravenous route, and whether eliminated by the liver or nonhepatically—is not a function of f_u. Again, changes in protein binding will not result in changes in

the steady-state exposure to the unbound drug. It is important to emphasize that AUC_u refers to the AUC based on unbound concentrations. The AUC based on total concentrations, AUC_{tot} , can be calculated from this equation: $AUC_{tot} = AUC_u/f_u$. If the protein binding of a drug changes and f_u is doubled, AUC_{tot} will be halved, and AUC_u will remain the same. The expression for AUC_u retains the f_u term for all high-clearance drugs administered intravenously (regardless of clearance route) and for high-clearance drugs administered orally that are eliminated by extrahepatic pathways.

To address this issue, Benet and Hoener reviewed pharmacokinetic data on 456 drugs from the literature. No orally administered drug with a high extraction ratio and nonhepatic clearance met the criterion for significant (>70%) protein binding. Only 25 (5%) of the 456 drugs had high extraction ratios, were not administered by the oral route, and met the criterion for which protein binding may influence drug exposure. However, many of these 25 agents are routinely used in critical care (Table 152-1).

In critically ill patients, protein concentrations can change quickly. This is particularly true of the acute-phase reactant, α_1 -acid glycoprotein (AAG). In addition, some patients (e.g., those undergoing dialysis or those with cachexia) have altered protein binding.¹² The extent of protein binding, route of administration, route of elimination, and extraction ratio of the drug all should be considered when

determining whether a change in binding is likely to result in a change in effect.

As a final note on protein binding, care must be taken when evaluating total drug concentrations in patients with altered protein binding. Consider the case of phenytoin. The percentage of unbound drug is typically 10% but is approximately doubled in patients receiving hemodialysis (Table 152-2). If phenytoin were administered as a standard dose to all patients, there would be no problem; phenytoin is a low-clearance drug, and protein binding should not influence overall unbound exposure whether the drug is administered orally or intravenously. However, phenytoin concentrations are often obtained for the purposes of therapeutic drug monitoring, and efforts are made to achieve circulating levels within the commonly accepted therapeutic range of 10 to 20 mg/L. In patients with normal protein binding, this exposure equates to an unbound therapeutic range of 1 to 2 mg/L. In patients with 20% unbound drug, the desired unbound range is still 1 to 2 mg/L, but the range based on total concentration is approximately halved. In cases of higher f_u , if phenytoin dosing is increased to achieve 10 to 20 mg/L, toxicities may be observed because the unbound concentration will be twice the desired value.

■ NONLINEAR PHARMACOKINETICS

The application of pharmacokinetics to therapeutic drug monitoring becomes considerably more difficult with drugs that exhibit nonlinearities. With linear pharmacokinetics, parameters are stable over time and across concentrations. Doubling of the dose results in doubling of the concentration, and a given dose provides the same AUC regardless of the dosing history. *Nonlinear pharmacokinetics* is a term used when the principle of superposition no longer holds. An increase in dose may result in an increase in concentration that is more than or less than proportional, or it may result in clearance changes over time. There are several common types of nonlinearities that occur in the clinical setting.

Phenytoin is the classic example for nonlinear elimination. Increases in a phenytoin dose can result in greater than proportional increases in concentration. In any pharmacokinetic system, clearance is defined as the rate of elimination relative to the concentration. Hence, an instantaneous rate of elimination can be defined as follows:

$$\text{Rate of elimination} = CL \times C \quad (\text{Equation 15})$$

In a linear elimination process, clearance is constant, and doubling the concentration doubles the rate of elimination. In the case of phenytoin with nonlinear elimination, clearance is not constant. Nonlinear elimination occurs because the metabolic pathway responsible for the elimination of the drug is saturable. The enzyme system has a maximum rate of metabolism that can be approached at therapeutic concentrations of phenytoin. These principles can be better understood by considering the rate of elimination described by the Michaelis-Menten equation (Fig. 152-9). It has two parameters, the *maximum rate of elimination* (V_{max}) and the *concentration that results in one-half the maximum rate* (K_m):

TABLE 152-1

25 Drugs for Which Changes in Protein Binding May Influence Clinical Drug Exposure After Intravenous or Intramuscular Administration*

| | |
|------------------------|--------------------|
| Alfentanil | Itraconazole |
| Amitriptyline | Lidocaine |
| Buprenorphine | Methylprednisolone |
| Chlorpromazine | Midazolam |
| Cocaine | Milrinone |
| Diltiazem | Nicardipine |
| Diphenhydramine | Pentamidine |
| Doxorubicin | Propofol |
| Erythromycin | Propranolol |
| Fentanyl | Remifentanyl |
| Gold sodium thiomalate | Sufentanil |
| Haloperidol | Verapamil |
| Idarubicin | |

*Criteria for selection included >70% protein binding and hepatic clearance >6.0 mL/min/kg or nonhepatic extraction ratio clearance $\geq 0.28 \times$ renal blood flow (>4.8 mL/min/kg). Modified from Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. Clin Pharmacol Ther 2002;71:115–121.

TABLE 152-2

Effect of Decreased Protein Binding on Bound and Unbound Concentrations of Phenytoin

| CONCENTRATION | CONCENTRATIONS OF PHENYTOIN AT THERAPEUTIC RANGE (mg/L) | | RESULT OF ERRONEOUS INCREASE IN PHENYTOIN DOSE IN PATIENT WITH DECREASED PROTEIN BINDING* |
|---------------------|---|---|---|
| | TYPICAL PATIENT | PATIENT WITH PROTEIN BINDING DECREASED BY 50% | |
| Total (C_{tot}) | 20 | 10 | 20 |
| Unbound (C_u) | 2 (10%) | 2 (20%) | 4 (20%) |
| Bound (C_b) | 18 | 8 | 16 |

*Because of the altered protein binding, C_{tot} is less when C_u is in the therapeutic range (i.e., 2 mg/L). During therapeutic drug monitoring, it is the C_{tot} that is measured. If the decreased protein binding is not taken into account and the phenytoin dose is increased to achieve a C_{tot} of 20 mg/L, the actual C_u will double and toxic effects could ensue.

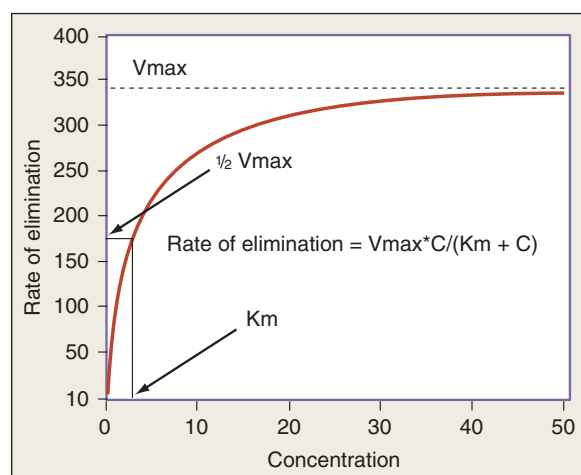


FIGURE 152-9 ■ The Michaelis-Menten model demonstrates elimination as a nonlinear function of concentration, with characteristics including a maximum rate of elimination (V_{\max}) and a concentration at which one-half of the maximum rate of elimination occurs (K_m).

$$\text{Rate of elimination} = \frac{V_{\max} \times C}{K_m + C} \quad (\text{Equation 16})$$

Although the parameters V_{\max} and K_m are constant, it can be seen that clearance is a function of concentration (C). The clearance of a drug decreases as the concentration increases:

$$CL = \frac{\text{Rate of elimination}}{C} = \frac{V_{\max}}{K_m + C} \quad (\text{Equation 17})$$

Although enzyme systems do have maximal rates, the usual drug concentrations attained in the clinical setting are considerably lower than K_m , the quantity $V_{\max}/(K_m + C)$ is minimally influenced by concentration, and clearance becomes constant. Therefore, even

though many drugs are metabolized by hepatic enzymes, few drugs of clinical interest display detectable nonlinear elimination.

At steady state, the amount of drug eliminated every day must equal the dose taken, and the elimination rate equals the dosing rate. After rearranging the equation for the C_{ss} :

$$C_{ss} = \frac{\text{Dosing rate} \times K_m}{V_{\max} - \text{Dosing rate}} \quad (\text{Equation 18})$$

This equation shows that an increase in dosing rate produces a greater than proportional increase in the C_{ss} . Furthermore, if the dosing rate exceeds V_{\max} , a C_{ss} will never be attained.

Another type of nonlinearity is time-dependent pharmacokinetics as demonstrated by carbamazepine inducing its own metabolism.¹³ This autoinduction causes the clearance of carbamazepine to increase over time. It is important to gradually increase the dose of carbamazepine during the first few weeks of therapy up to the expected maintenance dose to avoid toxicities related to elevated concentrations.

Protein binding also can become saturable with some drugs. Intuitively, one might think that saturation of protein binding would result in higher unbound drug concentrations available to exert desirable effects and toxicities, but it must be kept in mind that the organs responsible for drug clearance are eliminating unbound drug. Therefore, unless the clearance of a drug also changes, the steady-state unbound concentration will remain constant in the face of saturable protein binding. The total concentration is a function of the unbound concentration and the fraction unbound:

$$C_{\text{tot}} = \frac{C_u}{f_u} \quad (\text{Equation 19})$$

If the fraction unbound increases at higher unbound concentrations, total concentrations do not increase in proportion to unbound concentrations. This can be perplexing in therapeutic drug monitoring situations. Increases in dose produce less than expected increases in total concentration. As the dose is pushed higher to reach desired total concentrations, toxicities may be observed because saturable binding causes the unbound concentration to be greater than expected.

KEY POINTS

1. Pharmacokinetic analysis is likely to be useful when there is a strong relationship between drug concentration and the pharmacologic response associated with a given drug concentration.
2. Although many of the complex underlying principles of drug distribution and elimination are simplified by the one-compartment model, it is widely employed for patient care because it successfully predicts future drug concentrations with sufficient accuracy to be clinically useful.
3. Volume of distribution (V) reflects the resulting concentration from a given drug dose and is not directly associated with a physiologic space.
4. Drug half-life ($t_{1/2}$) is a measure of how quickly a drug is eliminated from the body; it is related to the first-order elimination rate constant (K) by the equation: $t_{1/2} = 0.693/K$.
5. Clearance (CL) is a primary pharmacokinetic parameter that describes the efficiency of the body in eliminating a drug and is given by the volume of blood completely cleared of drug per unit time.
6. The area-under-the-concentration–time curve (AUC) is a measure of drug exposure; it is determined by the dose of drug and the clearance through the relationship: $AUC = \text{Dose}/CL$.
7. In a one-compartment pharmacokinetic model, the change in drug concentration (ΔC) can be predicted by the dose of drug and volume of distribution through the relationship: $\Delta C = \text{Dose}/V$.
8. Half-life ($t_{1/2}$) measures the amount of time needed for a drug concentration to decrease by 50%; it changes in proportion to changes in either V or CL , as reflected by the equation $t_{1/2} = 0.693 \times V/CL$.
9. Most drugs demonstrate at least two compartments when pharmacokinetics is examined closely; changes in concentration reflect a short distribution phase (α) and a longer elimination phase (β).
10. After five half-lives of either α (the distribution $t_{1/2}$) or β (the elimination $t_{1/2}$), a drug will be 97% distributed throughout the body or eliminated from the body.
11. The extent of drug absorption is termed *bioavailability* (F); it is generally referenced to concentrations when the drug is intravenously administered.
12. The *first-pass effect* refers to the elimination of drug that is absorbed orally but then metabolized and/or secreted by enzymes in either the liver or the gut wall before reaching the systemic circulation.

KEY POINTS—cont'd

13. Pharmacodynamics is the study of the relationship between the concentration of drug and its pharmacologic effect.
14. The Emax pharmacodynamic model defines a hyperbolic relationship between effect and dose that allows less than proportional increases in response as concentrations increase.
15. Observed pharmacologic effects often lag behind the serum concentration eliciting the effect and can be observed as a hysteresis loop when effect-concentration pairs are connected in time order.
16. Antagonists may inhibit an effect at a receptor through concentration-dependent competitive blocking or by binding irreversibly to the receptor.
17. Although many drugs are bound to some extent by plasma proteins, their effect is determined by the unbound concentration; changes in protein binding do not have a clinically significant effect in most clinical patients.
18. Nonlinear elimination is exhibited when CL changes with changes in drug concentration, as reflected by the Michaelis-Menten equation, $CL = V_{max}/(K_m + C)$, wherein V_{max} is the maximum rate of elimination, K_m is the concentration of drug that results in one-half the maximum rate, and C is the concentration of drug.

ANNOTATED REFERENCES

Benet LZ, Hoener B. Changes in plasma protein binding have little clinical relevance. *Clin Pharmacol Ther* 2002;71:115–121.

In an easily understood manner, this manuscript systematically presents the physiology and mathematics needed to understand why changes in protein binding have little clinical relevance.

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This is an excellent reference article that contains an exhaustive compilation of drugs with their therapeutic, toxic, and fatal concentration ranges. The article also provides half-lives and references for each drug.

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Poisoning: Overview of Approaches for Evaluation and Treatment

Brenna Farmer and Donna L. Seger

Patients presenting to the hospital with overdoses and poisonings should undergo an initial evaluation to determine if a specific poisoning can be determined that would lead to specific management options. History and physical examination are key to determine what poisoning, such as a toxidrome, a syndrome related to a toxic exposure (cholinergic, anticholinergic, sympathomimetic, opioid, sedative-hypnotic, or withdrawal syndromes), could be causing a patient's presentation. Once a poisoning or overdose has been identified, management can be determined. Management options can include gastrointestinal decontamination, enhancing elimination, and/or use of antidotes. Additionally, some poisonings and overdoses only require supportive care.

HISTORY

A thorough poison history should be obtained. Necessary elements include suspected ingestion, amount ingested, time of ingestion, and any possible coingestants. Other important elements include past medical history, medication history, social history, and family history. Access to other medications in the home, including dietary and herbal supplements and over-the-counter medications, must be determined. Review of symptoms, including if vomiting was present, will also be important when determining if gastrointestinal decontamination would be useful.

PHYSICAL EXAMINATION

Poisoned patients should undergo a thorough physical examination to determine if a toxidrome is present. Specific elements of the examination that allow for this determination include mental status; pupil size and reactivity; mucous membrane evaluation; cardiac and pulmonary examinations; abdominal examination for bowel sounds and presence of palpable bladder; skin examination for temperature, flushing, and perspiration; muscle tone; and neurologic examination for presences of tremors, clonus, and reflexes. See [Table 153-1](#) for toxidrome physical exam findings.

LABORATORY ANALYSIS

While determining if a poisoning has occurred or trying to determine the cause of an undifferentiated poisoning, some laboratory values can be helpful. Common laboratories to obtain include basic metabolic panel for electrolytes and to determine anion gap; ethanol, acetaminophen (paracetamol), and salicylate concentrations; liver function tests for transaminases; serum osmolality if toxic alcohol is suspected; blood gas for pH. These laboratories can aid in narrowing the differential diagnosis when a patient has overdosed or make the diagnosis in acetaminophen or salicylate poisoning.

TOXICOLOGY LABORATORY

Urine drug screens are usually obtained in poisoned patients; however, there is no standardized screen. Interpretation of urine drug screen results depends on the clinician's knowledge of which toxins have been screened and whether confirmatory testing (ideally performed by a different analytic method) will follow. The length of time required to

receive results varies among hospitals. Quantitative serum drug testing is done when quantitation of a toxin is clinically relevant, as is the case for acetaminophen, anticonvulsant agents, salicylates, digoxin, ethanol, ethylene glycol, methanol, iron, lithium, and theophylline. The clinician caring for the poisoned patient should discuss drug testing with the analytic toxicologist so that the results of testing can be appropriately interpreted. The clinical value of analytic toxicology testing depends on the clinician's ability to understand and interpret the results.

Once a poisoning has been identified, specific management options may be necessary, from gastrointestinal decontamination and enhancing elimination, to use of specific antidotes.

GASTROINTESTINAL DECONTAMINATION

The theory of gastric decontamination is that removal of toxins is done first from the stomach (where absorption is poor) before they move into the small intestine (where absorption is more rapid) so as to decrease the toxicity of the poisoning. Because of controversies regarding the role of gastrointestinal decontamination (GID), senior toxicologists from the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists (EAPCCT) agreed to collaborate on the production of Position Statements on GID treatments. These statements, published in 1997, are systematically developed guidelines founded on a criteria-based critical review of all relevant scientific literature.¹ All Position Statements were updated in 2004, with some getting new updates in 2014 ([Table 153-2](#)). GID included ipecac, gastric lavage, single-dose activated charcoal, cathartics, and whole-bowel irrigation.

Ipecac

Ipecac, prepared form of the *Cephaelis acuminata* or *Cephaelis ipecacuanha* plants, is no longer recommended for routine use in the management of poisoned patients as there is no evidence that it improves outcomes.² Vomiting within 30 minutes after administration is caused by local irritation of the gastric mucosa, and after 30 minutes vomiting is centrally induced.³ In experimental studies, the amount of marker removed by ipecac treatment was highly variable and diminished with time.²

Gastric Lavage

Gastric lavage should not be employed routinely in the management of poisoned patients as there is little clinical evidence of benefit and no controlled trials showing benefit.⁴ If performed due to a potentially life-threatening poison ingestion, an experienced provider should perform the lavage due to the complications that can occur.⁴ Gastric lavage involves a large-bore (36F-40F) orogastric tube passed into the stomach, after which small volumes (200-300 mL) of liquid are alternately administered and aspirated. Comatose patients and those with loss of their protective airway reflexes should have an endotracheal tube placed prior to this procedure. An oral airway prevents biting of the tube. The amount of stomach contents removed via this procedure is highly variable and decreases with time.⁵⁻⁷ The procedure can actually push stomach contents into the intestine.⁸ Contraindications

TABLE 153-1 Toxidrome Physical Exam Findings

| TOXIDROME PHYSICAL EXAMINATION | CHOLINERGIC | ANTICHOLINERGIC | SYMPATHO- MIMETIC | OPIOID | OPIOID WITH- DRAWAL | SEDATIVE- HYPNOTIC | SEDATIVE- HYPNOTIC WITHDRAWAL |
|--------------------------------------|--|-----------------------|----------------------|--|---------------------------|-----------------------|-------------------------------------|
| Mental status | Awake | Obtunded or delirious | Awake | Depressed | Awake | Depressed | Agitated, awake, delirious |
| Pupils | Pinpoint Reactive | Dilated Unreactive | Dilated Reactive | Pinpoint Reactive | Dilated Reactive | Normal | Dilated Reactive |
| Mucous membranes | Wet | Dry | Normal | Normal | Normal | Normal | Normal |
| Cardiovascular | ↓ Heart rate | ↑ Heart rate | ↑ Heart rate | Normal | Normal | Normal | ↑ Heart rate |
| Pulmonary | Wheeze, rhonchi ↑ Respiratory rate | Normal | Normal | ↓ Respiratory rate ↓ Depth of breathing | Normal | Normal | Normal |
| Bowel sounds | ↑ | ↓ | Normal | ↓ | ↑ | Normal | Normal |
| Bladder | Not palpable | Palpable | Normal | May be palpable | Normal | Normal | Normal |
| Skin temperature | ↓ | ↑ | ↑ | Normal | Normal | Normal | ↑ |
| Skin color | Normal | Flushed | Flushed | Normal or cyanotic | Normal | Normal | Normal |
| Perspiration | Present | Absent | Present | | | | Present |
| Antidote | Atropine Pralidoxime | Physostigmine | Benzo- diazepines | Naloxone | | | Benzodiazepines |

TABLE 153-2**Position Statement Summaries on
Gastrointestinal Decontamination
Treatments**

| MANAGEMENT | RECOMMENDATION |
|----------------------------------|---|
| GASTRIC DECONTAMINATION | |
| Ipecac | Syrup of ipecac should not be administered routinely for the management of poisoned patients. ² |
| Gastric lavage | Gastric lavage should not be employed routinely in the management of poisoned patients. ⁴ |
| Single-dose activated charcoal | Single-dose activated charcoal should not be administered routinely in the management of poisoned patients. ¹¹ |
| Cathartic | Administration of a cathartic alone has no role in the management of poisoned patients. Routine use of a cathartic in combination with activated charcoal is not endorsed. ¹⁸ |
| Whole-bowel irrigation | Whole-bowel irrigation should not be used routinely in the poisoned patient. ¹⁹ |
| ENHANCE ELIMINATION | |
| Multiple-dose activated charcoal | Multiple-dose activated charcoal should be considered if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. ²⁰ |
| Urinary alkalinization | Urinary alkalinization should be considered as first-line treatment in patients with moderately severe salicylate poisoning who do not meet the criteria for hemodialysis. Urinary alkalinization also should be considered for patients with severe poisoning due to 2,4-dichlorophenoxyacetic acid or mecoprop (MCP) poisoning. Urinary alkalinization is not recommended as first-line treatment for cases of phenobarbital poisoning, because multiple-dose activated charcoal is superior. ²¹ |

include loss of protective airway reflexes (unless the patient is endotracheally intubated), ingestion of a corrosive substance or a hydrocarbon, gastrointestinal pathology, and other medical conditions that could be worsened by the use of lavage. Complications of the procedure include aspiration, laryngospasm, hypoxia, hypercapnia, mechanical injury, and fluid and electrolyte imbalances in children.⁹

Single-Dose Activated Charcoal

Activated charcoal is made when coconut shells, peat, wood, or other materials undergo controlled pyrolysis and are subsequently activated by heating in steam or air at high temperatures. Activation creates multiple internal pores and the small particle size necessary for adsorption. The particles have a large surface area and are capable of adsorbing poisons with varying affinities. Although in vitro studies demonstrate adsorption of many drugs to activated charcoal, animal studies reveal variable reductions in the systemic uptake of marker substances.^{9,10} Volunteer and clinical studies have not demonstrated that single-dose administration of activated charcoal improves outcome. Therefore, single-dose activated charcoal should not be administered routinely in the management of poisoned patients. Administration of activated charcoal may be considered if a patient has ingested a potentially toxic amount of poison (that is known to be adsorbed to charcoal) not longer than 1 hour before treatment as its effectiveness decreases over time. There is no evidence that the administration of activated charcoal improves outcome.^{11,12}

Contraindications to the administration of activated charcoal include decreased level of consciousness and unprotected airway, ingestion of caustic substances or hydrocarbons, gastrointestinal pathology, and medical conditions that could be further compromised by the administration of activated charcoal. Complications include aspiration and direct administration of charcoal into the lung.¹¹

Because activated charcoal is an inert substance, it is thought that lung injury after aspiration of activated charcoal is caused by gastric

contents. Aspiration of gastric contents causes neutrophils to release neutrophil elastase, which increases pulmonary vascular permeability.¹³ In comparison, intratracheal administration of activated charcoal does not increase elastase in the bronchoalveolar fluid.¹⁴ Activated charcoal can activate alveolar macrophages, which are a potent source of oxygen radicals, proteases, and other inflammatory mediators. Charcoal also causes obstruction of small distal airways. Overdistention of alveolar segments in areas not occluded by charcoal leads to volutrauma in those areas, which increases microvascular permeability.¹⁵ Although case reports reveal long-term pulmonary pathology after aspiration or instillation of activated charcoal,^{16,17} the true incidence of chronic problems after charcoal aspiration is unknown.

Cathartics

Administration of a cathartic alone has no role in the management of poisoned patients. Routine use of a cathartic in combination with activated charcoal is not endorsed.¹⁸

Whole-Bowel Irrigation

Whole-bowel irrigation consists of administration through a nasogastric tube of an osmotically balanced, polyethylene glycol–based electrolyte solution to decontaminate the entire gastrointestinal tract by physically expelling intraluminal contents. As much as 1500 to 2000 mL/h can be administered to an “awake” adult patient. Negotiation to let the patient attempt to drink the solution only causes delay, because patients are unable to drink at a constant rate. Whole-bowel irrigation should not be used routinely in the poisoned patient. However, it can be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs and for drugs not likely to be adsorbed to activated charcoal (iron, lithium, potassium) and for the removal of illicit drug packets.¹⁹ Contraindications include bowel pathology, unprotected or compromised airway, hemodynamic instability, and intractable vomiting. Complications are nausea, vomiting, and abdominal cramps.¹⁹

Clinical Implications of Gastrointestinal Decontamination

There is no role for syrup of ipecac in the hospital setting. Gastric lavage may be considered for obtunded patients if it can be instituted within 1 hour after the ingestion. Single-dose activated charcoal should not be routinely administered to patients with mild to moderate degrees of poisoning. Whole-bowel irrigation should be considered for awake patients within the first hours after ingestion of a sustained-release preparation, ionic compounds (e.g., lithium), or packets of illicit drugs.

These guidelines refer to the routine management of poisoned patients. Cellular toxins require special consideration. The physician should always call the Poison Center (1-800-222-1222 in the United States) to discuss a patient with an ingestion and to seek further guidance on management.

ENHANCED ELIMINATION

Multiple-Dose Activated Charcoal

Multiple-dose activated charcoal is the repeated oral administration of activated charcoal to enhance drug elimination. If the drug concentration in the gut is lower than that in the blood, the drug will passively diffuse back into the gut. The concentration gradient, intestinal surface area, permeability, and blood flow determine the degree of passive diffusion. As the drug passes continuously into the gut, it is adsorbed onto the charcoal particles, a process called *gastrointestinal dialysis*. Multiple-dose activated charcoal also interrupts the enterohepatic and enterogastric circulation of drugs. Drugs with a prolonged elimination half-life, a small volume of distribution (less than 1 L/kg), and little

protein binding are the most amenable to this sort of management.²⁰ Multiple-dose activated charcoal should be considered if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. With all of these drugs, data confirm enhanced elimination, although no controlled studies have demonstrated clinical benefit.²⁰ Other ingestions may benefit from multiple-dose activated charcoal, but there are insufficient clinical data to routinely recommend its use.

The initial dose of charcoal is 50 to 100 g, and this treatment is followed every 1, 2, or 4 hours by a dose equivalent to 12.5 g/h. More frequent, smaller doses may prevent vomiting. Multiple-dose activated charcoal can be continued until the patient improves clinically. Contraindications include an unprotected airway, intestinal obstruction, and an anatomically abnormal gastrointestinal tract. Complications include bowel obstruction and vomiting with subsequent aspiration.²⁰

Urinary Alkalinization

Urinary alkalinization is the administration of intravenous (IV) sodium bicarbonate to produce urine with a pH \geq 7.5. The objective of treatment is pH manipulation, not forced diuresis. Hypokalemia is the most common complication. Alkalemia also can occur.²¹ Urinary alkalinization should be considered as first-line treatment in patients with moderately severe salicylate poisoning who do not meet the criteria for hemodialysis. Urinary alkalinization also should be considered for patients with severe poisoning due to 2,4-dichlorophenoxyacetic acid or mecoprop (MCP) poisoning. Urinary alkalinization is not recommended as first-line treatment for cases of phenobarbital poisoning, because multiple-dose activated charcoal is superior.²¹

SELECTED ANTIDOTES

Stabilization of the patient always should precede administration of antidote(s). The effects of the toxin can outlast the effects of the administered antidote. Patients receiving antidotes should be observed in a critical care setting.

Dextrose

Up to 8% of patients with altered mental status are hypoglycemic.²² Hypoglycemia can be a result of drug or toxin exposure, nutritional deprivation, or a medical complication (e.g., sepsis, hyperthermia). Glucose should be checked at the bedside for all patients with altered mental status.

Naloxone

Endogenous and exogenous opiates produce their effects by binding at one or more opiate receptors. Naloxone, nalmefene, and naltrexone are competitive opioid antagonists that bind at the mu (μ), kappa (κ), and delta (δ) receptors and competitively prevent the binding of endogenous and exogenous opiates at these receptors. The duration of action of naloxone is 15 to 90 minutes. Its clinical effects depend on the dose and route of naloxone administration as well as the dose and rate of elimination of the opiate agonist. Naloxone can be administered by IV, intramuscular, intratracheal, or sublingual routes. After IV administration, naloxone rapidly enters the central nervous system (CNS). In patients with opioid poisoning, respiration improves within 1 to 2 minutes, and consciousness is restored. The goal of naloxone administration is to restore respiratory function. Miosis, inhibition of baroreceptor reflexes, laryngospasm, and decreased gastrointestinal motility are also reversed.²³

Certain nonopiate drugs can cause release of endogenous opiates, contributing to CNS and respiratory depression as well as hypotension. Alternatively, nonopiate drugs and naloxone can compete for an unidentified nonopiate receptor that contributes to CNS depression and hypotension. Naloxone can reverse the toxicity caused by drugs that are not opioids, such as clonidine, angiotensin-converting enzyme

inhibitors, and sodium valproate. Naloxone should be administered to all patients with altered mental status or coma of unknown cause. Opioid-dependent patients should receive only small doses in an effort to restore respiratory function and prevent rapid withdrawal. If a patient is not opioid dependent, a reasonable starting dose is 2 mg, increasing to 10 mg (in increments) if there is no response. Large doses of naloxone may be necessary to reverse the effects of nonopioid drugs or of opioid drugs with high affinity for the δ and κ opiate receptors.

If respiratory depression returns, the initial dose of naloxone may have to be repeated or a constant infusion of naloxone initiated. The starting dose for a constant infusion of naloxone is hourly administration of about one-half to two-thirds of the bolus dose that reversed the opioid effects. If withdrawal is precipitated, it is short lived and not life-threatening. Complications of naloxone administration are very rare.²⁴

Flumazenil

Flumazenil competitively antagonizes the pharmacologic effects of drugs that act on the benzodiazepine receptor (e.g., all drugs in the benzodiazepine class). Receptor occupancy follows the law of mass action, and antagonism is dose dependent. The duration of action of flumazenil is variable and depends on the type of benzodiazepine ingested, relative doses of agonist and antagonist, presence of ongoing benzodiazepine absorption, and relative receptor binding affinities. Flumazenil also antagonizes the sedative effects of drugs other than benzodiazepines, such as zolpidem (Ambien), cannabis, ethanol, promethazine, chlorzoxazone, and carisoprodol. These drugs may have differing affinities for the γ -aminobutyric acid A (GABA_A) receptor, implying that the dose of flumazenil required to reverse the effects depends on the affinity of the specific drug for the receptor.²⁵

Flumazenil is safe and effective for reversing conscious sedation after short procedures such as endoscopy. This safety has been generalized to imply that flumazenil also is safe for patients with a multidrug overdose and that reversal of benzodiazepine-induced sedation prevents morbidity from procedures such as endotracheal intubation or computed tomography. However, many patients have experienced single or multiple seizures after flumazenil administration. Status epilepticus has been precipitated, leading to death. The data are insufficient to determine whether morbidity or mortality is increased as a result of flumazenil-precipitated seizures.^{26,27}

Flumazenil administration can precipitate seizures in patients with an overdose who have ingested both a benzodiazepine and a proconvulsant drug or just a proconvulsant drug. Flumazenil also can precipitate seizures in patients who have a history of seizures, chronic benzodiazepine ingestion, or head injury. Identification of patients at risk for seizures is difficult.²⁸ Before administering flumazenil to a patient with a benzodiazepine ingestion, it is reasonable to first obtain an electrocardiogram (to rule out exposure to proconvulsant tricyclic antidepressants) and a urine drug screen. Resedation occurs after 18 to 120 minutes in approximately half of patients awakened by flumazenil. Therefore, either continuous IV infusion or observation for a number of hours is required.²⁹

Administration of flumazenil to patients with an overdose should not be routine. It should be limited to the following situations: iatrogenic overdose with known patient history, obtundation in a toddler secondary to ingestion of benzodiazepine, and reversal of a paradoxical response to benzodiazepine.

Physostigmine

Physostigmine inhibits acetylcholinesterase, the enzyme responsible for the metabolism of acetylcholine (ACH). ACH is an endogenous neurotransmitter that mediates action by binding to muscarinic and nicotinic receptors. Accumulation of ACH stimulates cholinergic nerve endings. In the poisoned patient, physostigmine is most frequently administered to treat anticholinergic toxicity. Clinical signs of anticholinergic toxicity are recognized by the mnemonic, "Blind as a bat, Red as a beet, Hot as a hare, Dry as a bone, Mad as a hatter" (see

Table 153-1). Physostigmine administration should be considered if life-threatening clinical signs of anticholinergic peripheral effects (hypertension, tachycardia, and seizures) or central effects (painful psychosis) are present. However, it is extremely difficult to balance cholinergic and anticholinergic forces. Complications of cholinergic crises (caused by excessive doses of physostigmine) include hypertension, dysrhythmia, asystole, bronchorrhea, bronchoconstriction, seizures, and status epilepticus. Contraindications to physostigmine administration include bradycardia and conduction delays, reactive airway disease, peripheral vascular disease, intestinal or bladder obstruction, and treatment with a depolarizing neuromuscular blocking agent (e.g., succinylcholine). An acceptable dose of physostigmine is 1 to 2 mg IV over 10 minutes. This drug should be administered in the presence of a physician because of the potential for precipitation of life-threatening cholinergic effects.³⁰

HYPOTENSION IN THE POISONED PATIENT

Hypotension in the poisoned patient is most frequently caused by receptor blockade, drug-induced myocardial depression, or drug-induced vasodilatation. Clinicians reflexively initially treat hypotension by infusing IV fluids; however, unless the poisoned patient is hypovolemic, large volumes of fluid can predispose patients to the development of acute respiratory failure.

Catecholamines are the pressors of choice for treatment of hypotension in most intensive care unit (ICU) patients who are older, chronically ill, or acutely ill from an infectious process. The causative factors in sepsis-induced vasodilation and myocardial depression/ischemia are different from the factors that cause drug-induced vasodilation, myocardial depression, or ischemia. Treatment approaches must address the cause of the hypotension and not assume that all hypotensive patients should be treated in a similar manner.

Poisoned patients who are young and healthy respond to hypotension with an outpouring of endogenous catecholamines. Adrenergic receptors are sensitive in young patients. Administration of exogenous catecholamines is unlikely to be of much benefit, because catecholamine receptors are already maximally stimulated by endogenous catecholamines. Agents that must be considered for the treatment of hypotension in the poisoned patient are sodium bicarbonate (for a sodium channel-blocking agent), glucagon, and insulin/glucose.

Glucagon

The cardiovascular effects of glucagon are mediated by myocardial glucagon receptors that are catecholamine independent. Stimulation activates adenylate cyclase, leading to increased intracellular levels of the second messenger, cyclic adenosine monophosphate (cAMP). This cyclic nucleotide increases myocardial calcium uptake. Both the slope of phase zero of the action potential and the conduction velocity through the atrioventricular node are increased. Glucagon increases heart rate and stroke volume, thereby increasing cardiac output. After IV administration, augmented inotropy is seen within 1 to 3 minutes, with a peak effect in 5 to 7 minutes.³¹

Glucagon should be considered early in the treatment of hypotensive poisoned patients, especially those patients with beta-adrenergic antagonist toxicity. Treatment regimens vary. An acceptable regimen is 10 mg of glucagon given over 10 minutes (rapid administration causes vomiting), followed by 1 to 3 mg/h. If the patient wretches, the hourly dose of glucagon should be decreased. Elderly patients may be more sensitive to the emetic effects of the drug.

Insulin and Glucose

Insulin improves contractility in anoxic rat hearts and improves cardiac index after cardiopulmonary bypass surgery. During drug-induced shock, insulin shifts myocardial fatty acid oxidation to carbohydrate oxidation, which increases contractility, left ventricular

pressure, and rate of change of developed pressure. Enhanced fatty acid oxidation, such as occurs after epinephrine administration, transiently increases contractility at the expense of increased myocardial oxygen consumption.³²

Insulin and glucose treatment in poisoned patients is commonly referred to as high-dose insulin-euglycemia therapy (HIET). Insulin can be bolused at 0.5 to 1 U/kg, followed by an infusion at 0.5 to 1 U/kg/h.³³ The infusion can be titrated up to improve inotropy and contractility and to increase blood pressure. Case reports have had safe outcomes with large bolus and infusion doses.³³ Concurrent administration of glucose is used to maintain euglycemia. Hourly serum glucose checks are mandatory because hypoglycemia occurs frequently. Potassium should also be monitored due to intracellular shift.

CARDIAC ARRHYTHMIAS

ICU treatment regimens assume that a diseased heart is the cause of most cardiac arrhythmias. This assumption is invalid in poisoned patients. Treatment of the arrhythmia must take into consideration the pharmacology of the toxin causing the arrhythmia.

ACUTE RENAL FAILURE

In poisoned patients, acute renal failure (ARF) is most frequently the result of a decrease in extracellular fluid volume and renal hypoperfusion caused by drug- or chemical-induced vasodilation, drug-induced myocardial depression, or rhabdomyolysis. Attempts to prevent ARF are important because there is no specific therapy once ARF is established. Studies evaluating the efficacy of low-dose dopamine (0.5–3.0 mg/kg/min) in preventing ARF have not demonstrated any benefit, but the patient populations in these studies consisted of critically ill patients with established ARF or at high risk for developing ARF.³⁴ The efficacy of administration of low-dose dopamine after periods of hypotension in poisoned patients who typically are younger and without chronic disease has not been evaluated. When dopamine is administered to normal human subjects, there is a dose-dependent increase in renal blood flow, sodium excretion, and glomerular filtration rate.³⁵ Low-dose dopamine also limits adenosine triphosphate (ATP) utilization and oxygen requirements in nephron segments at risk for ischemia.³⁶ Although there are no studies regarding the efficacy of low-dose dopamine in cases of drug-induced hypotension, one may consider administration in previously healthy poisoned patients who have adequate vascular volume and remain oliguric or anuric despite maximal diuretic therapy.

SEIZURES

Blood pH can be as low as 7.17 at 30 minutes and 7.20 at 60 minutes after resolution of a 30- to 60-second seizure.³⁷ Acidosis decreases cardiac output, oxygen extraction, and left ventricular end-diastolic pressure and impairs myocardial contractility. If a patient has ingested a cardiotoxic drug (e.g., a tricyclic antidepressant) that causes significant myocardial depression, the consequences of acidosis can increase the toxicity of the drug. Ictal increases in plasma epinephrine levels can add to the potential risk for cardiac arrhythmias. Additionally,

airway reflexes are inhibited postictally, which adds to the potential for aspiration.³⁸

Whether seizures increase morbidity and mortality in poisoned patients is difficult to ascertain. Deaths of poisoned patients who sustain seizures are usually attributed to the toxicity of the drug. Because of the number of variables, it is impossible to know whether the risk for mortality is influenced by the presence of convulsions. Accordingly, the physician should take an aggressive approach toward terminating seizures in poisoned patients. Benzodiazepines are the drugs of choice to quickly terminate seizures because they are lipophilic and rapidly enter the CNS.

MECHANICAL VENTILATION AND EXTUBATION

Endotracheal intubation is commonly indicated for the management of poisoned patients on the basis of respiratory depression or impaired protective airway reflexes or both. As the drug is metabolized, its effects abate, and the patient's sensorium improves. The patient may become alert slowly or very suddenly. The patient should be extubated if ability to protect the airway is evident and ventilation is adequate for 15 to 60 minutes with minimal respiratory support (e.g., 5-cm H₂O positive end-expiratory pressure and 5-cm H₂O pressure support). Unnecessary or excessive administration of sedatives or anxiolytics in an attempt to make the patient more comfortable can delay weaning from mechanical ventilation and extubation and increase the risk for complications.

KEY POINTS

1. The theory of gastric decontamination is that removal of toxins from the stomach (where absorption is poor) before they move into the small intestine (where absorption is more rapid) decreases the toxicity of the poisoning.
2. Stabilization of the patient should always precede administration of antidote(s). The effects of the toxin can outlast the effects of the administered antidote. Patients receiving antidotes should be observed in a critical care setting.
3. Treating hypotensive, poisoned patients with large volumes of intravenous fluids can increase the risk for acute respiratory failure.
4. Efforts to prevent development of acute renal failure (ARF) in the poisoned patient are important because there is no specific therapy once ARF is established.
5. An aggressive approach should be taken toward terminating seizures in the poisoned patient. Benzodiazepines are the drugs of choice to quickly terminate seizures, because they are lipophilic and rapidly enter the central nervous system (CNS).
6. The clinical value of analytic toxicology testing depends on the clinician's ability to understand and interpret the results.

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remaining 11 patients, a severe complication occurred in 1. There was no difference in outcome measures between those patients who received flumazenil and those who did not.

Merigian K, Glaho K. Single-dose oral activated charcoal in the treatment of the self-poisoned patient: a prospective, randomized controlled trial. *Am J Ther* 2002;9:301–308.

A total of 1479 patients with overdose were randomly assigned to receive or not receive activated charcoal. Gastric emptying was not performed. There were no differences between the two groups in length of intubation time, length of hospital stay, or complication rate.

Orringer DE, Eustace JC, Wunsch CD, Gardner LB. Natural history of lactic acidosis after grand mal seizures. *N Engl J Med* 1977;15:796–799.

This classic article demonstrated that significant acidosis can occur for up to 1 hour after a single 30- to 60-second seizure.

Pond SM, Lewis-Driver DJ, Williams GM, et al. Gastric emptying in acute overdose: a prospective randomized controlled trial. *Med J Aust* 1995;163:345–349.

This was a randomized study of gastric emptying versus no gastric emptying. A total of 342 patients underwent lavage or no gastric lavage before administration of charcoal. There were no significant differences between the two groups in incidence of clinical deterioration or improvement during the first 6 hours. However, only 55 patients presented within 1 hour, of whom just 14 were not lavaged.

Sauvadet A, Rohn T, Pecker F, et al. Arachidonic acid drives mini-glucagon action in cardiac cells. *J Biol Chem* 1997;272:12437–12445.

Glucagon triggers release of arachidonic acid (AA) and is then processed by cardiac cells into a terminal fragment mini-glucagon, which is an essential component of the contractile positive inotropic effect. AA and cAMP are both second messengers.

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Balock's fundamental work on shock showed that injury precipitated obligatory local and regional fluid losses, the effects of which could be ameliorated by vigorous restoration of intravascular volume. This concept became a cornerstone to the understanding of the pathophysiology of shock and provided the fundamental rationale for IV therapy for hemorrhage and hypovolemia.¹

The introduction of blood transfusions as the result of contributions by surgeons during World War I and World War II dramatically changed outcomes in cases of severe hemorrhage. During the Korean War, fluid overload became a common and lethal side effect of resuscitation, owing to a lack of knowledge about how infusates disperse and are eliminated during trauma. Between the Korean War and the Vietnam War, Shires and colleagues described the shifts of fluid and electrolytes into cells after severe hemorrhagic shock. As a consequence, treatment of patients with shock was altered during the Vietnam War, leading to better outcomes and a lower incidence of acute renal failure. It has taken two more wars since 911 to return to the basic concept that patients who lose whole blood should be given whole blood or at least the right ratio of blood's main components, plasma, platelets, and red cells as early as possible.^{2,3}

Mechanisms of injury and severity of blood loss as well as prehospital interventions vary widely among trauma centers worldwide. The number of preventable deaths due to hemorrhage are still significant. Therefore, prompt and definitive control of hemorrhage and innovative resuscitative strategies continue to be the cornerstone of treatment.⁴

RESUSCITATIVE STRATEGIES IN HEMORRHAGIC SHOCK

The mainstays of therapy in hemorrhagic shock are bleeding control, tissue oxygenation, coagulation support, and maintenance of normothermia.⁵ Fluid resuscitation strategies in prehospital and hospital settings are important.

Vascular Access for Patients with Severe Hemorrhage

In the trauma patient presenting with multiple serious injuries and hemorrhagic shock, vascular access is necessary. Venous access should never be initiated on an injured limb. When thoracoabdominal injury is suspected, it is prudent to obtain infradiaphragmatic and supradiaphragmatic access.

Advanced trauma life support (ATLS) guidelines recommend rapid placement of two large-bore (16 gauge or larger) IV catheters. The most suitable veins are at the wrist, on the dorsum of the hand, at the antecubital fossa in the arm, and on the saphenous in the leg. If peripheral IV catheters are unable to be placed, catheters can be placed in the central veins. The femoral vein is the most frequent central vein cannulated. The subclavian vein is another alternative and can be placed safely in experienced hands. The internal jugular vein is rarely used in trauma patients because of the possibility of cervical spine injuries and the need for cervical immobilization with a collar. Patients with absent pulses may need to undergo cutdown to cannulate the femoral vein under direct vision to obtain IV access. Currently, prehospital personnel are well trained to use intraosseous (IO) needles. It is a technique best applied under difficult circumstances such as in a

moving environment, in the helicopter, or on poor roads. IO needles are now standard practice for trauma care in many prehospital settings. This technique is taught easily, and clinical competencies are acquired rapidly. IO lines allow for the use of medication and blood transfusion if necessary in desperate cases.^{6,7} IO access is increasingly being used in the emergency department when peripheral lines cannot be obtained and hypovolemia makes central vein cannulation difficult.

Resuscitative Fluids and Interventions

Prehospital Fluid Resuscitation

There are several recent studies currently undertaken to evaluate the effectiveness of prehospital use of plasma, packed red blood cells (PRBC), and whole blood. The use of PRBC in the prehospital setting was independently associated with a lower risk of 24-hour mortality, 30-day mortality, and trauma-induced coagulopathy in severely injured patients with blunt trauma. Early resuscitation incorporating PRBC transfusion initiated before arrival of the patient at the trauma center without a delay in transport was associated with improved outcomes.⁸ Two additional studies are also being completed to test the efficacy of administering thawed plasma in the helicopter and the role of using prehospital administration of tranexamic acid (TXA).^{9,10}

The Prehospital Air Medical Plasma (PAMPer) trial is aimed at determining the effect of prehospital plasma transfusion during air medical transport on 30-day mortality in patients at risk for traumatic hemorrhage. This study is a multicenter, cluster-randomized clinical trial. The trial will enroll trauma patients with profound hypotension (SBP \leq 70 mm Hg) or hypotension (SBP 71-90 mm Hg) and tachycardia (HR \geq 108 bpm) from six level I trauma center air medical transport programs. This trial is one of three awards funded by the Department of Defense (DoD) to investigate prehospital plasma transfusion in traumatic shock. The Control of Major Bleeding after Trauma (COMBAT) trial will assess the effect of ground ambulance plasma administration, looking at the effect on trauma-induced coagulopathy (TIC), transfusion requirements, metabolic recovery, organ failure, and mortality.¹¹ The Prehospital Use of Plasma for Traumatic Hemorrhage (PUPTH) trial will also examine the impact of using thawed prehospital plasma on mortality and coagulopathy.¹²

Tranexamic Acid for Trauma Patients

A recently published landmark trial that studied the safety and efficacy of tranexamic acid (TXA) deserves special attention. This is a clinical randomization of the use of an antifibrinolytic agent in significant hemorrhage (CRASH-2) in trauma resuscitation. The results of this trial showed that use of TXA resulted in a reduction in all-cause mortality and death as a result of bleeding. This study was performed in a rigorous manner that reflected real-world clinical practice across a wide variety of settings, including austere environments. CRASH-2 provides level I evidence for the use of TXA to reduce mortality in trauma patients. The inclusion criteria for this study were clinical, not laboratory based, and very broad. As a result, the population truly at risk for hemorrhagic death was much smaller than the overall study population, as further evidenced by the fact that slightly fewer than 50% of patients in each arm underwent surgical interventions. The fact that a significant reduction in death as a result of hemorrhage was observed is therefore even more remarkable and suggests an important

treatment effect in critically injured patients with a risk of bleeding.¹³ Further testing is warranted before this should become standard of care.

Trauma-Induced Coagulopathy, Coagulation Factors, and Platelets

Severe bleeding, surgery, and massive transfusion interact synergistically to lead to the lethal triad: hypothermia, acidosis, and coagulopathy. Coagulopathy promotes bleeding and hypotension, which leads to hypothermia and acidosis. Hypothermia and acidosis impair thrombin generation and decrease fibrinogen levels.¹⁴

Failure of coagulation in trauma is multifactorial and is characterized by the combined presence of coagulation abnormalities resembling disseminated intravascular coagulation (DIC), excessive fibrinolysis (likely caused by release of tissue plasminogen activator [TPA] from damaged tissues), dilutional coagulopathy due to excessive fluid treatment, and massive transfusion syndrome resulting in dilution of coagulation factors and platelets.¹⁵

Until recently, coagulopathy associated with trauma was thought to be a secondary phenomenon resulting mainly from loss of coagulation factors during hemorrhage and dilution from resuscitation fluids. However, there is strong evidence showing that there is an early almost immediate trauma-induced coagulopathy (TIC) that occurs within minutes of injury and is associated with a fourfold increase in mortality.¹⁶ This is a multifactorial phenomenon partly due to an endogenous coagulopathy that occurs as a result of tissue damage in severe shock. The more we learn about TIC, the more we realize that it is a complex multifactorial event. The severity of trauma correlates with the degree of the coagulopathy, however; standard coagulation tests fail to adequately describe the complex processes occurring in TIC and thus have limited value. There is a lack of agreement about the clinical definition, and currently there are no operational scales that could aid in a clinical classification that covers a rational spectrum of bleeding abnormalities after injury.¹⁷ Many alterations have been described, including activation of protein C as well as autoheparinization following glycocalyx disruption as important instigators of TIC, but fibrinogen depletion and platelet dysfunction must also be taken into account to fully treat the hemorrhagic process. In addition to all these challenges, the event *per se* is very dynamic and can occur in a short time, thus precluding the use of time-consuming and cumbersome coagulation tests that are usually being measured at the same time that TIC is being aggressively treated.

The role that platelets play in TIC is difficult to elucidate, in part due to the fact that classic plasma-based clotting test do not assess platelet function, and light transmittance aggregometry, considered a gold standard for platelet function, is both labor intensive and time consuming. Extensive ADP metabolism secondary to endothelial cell injury in combination with “platelet exhaustion” due to overwhelming immediate activation may be all factors that generate platelet dysfunction in early trauma. A prolonged refractory state could explain why platelet counts often remain in a normal range despite being dysfunctional.

These difficulties have led to a renewed interest in the use of thromboelastography (TEG)—a point of care assessment of clot generation, strength, and breakdown. This procedure has the potential to provide a rapid assessment of the whole clotting process, but it requires further validation in the acute setting. In the absence of a validated diagnostic test at the point of care, management is therefore blind to the status of the coagulation system and relies on clinical judgment and empiric therapy.¹⁸

A recent prospective observational multicenter study using TEG and platelet mapping in 51 trauma patients showed that platelets were inhibited in 86.1% of trauma patients, compared to 4.2% in healthy volunteers using as an activator.¹⁹ Patients with a high base deficit also had worse platelet inhibition.

The clinical importance of platelet inhibition after trauma is significant. Close to 45.5% of critically injured patients had “platelet hypo-

function” upon admission, and 91.1% experienced dysfunction during their ICU stay. Twenty-four-hour and in-hospital mortality was significantly higher: up to tenfold increase in 24-h mortality with platelet hypofunction.²⁰

Despite our lack of complete understanding of the TIC phenomenon it is clear that a systematic approach to resuscitation must include early management, rapid scene-to-hospital transport, swift hemorrhage control (including surgical intervention, interventional radiology, or innovative balloon occlusive techniques such as resuscitative endovascular balloon occlusion of the aorta (REBOA²¹), and the avoidance of excessive crystalloid resuscitation. Existing pharmaceutical treatments such as TXA may become a standard of care and if used should be administered very early after trauma. Trauma centers and hospitals caring for injured patients need to develop and institute standard protocols for diagnosing and treating this early manifestation of trauma.

TIC and the need to administer a massive transfusion protocol are two concepts inexorably linked to the management of severe hemorrhage. Predictive scores to determine the need for massive transfusion have been recently proposed. The ABC (Assessment of Blood Consumption) score accounts for four dichotomous components that are easily obtained at the bedside for early evaluation of injured patients. The presence of any one component contributes one point to the total score for a possible range of scores from 0 to 4. Parameters include penetrating mechanism (0 = no, 1 = yes); emergency department systolic blood pressure of 90 mm Hg or less (0 = no, 1 = yes); emergency department heart rate of 120 beats/min or greater (0 = no, 1 = yes); and positive abdominal sonogram (0 = no, 1 = yes).

The ABC score was validated in a multicenter study and yielded a predictive value consistent across several trauma centers examined. The negative predictive value was 97%, and less than 5% of patients who will require massive transfusion will be missed using the ABC score.^{22,23}

Most recently, a quantitative scoring system for TIC and a clinical outcomes definition for postinjury mortality due to coagulopathy have been proposed. This classification offers standardized clinical scoring and death criteria in patients with TIC and should be useful for research in TIC, ultimately leading to an improvement in patient outcome.¹⁷

Red Cells, Platelets, and Plasma—the Ideal Ratio and the Prospects of Whole Blood Resuscitation

Only after the implementation of radical changes in blood banking practice in the early 70s that imposed the usage of separate components of blood in transfusion medicine, the use of whole blood was historically the gold standard for treating hemorrhagic shock during military conflicts.²⁴ After the recent experience in the Middle East, the main principles of current resuscitation strategies has now shifted toward preventing or reversing the effects of coagulopathy by means of using a balanced ratio of whole blood's main components as early as possible (1:1:1—plasma: packed red blood cells: platelets).²

This combination approach is referred to as *whole blood-like* resuscitation despite being suboptimal from a compositional when compared to whole blood.^{25,26} The use of whole blood continues to increase across trauma centers in the United States and is thought to provide the bleeding patient the identical components he or she is losing while maximizing the resuscitative and hemostatic effects.^{27,28}

Additional benefits may include minimization of donor exposure, as the requirements for whole blood storage and resuscitation would lower overall age of the transfused products as compared to balanced component resuscitation.

While the use of whole blood is researched and eventually generalized, current available options are type O-negative, type-specific, typed and screened, or typed and cross-matched packed red blood cells. The initial choice depends on the degree of hemodynamic instability. Type O-negative red cells have no major antigens and can be used safely for patients with any blood type. Unfortunately, only 8% of the population has O-negative blood, and blood bank reserves for O-negative blood

are low. O-positive blood can be used in male patients but may be a problem in female Rh-negative patients.

Early identification of severe injuries with the likelihood of hemorrhage should suffice for the trauma team leader to alert the blood bank. Hematocrit levels should not guide the decision for transfusion in acute hemorrhage. Protocols for massive transfusion should be established, and the blood bank should automatically begin preparation of fresh frozen plasma and platelet packs if massive bleeding is anticipated.

If 50% to 75% of the patient's blood volume has been replaced with type O blood, one should continue to administer type O red cells. Otherwise, the risk of a major cross-match reaction increases, since the patient may have received enough anti-A or anti-B antibodies to precipitate hemolysis if A, B, or AB units are subsequently given. Obtaining type-specific red cells requires 5 to 10 minutes in most institutions.

When blood is typed and screened, the patient's blood group is identified, and the serum is screened for major blood group antibodies. A full cross-match generally requires about 45 minutes and involves mixing donor cells with recipient serum to rule out antigen/antibody reactions.

Massive transfusion protocols have been developed and utilized in major trauma centers. Activating the massive transfusion protocol gives a fixed ratio of red cells to plasma to platelets. High plasma- and platelet-to-red cell ratio has been shown to increase survival in retrospective studies.²⁹ Military data showed an increase in survival with a red cell-to-plasma ratio approaching 1:1.³⁰ Civilian trauma centers are increasingly adopting a 1:1:1 ratio for massive transfusion protocols. The Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study demonstrated that clinicians were transfusing patients with a blood product ratio of 1:1:1 or 1:1:2 and that early transfusion of plasma (within minutes of arrival to a trauma center) was associated with improved 6-hour survival after admission.^{31,32}

In 2015, the first multicenter, randomized clinical trial was completed in order to address the effectiveness and safety of a 1:1:1 transfusion ratio compared with a 1:1:2 transfusion ratio in patients with trauma who were predicted to receive a massive transfusion. The Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial showed that in patients with severe trauma and major bleeding,

early administration of plasma, platelets, and RBCs in a 1:1:1 ratio compared with a 1:1:2 ratio did not result in significant differences in mortality at 24 hours or at 30 days. However, more patients in the 1:1:1 group achieved hemostasis, and fewer experienced death due to exsanguination by 24 hours. As expected, though there was an increased use of plasma and platelets transfused in the 1:1:1 group, no other safety differences were identified between the two groups.³³

Putting It All Together: A Comprehensive Approach for Management of Shock and Severe Bleeding

Resuscitation management should start at the very moment that the patient is found at the scene. The use of tourniquets must be liberal and competencies for proper application by EMT personnel should be part of all EMS systems. Hemostatic dressings and hypotensive resuscitation must also be available in the prehospital setting.

If possible, a balanced blood product transfusion should be initiated early; ideally providing thawed plasma and PRBCs. Once the patient arrives to the trauma center, TEG, hemoglobin, and a venous blood gas are immediately obtained.

Patients in shock or hypotensive or with an ABC score >2 should be signaled as candidates for a massive transfusion. Initially they must receive blood components in a 1:1:1 ratio. Need for surgery or angio-embolization is determined soon and implemented immediately. At this point, it is critical to assess the effectiveness of the resuscitative interventions, and therefore, conversion to a goal-driven management of TIC is warranted in order to specifically manage the impaired coagulation depicted by rapid TEG. It is imperative to reduce to a minimum the use of crystalloids and artificial colloids. TXA should be infused early in those patients with TEG evidence of fibrinolysis.

Damage control and staged procedures must be carefully planned, and multidisciplinary communication with the ICU team and other consultants is key in maintaining the proper order of priorities and in the implementation of ancillary care. Measured and titrated fluid administration will aid in securing definitive facial closure of patients with open abdomen undergoing damage control. It is fundamental to exercise an individual assessment of the patient and his or her response to therapy and adjust all resuscitative options throughout this critical early stage.

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Mediastinitis includes a variety of thoracic infections that occur in the space between the sternum and the spine, above the diaphragm, and below the thoracic outlet. The diagnosis, treatment, and prognosis of mediastinitis are determined by their location and etiology. The mediastinum can be divided anatomically into superior and inferior compartments at the sternal angle, the inferior with further division into three clinically relevant compartments: anterior (between the posterior sternum and the anterior pericardium), middle (the intrapericardial contents), and posterior (bounded anteriorly by the posterior pericardium and posteriorly by the spine). The pleural cavities are the lateral boundaries for each of these mediastinal spaces (Fig. 155-1).

With respect to etiology, mediastinitis can be either primary, arising without prior intervention, or secondary, occurring post intervention. Clinically, the anatomic anterior and middle compartments can be considered together, as mediastinitis occurs most commonly in those combined spaces secondarily as a postoperative complication of cardiac operations.

Esophageal pathology accounts for the overwhelming majority of the mediastinal infections of the posterior compartment.

Other more unusual forms of mediastinal infections or inflammation include those that migrate into the mediastinum from adjacent fascially contiguous spaces and those that are more indolent than acute and are characterized by chronic inflammation and fibrosis.

Accordingly, this presentation of the subject will follow these anatomic and etiologic distinctions: acute anterior mediastinitis, acute posterior mediastinitis, and migratory and chronic mediastinal inflammation.

■ ACUTE ANTERIOR MEDIASTINITIS

The most common form of acute anterior mediastinitis is that occurring after sternotomy for a cardiac operation. Rarely, it may occur after traumatic sternal fracture¹ or following descending cervical infections.

The term *mediastinitis* after cardiac operations should strictly refer to an infection involving the space deep to the sternum. Other forms of postoperative infection can be identified as superficial sternal wound infection (SWI; above the fascia without sternal involvement) and sternal osteomyelitis (without deeper infection).

As no impervious anatomic barrier exists between the posterior cortex of the sternum and the space behind it, any infection posterior to the sternum is considered an infection of the anterior mediastinum.

Clinically, especially in more obese patients, it is sometimes unclear as to whether one is initially dealing with a superficial problem (anterior to the fascia), a sterile dehiscence, or a deeper infection. More than a small amount of drainage, any sternal instability, or evidence of separation suggest at least a sterile dehiscence and the need for re-exploration, deep cultures, and appropriate reclosure.

Incidence, Pathology, and Prevention

Over the past 2 decades, there may be a trend toward lower reported rates of mediastinitis after sternotomy (more large series with <1%

incidence); however, the reported range remains wide, from 0.24% to 4% of cardiac operations, due in part to the various definitions of mediastinitis itself.^{2,3,4} Increasingly, as the postoperative length of stay decreases, mediastinal infections are diagnosed days or even months after hospital discharge, with the median time to diagnosis variously reported at around 10 days after surgery.

A number of host factors that increase the risk of post-cardiac surgery mediastinitis have been identified. Among these are diabetes, increased body mass index, older age, renal failure, prolonged preoperative hospitalization, immunosuppression, chronic obstructive pulmonary disease, cigarette smoking, reoperation, preoperative atrial fibrillation, and elevated C-reactive protein.^{3,5-7}

An increased incidence of deep SWI (DSWI) or dehiscence has been associated with intraoperative factors such as bilateral internal mammary use (5% versus 1% in most series), off-midline sternotomy, prolonged operative time, and the use of an intraaortic balloon pump.⁷

In multiple studies, bone healing was significantly impaired by using bone wax for sternal hemostasis when compared with water-soluble polymer wax, suggesting the use of the latter as a useful alternative, since bone healing immediately postoperatively is the most critical time frame for the prevention of sternal nonunion and infection.⁸

In high-risk patients, sternal closure with rigid plate fixation showed a significant decrease in the incidence of postoperative mediastinitis when compared to a similar population of patients whose sterna were closed with wire, as reported by Songa et al.⁹

Furthermore, several studies have shown that the use of cyanoacrylate glue decreases the infection rates of deep surgical and superficial surgical sites in patients who have sternal detachment or are at high risk for developing infection.¹⁰

Postoperatively, increased glucose levels (>200 mg/dL),¹¹ re-exploration, and prolonged ventilator use are associated with a higher incidence of deep sternal infection.⁷ Glucose values as low as ≥130 mg/dL have been linked to such infection in children.¹²

Avoiding sternotomy entirely, as can be done with less chest wall-invasive approaches, appears to dramatically reduce or eliminate the risk of mediastinal infection after cardiac operations.⁷

Postoperative tracheostomy is required in some poststernotomy patients, and many of these have some of the risk factors that are also predictive of DSWI. Early tracheostomy for patients with prolonged ventilator dependence, once deferred 2 or more weeks after sternotomy for fear of contaminating the anterior mediastinal space, has not been shown to be associated with an increased incidence of mediastinitis (mean of 5.6 days post cardiac operation).¹³ Tracheostomy per se is not a risk factor for DSWI, whereas it serves as a surrogate for respiratory failure.^{14,15} Specifically, the technique of percutaneous tracheostomy has not been associated with a subsequent increase in mediastinal infection.¹⁶

Staphylococcal species are the most common organisms seen in patients with poststernotomy deep wound infection, and these are increasingly methicillin resistant.¹⁷ Coagulase-negative resistant organisms are more common in patients who have prolonged hospitalizations.¹⁸ Gram-negative organisms may be cultured, particularly from diabetics, in patients with gram-negative pneumonia prior to operation or in those who require re-exploration.¹⁹

Given the most common organisms causing these infections, a second-generation cephalosporin is still the most accepted preoperative prophylaxis. Vancomycin is substituted in patients with penicillin allergy, and the addition of preoperative gram-negative coverage (e.g., gentamicin) is appropriate in such cases, given vancomycin's poor

*This chapter is a revision and update of that included in the previous edition of this book written by Robert G. Johnson.

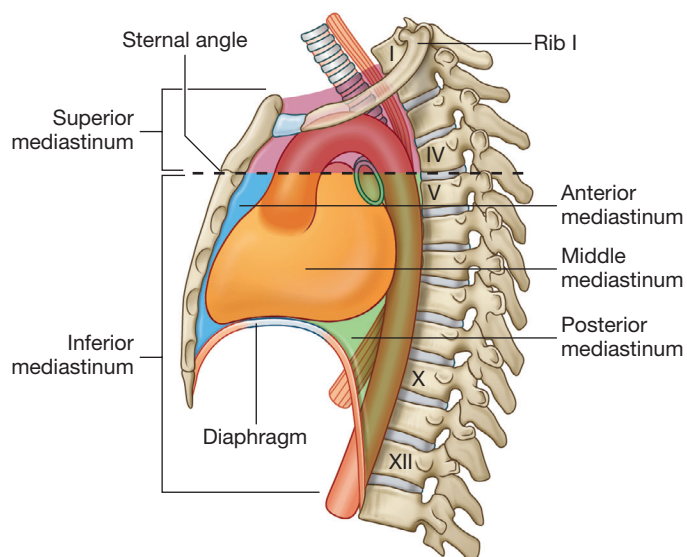


FIGURE 155-1 ■ With respect to etiology, mediastinitis may be either primary, arising without prior intervention, or secondary, occurring post intervention. Clinically, the anatomic anterior and middle compartments can be considered together, as mediastinitis occurs most commonly in these combined spaces secondarily as a postoperative complication of cardiac operations. Esophageal pathology accounts for the overwhelming majority of mediastinal infections of the posterior compartment. (From Drake RL, Vogl AW, Mitchell AW: *Gray's Anatomy for Students*, 2/e. Philadelphia: Churchill Livingstone, 2009. Fig 3-5.)

coverage of such organisms.²⁰ Topical vancomycin has been shown to be effective in decreasing the incidence of sternal infections, and it is used routinely in some practices.²¹ Evidence-based guidelines from the Society of Thoracic Surgeons recommends gram-positive prophylaxis for no more than 48 hours, in addition to preoperative nasal mupirocin.^{17,20}

Diagnosis

Patients with mediastinitis after sternotomy generally have clinical signs of wound drainage and sternal instability, but neither may be present initially. Fever and leukocytosis are common. Some patients manifest signs of sepsis, with mental status changes and hemodynamic compromise. Mediastinitis can very rarely appear as early as 1 day after operation or as remotely as months after an operation.

Rarely, those patients who have an indolent course presenting many months after operation may have isolated deep involvement, tracking down to the aorta and/or involving some artificial material such as a plectet or a braided suture.

The variable diagnostic accuracy of imaging techniques for the diagnosis of mediastinitis permits them to be supportive²² but rarely, if ever, definitive. This is especially true during the early time frame (<30 days), when the vast majority of patients present. During this time, fluid collections and mediastinal soft-tissue changes are common, if not universal, with both being nonspecific for infection.²³

Technetium-99m leukocyte imaging can identify patients who have DSWI and require aggressive surgical débridement.²⁴ In one study, the patterns of intense uptake at 4 and 20 hours or increasing uptake between 4 and 20 hours were 100% sensitive and 89% specific for the detection of DSWI. The scan is useful in patients with suspected DSWI when clinical examination fails to confirm a diagnosis or when deep sternal aspirates of the SWI are equivocal. Leukocyte imaging is not useful for detecting superficial SWIs.²⁵

A profile of abnormal cytokine levels has been characterized,²⁶ with the terminal SC5b-9 complement complex concentration being substantially higher in patients with mediastinitis and having no overlap with the values in nonmediastinitis, post-cardiac surgery controls. In difficult-to-diagnose cases, blind retrosternal, subxiphoid needle aspiration and culture have been variably employed, and aspiration with ultrasound guidance has been reported after cardiac transplantation.²⁷ A recent small series suggested diagnostic success in patients without classic signs of infection by anteriorly inserting a 22-gauge needle percutaneously and aspirating between the recently closed sternal edges. Cultures and Gram stains were used to establish the presence of infection, with a high degree of specificity and sensitivity.²⁸

Treatment

The different technical approaches to treat anterior mediastinitis are related to the interval since the antecedent operation, the depth extent of the infection, and the acuity of the patient.²⁹

The classification by Pairolero and Arnold,³⁰ which is based on clinical rather than microbiologic features, can be used to practically approach the different types of clinical entities. There are three major types of sternomediastinitis in this system.

Type I sternomediastinitis manifests with serosanguineous drainage within a few days after sternotomy. Pus, osteomyelitis, and chondritis are notably absent. Mediastinal tissues are still soft and pliable. Bacterial cultures are initially negative or yield staphylococci. In such cases, the sternotomy is reopened, all blind pockets are eliminated, and the mediastinum is irrigated. This type of infection is best managed by the reinsertion of drainage tubes and reclosure of the sternum with either a variation of the Robicsek³¹ weave or a commercially available plate fixation device. Aggressive intravenous and topical antibiotic treatment should be used in these cases.

Type II sternomediastinitis is a fulminant process that occurs 1 to 3 weeks after surgery. In addition to reopening, drainage, and irrigation, these patients also require débridement of the necrotic soft tissue, bone, and cartilage. This may be performed initially, when the wound is reopened but may be delayed if the patient is septic or if his or her general condition is too critical to allow a major intervention. An effort should be made to remove all foreign materials such as felt pledgets and pacing wires. Exposed suture lines can be reinforced with autologous tissue, such as fascia lata, or covered with muscle flaps. The wound is then kept open and treated with daily dressing.

Type III sternomediastinitis occurs 1 month to 1 year after surgery. The patient typically presents with chronic draining sinus tracts that lead to the infected sternum, cartilages, or retained foreign bodies. Repair requires wide exposure, extensive débridement, often total sternectomy, and flap coverage using autologous tissues.

Diluted antibiotic, povidone iodine, and aqueous acid solutions have been reported as irrigation protocols.^{29,32} The duration of irrigation has varied from 3 days to 1 week, while systemic antibiotics are continued, as would be the case for other adult bone infections.³³

The cultures obtained at operation dictate the systemic antibiotics that will ultimately be used, but initial coverage may include a second-generation cephalosporin and gram-negative coverage until a Gram stain or the culture results are definitive.

If a two-stage approach is indicated, the approach involves an interval during which the sternum and skin are left open and a wound vacuum device placed.^{34,35} Open management of sternal wounds is associated with a risk of sudden cardiac hemorrhage from the exposed grafts, the aorta, or (most frequently) the right ventricle. The risk of death in such patients is very high (>50%).³⁶⁻³⁸ Given these risks, it has been recommended that close attention be paid to the proximity of the sternal edges and the right ventricle or grafts. Decreased abrasive contact may be afforded by the use of sedation, possible muscle paralysis, and mechanical ventilation until coverage can be achieved.

Whether used as an initial single-stage procedure or as a secondary procedure, tissue transposition into the anterior mediastinum has

dramatically changed the prognosis of this once often fatal complication.³⁹ Well-vascularized omentum or a variety of muscle flaps can be used.

The sternum may be left open with the tissue flap between the remnant edges, or rarely, it may be closed over the flap. Either way, closed suction drains are required for the large, mobilized skin flaps and sometimes beneath the transposed tissue flap.

The use of omentum versus any specific muscle flap may be dictated by availability (e.g., in patients with prior laparotomies), but when the option exists, the use of omentum has been touted as advantageous over muscle flaps,⁴⁰ although it has also been associated with poorer survival,⁴¹ perhaps related to patient selection. Omentum has also been successfully employed in infections after ascending aortic replacement for its properties of improving oxygen supply, enhancing antibiotic delivery, and enhancing the immunologic response while absorbing secretions that can lead to bacterial proliferation.⁴² Skin coverage over a transposed flap may be accomplished by primary presternal skin reapproximation or split-thickness skin grafting, or, with the rectus muscle, a skin paddle may be transposed as well.

As noted earlier, debrided sternal wounds may be prepared for flap coverage by the use of a closed high-pressure vacuum system in which a polyurethane foam (400- to 600- μ m pore size) is cut to fit the anterior mediastinal space and sealed to the skin, permitting a vacuum (-50 mm Hg) to be generated over the entire wound surface. The device is changed regularly to avoid tissue ingrowth, and whenever the anterior surface of the heart is in contact with the foam, it should be changed at least every 72 hours to avoid adhesions, which could have catastrophic consequences. Particularly with smaller wounds, the vacuum treatment may obviate the use of a flap coverage, as the wound heals secondarily, with obliteration of the space over a period of weeks.^{43,44}

Prognosis

Although the mortality of mediastinitis has improved dramatically over the past 2.5 decades, the likelihood of death remains high, as reported in a larger series (12.8% to 47%), more often from associated comorbidities or complications such as an additional infection.⁴⁵ Early detection with expeditious operative débridement and tissue coverage are the major advances that have allowed this improvement to take place. Importantly, it is not merely acute mortality that is elevated in patients with post-cardiac surgery mediastinitis. In studies from the Northern New England Cardiovascular Disease Study Group, with adjustment for various comorbidities, the 4-year mortality for patients with a postoperative deep sternal infection was three times greater than that for patients without this complication, and this increased all-cause mortality rate persisted with up to 10 years of follow-up. For patients surviving for longer than 6 months after a cardiac operation, the incidence of death was 70% higher than the rate among patients who did not have a mediastinal infection.⁴⁶

POSTERIOR MEDIASTITIS

Acute infections that arise in the posterior mediastinum generally result from disease that may be primary to the esophagus or, more commonly in the United States, secondary to esophageal intervention.⁴⁷

Primarily, esophagitis (e.g., in immunocompromised patients with fungal or viral organisms) may extend through the esophagus, resulting in mediastinitis. Abscess formation, presumably secondary to hematogenous spread, can occur.⁴⁸ Esophageal perforation (often at the gastric junction) from a swallowed foreign body has also been reported.⁴⁹

Esophageal operations may be the source of an infection due to anastomotic disruption, but as transhiatal esophagectomy is increasingly employed for patients with esophageal cancer, its cervical gastropharyngeal anastomosis mostly avoids the consequences of mediastinitis. Still, among patients with an intrathoracic esophagogastric

anastomosis, a leak may occur in 4.3% to 8.7% of patients.⁵⁰ Traumatic injuries to the trachea, proximal bronchi, or esophagus obviously may also result in the contamination of this space. Other causes of posterior compartment mediastinitis include the classic Boerhaave's syndrome characterized by the rupture of the lower esophagus post retching and, more rarely, the erosion of a broncholith from a partially or completely obstructed bronchus.⁵¹

Diagnosis

Given a relevant history, the presence of cervical pain and/or chest pain with a high fever would strongly suggest the diagnosis. Supraclavicular crepitus may be identified in patients with upper mediastinal pathology but is generally absent initially in those with middle or lower esophageal disease. Leukocytosis may be the singular early laboratory abnormality. Furthermore, sepsis with mental status changes and hypotension may occur. Certainly, in some of these patients, plain chest film may reveal a pleural effusion, and more rarely, air may be seen in the retropharyngeal space or other abnormal locations along the length of the mediastinum posterior to the pericardium. Computed tomography (CT) scan with oral Gastrografin is the mainstay for diagnosis and localization, as it can clearly demonstrate any abnormal air or fluid collections along the esophagus or esophagogastric junction, and water-soluble contrast may diagnose the presence of an esophageal leak. If there is any concern for possible aspiration, angiographic contrast agents are favored instead of Gastrografin, as the latter can cause more severe pneumonitis if aspirated, and barium will persist after the swallow, complicating the imaging of the future leak test. Transesophageal ultrasonography and fine-needle aspiration have been jointly used to diagnose a variety of periesophageal infections,⁵² and this bedside technique in critically ill patients likely has improved diagnostic accuracy over standard CT imaging.

Treatment

A contained esophageal disruption (extravasation of contrast that drains rather promptly back into the lumen) may be managed successfully in stable patients by serial clinical evaluation, limited oral intake, antibiotic therapy, and repeat imaging.⁵³ This may be particularly true in young children.⁵⁴

In patients with more frank mediastinal contamination not confined to the local perforation but identified within the first 24 hours, operation with primary repair and drainage is most often indicated.^{55,56} If the length of time since the perforation is sufficiently short and the injury is sufficiently small, so that local inflammation is limited, primary repair of a disruption—preferably with viable vascularized tissue buttressing—has been successfully employed,⁵⁶ even after 24 hours.⁵⁷ Success has also been recently reported with the use of covered self-expanding esophageal stents.⁵⁸ Image-guided nonoperative drainage with antibiotics has been successfully employed in selected cases where a defined collection or abscess could be identified.

In a case series reported by Ben-David et al., uncontained acute (less than 24 hours) esophageal perforations in the chest greater than 2 cm in size were successfully treated with a combination of endoscopically placed stent, minimally invasive laparoscopic/thoroscopic mediastinal drainage, and a laparoscopically placed gastrostomy or jejunostomy tube. By adopting this treatment algorithm, esophageal leak occlusion was confirmed in all patients within 24 hours of the esophageal stent placement, and 73% of the patients were able to begin a diet 48 hours after their esophagogram confirmed no further extravasation of contrast.^{59,60}

In patients with more extensive local inflammation, such as those diagnosed more than 24 hours after perforation and those who are more systemically ill, drainage with or without some esophageal diversion may be employed.

Continued sepsis and multiple organ failure are the most common causes of death among these patients, and multiple operations to excise

necrotic tissue and drain the space are sometimes required before definitive reconstruction.

MIGRATORY AND CHRONIC MEDIASTINAL INFLAMMATION

The mediastinum may be infected secondarily from contiguous acute infections involving adjacent anatomic spaces such as the pleurae, lungs, spine, intraabdominal processes, and retroperitoneum.⁶¹

Perhaps the most dramatic and well described of the migratory mediastinal infections are those that descend from the neck, which is known as *descending necrotizing mediastinitis*. These include those infections that arise as classic Ludwig's angina (odontogenic or non-odontogenic) or from cervical puncture wounds. Gravity and the negative pressure of the thoracic cavity have been cited as reasons for this descent through the pretracheal space into the upper posterior mediastinum. These patients are often young and may have a history of a dental infection. Cervical pain, cellulitis, necrosis, and abscess formation may occur, and a high index of suspicion leading to CT imaging can be diagnostic. Broad-spectrum antibiotics are essential and must be accompanied by cervical and mediastinal drainage directed by the clinical and radiologic findings.^{62,63} Drainage may be accomplished in a variety of ways including right thoracotomy, left-sided video-assisted

thoracoscopy, or an anterior clamshell incision. The mortality of this condition has historically ranged from 20% to 40% and increases directly with the interval between the onset of symptoms and diagnosis.

Oropharyngeal cervical infections descending into the mediastinum have been successfully managed with antibiotics and a combination of percutaneous drains and/or videoscopic débridement.^{61,64} In any case, aggressive imaging surveillance and a commitment to achieving and maintaining adequate drainage (multiple varied procedures) are necessary to successfully manage this relatively rare life-threatening disorder.⁶⁵

Mediastinal fibrosis is a chronic condition that may present precipitously when the process constricts a mediastinal structure, compromising its lumen. Pulmonary vein, pulmonary artery,⁶⁶ vena cava,⁶⁷ and tracheal stenoses are the most commonly seen. The diagnosis is generally established by CT or magnetic resonance imaging, which reveals a diffusely infiltrating, and sometimes calcified, mass. Bronchoscopy may contribute to the diagnosis.⁶⁸ The fibrosis is a benign, acellular proliferation of fibrous collagenous tissue that is idiopathic or may be an immunologic sequela of an intervention (e.g., radiofrequency ablation) or infection (mycotic, specifically, and most commonly, *Histoplasma*).^{69,70} Treatment may include steroid therapy⁷¹ and local dilation of the stenotic lumina with stents or operation.⁷²

■ References for this chapter can be found at expertconsult.com.

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Epistaxis is an acute hemorrhage from within the nasal cavity including the nasopharynx and accounts for 0.5% of all U.S. emergency department visits. Approximately 60% of individuals experience epistaxis at least once in their lifetime, although only 6% of cases require medical treatment.^{1,2} The peak incidence of epistaxis in adults is in the 45-65-year-old age group, and the incidence of severe posterior bleeding is greater.³ Special aspects regarding the care of critically ill patients with epistaxis including prevention, diagnosis, and management options will be discussed in this chapter.

ANATOMY

The vascular supply of the nasal cavity forms from the terminal branches of the internal and external carotid arteries. The majority of epistaxis (90%-95%) occurs on the anterior nasal septum at a region called *Little's area*. This area is supplied by Kiesselbach's plexus, a network of vessels from three large thin-walled arteries (sphenopalatine artery, anterior ethmoidal artery, and superior labial artery).⁴ Epistaxis is classified as anterior or posterior, although no clear landmarks separate the two.^{1,5} Melia and McGarry proposed that anterior bleeding is from a source anterior to the plane of the pyriform aperture (the anterior bony nasal aperture), which includes bleeding from the anterior septum and from the vestibular skin and mucocutaneous junction. Posterior bleeding is from a vessel situated posterior to the pyriform aperture and allows for further division into the lateral wall, septal, and nasal floor bleeding.⁶ The two primary sites of posterior epistaxis include the posterior lateral nasal wall and the posterior nasal septum, with the most common artery involved being the sphenopalatine artery. Epistaxis from the anterior ethmoidal artery is less common and is typically associated with midface trauma or iatrogenic injury during endoscopic sinus surgery.^{7,8}

DIAGNOSIS

It is important that the clinician wear appropriate safety clothing and equipment (disposable apron, gloves, surgical face mask, suction, and headlight). It is also important to gather details of the initial presentation, previous bleeding episodes, comorbid conditions, and current medications. Coagulation screening is only indicated when the clinical history suggests coagulopathy of a known use of anticoagulants.⁹ Warfarin is a commonly prescribed anticoagulant, and patients with epistaxis on warfarin are older, have longer mean hospital stays, and show trends that they require more aggressive treatment to control. In a review of patients taking warfarin with epistaxis, it was found that more than 75% of the patients were over-anticoagulated at the time of admission.¹⁰ Critically ill patients are frequently supine, with decreased alertness, and blood may drain into the nasopharynx and, subsequently, the stomach, making it difficult to differentiate from gastrointestinal bleeding. An anterior speculum exam with a good light source usually allows the identification of focal anterior bleeding. Generalized mucosal ooze in a patient with systemic coagulopathy and large amounts of bleeding that obscures visualization can make identification of the source difficult. In addition to the anterior/posterior classification system discussed above, bleeding can be classified as venous/

arterial or high/low flow based on the rate of bleeding. Venous bleeding can involve low flow, such as mucosal oozing, or it can be high flow from structures such as the cavernous sinus. Arterial bleeding can be low flow from oozing from small perforating vessels, or it can be high flow in carotid artery injuries.¹¹ Epistaxis can also be classified as primary or secondary when there is an underlying coagulopathy associated with anticoagulant/antiplatelet medications.⁶ For patients in which anterior bleeding is not easily identifiable, nasal endoscopy has been shown to identify over 80% of bleeding sites not otherwise seen and reduce the duration of hospital admission. Chiu and McGarry reported positive identification of 94% of posterior bleeding sites in 50 consecutive patients, while Supriya et al. identified 38 of 47 posterior bleeding sites in a series of 100 patients, with an overall positive identification rate of 91%.^{8,12}

TREATMENT

General management includes the protection of the airway, addressing hemodynamic compromise, and controlling active hemorrhage. Patients with a reduced level of consciousness or head injury are at risk of aspiration and should require consideration of airway protection with endotracheal intubation. Intravenous access and fluid resuscitation should be addressed quickly, as patients can become unstable. The first priority is to control or slow the active hemorrhage with some form of temporizing packing. Commercially available anterior or posterior balloon combination packs can be used with the goal of slowing the rate of blood loss while the setup of anticipated equipment is established. Prior to insertion of these packing materials, an attempt can be made by simply applying pressure to the nose, while the patient is positioned upright and leaning forward for 20 minutes. The goal here is to slow the blood loss rate by collapsing the bleeding vessels and forming a clot.

Treatment—Anterior Bleeding

Cautery of an identified bleeding point is the optimal method of management in adult epistaxis and can successfully control anterior bleeding, with silver nitrate and electrocautery as options. Silver nitrate is applied by rolling the applicator stick between your thumb and first finger while gently applying the tip to the area you wish to cauterize for about 5 to 10 seconds. Care should be taken not to burn the nasal skin as you enter the nose or aggressively use it on the septum. Start adjacent to the vessel, making an orbit around the vessel before rolling the tip in to the center, as re-bleeding is common when going straight for the site. Shargorodsky et al. found that cautery had a significantly lower treatment failure rate (defined as a re-bleed requiring intervention by a physician within 7 days) and a lower mean number of interventions required to achieve lasting hemostasis with nondissolvable packing. Among the patients who required admission, those who underwent directed vascular control had fewer inpatient days.¹³ If cautery does not control the bleeding, a nasal pack will be required. Nasal packs should be introduced into the nose directly front-to-back following the floor of the nose. Never place it upward, as this does not work, is painful, and increases the risk of complications. Commercially

available packs are available and consist of balloon/hydrocolloid fabrics that expand after placement into the nasopharynx. Most of these have a string or tubing that should be taped to the patient's cheek to secure it.

Treatment—Posterior Bleeding

Severe idiopathic nontraumatic posterior bleeding typically occurs in the elderly, who often have underlying cardiac and respiratory comorbidities. It should be suspected after appropriate anterior control measures have been taken and bleeding continues. Typically, a 12 French Foley catheter or similar item is used in conjunction with a ½-inch ribbon gauze or commercially available anterior packing supplies. The catheter balloon should be tested with saline prior to use. A nasal decongestant and topical local anesthetic solution should be administered to the nasal cavity and on the ribbon gauze. The catheter is lubricated and advanced into the nose until the tip can just be seen passing the soft palate in the mouth. At this point, the catheter needs to be pulled back 1 cm as the balloon inflates in the nasopharynx. Between 5 to 10 mL of saline is used to inflate the balloon, and once inflated, the catheter is pulled taut so that the balloon is effectively occluding the posterior nasopharynx at the back of the nasal cavity. Anterior packing is then performed by folding layers of the ribbon. These patients are at risk for adverse events such as re-bleeding and hypoxia, likely due to comorbidities such as cardiovascular disease, pulmonary disease, renal disease, obesity, and obstructive sleep apnea.^{14,15} For continued bleeding, surgery or embolization is an option. Moshaver et al. showed that compared with surgical intervention, posterior nasal packing resulted in a significantly shorter mean hospital stay and reduced health care costs. The overall success rate was 89%, and no difference was found in the complication rates between the two treatment options.¹⁶ Arterial embolization appears similar to surgery in terms of its success in controlling intractable epistaxis, with several recent studies showing success rates of 80% to 90%.¹⁷⁻²¹ The advantage of surgery is a lower risk for major complications such as stroke, blindness, and soft tissue ischemia. The advantage of embolization is the ability to perform the procedure under local anesthesia, thus avoiding general anesthesia in patients with comorbidities, as well as the improved diagnosis of vascular abnormalities such as malformations and pseudoaneurysms.

Treatment—After Packing the Nose

The packing is usually kept in for 5 days, but this is usually physician and institution dependent. Patients do not tolerate nasal packing well. Shargorodsky et al. examined whether the duration of packing was associated with the recurrence of epistaxis following removal and did not demonstrate a significant difference between the recurrence rate and the number of pack days, showing no evidence that removing the packing after fewer than 5 days was associated with increased recurrence of epistaxis.¹³ Furthermore, good results have been shown in packing durations of 1 to 3 days, with the control of bleeding as high as 85% for anterior epistaxis.²² Nasal packing of all types requires gram-positive coverage for prophylaxis against toxic shock syndrome. *Staphylococcus aureus* can be isolated from the nasal cavity in one-third of these patients, of whom 30% produce the exotoxin responsible for toxic shock syndrome.²³ Other complications include pressure necrosis of the palate, alar, or skin and displacement with airway obstruction.

MEDICOLEGAL THOUGHTS

The absence of a defined management algorithm, wide therapeutic options, and the potential for severe complications all contribute to epistaxis as a target for medicolegal cases. Understanding the variables will assist in advancing strategies and enhancing patient care. The most common reason has been due to the alleged failure of the treating physician to recognize complications in a timely manner and delays

in the subsequent diagnosis, such as cancer and retained foreign bodies.²⁴⁻²⁶ It is important to realize that epistaxis is a sign, not a diagnosis. Other cases have been related to the failure of recognition of anatomic variations, which led to blindness and stroke due to inadvertent embolization.^{5,27} This shows the importance of preinterventional imaging. Last, malposition or inadequate nasal packing with complications such as aspiration and dislodgment have been found throughout the hospital stay.²⁸

SPECIFIC INTENSIVE CARE UNIT SITUATIONS—NASAL INTUBATION

Nasotracheal intubation commonly causes epistaxis from injury to the nasal mucosa or turbinate. Good mucosal preparation for nasotracheal intubation should include adequate lubrication, topical local anesthetics, and vasoconstrictors. Moreover, if resistance is met, the tube should be slightly rotated to allow better passage or the other nare should be attempted.^{29,30} The inferior turbinate and the adjacent septum are the most common sites of nasal damage.^{31,32} Placement into intracranial compartments has occurred in the setting of skull base trauma. Blind placement in these situations may be associated with severe complications. Although posterior nasal packing should not be performed in the presence of nasal bone fractures, severe epistaxis may necessitate nasal packing with the use of balloon systems or arterial embolization ligation.^{33,34} Cribriform plate fractures are the most common site for intracranial catheter placement and can occur with even small amounts of pressure.

SPECIFIC INTENSIVE CARE UNIT SITUATIONS—POSTOPERATIVE EPISTAXIS

Sellar and parasellar lesions are typically approached through transphenoidal surgery, and postoperative bleeding originates from the external carotid system. Redundant mucosa, highly vascular and friable mucosa, large septal deviations, septal spurs, and complex sphenoid septations can make endoscopic transphenoidal surgery difficult and increase the risk for epistaxis.³⁵ Management of bleeding immediately postoperatively involves nasal packing and re-exploration in the operating room if the packing is not successful. In delayed bleeding, otorhinolaryngologic services typically perform endoscopic packing, balloon tamponade, silver nitrate application, and/or electrocautery. If these measures do not stop the bleeding, angiography followed by embolization can be performed.³⁶ Postoperative hypertension is generally viewed as a risk factor for epistaxis and is also an independent risk factor for persistent spontaneous epistaxis.³⁷

SPECIFIC INTENSIVE CARE UNIT SITUATIONS—MASSIVE FACIAL TRAUMA

Traumatic pseudoaneurysms of the internal carotid artery are rare but can be a fatal cause of epistaxis, with a mortality rate as high as 50%.^{38,39} Pseudoaneurysms or localized arterial disruptions are caused by blunt or penetrating trauma. Shearing forces and hemorrhages in the arterial wall weaken the artery and allow formation, and the continued pulsatile forces cause erosion on the thin bone layer.^{40,41} The Maurer's triad, which consists of unilateral blindness, orbital fracture, and massive epistaxis, is considered pathognomonic for internal carotid artery pseudoaneurysms.⁴² The diagnosis is often delayed because of a latency period between the trauma and the bleeding, which averages 3 weeks in 88% of cases.^{43,44} Angiographic imaging is the gold standard, with endovascular techniques being the preferred therapeutic approach.

NOVEL AND ADJUNCTIVE THERAPIES

Vasoconstrictors, hot water irrigation, and topical hemostatic compounds have all been used as adjunctive therapies to the abovementioned procedures for the control of bleeding. Hot water irrigation via a balloon placed in the nasopharynx for approximately 3 minutes at

50°C to induce mucosal edema (and occlude the bleeding vessel) has been shown to control posterior epistaxis.^{45,46} Topical hemostatic compounds are now available, consisting of gelatin granules and human thrombin. Studies show higher effectiveness, ease of application, and lower discomfort scores for their insertion and removal.⁴⁷

KEY POINTS

1. In the critically ill patient, diagnosis of epistaxis may be more difficult due to supine positioning and decreased alertness and is often confused with upper gastrointestinal bleeding.
2. Epistaxis is a sign and not a diagnosis; once bleeding is controlled, the search for the etiology should be conducted. Coagulation studies should be performed in those on anticoagulant/antiplatelet medications, with consideration of correction.
3. For intractable epistaxis, options should include surgery or embolization. Surgery has the advantages of decreased complication rates of stroke and blindness, while embolization has the advantage of avoiding general anesthesia in patients with nasopharyngeal bleeding.
4. Aspiration, hypoxia, and dislodgment complications with nasal packing must be continuously evaluated for, especially in patients with severe comorbidities.

■ References for this chapter can be found at expertconsult.com.

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The initial days of care for a cardiac surgery patient present multiple challenges for an intensivist. The intensive care unit (ICU) stay for most patients lasts for 24 to 48 hours, but during this critical period, life-threatening problems such as low cardiac output (CO), arrhythmias, and coagulopathy may occur. After 48 hours, the problems encountered tend to become more like those experienced by other groups of critically ill patients.

CARDIAC SURGERY PATIENT IN THE INTENSIVE CARE UNIT

History of Cardiac Surgery Linked to the History of Intensive Care

The development of modern cardiac surgery is intimately related to the development of the ICU. Until the 1950s, cardiac surgery was limited to the control of traumatic injuries and the closed repair of valves. The development of the extracorporeal pump oxygenator in 1953 ushered in the era of open-heart surgery.¹ Heart valve replacement then became possible, and subsequently in the 1960s, coronary artery bypass grafting (CABG) for ischemic heart disease was developed and rapidly popularized.²

Several studies have demonstrated that risk-adjusted mortality rates after CABG vary significantly among surgeons and hospitals and that mortality is related both to the number of surgeries performed by each surgeon and the total volume of procedures performed at the hospital.³⁻⁶ For high-risk surgical patients, survival is also related to the characteristics of the ICU care.⁷

Changing Epidemiology of Cardiac Surgery

Over the past decade, the population of patients treated with cardiac surgery has changed dramatically. Advances in cardiology including reperfusion therapy, angioplasty, stenting, and drug-eluting stents have obviated the need for surgical approaches to treatment except for particularly complex problems or after failure of other less invasive modalities. In the year 2000, 561,000 patients in the United States underwent percutaneous transluminal coronary angioplasty (PTCA), an increase of 262% relative to 1987. In the same year, 314,000 patients underwent CABG. Multiyear trends, represented in Figure 157-1, show a leveling off and subsequent decrease in the overall number of patients undergoing CABG.⁸ Studies comparing the use of stents versus CABG for left main disease have found no significant difference in rates of death, Q-wave infarction, or stroke; however, stenting was associated with higher rates of target vessel revascularization than was CABG.⁹

Even as younger patients are being treated with interventional techniques, the elderly are increasingly referred for operation. Although these operations are successful even in most octogenarians, they are associated with increased hospital mortality and longer ICU and hospital stays. It is clear, however, that good results in terms of long-term survival and quality of life are achievable.

Alternative Techniques for Cardiac Surgery

The increasing age of patients undergoing cardiac surgery and the relatively high incidence of adverse effects related to cardiopulmonary bypass (CPB) have led to the development of less invasive cardiac surgical techniques. These techniques are intended to decrease postoperative morbidity, reduce length of hospital stay, reduce costs, and hasten recovery of lifestyle (Table 157-1). Three major techniques have been proposed.

Minimally invasive direct coronary artery bypass (MIDCAB) differs from conventional CABG mainly in the type of surgical incision. Instead of median sternotomy, access is obtained via a left or right thoracotomy, a parasternal incision, or a partial sternotomy. Although the proposed benefit of such an approach is the reduction in morbidity related to median sternotomy, this advantage has not been demonstrated. MIDCAB grafting is a challenging technique and should be performed only in selected patients with favorable coronary anatomy. Both bare-metal and drug-eluting stenting have been shown to be inferior to MIDCAB for proximal left anterior descending coronary artery lesions, owing to higher reintervention rates and similar results in mortality and morbidity.^{4,10}

Off-pump coronary artery bypass (OPCAB) is performed on a beating heart without the benefit of CPB. The proposed advantage of this procedure is reduction of morbidity related to hypothermia and CPB. The procedure is undertaken using partial to full heparinization. Extubation may be achieved earlier in these patients because they do not require rewarming and are less coagulopathic. A subset of patients cannot tolerate the extent of retraction of the heart required for the surgery and need to be urgently placed on CPB. These patients may suffer ischemic myocardial injury and require support with inotropes or intraaortic balloon pumping (IABP) during the postoperative period.

A third method of minimally invasive cardiac surgery is the port-access technique. This operation entails obtaining access for CPB with the use of endovascular catheters. It allows surgery to be performed using CPB via either a left or a right thoracotomy. The technique is particularly useful for mitral valve replacement through a right thoracotomy and for redo CABG (avoiding the complications associated with repeat sternotomy). The port-access technique has been shown to be safe and is associated with shorter lengths of stay, reduced transfusion requirements, fewer infections, decreased incidence of renal failure, and less atrial fibrillation (AFib) compared with conventional techniques.¹¹ Widespread adoption of this technique has been limited by the technical complexity of placing the required catheters, which requires both extra time and a specially trained, skilled operative team. As the techniques of minimally invasive cardiac surgery continue to evolve, the intensivist caring for cardiac surgical patients must continue to keep abreast of these new methods.

Organization of the Postoperative Cardiac Surgery Unit

Optimal results from cardiac surgery require a skilled, dedicated, and multidisciplinary ICU team. Patients undergoing cardiac surgery are

usually admitted to the hospital on the day of surgery and arrive in the ICU directly from the operating room (OR). A typical patient is transferred to a step-down unit on the morning after surgery. This unit allows continued monitoring with telemetry for an additional 24 to 48 hours. Patients remaining in the ICU beyond 48 hours tend to become similar to a standard ICU population, as they develop secondary complications such as sepsis, pneumonia, and acute respiratory distress syndrome (ARDS).

Guidelines developed by the American Heart Association and the American College of Cardiology outline the requirements for cardiac surgical ICUs.¹²⁻¹⁴ These include the development of protocol-driven care, a minimum number of cardiac surgical ICU beds that is half the number of surgeries performed per week, and one-to-one nursing care during the first night in the unit. The ICU coverage by a dedicated intensivist has been shown to improve outcomes in other types of

major surgeries and should be recommended after cardiac surgery as well.⁷

SEPARATION FROM CARDIOPULMONARY BYPASS AND THE END OF SURGERY

Successful management of a postoperative cardiac surgery patient begins by understanding what occurs in the OR because operative problems often persist after transfer to the ICU. An understanding of the technical and pathophysiologic aspects of CPB may help an intensivist to better manage the postoperative cardiac surgical patient.

Cardiopulmonary Bypass

The goal of CPB is to separate the heart and lungs from the systemic circulation so that the heart may be arrested while the surgical repair is performed. Blood is drained from the right side of the heart via a cannula in the right atrium or via the femoral vein advanced into the right atrium. The blood is collected in a reservoir and then pumped through an oxygenator that contains a membrane where the blood is oxygenated and carbon dioxide is removed (Fig. 157-2). A perfusionist controls both the fraction of inspired oxygen and the rate of oxygen flow through the circuit, thereby controlling the patient's arterial oxygen and carbon dioxide levels, respectively. The treated blood then passes through an air filter and is returned to the patient via an arterial cannula placed in either the ascending aorta or the femoral artery. The perfusionist controls the amount of systemic flow provided to the patient (i.e., CO). Mild to moderate systemic hypothermia (28°C–34°C) is used during bypass to minimize oxygen consumption by both the body and the brain. After adequate CPB is established, an aortic cross-clamp is applied to the ascending aorta, between the aortic cannula and the heart. The interval when the cross-clamp is applied is

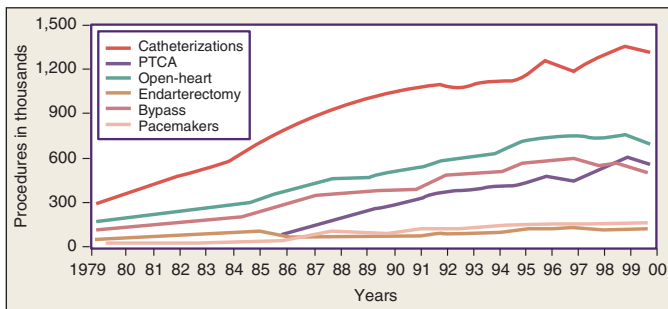


FIGURE 157-1 ■ Trends in cardiovascular operations and procedures in the United States, 1979–2000. PTCA, percutaneous transluminal coronary angioplasty. (From American Heart Association. Heart disease and stroke statistics—2003 update. Dallas, TX: AHA; 2003.)

TABLE 157-1 Comparison of Minimally Invasive Cardiac Surgery Techniques

| TECHNIQUE | INCISION SITE | CANNULATION SITE | ADVANTAGES | DISADVANTAGES |
|-------------------|---|---|---|---|
| Conventional CABG | Median sternotomy | Ascending aorta | Excellent exposure | Mediastinitis |
| | | Right atrium | Stable closure Extensive experience | Slow recovery of upper extremity function Postoperative cough limited by pain |
| MIDCAB | Left thoracotomy, or Paramedian or right thoracotomy, or Partial sternotomy | Ascending aorta Right atrium | Avoids median sternotomy Useful for redo procedure Hastens recovery of upper extremity function* | Limited exposure No cost savings May require multiple incisions |
| Port-access | Right anterior thoracotomy, or Paramedian or left thoracotomy | Ascending aorta via right paramedian port Femoral vein | Avoids median sternotomy Avoids atriotomy Access to mitral valve Smaller skin incision Decreases hospital stay* Decreases atrial fibrillation incidence* Decreases transfusion* Decreases rehabilitation time* | Increased cost of equipment Contraindicated in patients with ascending aortic pathology Limited operative exposure Significant learning curve unlikely to decrease cerebral emboli |
| OPCAB | Median sternotomy, or Right or left thoracotomy, or Partial sternotomy | None | Avoids aortic manipulation Avoids atriotomy and CPB Normothermia Decreases atrial fibrillation incidence* Decreases transfusion* Decreases neurologic morbidity† Decreases pulmonary morbidity† | Cost of equipment Slow recovery of upper extremity function Mediastinitis Increases intraoperative ischemia Undetermined graft longevity |

*Limited supporting evidence exists.

†Proposed benefit.

CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; MIDCAB, minimally invasive direct coronary artery bypass; OPCAB, off-pump coronary artery bypass.

Adapted from Reves JG, Hill SE, Sum-Ping ST, et al. Perioperative management of the cardiac surgical patient. In: Murray MJ, Coursin DB, Pearl RG, Prough DS, editors. Critical care medicine: perioperative management. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2002: 356.

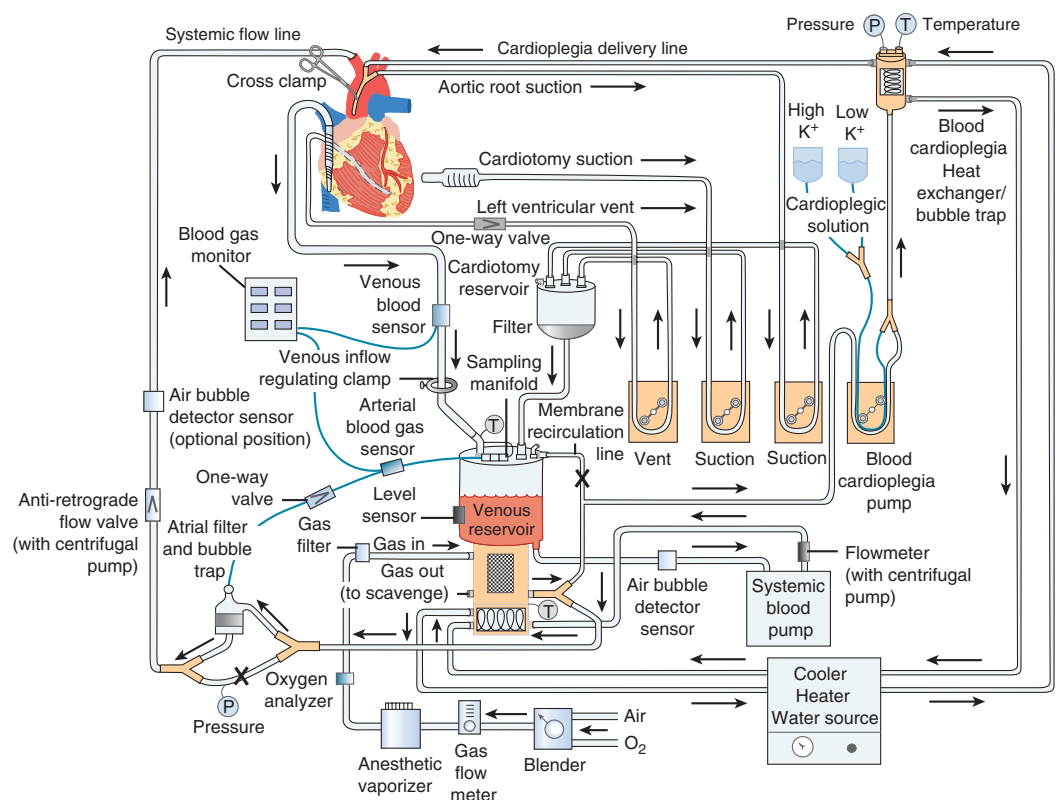


FIGURE 157-2 ■ Cardiopulmonary bypass circuit. (Adapted with permission from Gravlee GP, Davis RF, Kurusz M, Utley JR, editors. *Cardiopulmonary bypass: principles and practice*. 2nd ed. Baltimore: Lippincott Williams & Wilkins; 2000: 70.)

referred to as *ischemic* time, because no blood is circulated through the heart during this period. The heart is arrested by infusing a high-concentration potassium solution into the native coronary arteries (antegrade cardioplegia) via a cannula placed between the aortic cross-clamp and the heart. Cardioplegia may also be given “backward,” through the venous system of the myocardium (retrograde cardioplegia) via a catheter placed in the coronary sinus. Potassium is used as the arresting agent because it stops the heart from beating and minimizes myocardial oxygen consumption.

Myocardial Protection

Several measures are taken to protect the heart during ischemic time, because irreversible myocardial damage may otherwise occur. Electromechanical arrest is the most important protective measure, because the beating action of the heart accounts for about 85% of the heart's total oxygen consumption. The heart is usually cooled to about 10°C with a cold cardioplegia solution (4°C) supplemented with topical ice slush. Additionally, the left ventricle is “vented” to prevent distention, which could lead to subendocardial ischemia. Finally, various additives are included in the cardioplegia solution to minimize myocardial edema, maintain normal intramyocardial pH, and provide substrates for anaerobic metabolism. The adequacy of intraoperative myocardial protection is critical for determining the subsequent course and final outcome for a patient.

Separation from Cardiopulmonary Bypass

Weaning from CPB is the process whereby cardiopulmonary function is transferred from the bypass system back to the patient's own heart and lungs. Successful separation from CPB requires that the metabolic, cardiac, and respiratory parameters are as close to normal as possible.

Separation from CPB implies that the native circulation will be required to support the body's metabolic demands. The surgical team manipulates the heart rate and rhythm, preload, afterload, and myocardial contractility to achieve this goal.

In most cases, normal sinus rhythm is restored after discontinuation of cardioplegia and rewarming of the heart. Occasionally, discontinuation of cardioplegia and rewarming lead to the onset of ventricular fibrillation; in such cases, electrical defibrillation is required. Other dysrhythmias commonly encountered are atrioventricular dissociation and atrial fibrillation (AFib). An attempt should be made to convert these to sinus rhythm by pharmacologic means. Bradyarrhythmias are treated by pacing, using temporary epicardial wires placed by the surgeon after completion of the repair. A heart rate of 70 to 90 beats/min usually is optimal. Pharmacologic support of the circulation may be needed to provide appropriate afterload or systemic vascular resistance (SVR) during separation from CPB. Most patients are vasodilated to some extent, possibly as a result of a systemic inflammatory response to CPB or the effects of rewarming, or both. As a consequence, the infusion of a vasoconstrictor is often required. Care must be taken to strike a proper balance so that increased SVR maintains adequate arterial blood pressure without excessively increasing left ventricular afterload and compromising CO.

Most often, myocardial function is adequate, and the infusion of an inotrope is not necessary. However, inotropic support is often needed for patients with a poor preoperative ventricular function or inadequate myocardial protection or revascularization during CPB. The optimal inotrope in this situation is a matter of considerable debate, and data are lacking to support a strong recommendation for a specific agent. Epinephrine, norepinephrine, dopamine, dobutamine, amrinone, and milrinone have all been used successfully. Intraoperative monitoring using transesophageal echocardiography (TEE) is particularly useful for titration of inotropic therapy.

Once all preparations for separation from CPB have been made, the perfusionist begins to wean the patient from bypass. This is done by slowly decreasing the amount of blood drained from the right atrium while simultaneously reducing flow into the aorta. Once the patient is off CPB (i.e., no blood is being drained from the right atrium into the circuit), the perfusionist, at the direction of the anesthesiologist or surgeon, may continue to infuse through the aortic cannula. This maneuver allows optimization of ventricular filling or preload. However, care must be taken not to overdistend the heart; also, during this period, TEE is extremely useful.

Reversal of Anticoagulation

After weaning from CPB, protamine is given to neutralize any residual heparin. Dosing may be based on the patient's weight, the total amount of heparin given, or an assay of residual heparin activity. Institutional preference governs the technique employed, but all have been proven effective. Several adverse responses to protamine administration are possible, including histamine-induced systemic hypotension, immunoglobulin E-mediated allergic reactions, and complement-mediated catastrophic pulmonary hypertension.

Transport and Admission to the Intensive Care Unit

After chest closure, confirmation of hemodynamic stability, and adequate medical and surgical hemostasis, the patient is transferred to the ICU. Transport of a critically ill patient is a potentially dangerous process and requires extreme vigilance. Transport between the OR and the ICU should be done with the same degree of monitoring as would be available at either end. This usually includes continuous monitoring of arterial blood pressure, pulmonary artery pressure and/or central venous pressure (CVP), electrocardiogram (ECG), and pulse oximetry. The transport bed should be equipped with a full oxygen tank, a bag valve mask, intubation equipment, resuscitation drugs, and a defibrillator. Care must be taken to ensure that infusions of vasoactive drugs are not interrupted.

On arrival in the ICU, the intensivist-led team assumes patient care. A detailed sign-out from the operative team ensures continuity of care. The sign-out should include a detailed history including an assessment of preoperative cardiac functional status, a list of preoperative medications, and a detailed description of the surgery. Key facts are the type of repair performed, target vessels (if the patient has undergone CABG), duration of CPB and cross-clamping, difficulties encountered in separation from CPB, presence of abnormal bleeding, and postoperative assessment of cardiac function. All treatments administered in the OR should be detailed, in particular, fluids, blood products, and vasoactive drugs.

Once care has been handed over to the ICU team, a thorough examination of the patient should immediately follow. This examination should include verification of endotracheal tube placement, type and position of arterial or central venous lines, chest tube position and patency, and presence and location of any epicardial pacing wires.

MONITORING THE POSTOPERATIVE CARDIAC SURGERY PATIENT

Hemodynamic Monitoring

All patients admitted to the ICU after cardiac surgery will have their blood pressure continuously monitored using an intraarterial line, which is usually placed in either a radial or a femoral artery. Accuracy of the measurements depends on strict attention to calibration, leveling, and removal of air from the tubing. After CPB, femoral arterial pressure may more accurately reflect central aortic pressures,¹⁵ but this problem is usually resolved by the time the patient arrives in the ICU. If the radial artery is cannulated, the hand should be examined for signs of ischemia.¹⁶ Vascular complications of femoral arterial lines are

extremely rare, but femoral catheters may be associated with an increased incidence of infection.¹⁷

Central venous access is required in all patients for drug administration and hemodynamic monitoring. In low-risk patients, a CVP catheter may be all that is needed, particularly if echocardiography is available as a backup. Pulmonary artery catheters have the advantage of allowing measurement of pulmonary artery occlusion pressure (PAOP), thermodilution, and CO, as well as sampling of the mixed venous blood saturation (SvO₂). Use of the pulmonary artery catheter remains controversial. Improved outcome due to the use of a pulmonary artery catheter for monitoring of cardiac surgical patients has not been demonstrated.¹⁸ Some studies showed an increased risk of death or adverse outcome when treatment was guided by the use of a pulmonary artery catheter.^{19,20} However, many of these studies have been criticized on methodological grounds, and the use of a catheter in cardiac surgery remains widespread.²¹ Current guidelines recommend the use of a pulmonary artery catheter in high-risk patients undergoing surgery in an appropriate practice setting.²² Such a setting is the one in which the physician and nursing staff are familiar with the catheter and trained to properly interpret the information obtained. If echocardiography is readily available, it is possible to manage even high-risk patients using a CVP catheter.

Electrocardiography

On admission to the ICU, the patient is connected to a continuous ECG monitor, and a formal 12-lead ECG is obtained. The cardiogram is examined for rate, rhythm, QRS complex morphology, and signs of myocardial ischemia. For patients who are being paced postoperatively, the type of pacing and the degree of capture should be assessed.

Continuous ECG monitoring allows detection of arrhythmias. If an arrhythmia is detected, a 12-lead ECG should be obtained, and serum electrolyte concentrations should be measured. Treatment of arrhythmias should be carried out using established protocols.²³ If a malignant arrhythmia occurs, myocardial ischemia should be considered as a possible precipitating cause.

Monitoring of trends in ST-segment elevation or depression allows early detection of postoperative myocardial ischemia. Although transient ST-segment changes are relatively common and of unclear significance, persistent changes should be investigated by obtaining a 12-lead ECG and measuring circulating levels of creatine kinase myocardial band (CK-MB), troponin-T, or troponin-I.^{24,25} If ischemia is strongly suspected, then echocardiography followed by coronary angiography should be considered. Findings from these studies may indicate the need for further coronary revascularization.

Chest Radiography

The postoperative chest radiograph should be systematically evaluated. Proper placement of the endotracheal tube and any central lines inserted should be confirmed. If a pulmonary artery catheter is placed, the location of its tip should be noted and adjusted as needed. The lung fields should be examined for the presence of pneumothorax (PTX) or consolidation. Additional air may be noted as subcutaneous emphysema or pneumopericardium, although these findings are of little clinical significance. Further examination of the lung fields commonly shows small areas of atelectasis and pleural effusion. The cardiac silhouette is often enlarged after surgery as a result of myocardial edema and accumulation of fluid in the open pericardial sac. Increasing size of the cardiac silhouette or pleural effusions on serial chest radiographs may be evidence of ongoing mediastinal bleeding.

Echocardiography in the Intensive Care Unit

Echocardiography is an excellent tool for evaluating chamber size and function and the adequacy of valve repair or replacement. Indications include postoperative assessment of left ventricular function, assessment of unexplained sudden hemodynamic deterioration, evaluation

to rule out pericardial tamponade, and workup of new cardiac ischemia. Limitations to transthoracic echocardiography include inadequate windows early after operation due to air and edema in the soft tissues and wound dressings.

TEE is increasingly being used as a tool to facilitate decision making in managing critically ill patients, including cardiac surgical patients. In the cardiac surgical ICU, this modality may have a particularly high yield when used to establish the cause of postoperative hypotension.²⁶ In one large series, a new diagnosis was established or an important pathology was excluded in 45% of TEE examinations performed in the ICU. Pericardial tamponade was diagnosed in 34 cases (11%) and excluded in 36 cases (12%). Other diagnoses included severe left ventricular failure and presence of large pleural effusions. The results of TEE had an impact on therapy in 220 cases (73%) by leading to a change of pharmacologic treatment and/or fluid administration, reoperation, or a decision that reoperation was unnecessary.²⁷

CLINICAL MANIFESTATIONS OF THE POSTBYPASS PERIOD

The Normal Course

Patients are typically admitted to the ICU intubated and ventilated. Sedation with a short-acting agent, typically propofol, is continued until the patient is ready for extubation.^{28,29} Once hemodynamic stability is ascertained and chest tube drainage is judged to be under control, the patient is allowed to awaken. There is no need for prolonged weaning from mechanical ventilation. A short trial of spontaneous ventilation is sufficient to determine whether respiration will be adequate without mechanical support. The rapid shallow breathing index (RSBI) has been shown to be a sensitive way to assess the likelihood of successful extubation.³⁰ The RSBI is calculated by dividing the respiratory rate (in breaths/min) by the tidal volume (in liters). Values of RSBI lower than 105 predict successful extubation. Chest tubes are commonly removed on the first postoperative day. The pulmonary artery catheter, if present, is discontinued, and the patient may be transferred to a step-down unit.

Fast-tracking of cardiac surgical patients refers to a comprehensive program designed to reduce both length of stay and hospital costs.^{31,32} As a part of this program, multiple anesthetic techniques designed to allow earlier postoperative extubation have been proposed, studied, and shown to be safe. These techniques may allow extubation in the OR.³³ The key to proper use of this technique is patient selection. Patients with unstable angina or a high degree of congestive heart failure (CHF) are generally not appropriate candidates for fast-tracking. The fast-track group has been shown to have shorter extubation times, shorter ICU or postanesthesia care unit stays, and a lower incidence of low CO syndrome.²⁹

Low Cardiac Output

Low CO is the most common problem encountered in the postoperative cardiac surgical patient. A hallmark of low CO is low blood pressure. However, a patient may have a low CO with tissue hypoperfusion and still maintain what appears to be an adequate blood pressure. In the postoperative state, the physician must continuously examine and monitor the patient for signs of hypoperfusion. Physical signs of inadequate tissue perfusion include altered mental status; cool, pale, or even cyanotic extremities; diaphoresis; and low urine output. Global measures of hypoperfusion include increased base deficit, elevated blood lactate concentration, and decreased SvO_2 . Although the clinician must consider CO in terms of adequacy of perfusion, blood pressure per se is still important. Both the brain and kidneys depend on adequate blood pressure to maintain tissue perfusion. Additionally, coronary artery blood flow is dependent on the diastolic blood pressure.

When assessing a patient with hypotension or signs of hypoperfusion, it is useful to consider the problem in relation to the components of CO—namely, preload, contractility, afterload, and rate and rhythm.

Preload

Preload refers to the stretch of the left ventricle at the end of diastole and is determined by the extent of diastolic ventricular filling. Adequate filling is required to ensure ejection in the subsequent systole. The most common cause of inadequate preload in postoperative patients is hypovolemia. Intravascular volume status should be continually monitored by assessing changes over time with respect to physical examination, chest tube output, and filling pressures (CVP, PAOP, or pulmonary artery diastolic pressure). Because none of the clinically measured filling pressures correlates perfectly with actual ventricular preload (i.e., end-diastolic volume) and correlation is particularly poor when the heart is diseased, it is often useful to obtain a snapshot of ventricular filling using echocardiography. By this means, it is possible to assess the relationship between measured filling pressures and actual preload in a specific patient. Preoperative catheterization data may also be helpful for determining this relationship. Hypovolemia should be treated with fluid replacement. Crystalloids are generally used. Surprisingly, there is no generally accepted hemoglobin concentration or hematocrit that should be used as a trigger for ordering transfusion of packed red blood cells.³⁴ Red cell transfusion has been associated with early morbidity and long-term adverse sequelae.

In some cases, low preload is not caused by absolute hypovolemia but by relative or distributional hypovolemia. CPB and subsequent rewarming may lead to vasodilatation and a subsequent hypotension. Intravascular volume expansion may be required to maintain perfusion. An acceptable alternative is administration of a low dose of vasopressor such as phenylephrine or norepinephrine to maintain an adequate perfusion pressure. Vasopressin in doses between 0.01 and 0.1 units/min has been demonstrated to be effective in this situation.^{35,36} Vasodilatation is usually a transient problem that resolves during the first several hours after separation from CPB. Continued vasodilatation after this period should prompt a search for another cause, particularly infection.

Pump Failure

Either or both ventricles may fail postoperatively. Decreased myocardial contractility may be caused by impaired preoperative function, inadequate revascularization at surgery, post-CPB reperfusion injury, or perioperative myocardial ischemia or myocardial infarction (MI). The incidence of infarction is approximately 5% in a large series.³⁷ Preoperative myocardial function and the adequacy of revascularization at surgery should be clear from the history. Determination of circulating levels of CK-MB or troponin postoperatively may provide evidence of perioperative ischemia or infarction.^{24,25} Often, diminished contractility after operation is caused by inadequate myocardial protection during surgery. Decreased myocardial contractility secondary to inadequate myocardial protection usually resolves within the first 24 hours postoperatively.

Persistent new myocardial dysfunction associated with ECG changes and echocardiographic evidence of new wall-motion abnormalities should raise suspicion that the problem is an occluded graft and MI. Measurements of CK-MB in serum are of limited usefulness because levels of this enzyme are commonly elevated after surgery as a result of manipulation of the heart and incision of the atria. If CK-MB levels are very high (>80 mg/dL), then perioperative MI is likely.³⁸ Cardiac troponins are more specific for diagnosing perioperative infarction. A comparison of CK-MB, troponin-T, and troponin-I showed that a troponin-I level of greater than 5 μ g/L was the most accurate indicator of MI.³⁹ Elevated serum concentrations of troponin-I are associated with a cardiac cause of death and major postoperative complications.⁴⁰ In addition, troponin-T concentrations measured after surgery are an independent predictor of in-hospital death after cardiac surgery.²⁵ If ischemia or MI is diagnosed, the patient may be taken urgently for angiography or reexploration and revascularization.

Postoperative valvular insufficiency may occur not only in patients with preexisting valvular lesions but also as a result of injury during surgery. The mitral valve is most commonly affected. Ischemia of the

papillary muscles due to inadequate myocardial protection or perioperative MI may lead to acute mitral regurgitation in the postoperative period. Diagnosis is often made by TEE in the OR, but inadequate CO and a new systolic murmur should prompt echocardiographic evaluation.

Rate and Rhythm

CO is the product of heart rate and stroke volume. Many dysrhythmias may adversely affect CO. If the heart rate is too low, CO may be compromised. If the heart rate is too fast, ventricular diastolic filling may be impaired, thus decreasing CO. Rhythm disturbances are common after cardiac surgery and may be divided into bradyarrhythmias and tachyarrhythmias; these categories are further divided into atrial and ventricular arrhythmias.

Bradycardia may lead to ventricular distention, increasing wall tension and decreasing coronary perfusion pressure, factors that may promote the development of ischemia and heart failure. A heart rate of 80 to 90 appears to be optimal, allowing adequate filling and preventing overdistention but not causing rate-related ischemia. Bradycardia may be corrected by pacing. In general, epicardial pacing wires are left in place after chest closure and are attached to an external pacemaker in the immediate postoperative period. If the dysrhythmia is sinus bradycardia, atrial pacing is usually optimal. The second most common cause of bradyarrhythmia after cardiac surgery is atrioventricular dissociation. The combination of atrial and ventricular leads allows atrioventricular pacing for managing dissociation. Synchronization of the atrioventricular interval between 0.1 and 0.225 seconds optimizes CO.⁴¹

AFib is the most common tachyarrhythmia. It occurs in 10% to 35% of patients after cardiac surgery, usually on the second or third postoperative day. Postoperative AFib is associated with increased morbidity and mortality and with longer, more expensive hospital stays.⁴² Independent predictors of postoperative AFib include advanced age, male sex, history of AFib, history of CHF, and pre-CPB heart rate greater than 100 beats/min.⁴³ Surgical practices such as pulmonary vein venting, bicaval venous cannulation, postoperative atrial pacing, and longer cross-clamp times also were identified as independent predictors of postoperative AFib. Patients who developed postoperative AFib had longer lengths of stay, both in the ICU and in the ward, compared with patients who did not develop the complication.

Although premature ventricular contractions are common, sustained ventricular arrhythmias are far less frequent. Severe ventricular arrhythmias occurring after cardiac surgery are related to ischemia, hypoxemia, hypovolemia, electrolyte abnormalities, effects of vasoactive drugs, or underlying preexisting cardiomyopathy.⁴⁴ In a series of 2100 cardiac operations, only 16 patients (0.8%) developed ventricular fibrillation or sustained ventricular tachycardia during an interval from 3 days to 3 weeks after surgery. Ten of these patients had undergone valve surgery.⁴⁵ Prognosis in these patients is dependent on the preoperative ventricular prognosis. In those with a left ventricular ejection fraction of less than 40%, the mortality rate may be as high as 75%.⁴⁶

Afterload

Ventricular afterload is the impedance to ventricular ejection during systole. Hypertension develops in as many as 60% of patients after surgery. Increased arterial blood pressure occurs even among patients without a preoperative history of hypertension. Predisposing factors include hypoxemia, hypercapnia, inadequate rewarming, pain, fluid overload, and increased sympathetic tone. Perioperative discontinuation of β -adrenergic blockers also may contribute to the development of postoperative hypertension. Hypertension and increased afterload may lead to myocardial ischemia by augmenting ventricular stroke work. Additionally, hypertension may lead to bleeding from surgical sites, aortic dissection, and increased risk of stroke.

Tamponade

Tamponade refers to the hemodynamic consequences of a collection of blood or other fluid in the pericardial sac. In postsurgical patients,

the presentation of tamponade may be subtle and differ significantly from classic descriptions. Equilibration of filling pressures typically is not seen. More commonly, patients present with isolated elevation of right atrial pressure caused by compression of the right atrium and superior vena cava. After cardiac surgery, as many as 66% of pericardial fluid collections are loculated posterior effusions.⁴⁷

Bleeding from the atrial cannulation site is a common cause of tamponade. As the pressure on the right atrium increases, ventricular filling is impaired, and CO decreases. Diagnosis of tamponade is made difficult by the high overall frequency of pericardial effusions after surgery. Echocardiographic studies have shown that moderate effusions are present in 30% of patients on the eighth postoperative day, with 2% of patients having large effusions.⁴⁸

Diagnosis of tamponade in the postoperative patient requires a high index of suspicion and prompt intervention. Any hemodynamic instability should be assessed for tamponade. Low CO, hypotension, and tachycardia accompanied by an elevation of the left, right, or both atrial pressures should lead to a prompt echocardiogram. Other signs that may be present include a widened mediastinum on chest radiography, dysrhythmias, and decreased ECG voltage. Because of the influence of positive pressure ventilation, the classic sign of pulsus paradoxus may not be present.

If time permits, the diagnosis of tamponade may be confirmed with the use of echocardiography. Although effusions are common, signs of compression or collapse of either atrium or right ventricle are diagnostic.⁴⁹⁻⁵¹ It is important to remember that the diagnosis may be made on clinical suspicion alone, and that treatment should not be withheld to await confirmation. Once tamponade is diagnosed, volume transfusion may temporize the situation. Pericardiocentesis is not effective in this situation, and prompt reexploration for hemostasis and evacuation of clot is indicated.

Respiratory Complications

Patients undergoing cardiac surgery are at risk for multiple pulmonary complications. These include PTX and pleural effusion in the immediate postoperative period. After the first 24 hours, patients sometimes develop acute lung injury (ALI), ARDS, or pneumonia. Diaphragmatic dysfunction secondary to phrenic nerve injury may occur.

Residual PTX is often seen on the initial postoperative chest radiograph and is commonly on the left side as a result of opening the left parietal pleura during dissection of the left internal mammary artery. The PTX usually resolves spontaneously as the chest tubes are placed on suction. Occasionally, a PTX is seen on the right side as a result of accidental incision of the right parietal pleura. Right PTX may progress to tension PTX and significant hemodynamic deterioration. This diagnosis should be considered in any unstable patient. Treatment consists of insertion of an additional chest tube.

Pleural effusion in the first 24 hours after cardiac surgery should raise the suspicion of hemothorax. Effusions should be watched carefully for expansion and correlated with other signs and symptoms of continued bleeding. Massive, expanding hemothorax is an indication for immediate reexploration and hemostasis. Pleural effusion after the first 24 hours is generally a benign process. Most pleural effusions resolve spontaneously. Thoracentesis should be performed only if the effusion occupies more than 50% of the lung field on radiography or if the patient has significant impairment of respiratory function.

ALI and ARDS are rare (<0.5%) complications after cardiac surgery, CPB, and blood transfusion. The mortality rate associated with this complication ranges between 15% and 70%.⁵² During the postoperative period, patients with ARDS were more likely to have had prior cardiac surgery or received more blood products and developed shock more frequently than patients without ARDS.⁵³

Nosocomial pneumonia may complicate any ICU stay. Patients who require mechanical ventilation for longer than 48 hours are at a particular risk. These pneumonias are usually caused by aspiration of oral or gastric secretions into the lungs. The incidence of nosocomial pneumonia may be reduced by diligent mouth care to prevent pooling

of secretions and elevation of the head of the bed to greater than 30 degrees. Nosocomial pneumonia carries a mortality rate of 24% to 50% and warrants appropriate broad-spectrum antimicrobial therapy.⁵⁴ Early broad-spectrum antibiotics (based on the cardiac ICU-specific antibiogram) should be initiated and then deescalated once the results of quantitative cultures are available.

Diaphragmatic dysfunction is usually caused by a cold-induced injury of the phrenic nerve as a result of the application of ice slush to the heart as part of the cardioplegia regimen. This complication occurs in up to 2% of patients undergoing cardiac surgery with topical hypothermia.^{55,56} While the patient is being ventilated with positive pressure, this injury will not be apparent. If preoperative pulmonary function was normal, unilateral diaphragmatic paralysis usually is well tolerated. Pulmonary function may be severely compromised if pulmonary problems were present preoperatively or if bilateral diaphragmatic injury occurs.⁵⁷ Such patients are at an increased risk of developing nosocomial pneumonia, failing to wean from the ventilator, and succumbing to death. Diaphragmatic dysfunction usually resolves spontaneously within 3 to 4 months.

Continued Bleeding

Continued bleeding is a common problem and requires immediate and aggressive management before the onset of further complications. The reasons for continued bleeding are often multifactorial and include inadequate surgical hemostasis, platelet dysfunction, coagulopathy, and inadequate heparin reversal. Often these factors occur in combination, and patients undergoing valve replacement are at an increased risk.⁵⁸

Multiple clotting abnormalities are possible, most of which result either directly or indirectly from the use of CPB.⁵⁹ The tubing, blood reservoir, and oxygenator membrane are all foreign surfaces that may activate the clotting cascade. Because the pump must be primed with either normal saline or lactated Ringer's solution, the priming process leads to substantial dilution of all blood components including red blood cells, platelets, and clotting factors. After CPB, the platelet count is decreased, and the remaining platelets are functionally deranged.^{60,61} There is sequestration of platelets in the liver, spleen, and CPB circuit itself. Systemic fibrinolysis due to activation of this system by the CPB circuit occurs.

Inadequate reversal of heparin should be diagnosed at the bedside by the activated coagulation test (ACT) or by measuring the activated partial thromboplastin time (APTT). Because the half-life of heparin is longer than that of protamine, heparin-induced anticoagulation may rebound in the immediate postoperative period. The treatment is administration of additional protamine.

Renal Dysfunction

Mild renal dysfunction is a common postoperative event (7%),⁶² with approximately 1% of patients diagnosed with acute renal failure (ARF) requiring renal replacement therapy. These patients have increased morbidity and mortality with prolonged ICU length of stay as much as fivefold.⁶²

A multicenter study of 2222 patients undergoing CABG identified 5 independent preoperative predictors of renal dysfunction: age 70 to 79 years or 80 to 95 years, CHF, previous myocardial revascularization, type 1 diabetes mellitus (DM) or preoperative serum glucose levels exceeding 300 mg/dL, and preoperative serum creatinine levels of 1.4 to 2.0 mg/dL. Independent perioperative factors that exacerbated risk were CPB lasting 3 hours or longer and various measures of ventricular dysfunction.⁶² The predominant predisposing factor appears to be low CO exacerbated by concurrent use of vasopressors such as phenylephrine.⁶³

Renal dysfunction tends to follow one of the three main patterns.⁶⁴ *Abbreviated ARF* (creatinine peaks on post-op day 4) is a transient event, most probably related to intraoperative renal ischemia. *Overt ARF* (creatinine peaks at a higher level than abbreviated ARF and then

decreases over weeks) occurs when the duration of the predisposing insult, usually low CO, is longer. *Protracted ARF* (frequently irreversible renal failure) occurs when a second insult, commonly sepsis or hypotension, is superimposed on the resolving renal function.

Neurologic Complications

Neurologic sequelae of CPB range from subtle neurocognitive deficits (appearing in up to 80% of patients) to stroke. To estimate the relative risks of neurologic sequelae associated with various clinical factors, a logistic regression model was applied to prospectively collected data from 273 patients enrolled at 24 American medical centers.⁶⁵ Adverse cerebral outcomes occurred in 16% of patients and were almost equally divided between type I (8.4%; 5 cerebral deaths, 16 nonfatal strokes, and 2 new transient ischemic attacks) and type II outcomes (7.3%; 17 new cases of intellectual deterioration persisting at hospital discharge and 3 cases of newly diagnosed seizure disorder). Resource utilization for these patients was significantly increased; median ICU stay was prolonged from 3 days to 6 to 8 days, and total duration of hospitalization was increased by 50% (type II outcomes) to 100% (type I outcomes). After discharge from the acute care setting, specialized care was required for 69% of the patients with adverse neurologic sequelae. Risk factors for type I outcomes related primarily to embolic phenomena including proximal aortic atherosclerosis, intracardiac thrombus, and intermittent clamping of the aorta during surgery. Risk factors for type II outcomes included, in addition to these factors, a preoperative history of endocarditis, alcohol abuse, perioperative dysrhythmia, poorly controlled hypertension, and low CO after CPB.

Gastrointestinal Complications

Acute abdominal complications are relatively rare after cardiac surgery. If they do occur, they are associated with extremely high rates of morbidity and mortality. One prospective study of 1116 patients undergoing CPB found that abdominal complications occurred in 23 (2.1%). Ten of these patients underwent subsequent abdominal surgery, and 20 died. Early complications occurred on postoperative days 6 and 7 and consisted of bowel ischemia or hepatic failure. These complications are probably related to perioperative hypotension and low CO.⁶⁶ Late complications consisted of pseudomembranous colitis, cholecystitis, pancreatitis, and rupture of a septic spleen.⁶⁷

Mild transient increases in circulating levels of hepatocellular enzymes are common after surgery. These changes are generally of no consequence; however, increased serum transaminase levels, if sustained or very high (e.g., serum alanine aminotransferase concentration >500 IU/L), may represent evidence of severe ischemic injury of the liver and carries a high risk of mortality. This complication is strongly associated with low CO and increased filling pressures, suggesting that liver ischemia is induced by a combination of decreased perfusion and venous congestion.⁶⁸

MANAGEMENT OF COMMON POSTOPERATIVE PROBLEMS

Optimization of Cardiac Output

Treatment of hypotension and low CO must be tailored to the cause. Again, it is useful to consider treatment in terms of preload, contractility, afterload, and rate and rhythm. Inadequate filling pressures are treated with volume infusion. The intravascular volume expander may be a crystalloid solution, a colloid solution, or packed red blood cells if hematocrit is low or there is evidence of ongoing bleeding. It is important to remember that inotropic therapy is ineffective and possibly detrimental if adequate blood volume is not restored.

If CO or blood pressure remains low despite intravascular volume resuscitation, then it is necessary to institute an inotropic or vasopressor support. No single agent is optimal in all cases. Rather, selection of the agent should be based on the suspected cause of low CO or

TABLE 157-2 Comparison of Relative Activity of Available Vasoactive Agents

| AGENT | α_1 | β_1 | β_2 | PHOSPHODI- ESTERASE INHIBITION | DOSE (mcg/kg per Minute) |
|----------------|------------|-----------|-----------|--------------------------------------|--------------------------------|
| Epinephrine | ++ | +++ | + | — | 0.01-0.15 |
| Norepinephrine | ++++ | +++ | + | — | 0.01-3 |
| Dopamine | ++ | ++ | + | — | 2-20 |
| Dobutamine | + | +++ | + | — | 2-20 |
| Phenylephrine | +++ | — | — | — | 0.4-9.1 |
| Milrinone | — | — | — | +++ | 0.375-0.75 |

—, no activity; +, mild activity; ++, moderate activity; +++, strong activity.

hypotension and knowledge of pharmacologic effects of the various inotropic and vasopressor drugs that are available (Table 157-2). If the primary cause of hypotension appears to be vasodilatation, administration of a vasoconstrictor (e.g., phenylephrine, norepinephrine, or vasopressin) is indicated. If hypotension is related to inadequate ventricular ejection, then inotropic therapy (e.g., epinephrine, norepinephrine, dopamine, or dobutamine) with a β -adrenergic agent should be instituted. In patients with chronic systolic dysfunction, response to these agents may be impaired. Chronically elevated levels of circulating catecholamines deplete myocardial norepinephrine stores and downregulate the expression of myocardial β -adrenergic receptors. In these patients, tachyphylaxis to β -adrenergic agonists may develop rapidly. Adding a phosphodiesterase inhibitor (e.g., amrinone or milrinone) is often effective in these patients.^{69,70} In all cases, agents should be titrated to achieve adequate end-organ perfusion.

Mechanical Support of the Circulation

Failure to respond to appropriate vasopressor or inotropic therapy may necessitate mechanical support of the circulation. IABP is the most commonly used method. The balloon is positioned in the aorta just distal to the take-off of the left common carotid artery. Inflation of the balloon during diastole increases the diastolic pressure above the balloon, thereby increasing the coronary perfusion pressure. Conversely, deflation during systole decreases the left ventricular afterload. This combination of hemodynamic effects ameliorates myocardial ischemia and improves CO.

Ventricular assist devices (VADs) are more effective than IABP for maintaining CO. Either the left ventricle or the right ventricle or both may be supported with VADs. Currently, VADs may be used either as a bridge to transplantation or as a bridge to recovery. Either situation assumes that the VAD is a time-limited intervention. There are some data to support the view that resting the heart through the use of a VAD may allow some recovery of acutely injured myocytes, permitting eventual withdrawal of mechanical support. If the heart is chronically diseased, there is little hope of recovery, and the VAD serves to support the patient until transplantation becomes possible.⁷¹⁻⁷³

Ongoing clinical trials are investigating the use of VADs as definitive therapy rather than as a bridge to transplantation. Implantation of these devices may increase the long-term survival of patients with end-stage heart failure.⁷⁴

Correction of Arrhythmias

AFib is the most commonly encountered arrhythmia after cardiac surgery. Prophylactic use of β -adrenergic blockers reduces the incidence of postoperative AFib, and they should be administered after cardiac surgery to all patients unless specific contraindications are present.⁷⁵ Prophylactic treatment with amiodarone and atrial overdrive pacing should be considered for patients who are at a high risk for

postoperative AFib (e.g., those with a history of previous AFib or mitral valve surgery).^{42,76}

If AFib develops after cardiac surgery, the intensivist needs to determine whether the primary strategy should be to control the ventricular rate or to restore normal sinus rhythm. If AFib is associated with hemodynamic instability or anticoagulation is contraindicated, rhythm management using electrical cardioversion or amiodarone is preferred.^{77,78} Overdrive pacing using atrial pacing wires also may be effective. The appropriate strategy for most stable patients may be control of ventricular rate, because most will spontaneously revert to sinus rhythm within 8 weeks after discharge.^{79,80} Appropriate agents to achieve ventricular rate control include intravenous or oral β -adrenergic blockers or calcium channel blockers. All patients with AFib persisting for longer than 24 to 48 hours should be anticoagulated unless there is a specific contraindication. Long-term outcomes are similar regardless of whether the rate-control strategy or the rhythm-control strategy is selected.^{81,82}

Postoperative ventricular arrhythmias should be treated immediately according to the current advanced cardiac life support protocols.²³ Any postoperative ventricular arrhythmia should prompt a search for an underlying cause. Importantly, ischemia should be ruled out. Patients with sustained ventricular arrhythmias should undergo electrophysiologic testing before long-term antiarrhythmic therapy is instituted. The implantable cardioverter-defibrillator device has been shown to be superior to drug therapy for patients with hemodynamically significant arrhythmias.⁸³

Hypertension in the Postoperative Period

Hypertension leading to an increase in ventricular afterload is a common cause of decreased CO. Hypertension may be controlled by an intravenous infusion of sodium nitroprusside, nitroglycerin, β -adrenergic antagonists, or calcium channel blockers. These agents should augment CO by reducing blood pressure and afterload in the hypertensive patient. Frequently, acute hypertension resolves within 24 to 48 hours postoperatively. If hypertension persists beyond this initial period of recovery, intravenous agents should be weaned and oral therapy initiated. Both β -adrenergic blockers and angiotensin-converting enzyme inhibitors have been shown to confer a long-term mortality benefit and should be started. If hypertension was not a problem preoperatively, prolonged antihypertensive therapy postoperatively usually will not be necessary.

Correction of Coagulopathy

Postoperative coagulopathy may promote bleeding and accumulation of blood in the chest or pericardial cavity. Aggressive measures must be used to correct the coagulopathy. A systemic approach to the evaluation and treatment of continued bleeding is needed; one such approach is outlined in Table 157-3. Hypothermia may contribute to coagulopathy. Therefore, profoundly hypothermic ICU patients must be actively rewarmed with the use of transcutaneous warming. Laboratory evaluation of suspected coagulopathy should include measurements of platelet count, prothrombin time (PT), APTT, ACT, and bleeding time. The use of thromboelastography (TEG) may be useful to guide component transfusion requirements.

Postoperative Bleeding

Bleeding that continues after correcting coagulopathy needs to be treated aggressively. Venous bleeding in the chest may be partially controlled by applying positive end-expiratory pressure (PEEP).^{84,85}

Continuing mediastinal hemorrhage, or the suspicion of cardiac tamponade, is an indication for immediate reexploration. Exsanguinating hemorrhage or impending arrest from tamponade may require that reexploration be carried out at the bedside in an ICU. Bleeding that is unresponsive to medical therapy and requires reexploration is usually associated with a surgical source. Accepted guidelines for reoperation include bleeding rates of 400 mL/h for 1 hour, 300 mL/h for 2 hours,

TABLE 157-3 Evaluation and Treatment of Postoperative Coagulopathy

| COAGULATION TEST | NORMAL RANGE | SUGGESTED TREATMENT |
|------------------|--------------------------|---|
| Body temperature | — | If less than 35.5°C, the patient should be actively rewarmed. |
| PT | 11-13.3 seconds | Administer fresh-frozen plasma. |
| PTT | 21-32 seconds | Consider additional protamine.* |
| Platelets | 140,000-440,000/ μ L | If <100,000, transfuse platelets. |
| Fibrinogen | 150-360 mg/dL | If <100, transfuse cryoprecipitate. |
| Bleeding time | 2.5-9.5 min | If prolonged and platelet count is normal, consider platelet dysfunction and treat with DDAVP and/or cryoprecipitate. |
| ACT | 90-120 seconds | Consider additional protamine.* |

*Excessive protamine may itself cause bleeding.¹⁰⁵

ACT, activated coagulation test; DDAVP, desmopressin acetate; PT, prothrombin time; PTT, partial thromboplastin time.

or 200 mL/h for 3 hours. A sudden decrease or total cessation of drainage from mediastinal tubes may be equally ominous. Cessation of drainage from a mediastinal or chest tube may be caused by clotted blood occluding the tube. If bleeding persists but drainage ceases, the result may be tamponade.

Reexploration is associated with increased morbidity and mortality. However, this increased mortality and morbidity may be partially explained by delays in the decision to reexplore that lead to avoidable open-chest resuscitations in the ICU.^{58,86,87}

Postoperative Renal Failure

The cornerstone of prevention and treatment of renal failure in the cardiac surgical patient is the maintenance of adequate renal perfusion. This goal is best achieved by optimizing circulating blood volume and CO. Multiple pharmacologic regimens for renal protection have been described. Dopamine at low “renal” doses (1-3 μ g/kg per minute) has been used. The rationale for this strategy is that dopamine activates type 1 dopaminergic (DA1) receptors, leading to renal artery dilation, natriuresis, and diuresis. However, numerous human studies have failed to show that low-dose dopamine prevents renal failure or improves survival.⁸⁸ Even low doses of dopamine increase CO, and this may be the basis for any increase in urine output observed.⁸⁹ Fenoldopam⁹⁰ and dexmedetomidine⁹¹ are DA1 receptor antagonists that have also been proposed as renal protective agents and used with mixed success.⁹²

Loop diuretics such as furosemide have been proposed as renal protective agents, not only because of their ability to produce diuresis and natriuresis but also because these drugs may reduce medullary tubular oxygen consumption. Mannitol, an osmotic diuretic, has been used to prevent the development of ARF. Neither mannitol nor furosemide has been shown to improve outcomes in patients with ARF.⁶² Indeed, these drugs may be deleterious because of their ability to promote diuresis and thus exacerbate hypovolemia and inadequate renal perfusion. Some success has been reported with the combination of mannitol, furosemide, and dopamine.⁹³ Infusing a solution containing these three agents promoted diuresis in patients with acute postoperative ARF and adequate CO and significantly decreased the need for dialysis in the majority of patients.⁹¹ Early administration of this solution in ARF caused early restoration of renal function to the normal or baseline status.⁹³

The failure of pharmacologic means of preventing and treating renal failure has led to interest in other methods. Early and intensive use of continuous venovenous hemofiltration achieved a better than

predicted outcome in a series of 65 consecutive patients with severe ARF who underwent cardiac operations.⁹⁴

Glucose Control

Studies have shown that tight control of blood glucose level in the ICU is associated with an increase in morbidity and mortality (Table 157-4). Hyperglycemia and insulin resistance are common in critically ill patients, even those who have not previously had DM. Results of a prospective randomized controlled study⁹⁵ in which 6104 critically ill adult patients were randomly assigned to receive either intensive insulin therapy (maintaining blood glucose concentration between 80 and 108 mg/dL) or conventional treatment (infusing insulin to keep blood glucose level 180 mg/dL or less) showed that, at 3 months, the intensive insulin therapy group had an increase in hypoglycemic episodes and ICU mortality.

Mechanical Ventilation

In uncomplicated recoveries, patients require only a short period of mechanical ventilation. Typically, volume-controlled ventilation is used until sedation is discontinued and the patient awakens. Once the patient is awake, hemodynamically stable, and without evidence of bleeding, a short trial of spontaneous ventilation is performed. If the weaning trial is successful, the patient is extubated. If continued mechanical ventilation is required because of respiratory failure or hemodynamic instability, either conventional volume-controlled ventilation or pressure support ventilation may be employed.

A small number of patients develop ALI or ARDS. In a large prospective trial of medical and surgical patients with ARDS or ALI, it was clearly beneficial to employ a lung-protective strategy (6 mL/kg ideal body weight) for mechanical ventilation.⁹⁶ No such study has been performed in cardiac surgical patients, but it seems reasonable to adopt the same guidelines. These recommendations apply only to patients with established ALI/ARDS; use of low tidal volumes has not been shown to be effective when used prophylactically.

Patients with ALI or ARDS typically require increasing levels of PEEP to support oxygenation. The effect of PEEP on ventricular output is controversial. There is evidence that the application of PEEP up to 30 cm H₂O decreases CO by reducing ventricular preload and displacing the interventricular septum toward the left, which restricts left ventricular filling.⁹⁷ Other studies have not supported this view. When adult patients with normal preoperative respiratory status were randomly assigned to treatment with graded degrees of PEEP between 0 and 10 cm H₂O during mechanical ventilatory support, there were no significant differences in cardiac index among the groups.⁹⁸ It is likely that the effects of PEEP on the circulation are widely variable among patients and that the appropriate strategy is upward titration of PEEP under close monitoring.

OUTCOMES OF CARDIAC SURGERY

Increasingly, health care is being driven by outcome data. Cardiac surgery has been one of the leading specialties in this field. It is difficult to assess results from crude mortality data, because these do not take into account case complexity and differing preoperative risks among patients. Crude comparisons of death rates may be misleading and may encourage surgeons to practice risk-averse behavior. Death rates should be stratified by risk. It is, however, possible to make some generalizations. Among low-risk patients undergoing CABG, mortality rates lower than 2% are achievable.⁹⁹ Higher mortality rates are to be expected in selected subgroups of patients with major preoperative risk factors (e.g., poor ventricular function, advanced age, and comorbid conditions) or major operative risk factors (e.g., reoperative surgery and complex operations).

A prospective cohort of 27,239 consecutive patients undergoing isolated CABG was examined to determine the risk factors for hospital mortality. After adjustment for patient and disease characteristics, the

TABLE 157-4 Protocol for Blood Sugar Control in the Postoperative Period

Decision to initiate IV insulin

If BG <200 mg/dL, begin D₅ ½ NS at 60-100 mL/h.

If BG >300 mg/dL, give stat dose of IV insulin, 0.1 U/kg body weight.



Initiate an hourly rate (total daily dose of insulin divided by 24).

For patients who have never taken insulin, give 0.02 U/kg body weight per hour.*



Check BG hourly and adjust according to the following table.

Recheck BG hourly.



If in desirable range (101-150 mg/dL), continue to check BG every 2 hours and adjust as necessary.

| CURRENT BG (mg/dL) | PREVIOUS BG (mg/dL) | | | | | | | |
|--------------------|---|---------------------------------------|-------------------------------------|---------------------------------------|---------|-------------------------------------|-------------------------------------|-------------------------------------|
| | <60 | 60-80 | 81-100 | 101-150 | 151-200 | 201-250 | 251-300 | 301-400 >400 |
| <60 | Withhold drip and give 1 ampule of 50% glucose; check BG every 30 min until >100 mg/dL, then reinitiate drip at 50% of previous rate. | | | | | | | |
| 60-80 | Withhold drip; check BG every 30 min until >100 mg/dL, then reinitiate drip at 50% of previous rate. | | | | | | | |
| 81-100 | ↓ Rate by 1 U/h | No change | | ↓ Rate by 25% or 0.5 U/h [†] | | ↓ Rate by 25% or 1 U/h [†] | | ↓ Rate by 50% or 2 U/h [†] |
| 101-150 | No change | | | ↓ Rate by 25% or 1 U/h [†] | | | | |
| 151-200 | ↑ Rate by 1 U/h | ↑ Rate by 0.5 U/h | | ↑ Rate by 25% or 1 U/h [†] | | No change | | ↓ Rate by 25% or 1 U/h [†] |
| 201-250 | ↑ Rate by 25% or 2 U/h [†] | | ↑ Rate by 25% or 1 U/h [†] | | | ↑ Rate by 1 U/h | | No change |
| 251-300 | ↑ Rate by 33% or 2.5 U/h [†] | ↑ Rate by 25% or 1.5 U/h [†] | ↑ Rate by 25% or 1 U/h [†] | ↑ Rate by 1 U/h [†] | | ↑ Rate by 1.5 U/h [†] | ↑ Rate by 25% or 2 U/h [†] | No change |
| 301-400 | ↑ Rate by 40% or 3 U/h [†] | | | | | | | |
| >400 | ↑ Rate by 50% or 4 U/h [†] | | | | | | | |

BEFORE DISCONTINUING INSULIN INFUSION

Ensure that the patient is able to tolerate oral intake.

Write orders for alternative glycemic management.

Precede discontinuation by 1-2 hours with subcutaneous dose of very rapid or rapid insulin. If patient has never taken insulin, use a dose equal to twice the hourly rate of IV insulin. Otherwise, use the dose of insulin or oral agent given before surgery/admission.

*For patients undergoing major surgery (e.g., cardiothoracic surgery, transplantation), higher doses may be necessary.

[†]Whichever is greater.BG, blood glucose concentration; D₅ ½ NS, 5% dextrose in half-normal saline; IV, intravenous; U, units.

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following comorbid conditions were found to be related to postoperative mortality: DM, vascular disease, chronic obstructive pulmonary disease, peptic ulcer disease, and dialysis-dependent renal failure.¹⁰⁰

Cardiac surgery is being performed more frequently in patients aged 80 years and older. In one study, the 30-day mortality rate for patients aged 65 to 75 years was 3.4% and for those older than 80 years was 13.5%. Older patients had longer ICU and postoperative lengths of stay. Although emergency operations and complex procedures carry high risks for octogenarians and increasing costs for the society, most of these patients may be offered operation with short-term morbidity, mortality, and resource use that only modestly exceed those of younger patients.¹⁰¹ Once discharged from the hospital, older patients report a high quality of life.¹⁰²

Overall, fewer than 10% of cardiac surgical patients spend more than 48 hours in the ICU. Most survive and eventually report improved functional status and a reasonable quality of life.^{103,104}

CONCLUSION

Most cardiac surgical patients may be discharged from the ICU to a step-down unit within 24 to 48 hours after operation, but an increasing number cannot. Patients who require longer and more intensive services in the ICU are typically older and sicker preoperatively. Adherence to best practices in the ICU optimizes the opportunity for even these high-risk patients to survive their operation and achieve a good quality of life after hospitalization.

The ongoing development of less invasive techniques in cardiology and cardiac surgery will, paradoxically, bring about a further increase in the complexity of cases treated in the cardiac surgical ICU as patients who are less sick are treated elsewhere. This trend will lead to increasing challenges for intensivists working in these units and allow them to continue to be at the forefront of critical care medicine.

KEY POINTS

1. Developments in interventional cardiology have led to older and medically complex populations being referred for cardiac surgery.
2. Much of the care of cardiac surgical patients should be protocol driven and conducted in specialized units.
3. Most patients undergoing cardiac surgery require only a shorter ICU stay.
4. Patients may be extubated once hemodynamic stability is achieved and mediastinal bleeding is deemed to be under control.
5. Low CO after surgery should be treated based on the components of the CO: rate, rhythm, preload, afterload, and contractility.
6. AFib continues to be a cause of significant morbidity.

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■ References for this chapter can be found at expertconsult.com.

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OVERVIEW OF LUNG TRANSPLANT

Lung transplantation offers hope for improved survival and quality of life for selected patients with end-stage lung disease. The availability of suitable donor organs and preservation injury remain the initial limiting factors to successful transplantation. Novel techniques aiming to extend the donor pool have resulted in the ability to offer transplantations to more patients both by allowing for better evaluation of questionable organs as well as by allowing potential treatment and repair of injured organs.^{1,2} Like other solid organ transplants, rejection and infection, as well as organ system dysfunction associated with the perioperative course, remain challenges.³ However, over 40 years of experience has led to substantial improvements in early outcome. This experience has been reflected in changes in various aspects in the field, including a different allocation system where priority is given based on medical urgency and expected outcome,⁴ donor and recipient assessments, innovative surgical techniques, better understanding of early complications, and the development of newer immunosuppressive medications.

Diagnoses for which adults undergo lung transplantation include chronic obstructive lung disease (COPD) from emphysema (32%), interstitial lung disease (24%), cystic fibrosis (16%), alpha-1 antitrypsin deficiency (5%), and others including sarcoidosis, congenital heart disease, and connective tissue disease complicated by advanced lung disease.³ Over the past 2 decades, the number of single lung transplant (SLT) procedures has remained stable, and the number of bilateral lung transplant (BLT) procedures has seen a steady increase. In recent years, most recipients who had the most common indications for lung transplantation underwent bilateral procedures, with COPD, either from emphysema or alpha-1 antitrypsin deficiency, being the most frequent diagnosis of transplantation. This has been the scenario where the trend toward bilateral transplantation has been more noticeable.³

Donor selection, procurement, and lung preservation protocols tend to be individualized on an institutional basis. The limited availability of donor lungs, however, has increased the scrutiny with which organs are judged in order to avoid rejecting them inappropriately. Significant lung contusion, smoking-related lung damage, pneumonia, pulmonary edema, and significant aspiration are prime concerns in evaluating the suitability of donor organs. Although already described as an independent association for primary graft dysfunction (PGD),⁵ donor's older age is being challenged at some centers as a risk factor for worsened outcomes. More transplants have been performed where the donor does not meet stringent criteria.⁶ Procurement and lung preservation protocols often include administration of antiinflammatory agents, pulmonary vasodilators, and antioxidants.

The surgical technique involves thoracotomy for SLT or transverse thoracosternotomy (clamshell incision) for BLT transplants. Minimally invasive techniques are being developed in some centers as well. The surgical procedure includes anastomoses of the pulmonary artery, atrium, and bronchus. Cardiopulmonary bypass (CPB) is avoided in the case of SLT and BLT, unless preexisting pulmonary hypertension precludes cross-clamping of the pulmonary artery or if cardiorespiratory stability cannot otherwise be maintained. On completion of the operation, a double endotracheal tube (EBT) is exchanged for a standard endotracheal tube (ETT), unless allograft function appears tenuous or there is evidence of air trapping. Heart-lung transplants are

performed utilizing either a clamshell incision or sternotomy. CPB is obviously a requirement in these patients. The vascular anastomoses include the aorta and a cuff of right atrium including both vena cavae. Bi-bronchial airway anastomoses, which are associated with less dehiscence than a single tracheal anastomosis, are performed.

MANAGEMENT OF CRITICALLY ILL LUNG TRANSPLANT CANDIDATES—BRIDGE TO LUNG TRANSPLANT

In recent years, the proportion of candidates requiring support beyond noninvasive measures including mechanical ventilation and extracorporeal life support (ECLS) has increased, resulting in a larger proportion of patients requiring intensive care management and support before transplantation.⁷

The field has learned that, in large-volume centers,⁸ outcomes are unaffected and that the technology around ECLS support has evolved to become simpler.⁹⁻¹² Technologic advances include heparin-coated circuits, development of polymethylpentene oxygenator membranes, introduction of centrifugal pumps, dual lumen cannulas, and miniaturized systems. Although these have translated into an increased interest toward the earlier implementation of ECLS, its use has been described as a risk factor for airway dehiscence, stroke, infection, and thromboembolic complications after transplantation.¹¹ Efforts toward ECLS without mechanical ventilator support—"awake ECLS"—aim to offset the risks of prolonged sedation and subsequent postoperative deconditioning.¹³ Awake ECLS has resulted in improved early outcomes.¹³

Intraoperative Issues

The choice of the type of surgical incision (clamshell incision vs. anterolateral thoracotomies vs. median sternotomy) for lung transplantation depends on several factors, which include single or bilateral lung transplantation, CPB use, history of prior surgery in the recipient, and surgeon's preference. Bilateral anterior thoracotomy (sternal sparing) performed for BLT has a lower rate of sternal infections and healing complications than clamshell incision.¹⁴ During surgery, three anastomoses are made on each side. From posterior to anterior, they include the bronchus, pulmonary artery, and pulmonary veins to the left atrium. Bronchial artery anastomosis is usually not made. In addition, lymphatic and nerve ending anastomoses are not made. About 30% to 40% of patients require CPB support, intraoperatively for hemodynamic instability or hypoxemia that occurs after clamping the first or second pulmonary artery. CPB is commonly required in recipients with pulmonary hypertension or in situations where independent lung ventilation is not possible.¹⁵ The tubing, cannulae, membrane oxygenators, and pumps used in the CPB machine trigger a systemic inflammatory response, and patients tend to be hypotensive from the resulting vasoplegia. Intraoperative extracorporeal membrane oxygenator machines have several advantages. They decrease the amount of circuit, thus decreasing the blood-air interface. There are a fewer number of blood products that are transfused and a lower incidence of PGD.¹⁶ At the conclusion of the surgery, the double-lumen endotracheal tube used for independent lung ventilation is changed to a

single-lumen tube. The patient is transferred to the intensive care unit (ICU) after chest closure. The patient is then weaned off of the ventilator and/or extracorporeal membrane oxygenation (EMCO) in the ICU.

Lung transplant recipients who have pulmonary hypertension require special attention. During surgery, every effort is made to prevent a sudden rise in pulmonary pressure that may cause right ventricular failure. Intraoperative transesophageal echocardiography (TEE) helps monitor the right ventricular function very closely. Inhaled nitric oxide (iNO), inhaled prostacyclin, and intravenous milrinone are used to support right ventricular function intraoperatively and during the immediate postoperative period.¹⁷

Immediate Postoperative Intensive Care Unit Management

Weaning the patient off of the mechanical ventilator and ECMO is performed by the ICU physician who works in close collaboration with the thoracic surgeon.¹⁸ Stabilization of respiratory function and ventilator weaning are the initial goals when the patient arrives in the ICU from the operating room. Either pressure or volume target ventilation is used. The goal is to keep the airway pressures low to avoid barotrauma to the fresh bronchial anastomoses and prevent atelectasis. Lung protective ventilation strategy with tidal volumes (VT) around 6 mL/kg of predicted body weight and low to moderate PEEP (positive end-expiratory pressures) should be used.¹⁹ High PEEP should be avoided. In patients who undergo SLT, it might be challenging to ventilate the graft as the compliance of the native lung will be different. Care should be taken to avoid overinflation of the native emphysematous lung as this might lead to hemodynamic compromise from auto-PEEP or intrinsic PEEP. Patients typically present with hypoxemia, hypercapnia, and hemodynamic instability. Decreasing the respiratory rate, increasing the expiratory time, and decreasing the PEEP can help. If the above measures do not help, brief disconnection from the ventilator circuit should be considered. If the situation continues, placement of a double lumen tube and independent lung ventilation should be considered.²⁰ Likewise, the compliance of the native fibrotic lung will be worse when compared to the new graft. This might risk overinflation of the new transplanted allograft. Mild pulmonary edema is a common finding in transplanted lungs due to the absence of lymphatic drainage. This usually clears up in the first few days. If end organ perfusion is adequate, increase in preload is avoided.^{19,21} iNO is routinely used in patients with pulmonary hypertension and right ventricular failure in the operating room. However, the intraoperative use of iNO does not seem to decrease the incidence of PGD.^{22,23} The patient is rapidly weaned from iNO in the ICU. As soon as clinical stability is achieved, weaning from the mechanical ventilator is started. The oxygen fraction is rapidly decreased, if tolerated.¹⁹ The majority of the patients will be weaned and extubated within the first 24 hours.^{20,23} Early extubation minimizes the chance of pulmonary infections and stress on the bronchial anastomoses. Patients can be extubated to noninvasive positive pressure ventilation (NIPPV). This helps in unloading of the respiratory muscles, decreasing respiratory rate, dyspnea, and improving ventilation/perfusion mismatch. NIPPV can also be used in recipients who demonstrate phrenic nerve dysfunction.²⁴ For patients requiring prolonged mechanical ventilation, a complicated postoperative course should be considered for early tracheostomy.²⁴ If there is difficulty in liberating from the mechanical ventilator, early tracheostomy should be considered as this would minimize sedation and help with physical therapy while providing easier access for secretion clearance.¹⁵ Patients who require reintubation can also be considered for tracheostomy. In debilitated patients, early tracheostomy may provide considerable benefit if prolonged mechanical ventilation is required. If patients cannot be extubated, the decision to perform a tracheostomy should be made early on in the first week.²⁵ Although lung transplant recipients who end up with a tracheostomy tend to be sicker, have a longer ICU stay, and be on prolonged ventilation, there is no difference in their short- and long-term survival compared to recipients who do not have a tracheostomy.

Tracheostomy in this population is an important option that enables weaning from the mechanical ventilator and is associated with better patient tolerance.²⁶ An early tracheostomy decreases the use of sedation and helps with weaning, mobilization, and physical therapy.²⁵ Chest tube removal depends on the 24-hour drainage from each tube. Apical chest tubes are removed first, followed by the basilar tubes, provided their drainage is less than 150 mL/24-hour period.¹⁵ Vigorous airway clearance techniques to mobilize secretions are an essential component of the recovery process after extubation. These include bronchodilators, incentive spirometry, flutter valve, chest physiotherapy, and nebulized hypertonic saline.

Pain control is an essential component of the postoperative ICU care. Adequate analgesia is essential to prevent splinting of the chest that would cause atelectasis. Fentanyl infusion and patient-controlled analgesia pumps are used once patients are more awake. Morphine is avoided as the patients' creatinine clearance tends to fluctuate with the initiation of calcineurin inhibitors, and there is a risk of accumulation of toxic metabolites of morphine. During surgery, patients undergo stretching of thoracic joints, ribs, vertebrae, and muscles; manipulation of pleura and lungs; and placement of chest tubes. All of the above cause considerable amount of pain when patients wake up from anesthesia. Poor pain control prevents patients from coughing and expanding the graft, thus increasing the risk of pulmonary complications. Moreover, the transplanted lungs are denervated and lack the cough reflex. Patients tend to splint from pain and as a result, diaphragmatic excursions are prevented, further causing retention of mucus that leads to atelectasis. Thoracic epidural analgesia is used for unilateral or bilateral thoracotomy. Epidural analgesia also decreases opiate requirements, thus decreasing sedation from opiates and enabling patients to participate more in mobilization and physical therapy.²⁷ An oral regimen consisting of oxycodone is started once patients are extubated and able to tolerate oral medications. Nonsteroidal antiinflammatory drugs are avoided for analgesia as they tend to worsen renal function, especially in patients who are on tacrolimus or cyclosporine.

Immunosuppression

Immunosuppression is initiated in the operating room. The first dose of an induction agent, like basiliximab (used in our center), is administered on the day of surgery. The second dose is repeated on the fourth postoperative day. The first dose of solumedrol (10 mg/kg) is administered just before perfusion of the first graft. This is followed by 1 g of intravenous mycophenolate mofetil. Tacrolimus is initiated after the arrival of the patient in the ICU. This practice might vary slightly from one center to another.

The main immunosuppressive drugs after transplantation include a combination of calcineurin inhibitors (tacrolimus or cyclosporine), antimetabolites (mycophenolate mofetil or azathioprine), and steroids. Calcineurin inhibitors are the cornerstone of the regimen. We default all patients to tacrolimus, mycophenolate mofetil, and prednisone. The dose of tacrolimus is gradually titrated to a tacrolimus trough level of 10 to 14 ng/mL, while monitoring the serum creatinine levels closely. Mycophenolate mofetil is administered at a dose of 1 g twice daily while cautiously monitoring for cytopenias.

Antimicrobials

Broad-spectrum antibiotics that would cover gram-positive and gram-negative organisms are initiated prior to making skin incisions on the recipient. Typical antibiotics include a combination of vancomycin and cefepime. Donor bronchus culture and prior cultures from recipient sputum guide the types and duration of the antibiotics. Trimethoprim-sulfamethoxazole, a prophylaxis against *Pneumocystis jiroveci* is started and given three times a week. Antifungal prophylaxis depends on pretransplant risk factors for aspergillus. Recipients with cystic fibrosis and cavitary disease are thought to have a high risk and are prophylaxed with oral voriconazole or posaconazole and inhaled

amphotericin. Patients who are at low risk for aspergillosis are prophylaxed with itraconazole. The oral prophylaxis is continued for 3 months. CMV prophylaxis depends on the CMV serologic status of the donor and recipient. If the donor is positive and the recipient is negative (D+/R−, CMV mismatch), the recipient is prophylaxed with daily valcyte. If the donor is CMV negative and the recipient is CMV positive (D−/R+) or if the donor and recipient are CMV positive (D+/R+), (intermediate-risk group) the recipient is prophylaxed with valcyte for 6 to 12 months. If the donor and recipient are CMV negative (D−/R−, low-risk group), the recipient is prophylaxed with acyclovir, which is effective against all herpesviruses other than CMV.

General Measures

Patients tend to get constipated from immobilization and opiate analgesics used in the immediate postoperative period. This is prevented by instituting scheduled laxatives. Constipation and ileus also interfere with absorption of immunosuppressive medications. Hence, great care is taken to prevent constipation and the slowing of gut motility. This is especially true in patients with cystic fibrosis who might require more aggressive measures that include osmotic laxatives, in addition to stimulant laxatives.¹⁸ On a similar note, electrolyte imbalance could make constipation and ileus worse. Magnesium, calcium, potassium, and creatinine levels need to be monitored closely. Hypomagnesemia results from the use of tacrolimus, proton pump inhibitors, and diuretics in the initial postoperative period. Intracellular levels of magnesium might be lower despite normal serum levels. This should be aggressively corrected to minimize neurotoxicity and cardiac dysrhythmias. Magnesium is a cofactor in muscle function and gastrointestinal motility.¹⁸ The incidence of venous thromboembolism in lung transplant recipients is much higher than in other populations. In fact, it is thought to be between 8% and 29%. As a result, deep vein thrombosis prophylaxis is enforced as soon as possible with low-molecular-weight heparin.²⁸

Lung transplant recipients have a high risk of gastroesophageal reflux from underlying esophageal dysmotility and recent thoracic surgery. Measures to control acid reflux and aspiration include keeping the head end of the bed elevated at a 30-degree angle or more and using a proton pump inhibitor.

Early and aggressive physical therapy is crucial in the success of lung transplantation to avoid critical care illness polyneuromyopathy. Once patients are extubated, they are mobilized to sit in a chair, twice a day. If patients are able to achieve adequate analgesia, they are made to walk with assistance.

POSTOPERATIVE COMPLICATIONS

Infectious Complications

Infectious complications are higher in lung transplant recipients compared to other solid organ transplantations. This is most likely related to the fact that the allograft is exposed to the environment. Moreover, a greater magnitude of immunosuppression is used in lung transplantation.²⁹ Bacterial infections of the lower respiratory tract are the most common infectious complications. The risk factors for these include immunosuppressed status, mechanical ventilation, and blunted cough due to pain.

Bleeding Issues

Increased bleeding is seen in recipients who have had previous pleurodesis and use of intraoperative or preoperative extracorporeal circulation (ECMO/CPB). Coagulopathy should be rapidly corrected with the transfusion of blood products. If there is increased bloody chest tube drainage of more than 200 mL/30 min, exploratory surgery should be considered. Even if the source of bleeding is not identified, the evacuation of blood products prevents collapse of the graft and development of the compartment syndrome.¹⁹

Acute Renal Failure

Acute renal failure is a common complication due to the use of calcineurin inhibitors. It results from intense afferent arteriole vasoconstriction caused by tacrolimus or cyclosporine resulting in decreased renal blood flow and glomerular filtration rate. Presence of systemic hypertension further worsens renal function. Hence, blood pressure should be well controlled, preferably with calcium channel blocking agents.^{15,29} Nonsteroidals should be avoided for analgesia. Diuretics should be used sparingly.

Atrial Tachyarrhythmias (Atrial Fibrillation, Atrial Flutter, and Supraventricular Tachycardia)

Atrial tachyarrhythmia is common in this population and occurs in 34% to 47% of the patients.¹⁵ The incidence is higher in double lung transplants than in single lung transplants and tends to occur 3 to 7 days after surgery. The incidence is also higher in older patients, patients who had been on CPB, and patients who had atrial manipulations. Electrolyte imbalance, sympathetic stimulation from pain, and anxiety precipitate atrial fibrillation. Rate control with beta blockers is preferred. Antiarrhythmic drugs are used if patients fail to respond to initial treatment. Amiodarone, sotalol, and propafenone have been used by different centers.³⁰⁻³²

Phrenic Nerve Injury and Diaphragmatic Paralysis

Phrenic nerve injury and diaphragmatic paralysis are underdiagnosed complications, with an incidence ranging from 3% to 40%. Difficulty weaning from the ventilator or thoracoabdominal asynchrony during spontaneous breathing trials, and a disproportionate elevation of the hemidiaphragm on postoperative chest X-rays should raise suspicion for this complication. Patients might also be hypercapneic on arterial blood gases. The diagnosis can be confirmed on a chest ultrasound or fluoroscopy when the recipient is breathing spontaneously. Absence of hemidiaphragmatic movement further confirms the diagnosis. Diaphragmatic weakness causes prolonged mechanical ventilation and increased length of hospital stay.¹⁹

Gastroparesis and Gastroesophageal Reflux

Vagal nerve injury during surgery might result in gastroparesis and gastroesophageal reflux. Patients might experience delayed gastric emptying, early satiety, epigastric fullness, nausea, vomiting and worsening acid reflux. Acid reflux increases the risk of microaspiration and injury to the new graft and can cause acute rejection. Hence, in the immediate postoperative recovery in the ICU, it is important to be vigilant of this complication. The head end of the bed has to be kept elevated to prevent aspiration. Likewise, prokinetics like azithromycin and metoclopramide are administered for gastroparesis until there is spontaneous recovery.¹⁹

Thrombotic Microangiopathy

Thrombotic microangiopathy is a life-threatening complication caused by small-vessel microthrombi. It results from endothelial injury, microcirculatory thrombosis, fibrin deposition, and platelet consumption. Microangiopathic hemolytic anemia, renal failure, thrombocytopenia, fever, and neurologic abnormalities are seen. This occurs due to tacrolimus or cyclosporine and is common in the first 3 months after transplantation.¹⁵ Incidence of thrombotic microangiopathy from calcineurin inhibitors is thought to be between 3% and 4.5%.³³ Low levels of ADAMTS-13 are not found in calcineurin-induced thrombotic microangiopathy, which is in sharp contrast to classic thrombotic thrombocytopenic purpura (TTP). Treatment includes discontinuation of the offending calcineurin inhibitor. Once the condition

improves, another calcineurin inhibitor can be attempted under close monitoring.

Hyperammonemia

Hyperammonemia occurs from a deficiency in hepatic glutamine synthetase, a urea cycle enzyme that plays an important role in processing nitrogenous waste.²⁹ This is a fatal complication that occurs in the first 30 days after transplantation. Symptoms include encephalopathy, lethargy, agitation, seizure, tremors, and coma.²⁹ Risk factors include total parenteral nutrition (TPN), lung transplantation for primary PAH. Treatment includes discontinuation of TPN, lactulose, neomycin, and aggressive hemodialysis.¹⁵

Bronchial Necrosis and Dehiscence

Bronchial circulation is not established during transplantation. Perfusion to airways and parenchyma is solely dependent on the blood supply from pulmonary arterial circulation. Pulmonary artery blood supply may be insufficient during the perioperative period, especially when vasopressors are used for hypotension. This might result in ischemic injury to the anastomosis or post anastomotic bronchus.³⁴ Relative ischemia exacerbated by intra- or postoperative hypotension and hemodynamic fluctuations makes anastomoses susceptible to necrosis, dehiscence, and infection. Severity of necrosis varies from commonly encountered mild focal necrotic sloughing to extensive necrosis, perforation, and bronchial dehiscence.³⁴ This usually occurs 1 to 5 weeks post operation with an incidence of 1% to 10%.³⁵ Hence, anastomosis should be examined carefully during every bronchoscopy. Clinical features include dyspnea, pneumomediastinum, subcutaneous emphysema, pneumothorax, lung collapse, and persistent air leaks in the early posttransplant period.³⁶ Since chest x-rays are unreliable, if bronchial dehiscence is suspected, computed tomography (CT) of the chest should be considered as it will very clearly delineate the bronchial defects and extraluminal air around the anastomosis.³⁴ Placement of self-expanding metallic stents that provoke granulation tissue can be used for healing.^{34,35}

Pulmonary Arterial Stenosis

Patients present with hypotension and evidence of severe right heart failure. This mimics a pulmonary embolism and can be treated with surgical correction or stent placement.

Pulmonary Vein Stenosis/Pulmonary Venous Obstruction

Pulmonary venous obstruction after lung transplantation is a very rare complication. It is associated with high morbidity and mortality unless recognized very early in the postoperative period. Patients present with progressive hypoxemia and infiltrates in the graft on chest x-ray, and it mimics acute pulmonary edema. Respiratory secretions in the endotracheal tube could be frothy pink or hemorrhagic. The pulmonary capillary wedge pressure could be high. This condition is diagnosed with TEE. The severity of the hypoxemia depends on the number of lungs transplanted, if pulmonary venous obstruction is unilateral or bilateral, and if the recipient had prior pulmonary hypertension. In patients who have undergone SLT and have prior pulmonary hypertension, pulmonary venous stenosis in the graft will cause severe hypoxemia and graft failure very early on. Bedside TEE is a very helpful tool to detect this condition. CT angiography is another option. Once diagnosed, patients need to be taken back to the operating room for reconstruction of the venous anastomoses.³⁷

Thoracic Compartment Syndrome

Thoracic compartment syndrome is seen in the immediate postoperative period, either immediately after chest closure or several hours

later. Patients present with hemodynamic instability. This complication is common in BLT, especially if there is a prolonged intraoperative course and transfusion of multiple blood products and/or use of CPB. Clinical features include high ventilator pressures, refractory hypotension, and progressive acidosis. Worsening lactic acidosis, tissue perfusion, renal function, and urine output are also noted. Immediate thoracotomy and delayed closure are recommended.³⁸

IMMUNOLOGIC CAUSES OF ALLOGRAFT DYSFUNCTION AFTER LUNG TRANSPLANTATION

Immunologic causes of allograft dysfunction after lung transplantation can be classified as immediate post-lung transplant complications (hyperacute rejection), within the first 72 hours after the transplant (PGD), and later events such as acute rejection (acute cellular rejection [ACR] and antibody-mediated rejection [AMR]), and chronic lung allograft dysfunction (CLAD). Other causes of allograft dysfunction such as infection, vascular anastomotic complications, and bronchial anastomotic complications have been discussed elsewhere.

Primary Graft Dysfunction

PGD is a form of acute lung injury that occurs within the first 72 hours after lung transplantation and is triggered by ischemia-reperfusion injury. PGD manifests as progressive hypoxemia and the presence of radiographic pulmonary infiltrates without other identifiable causes such as cardiogenic pulmonary edema, pneumonia, hyperacute rejection, or pulmonary venous anastomotic obstruction. It affects 10% to 35% of lung allograft recipients and is the major cause of early morbidity and mortality after lung transplantation.³⁹ In addition, PGD has been associated with an increased risk of CLAD, which is the major cause of late mortality after lung transplantation.⁴⁰

In 2005, the International Society of Heart and Lung Transplantation (ISHLT) Working Group on PGD proposed a standardized definition and grading system based on radiographic pulmonary infiltrates. A $\text{Pao}_2:\text{Fio}_2$ (P:F) ratio assessed immediately after lung transplantation (T0) and at 24 hours (T24), 48 hours (T48), and 72 hours (T72) post transplantation was suggested (Table 158-1).⁴¹ Subsequent validation studies using the standardized definition of PGD demonstrated a better discrimination of grade 3 PGD to predict early mortality. Grade 3 PGD at T72 accounted for 50% of all-cause mortality within the first 30 days post transplantation and demonstrated the most robust association with early and overall mortality after lung transplantation compared to the other grades of PGD.⁴²⁻⁴⁵

Prior studies have proposed several risk factors for the development of PGD based on the donor, recipient, and surgical variables (Table 158-2). Some of these risk factors are potentially modifiable (e.g., Fio_2 at reperfusion, obesity, cold ischemia time) and thus may suggest preventative strategies.⁴²

The pathogenesis of PGD is not well understood. The underlying etiology is thought to be an inflammatory cascade initiated by ischemia-reperfusion injury after lung transplantation, which ultimately leads to activation of the innate immune system and an influx of neutrophils into the lungs.^{49,50} During the past decade, several strategies targeting putative pathways in PGD have been studied, such as the use of iNO, modulation of the complement cascade, instillation of surfactant, and more recently, prevention of neutrophil extracellular traps (NETs) formation using an antiplatelet agent or intraalveolar disruption of NETs using DNase I.⁵¹⁻⁵³

Currently, the therapy for PGD remains generally supportive and draws from therapies applied in patients with ARDS, including lung-protective ventilation strategies. Additionally, pressure-controlled ventilation modes may be utilized to minimize barotrauma and airway anastomosis complications. Diuresis should be initiated, with blood pressure support, if needed, and excess fluid administration should be avoided.⁵⁴ Despite the encouraging results with iNO administration to

TABLE 158-1 2005 ISHLT Primary Graft Dysfunction Taxonomy

| GRADE AT T0, T24, T48, T72 | RADIOGRAPHIC INFILTRATES CONSISTENT WITH DIFFUSE PULMONARY EDEMA | PAO ₂ :Fio ₂ | SPECIFIC EXCEPTIONS |
|----------------------------|--|------------------------------------|--|
| 0 | — | Any | |
| 1 | + | >300 | On nasal cannula or Fio ₂ < 0.3 |
| 2 | + | 200-300 | |
| 3 | + | <200 | Any patients on ECMO or on NO with Fio ₂ > 0.5 MV |

ECMO, extracorporeal membrane oxygenation; Fio₂, fraction of inspired oxygen.

Adapted from Christie JD, Carby M, Bag R, et al. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2005 24:1454–1459.

TABLE 158-2 Risk Factors for Development of PGD Based on Donor, Recipient and Surgical Variables

| DONOR VARIABLES | RECIPIENT VARIABLES | SURGICAL VARIABLES |
|--------------------------------|-------------------------------|---|
| Any smoking history | Sarcoidosis | Use of cardiopulmonary bypass |
| African American race | Idiopathic pulmonary fibrosis | Large-volume blood product transfusion |
| Age > 45 | Pulmonary hypertension | |
| Head trauma | Overweight or obese | Single lung transplant |
| Prolong mechanical ventilation | | Elevated Fio ₂ during reperfusion (Fio ₂ > 0.4) |

Fio₂, fraction of inspired oxygen.

Adapted from references^{42,46-48}.

prevent and treat severe PGD suggested by several animal studies and case series,⁵⁵⁻⁵⁸ randomized, controlled studies did not support efficacy for iNO use in the clinical setting.^{22,59} However, despite the lack of an established role for iNO in prevention or treatment of PGD, its use may be justified as salvage therapy in selected cases for improving oxygenation, reducing mean pulmonary arterial pressure, and increasing mean systemic arterial pressure early after transplant.⁶⁰

Institution of venovenous (VV) ECMO in patients with profound respiratory failure due to PGD has gained in popularity with potentially good survival, if started early.^{61,62} In cases with refractory respiratory failure, retransplantation has been performed. However, predicted survival is poor, and it is generally not recommended.^{54,63}

Acute Rejection

Acute rejection after lung transplantation is common and continues to affect approximately 40% of lung transplantation recipients in the first year post transplantation.⁶⁴ The clinical manifestations are variable, nonspecific, and potentially confounded by coexisting diseases and processes. The presentations range from being asymptomatic with no radiographic changes, detected via routine posttransplantation surveillance biopsies, to a clinical picture resembling ARDS.⁶⁵ Acute rejection after lung transplantation encompasses ACR and AMR.

Acute Cellular Rejection

ACR is the result of an immune reaction against donor antigens that are expressed on the surface of donor cells and recognized by recipient lymphocytes. Recipient lymphocytes can react to various donor antigens such as blood group antigens and human leukocyte antigens (HLAs). HLAs are highly polymorphic cell-surface molecules and can

lead to a robust immune response when mismatched between donor organ and recipient. The lung is a rich lymphoid organ and possesses all immune cell lines necessary for initiation and maintenance of an immune reaction. Shortly after transplantation, the donor HLA proteins are presented to recipient T cells by the donor's own antigen presenting cells (APCs) ("direct pathway") or later by migrated recipient APCs to the transplanted lung ("indirect pathway"). APC stimulation induces naive T cells to become memory T cells capable of direct and rapid recognition of alloantigens and subsequent injury.^{66,67}

ACR is defined as the presence of perivascular and/or peribronchiolar lymphocytes in the absence of infectious etiologies. To date, bronchoscopic transbronchial biopsy remains the gold standard for diagnosis of ACR.^{68,69} However, multiple studies have been conducted in assessing less invasive tests such as bronchoscopy-guided airway brushings,⁷⁰ bronchoalveolar lavage (BAL),⁷¹⁻⁷³ or serum biomarkers for diagnosis of ACR.⁷⁴ Similarly, spirometry testing has utility but is not diagnostic.⁷⁵ Thus after several decades of attempts to find a less invasive, more precise, surrogate marker of ACR in lung transplantation, bronchoscopic tissue analysis remains the most reliable diagnostic modality.

Acute rejection can be seen as early as a week after lung transplantation. Although ACR is more often present as a nonspecific decline in spirometry with no significant radiographic changes, it can manifest as a fatal hypoxic respiratory failure with diffuse pulmonary infiltrates in its severe form. This can make the diagnosis and treatment of other ICU complications difficult. ACR presentation can mimic symptoms of pneumonia, and sometimes ACR can be triggered by earlier pneumonia. Therefore, development of new infiltrates after lung transplantation requires diagnostic evaluation using bronchoscopy with BAL and transbronchial biopsy. It is important to mention that ACR is directly responsible for only a small proportion of deaths in lung transplantation recipients. In fact, less than 4% of deaths are attributable to ACR in the first posttransplant month, and, at later time points, this incidence decreases to less than 2%.⁶⁴ Nevertheless, much attention has been paid to the early diagnosis and treatment of ACR as it remains the most significant risk factor for development of CLAD, which is the ultimate cause of mortality from lung transplantation.^{76,77}

The common first-line therapy for ACR is high-dose steroids with intravenous methylprednisolone; doses range from 10 to 15 mg/kg daily for 3 days, followed by a prednisone taper.⁷⁸⁻⁸⁰ The therapeutic plans for persistent or recurrent acute rejection are variable among centers, nevertheless warranting further augmentation of immunosuppression. This can be achieved by a repeat course of pulse steroids, optimization of maintenance immunosuppression,^{78,82} anti-T-cell agents such as polyclonal ATGs, or an anti-CD52 monoclonal antibody (alemtuzumab) in the treatment of severe and refractory ACR.^{80,83}

Antibody-Mediated Rejection

AMR is now a widely accepted complication after lung transplantation.^{80,84,85} AMR is mediated by donor-specific antibodies (DSA), produced by B cells or plasma cells, and upon binding to their cognate

antigen in the transplanted lung, they cause a deleterious effect via complement-dependent⁸⁶ and complement-independent pathways.^{86,87} DSA may be present at the time of transplantation (sensitized recipient) or develop de novo following transplantation.⁸⁸

The presence of DSA prior to transplantation can lead to hyperacute rejection, which is the most severe form of AMR, and occurs within minutes to hours after lung transplantation. The clinical manifestations are the rapid development of diffuse pulmonary infiltrates and hypoxia followed by systemic inflammatory response syndrome including coagulopathy, thrombocytopenia, oliguria, and hemodynamic instability.^{85,89-91} While hyperacute rejection is generally considered to be a fatal complication after lung transplantation, there are a few case reports of survival after enforcing aggressive immunotherapy strategies.⁹²⁻⁹⁴ Therapeutic approach to hyperacute rejection includes various combinations of high-dose steroids, plasmapheresis, cyclophosphamide, high-dose intravenous immunoglobulin, antithymocyte globulin (ATG), and rituximab, an anti-CD20 monoclonal antibody.^{85,89-94}

Aside from the risk for development of hyperacute rejection, the presence of DSA prior to lung transplantation has been associated with ACR, AMR, and CLAD.⁹⁵⁻⁹⁸ Therefore, prevention through the avoidance of the donor with known DSA HLA targets has been common, but it can significantly limit access to a transplant in the sensitized recipients.⁹⁹⁻¹⁰¹ Alternatively, pretransplantation desensitization using a combination of plasmapheresis, ATG, intravenous immunoglobulin (IVIG), and mycophenolate has been reported with equivalent post-transplantation outcomes to unsensitized patients.^{95,102-104} Overall, hyperacute rejection has become rare since the implementation of more sensitive methodologies for screening recipient HLA antibodies before transplantation.

Pretransplant DSA, as well as the de novo development of DSA after lung transplantation, can be asymptomatic (silent) or result in clinical manifestations of antibody-mediated rejection.^{95-97,103} The clinical presentations of ACR and AMR are indistinguishable. Additionally, ACR and AMR can copresent or one can trigger the other form of rejection.^{105,106} Unfortunately, AMR in lung transplantation has remained a diagnostic challenge.^{88,107} The lung transplant recipient presenting with an otherwise unexplained drop in lung function, anti-HLA DSA, a neutrophilic capillaritis, and positive C4d staining on transbronchial biopsy is highly likely to have AMR as the cause for graft dysfunction. In such cases, a diagnosis of “definite AMR” is suggested.^{88,90,107} However, this scenario is uncommon, and the more common clinical presentation is of a patient with an unexplained drop in pulmonary function and a new or increasing titer DSA. In these cases, lung biopsy does not suggest an alternative diagnosis or demonstrate confirmatory features of AMR. Therefore, the absence of confirmatory histology should not automatically rule out the diagnosis of AMR.^{90,107}

In general, there is no consensus agreement about the choice of agent or duration of therapy for AMR. Therapeutic options have been extrapolated from renal transplant and other areas of medicine without clinical trials. Treatment has generally consisted of multiple sequential interventions. It is very common to initiate therapy with pulse steroids (methylprednisolone 0.5-1 g daily for 3-5 days),¹⁰⁸ followed by plasmapheresis and high-dose IVIG.¹⁰⁹⁻¹¹² In recent years, there has been more interest in adding rituximab to the therapeutic regimen in order to deplete mature B cells and decrease the rate of recurrence of AMR.^{112,113} Additionally, a plasma cell-targeted therapy using proteasome inhibitors such as bortezomib has been used

successfully in management of AMR refractory to IVIG, plasmapheresis, and rituximab.¹¹⁴

Chronic Lung Allograft Dysfunction

CLAD is characterized by persistent loss of pulmonary function, which cannot be explained by other potentially reversible complications such as acute rejection, infection, or bronchial stenosis. It affects up to 50% of lung transplant recipients after 5 years and is the major cause of overall morbidity and mortality after lung transplantation.^{7,115,116} CLAD is an umbrella terminology embracing different phenotypes including obstructive CLAD and restrictive CLAD.^{116,117} Obstructive CLAD includes bronchiolitis obliterans syndrome (BOS), which is caused by recurrent inflammation, destruction, and eventual fibrosis of small airways, forming obliterative bronchiolitis (OB) lesions in the lung allograft. It presents as a persistent nonreversible obstructive ventilatory decline in spirometric measures of lung function with an essentially clear chest radiograph. High-resolution CT imaging of the chest often demonstrates air trapping, tree-in-bud opacities, or bronchiectasis. Due to the patchy distribution of OB lesions in lungs, transbronchial biopsy is insufficiently sensitive to achieve diagnosis. Therefore, the diagnosis of BOS is made by at least a 20% decline in FEV₁ from the best postoperative baseline, assessed by two measurements with a minimum interval of 3 weeks.^{116,118,119} BOS is thought to be irreversible; however, recently it became clear that 30% to 40% of patients with a diagnosis of BOS may respond to treatment with azithromycin. A placebo-controlled trial in patients with BOS confirmed that azithromycin was superior to placebo for improvement in FEV₁ in established BOS.^{120,121} Most patients who responded to azithromycin had elevated BAL neutrophilia during diagnosis. This observation led to a further subclassification of obstructive CLAD to BOS and a new phenotype known as *neutrophilic-reversible allograft dysfunction* or *azithromycin-responsive allograft dysfunction*.^{116,118,119}

Approximately 70% of CLAD is attributable to obstructive CLAD, and 30% to the restrictive phenotype of CLAD, also known as *restrictive allograft syndrome* (RAS).¹¹⁷ RAS is characterized by a restrictive pulmonary function decline and persistent parenchymal infiltrates on chest radiography. CT of the chest can demonstrate subpleural thickening and nonspecific interstitial changes. Additionally, organizing pneumonia, pleuroparenchymal fibroelastosis, and obliterative bronchiolitis may be seen in the histopathology.¹²² Unfortunately, the median survival after development of RAS is limited to 6 to 18 months, as opposed to 3 to 5 years in BOS.¹¹⁷

The medical management of CLAD centers around stabilizing rather than restoring graft functions. For management of BOS, current guidelines recommend conversion of cyclosporine to tacrolimus, antireflux surgery (e.g., Nissen fundoplication or Toupet fundoplication) in the case of documented gastroesophageal reflux, and a trial of azithromycin for a minimum duration of 3 months in patients with obstructive CLAD.^{118,119} Currently there are no formal guidelines for management of patients with restrictive CLAD. Some beneficial effects have been reported using pirfenidone and alemtuzumab in RAS.¹¹⁷ While selected cases may consider retransplantation for end-stage BOS, emerging data discourage this in RAS.^{118,119,123} For the majority of patients with end-stage CLAD, palliation becomes the priority. Symptom control in advanced disease remains challenging. Noninvasive ventilation for hypercapnia is generally ineffective, and ventilatory support and subsequent weaning are usually unsuccessful.¹²⁴

KEY POINTS

1. Lung transplantation continues to offer hope for many advanced lung disease processes. Much has been learned about the natural history of these otherwise terminal lung diseases, which has

influenced significant changes in the overall practice of lung transplantation, including the lung allocation system and the donor selection criteria.

KEY POINTS—cont'd

2. Primary graft failure (dysfunction) is a severe form of ischemia-reperfusion injury and carries enormous morbidity and mortality.
3. Lung transplant recipients with postoperative respiratory compromise should be maintained "on the dry side."
4. Growing evidence suggests that suboptimal early immunosuppression, as well as recurrent aspiration from reflux disease, are the two most modifiable risk factors associated with chronic rejection. Patient selection, consideration of antireflux surgery prior to transplantation or early after, and appropriate immunosuppression schedules should be implemented in protocols at every center.
5. Hyperammonemia continues to be a rare but feared complication after lung transplantation, given that its mechanism has yet to be understood. Aggressive management options including gut decontamination, high levels of dialysis, and pharmacologic treatments targeted at urea-cycle enzyme deficiencies are the only available tools but have yet to show promise in changing outcome.

ANNOTATED REFERENCES

Hachem RR, Trulock EP. The new lung allocation system and its impact on waitlist characteristics and post-transplant outcomes. *Semin Thorac Cardiovasc Surg* 2008;20:139–142.

This review clearly explains the current lung allocation process, which basically is geared toward making organs available to those who need them more urgently because of their underlying disease process and its expected outcome. A thorough comparison of the prior allocation process to the current one in terms of waiting time, waiting mortality, and more important, the steady proportional increase of idiopathic pulmonary fibrosis as the underlying cause of transplantation is made. This increase is explained by the comparable uncertainty of the disease's natural history and the high mortality of its exacerbations.

Christie JD, Edwards LB, Aurora P, Dobbels F, Kirk R, Rahmel AO, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-sixth official adult lung and heart-lung transplantation report—2009. *J Heart Lung Transplant* 2009;28:1031–1049.

This yearly document published by the International Society of Heart and Lung Transplantation summarizes and explicitly describes the statistical trends of lung and heart-lung transplantation. This

registry allows the reader to put in perspective the indications for transplantation, the donor characteristics, their impact on transplantation outcomes including rejection, complications and survival, as well as the centers offering transplantation and their influence on these outcomes in terms of the case load they are challenged with. It allows an organized chronologic understanding of lung and heart-lung transplantation outcomes.

Christie JD, Sager JS, Kimmel SE, Ahya VN, Gaughan C, Blumenthal NP, et al. Impact of primary graft failure on outcomes following lung transplantation. *Chest* 2005;127:161–165.

This single-center retrospective study conducted by field experts looked into the overall incidence of grade III primary graft failure in 255 consecutive procedures done in a period of over 10 years. It demonstrated an incidence of 11.3%, an increased mortality, worsened hospital length of stay, and increased duration of mechanical ventilation. Some 73.3% of patients who received the diagnosis of primary graft failure died during their hospitalization, versus 14.2% of those who did not. A 1-year follow up also demonstrated significantly affected physical function in those who had experienced primary graft failure.

■ References for this chapter can be found at expertconsult.com.

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Liver transplantation has been a successful surgical procedure for over 50 years. The pioneering work done by Thomas Starzl, who performed the first successful human liver transplant in 1967, defined both the surgical approach and efforts in controlling rejection.¹ The 1970s brought about advances in immunosuppression with the introduction of antilymphocyte globulin (ALG) developed at the University of Minnesota.² The early immunosuppressive regimens elevated liver transplantation as a viable surgical option for patients suffering from end-stage liver disease (ESLD). Orthotopic liver transplantation (OLT) is now offered more broadly, with more than 130 liver transplantation centers in the United States.³ Finally, the further advancement of immunosuppressive agents such as tacrolimus and interleukin (IL)-2 receptor blockers has paved the way for improved outcomes and survival. The current 1- and 5-year patient survival rates are 86% to 90% and 72% to 80%, respectively.⁴

Other advances have improved the outcomes of the field of liver transplantation including critical care management, surgical preparation of the graft, increases in preservation time, a smoother surgical procedure, and availability of organs less distant from the donor.^{5,6} Despite these advancements, the rates of liver transplantation have not changed dramatically for nearly 20 years.⁷ There are roughly 11,500 patients currently listed for liver transplantation with about 6000 liver transplantations performed in the United States in 2014.⁴ The majority of these were deceased donor, adult recipients.

■ PREOPERATIVE CONSIDERATIONS

Orthotopic Liver Transplantation Candidate Selection

OLT is the definitive treatment for many disease processes, including cirrhosis (both cholestatic and noncholestatic), biliary atresia, acute hepatic necrosis, metabolic disorders that result in hepatic failure, and malignancies of the liver or biliary tree as well as other rare causes of ESLD and even rarer causes of catastrophic traumatic liver injury.^{3,8,9} The savings of cost, morbidity, and mortality of patients receiving transplantation versus long-term management of severe liver disease makes this a viable option for many patients.

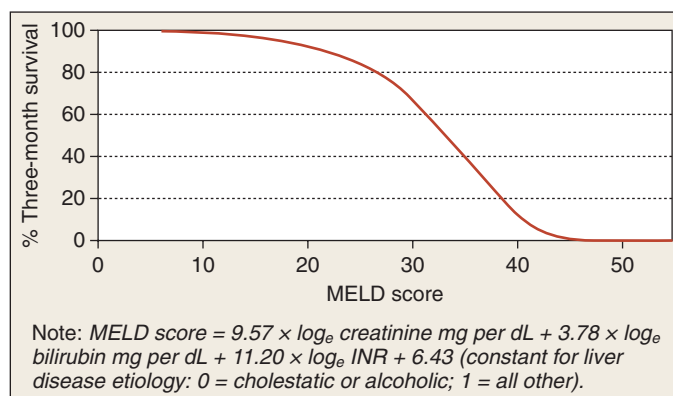
Of particular note is the indication of OLT in patients with hepatocellular carcinoma (HCC). The majority of cases in the United States and Europe are caused by chronic hepatitis C virus (HCV); however, in other parts of the world, hepatitis B virus (HBV) and exposure to aflatoxin B are the leading risk factors. Most develop HCC in the setting of preexisting cirrhosis, making surgical and oncologic treatments challenging.⁹ It is in this setting that OLT has become a standard treatment for patients who have minimal disease burden, and the refined selection criteria for this indication became known as the Milan Criteria. In 2002, researchers at UCLA demonstrated equivalent outcomes with a slight broadening of the Milan criteria.^{6,10} Other criteria, including the Kyoto criteria, have also led to acceptable results.^{11,12} Currently, both the Milan criteria and the UCLA criteria are recognized in the United States; however, expansion of these is likely to occur (Table 159-1).

In 2002, UNOS adopted the Model for End-Stage Liver Disease (MELD) and its pediatric counterpart, Pediatric End-Stage Liver Disease (PELD). The MELD calculation is used for all patients aged 12 and older for the purpose of listing patients for potential transplantation. The components of MELD include bilirubin (mg/dL), serum creatinine (mg/dL) or need for dialysis, and INR. For patients younger than 12, albumin, growth failure, and age at listing are also considered. The MELD score is predictive of mortality within 90 days of transplantation (Fig. 159-1). In 2012, a new policy called Share 35 helped distribute grafts more quickly to patients with a MELD score greater than 35.⁴ From a prognostic standpoint, it is helpful to understand the severity of the patients' ESLD for discussions of ongoing critical care goals.⁹ MELD/PELD scores can be easily calculated via multiple web-based calculators. The Organ Procurement and Transplantation Network (OPTN) website has multiple organ failure allocation calculators available with links to explanations for their use.¹³

Improvements in care over time (i.e., adoption of the Milan Criteria) have resulted in recipients who would previously have died while awaiting transplantation. Recipients are now more complex, older, have preexisting renal failure requiring dialysis (resulting in greater need for combined liver-kidney transplantation), require pretransplant hospitalization, and have longer wait times. For example, there are clear relationships that preoperative obesity and diabetes are related to early post-liver transplant morbidity. Prior to OLT, patients are often precipitously ill secondary to an inciting infection or fulminant hepatic failure. The success of performing transplantation in these patients is due to changes in immunosuppression therapy, surgical technique, and organ selection as well as anesthesia and critical care management in the early postoperative period.¹⁴⁻¹⁷ In addition to the Milan criteria, the stratification of recipients based on MELD scores have exception points given for portopulmonary syndrome to define those who will have the most successful posttransplant course.^{18,19} There is currently debate about whether these criteria are too broad as some patients have a much higher than expected survival while others perish while awaiting transplantation.^{18,20}

Donor Selection

In the past two decades, there has been a logarithmic increase in the demand for organs without a similar increase in donors. The concept of brain death, refined in the late 1960s, greatly expanded the donor pool. The concept of extended criteria donor (ECD) has emerged, making organs available for transplantation to those who would have otherwise died while on the waitlist.²¹⁻²⁵ Some of these characteristics include prolonged cold ischemia time (>12 h), HBV- or HCV-positive donors for HCV-positive recipients, elderly, nonhepatic solid cancers, severe electrolyte derangements, and evidence of parenchymal injury.²⁵⁻²⁸ This donor pool also includes patients with longer donor hospitalizations, donation after circulatory death (DCD), partial or segmented grafts (deceased and living), and even patients on extracorporeal membrane oxygenation.²⁹ This has led to organs procured from individuals who would not have been previously considered to be appropriate donors and transplantations to those who would not have otherwise received an organ at that time.³⁰⁻³² This is



| MELD score | Mortality at 3mo |
|------------|------------------|
| <9 | 1.9 |
| 10–19 | 6 |
| 20–29 | 19.6 |
| 30–39 | 52.6 |
| >40 | 71.3 |

FIGURE 159-1 ■ Model for end stage liver calculations. (From Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003;124:94. Fig. 2.)

TABLE 159-1

Liver Transplantation Criteria for Hepatocellular Carcinoma

| | MILAN | ULCA | KYOTO |
|------------------------------|---------------------|-----------------------|----------------|
| Single tumor | <5 cm | <6.5 cm | |
| # Tumors (each cm) | 3 tumors, 3 cm each | 3 tumors, 4.5 cm each | <10, 5 cm each |
| Total tumor size | | 8 cm | DCP <400 |
| 5-year survival | 75% | 52% | 82% |
| Disease-free 5-year survival | 83% | 79% | 93% |

conceptualized in the donor risk index, which is a method of predicting graft failure to help determine suitability of the organ to a recipient match.

There are many reports that support the use of ECD organs due to the fact that recipients are less ill at the time of transplantation and can have a more stable postoperative course. The average MELD scores are lower prior to transplantation, and the survival outcomes are equivalent, with most deaths attributable to the recipient age or other comorbidities rather than primary graft dysfunction.³³ Even hepatic lobar transplantation has been used in adults, although the reduced functional tissue mass has often resulted in delayed or inadequate liver function.³⁴ Last, another higher risk ECD transplant situation is what has been termed the *domino OLT*. In these cases, patients with ESLD secondary to familial or metabolic liver disease become both the donor and recipient in the same operation. Their somewhat diseased liver will then become the allograft into an otherwise nontransplantable host. The idea is that the second patient may have enough remaining graft function to allow for a more suitable donor to be identified.^{35,36} The intensivist should recognize that patients receiving ECD livers are at a higher risk of immediate graft malfunction or complications related to their comorbid state as compared to recipients of brain dead organs.

Recipient Operation

The more intricate details of liver transplant operation are beyond the scope of this chapter; however, a few salient points are worth mentioning as they can directly impact the immediate postoperative course. It cannot be stressed enough that any surgical procedure performed on a patient with long-standing portal hypertension is all the more difficult secondary to the vast venous collaterals that often lead to significant blood loss.³⁷ This is in addition to the blood that will be lost

during the usual course of the operation. Other factors, including cold and warm ischemia time, which may affect the quality of the graft; high-volume operative blood transfusion requirements; and reperfusion syndromes, make these patients challenging from a fluid, electrolyte, and organ function standpoint.^{38–41}

As with all types of OLTs, vascular anastomoses can prove troublesome. In cases of partial liver allografts, where there may be vessel size discrepancy or anomalous anatomy, vascular grafts may be used. Most often, this is an arterial graft (taken from the donor at the time of the procurement) and is used as a “jump” graft.^{42,43} Likewise, venous anastomoses can also be difficult but are most often performed primarily and, in rare cases, may also include a vascular graft to ensure adequate flow into the graft.

There are two main approaches to the anastomoses for biliary drainage of the liver graft: choledochocholedochostomy (duct-to-duct) and Roux-en-Y choledochojejunostomy. The duct-to-duct anastomosis may be done over a T-tube to assist in stenting the anastomosis and allowing for external monitoring of the graft. Many early biliary complications have been associated with T-tube use.^{44,45} The benefit of this approach is that postoperative ERCP can still be utilized for ductal evaluation and stent placement if needed (Fig. 159-2).

ACUTE POSTOPERATIVE MANAGEMENT

Respiratory Support

Postoperative respiratory disorders are commonplace following OLT, and many risk factors for post-OLT pulmonary complications have been identified.⁴⁶ Separate from portopulmonary hypertension (PPHTN) is hepatopulmonary syndrome (HPS), which is the hypoxia attributable to ventilation/perfusion (VQ) mismatch, intrapulmonary shunts, and capillary vasodilation with oxygen diffusion limitations secondary to portal hypertension. Liver transplantation effectively and rapidly reverses this dysfunction with graft function unless there are confounding comorbidities. Advanced ventilator maneuvers may be required, including the use of inhaled prostaglandins (Flolan) and inverse ratio ventilation.^{47,48} Ventilator wean failure requiring tracheostomy is unusual in OLT patients. Details of usual ventilation settings, approaches to mechanical ventilation wean, and extubation are described in Chapters 61 and 63. Inability to liberate from mechanical ventilation is predictive of graft failure and mortality at 1 year (Table 159-2).⁴⁹

Coagulopathy and Thrombocytopenia

Most liver transplant patients undergo surgery in the setting of ESLD and are coagulopathic at the time of surgery.^{50,51} The assumption that

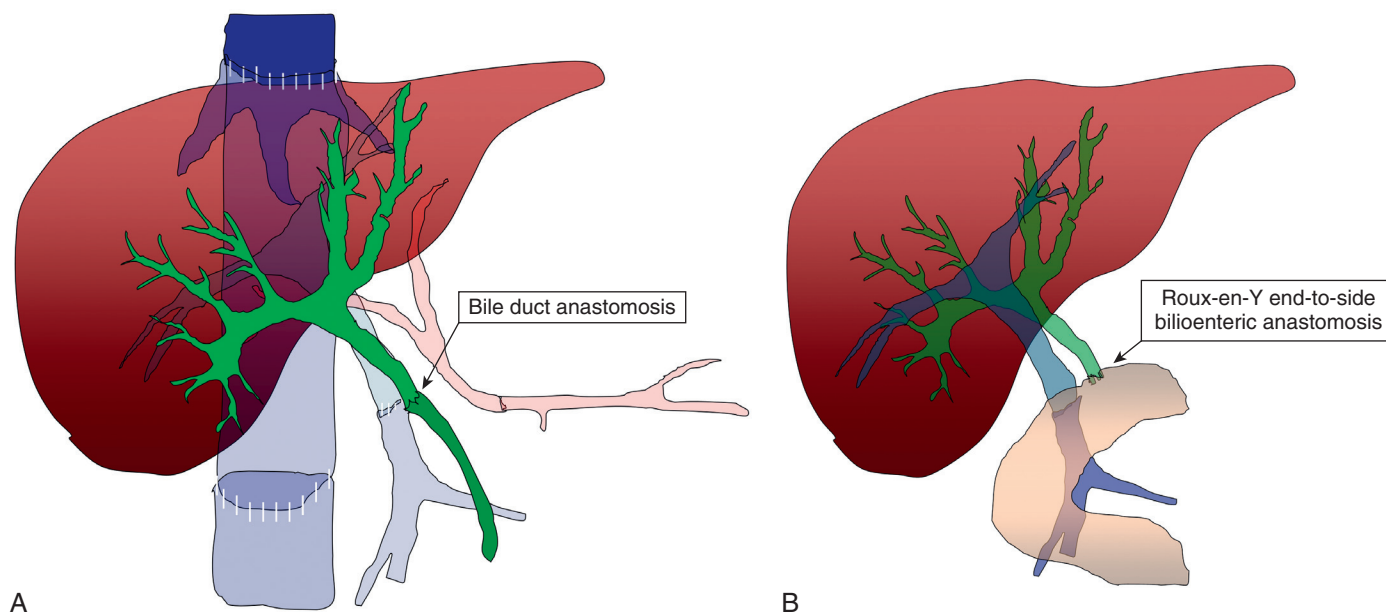


FIGURE 159-2 ■ Two common approaches to biliary anastomoses in orthotopic liver transplantation. (From Abu-Wasel B, Renfrew PD, Molinari M. Liver transplantation and endoscopic management of bile duct complications, endoscopy of GI tract, Associate Prof. Somchai Amornytin, editor, 2013, InTech, DOI: 10.5772/52630. Figs. 1E and 2A. Available from: <http://www.intechopen.com/books/endoscopy-of-gi-tract/liver-transplantation-and-endoscopic-management-of-bile-duct-complications>.)

TABLE 159-2 Risks for Postoperative Respiratory Failure in OLT

| |
|--|
| Age |
| MELD |
| AKF |
| Smoking |
| COPD |
| PPHTN |
| Preoperative PaO ₂ ≤ 44 mm Hg |

ESLD patients are hypocoagulable secondary to the loss of synthetic function of the liver is an incomplete understanding of the pathophysiologic process. It has been demonstrated that the complex balance between procoagulant forces and anticoagulant forces become rebalanced. The synthetic production of our innate anticoagulants is also depressed. Although it may seem counterintuitive, it is for this reason that frequent catastrophic spontaneous hemorrhage is not common.⁵² It is well recognized that these patients lack the usual reserves to maintain normal hemostasis, and they remain at risk for both bleeding diatheses and thrombotic events.

Technical and anesthetic advances have made minimal-transfusion liver transplantation a reality. That being said, there are many operative difficulties that can be encountered that result in massive blood loss to further derange homeostasis. It is important, then, to replace the blood that is being lost as a result of the operation and to correct coagulation using fresh frozen plasma (FFP) and cryoprecipitate to maintain normal fibrinogen levels. This results in fewer blood product transfusions, improved patient outcomes, and reduced costs.

Likewise, thrombocytopenia is common in OLT. In chronic liver disease, the only upregulation of procoagulant factors are of factor VIII and Von Willebrand factor.²⁸ The greatly reduced platelet number is thought to be secondary to multiple factors, including sequestration by the spleen resulting in hypersplenism, increased consumption,

bone marrow suppression, and reduced thrombopoietin levels. Despite the detrimental experimental evidence of platelet transfusion, most centers will transfuse OLT patients to keep the platelet counts greater than 20 K/dL or greater than 100 K/dL in uncontrolled nonsurgical bleeding.

Due to the inconclusive evidence that all blood product transfusions in OLT are more harmful than beneficial, the current literature supports consideration of the targeted use of blood products. Additional steps toward hemostasis using prohemostatic drugs such as aprotinin, lysine analogs, or prothrombin concentrates are warranted.⁵³

Immunosuppression

The advances in immunosuppression used in liver transplantation have dramatically improved the long-term quality of life and survival of patients. There are a few basic categories of commonly used drugs that we will discuss with the understanding that there are no global standardized regimens; the general approaches to these medications, however, are similar. Common regimens used for immunosuppression in OLT may include a combination of corticosteroids, azathioprine (AZT), mycophenolate mofetil (MMF), sirolimus, cyclosporine, tacrolimus, and antilymphocyte antibodies.

Corticosteroids enact their effect by suppressing antibody and complement binding resulting in a reduced synthesis of immunomodulatory cytokines. Steroids also inhibit secretion of IL-1 by macrophages required for antigen presentation and initiation of an acute allograft rejection.⁵⁴ Four corticosteroids are used most often in liver transplantation: hydrocortisone, prednisone, prednisolone, and methylprednisolone. Methylprednisolone is only available in intravenous (IV) formulation and requires hydrolyzation of a succinate moiety for biological activity, thereby requiring some liver function for biological activity. In addition, several biologically active metabolites are produced that prolong the half-life, making this drug unpredictable in liver transplant patients. All corticosteroids become metabolically inactivated by the cytochrome P450 system. Both prednisone and prednisolone are active drugs that do not require activation by the liver

and, therefore, have equivalent bioavailability in both oral and IV routes. Therefore, in the days following liver transplantation, the graft, having been crippled by warm and cold ischemia time, cannot inactivate steroids effectively. Clinically, this liver dysfunction allows for lower doses of steroid to be used with immunologic effectiveness.⁵⁵

MMF, also known by the trade name CellCept, is an ester derivative of mycophenolic acid (MPA) produced by *Penicillium* species. MMF is metabolized by the liver into MPA and inhibits cellular proliferation. It is relatively selective and renders lymphocytes unable to proliferate. MMF also has antiviral effects with activity against HCV and has been found to reduce the recurrence of HCV in patients transplanted for this disease.⁵⁶ Common side effects are gastrointestinal and hematologic, including gastritis, nausea, vomiting, and varying degrees of pancytopenia. Reduction of the dose usually results in resolution of the symptoms without having to completely withdraw the medication.

Cyclosporine and tacrolimus are calcineurin inhibitors. They suppress the immune system by preventing IL-2 production by T cells. Cyclosporine inhibits not only IL-2 but also T and B cell proliferation and differentiation.⁵⁴ Tacrolimus also inhibits the formation of IL-2 but is 100 times more potent than cyclosporine.⁵⁵ Both drugs are metabolized through the cytochrome P450 system.

The adverse effects of the calcineurin inhibitors are primarily nephrotoxicity and, in the case of tacrolimus, neurotoxicity. Renal dysfunction ranges from minimal to irreversible vasculopathic damage. Cyclosporine is also known to promote hypertrichosis and gingival hyperplasia. Tacrolimus, by contrast, has the potential for severe neurotoxicity that warrants immediate withdrawal of the medication. The half-life of cyclosporine is significantly prolonged when given in conjunction with tacrolimus, and thus this combination should be avoided.

Fluids and Electrolytes

The majority of patients undergoing OLT will have a significant positive total body fluid balance. This is due primarily to preoperative conditions that result in fluid accumulation, most notably the state of hyperaldosteronism.⁵⁷ This is aggravated by intraoperative fluid administration. A perioperative pulmonary artery (PA) catheter can determine intravascular volume as well as other hemodynamic parameters. Other methods of volume estimation are serial ultrasound examinations of IVC, RA and PA filling estimations, and noninvasive cardiac output monitoring devices such as FloTrac.

Not only do these patients have increased total body water and sodium levels, but they are also likely to have some degree of renal dysfunction. Dialysis-dependent recipients require judicious use of fluid resuscitation. The amount of volume that the patient receives intraoperatively is dependent upon the details of the surgical case. However, if large volumes of crystalloid or blood were required, these patients will often require early renal replacement therapy (RRT) to help manage the metabolic derangements as well as the fluid balance.^{58,59}

Protocolized fluid administration that focuses on hemodynamic goals has been shown to significantly reduce the volume of crystalloid required and the number of transfusions. These patients benefit from shorter number of ventilator days and reduced number of respiratory complications.^{15,57} In addition, there is a shorter return to antegrade bowel function and no suggestion of increased graft complications. While there is some critical care literature suggesting that a slight positive fluid balance may be beneficial in the general postoperative abdominal surgical patient, it appears that maintaining euvoolemia in OLT is beneficial.

Many patients with long-standing liver dysfunction prior to transplantation develop hyponatremia, which is corrected pre-, intra-, and postoperatively. The danger in rapid sodium correction is central pontine myelinolysis (CPM). Rapid correction may occur occultly and unintentionally via the unaccounted for sodium load in many IV medications, including sodium bicarbonate, albumin, and crystalloids, as well as the use of diuretics, blood products, or aggressive correction of hyperglycemia. Larger changes in sodium concentration have been

associated with prolonged intubation and neurologic complications in several patient populations including liver transplant recipients.⁶⁰

The most common electrolyte abnormalities in the posttransplant liver patient are hyponatremia and hypokalemia. These may persist from preoperative deficiencies and are due to a dilutional effect of the total body concentrations. Hypokalemia is induced intraoperatively to minimize cardiac event risk with the anticipation of labile potassium levels during revascularization of the graft. This is corrected by slow diuresis and judicious replacement with careful avoidance of sodium overload.

Hyperkalemia is a more serious problem and may signal primary graft dysfunction, hepatic necrosis, renal tubular necrosis, or drug toxicity. The usual treatment of hyperkalemia should be employed, including calcium, insulin, glucose, potassium-binding resins, systemic alkalization, and, in severe cases, emergent hemodialysis. Further evaluation as to the cause of the elevated potassium should follow to avoid missing the opportunity to intervene.

Nutritional Support

Resting energy expenditure (REE) of ESLD patients is much higher than one might anticipate.⁵² It is, indeed, a very catabolic state with an average requirement of 30 kcal/kg/day. Preoperatively, most of these patients are clinically malnourished.⁶¹ This can be determined both clinically and through laboratory testing, although assessment of the nutritional status of patients with ESLD can be problematic.⁶² Evaluation of the general muscle mass including the thenar prominence and the robustness of the temporalis muscle can give one a gross estimate of the patient's preoperative nutritional status. More sophisticated and accurate methods of determining the metabolic state of the OLT patient include the measurement from a metabolic cart.

The best predictor of postoperative malnutrition is the underlying cause and progression of ESLD; the more prolonged the course, the more nutritionally deplete these patients will be. Those patients that have a chronic disease leading to liver failure are likely to be in a more precarious nutritional state than the patient who developed acute fulminant hepatic failure from a drug overdose, for example.⁶³ What is clear is that the average liver transplant patient is likely to be nutritionally deplete, and careful attention to nutrition is imperative for success of the graft and the patient's recovery.

After transplantation, the best determinant of metabolic stress and ongoing nutritional needs is the allograft function.⁶⁴ In patients who have excellent early allograft function, nutritional goals are likely to be met with enteral diets, which is the preferred method for nutrition of the critically ill patient when possible. There are many benefits to enteral feeding for the liver transplant patient, including maintenance of the enterocyte mass and higher rates of visceral protein synthesis. Another benefit to enteral nutrition is the added avoidance of total parenteral nutrition (TPN)-induced cholestasis.⁶⁴ Not only can this be detrimental to the overall graft recovery, but it can also lead to confusion in the interpretation of the liver function tests. Patients who have difficulty tolerating enteral diets are often those who have delayed graft function, have received larger volumes of crystalloid and/or blood products, and are volume overloaded with concurrent bowel edema and ileus. These patients must be managed with parenteral nutrition. A more detailed description of nutritional support is found in a previous chapter.

SPECIFIC CONSIDERATIONS OF THE LIVER TRANSPLANT PATIENT

Operative Complications

Specific complications that arise from the surgical approach that would affect the postoperative course include portal vein thrombosis, hepatic artery thrombosis, and bile leaks. Complications following OLT are low but can be devastating. A summary report from UCLA demonstrated that early primary graft failure, hepatic artery

thrombosis, and portal vein thrombosis rates range from 0.7% to 6% for the adult populations.¹⁰ In their experience, they estimate that nearly 30% of OLT patients had complications that require reoperation. The most common cause of reoperation is bleeding. There are several risk factors identified for reoperation: higher MELD score, pretransplantation hospitalization, mechanical ventilation, vasopressor use, renal replacement therapy, longer ischemia times (both warm and cold ischemia), and more intraoperative transfusions.^{7,15,48,52} Later complications that should make one concerned about vascular compromise or rejection include biliary strictures, new-onset peritonitis, hepatic artery thrombosis, and cholangitis.^{44,45}

Thrombotic Events/Anastomotic Patency

Transplant surgical teams monitor the vascular anastomoses involved in liver transplantation in various ways. One approach is to leave an internal Doppler probe at the anastomosis and monitor the auditory wave output for bi- or triphasic flow. Another approach is to do diagnostic duplex ultrasound of the hepatic artery (HA) and portal vein (PV) within the early postoperative period.⁶⁵ The first method is more invasive and carries a small risk of increased infection, potential for anastomotic injury, inability to reposition the probe were it to become dislodged, as well as discomfort upon removal. Although bedside duplex of the graft and its anastomoses is noninvasive, it can be limited by bowel gas and is fairly uncomfortable in the immediate postoperative period unless the patient remains intubated and sedated.⁶⁶ In addition, it is not real-time monitoring and, unless previously scheduled, will be performed in a reactionary manner in response to metabolic or physiologic derangements. The use of one technique over the other is determined by the experience of the surgeon and the regional practices (Table 159-3).

Biliary Complications

Strictures, leaks, and biliary stones cause a significant morbidity for 30% to 50% of liver transplant recipients (higher in DCD OLT). The two most common reconstruction types are to either perform a duct-to-duct anastomosis (choledochocholedochostomy with or without T-tube) or a choledochojejunostomy (Fig. 159-3).⁶⁵ In the early postoperative period, bile leaks are the most common biliary complication. These are often difficult to detect, as they may be fairly asymptomatic, with only mild elevations of transaminases and bilirubin. The cause of the leak is often of more concern than the leak

itself; leaks can be caused by pure technical errors in the anastomosis, devascularization of the ductal tissue, or hepatic artery thrombosis.^{65,67} Further investigation is warranted. Dealing with biliary complications is often dependent upon the expertise and experience at each transplant center and may include ultrasound, angiography, cholangiography, MRCP, ERCP, and percutaneous drainage.⁶⁸ It is imperative to maintain a heightened awareness and close monitoring for these complications with aggressive treatment if detected to alleviate long-term sequelae and graft damage.

| TABLE 159-3 | | | Example of Immunosuppression Regimen: Adapted from the University of Minnesota for Orthotopic Liver Transplantation | |
|-----------------------|---|--|---|--|
| AGENT | ADULT—NORMAL KIDNEY FUNCTION | ADULT—POOR KIDNEY FUNCTION | | |
| Prednisone | 250 mg IV at reperfusion 200 mg POD#1 100 mg POD#2 50 mg POD#3 25 mg POD#4 10 mg POD#5 Stop POD#6 | 250 mg IV at reperfusion 200 mg POD#1 100 mg POD#2 50 mg POD#3 25 mg POD#4 10 mg POD#5 5 mg POD#6 and continue until tacrolimus levels are therapeutic, then stop | | |
| Mycophenolate mofetil | 1 g BID POD #0 Begin wean POD #90 Stop POD #120 | 1 g BID POD #0 Begin wean POD #90 Stop POD #120 | | |
| Basiliximab | 20 mg IV POD #1 and #5 | 20 mg IV POD #1 and #5 | | |
| Tacrolimus | Start when patient stable and renal function good 0.075 mg/kg BID Adjust dose to target trough level 0-3 months 10-12 mg/dL 3-6 months 8-10 mg/dL 6 months on 6-8 mg/dL | Start when renal function recovered (off dialysis, Cr < 2.5, UOP > 30 cc/h) 2 mg BID Adjust dose to target trough level 0-3 months 10-12 mg/dL 3-6 months 8-10 mg/dL 6 months on 6-8 mg/dL | | |

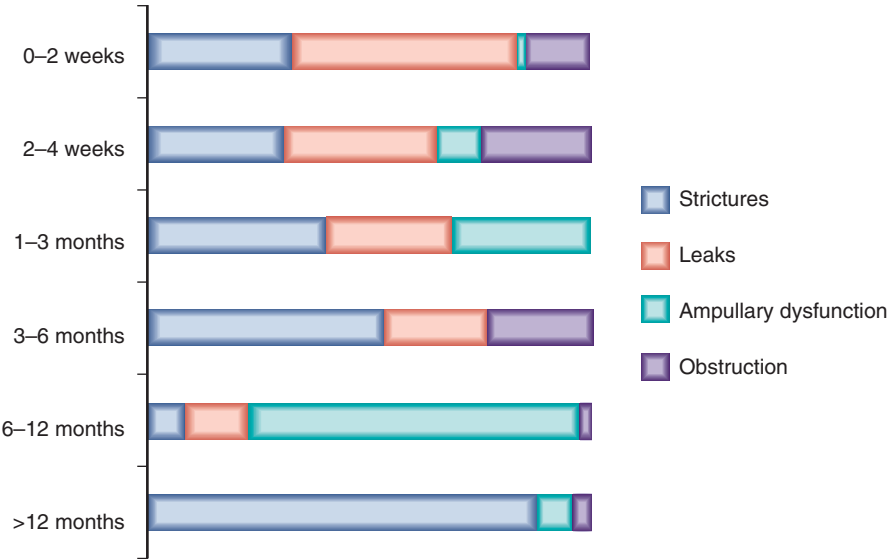


FIGURE 159-3 ■ Post-OLT biliary complications timeline.

■ ORGAN PHYSIOLOGY

Posttransplant Cardiomyopathy

ESLD patients often have preoperative hemodynamic abnormalities (e.g., hyperdynamic, hypotensive, vasodilated) resulting in high cardiac output, low systolic blood pressure, and low systemic vascular resistance.⁶⁹ This cirrhotic cardiomyopathy is thought to be secondary to the multiple arteriovenous communications, activation of the renin-angiotensin-aldosterone and sympathetic nervous system resulting in vasodilation, reduced circulatory blood volume, and sodium and water retention. The persistence of this hyperdynamic circulation is unpredictable but has been reported to take up to 2 years after successful liver transplantation for resolution.⁴⁶

Rarely, the OLT patient will develop overt cardiac failure after liver transplantation. Identification of the specific risk factors has not been successful. It is thought that elevated BNP and PA pressures in the early postoperative period may be a predictor.^{70,71} It is clear that the postoperative hemodynamic instability is worsened by anemia, PHTN, PPHTN, and cardiovascular disease. In the immediate postoperative period, the relative volume deficit of these patients is preferentially managed by resuscitation with colloids including albumin and blood products. Intravascular volume resuscitation using blood products with vasoconstrictors is used to maintain adequate perfusion for the new graft. This is done in an attempt to balance the additional morbidity of large volume with potential visceral ischemia.

Pulmonary

PPHTN is a long-standing fibroproliferative disorder of the pulmonary arteries that will result in pulmonary hypertension, hypoxia, dyspnea, and eventually right heart failure. This process is brought on by severe portal hypertension.¹⁶ Because of the insidious nature of the development of this disorder, it is an equally slow process to reverse once liver transplantation has been performed. However, liver transplantation is the definitive treatment for this disease process. Because 8% to 20% of OLT patients present with some degree of pulmonary hypertension, additional use of pulmonary artery vasodilators may be warranted, not only for pulmonary function but for reduced hepatic congestion as well.¹⁹ In these patients, it is not uncommon to employ additional hemodynamic monitoring devices to estimate pulmonary artery pressure and cardiac output. In cases of severe preoperative PPHTN, there is an increased risk of graft failure due to liver venous congestion and right heart failure; if severe or long-standing, these changes can become fixed and result in increased postoperative mortality.²⁰ It becomes important to manage these patients with perioperative pulmonary artery pressure and right heart pressure monitoring, most commonly accomplished by a PA catheter. However, this can also be supplemented with an indwelling miniaturized transesophageal echocardiography (mTEE) probe in centers that have a vast experience with these devices.⁷⁰

Renal

Hepatorenal syndrome (HRS) is the decline of renal function with a measured rise in creatinine to greater than 2.5 mg/dL and double the patient's preillness baseline.⁷² The onset may be insidious, as the urine output may remain relatively unchanged and may, therefore, go unnoticed. The etiology of HRS is due to the hemodynamic dysfunction associated with ESLD as described for PPHTN. Remarkably, however, the renal morphology is typically normal in this disease state. The long-standing renal dysfunction can result in permanent damage to the renal parenchyma. We will not discuss the combined liver-kidney transplant patient in any depth other than to recognize that prolonged renal failure prior to OLT is a marker for ongoing renal dysfunction and may, therefore, necessitate co-transplantation.

In the postoperative period, acute kidney injury is common and can occur in up to 60% of patients. There are suggested negative rela-

tionships between the use of prolonged vasoactive drugs, hypotension, higher MELD scores, and blood product administration with decreased renal function. Renal replacement therapy (RRT) is required in nearly 10% of these patients with a doubling of their mortality rate at 1 year.

Central Nervous System

Neurologic complications are common and can affect 30% to 60% of all solid organ transplant patients, including 15% to 30% of OLT recipients.⁷³ It has also been found that postoperative confusion is more common in OLT patients whose indication for transplant was alcoholic liver disease as compared to other causes of ESLD. Patients with minimal pretransplant encephalopathy, an uncomplicated surgical course, and adequate graft function should recover from anesthesia quickly. Any delay or decline in mental status warrants a thorough evaluation of other causes.

Similar to other solid organ transplant recipients, major complications include alterations in consciousness, seizures, cerebrovascular events, and CPM. The majority of these complications are secondary to opportunistic infections, drug toxicities, and metabolic changes. Although the preferred imaging modality is MRI, previous studies suggest that CT scan is utilized most often. The awareness that structural abnormalities play a much smaller role in postoperative mental status changes should direct a heavier use of MRI as the diagnostic imaging modality of choice.

Two of the most serious causes of coma in OLT are osmotic demyelination syndrome (ODS) and posterior reversible encephalopathy syndrome (PRES).⁷⁴ ODS includes the diagnosis of both central pontine (CPM) and extrapontine demyelination (ECM) processes. Differentiating PRES from ODS can be very difficult and cause significant diagnostic confusion. A closer evaluation as to the specific causes of each may help differentiate the etiology of the mental status change.

Hinchey et al. first described PRES in 1996 as vasogenic edema in the posterior circulation regions of the brain with the resulting altered consciousness, visual disturbances including cortical blindness, and eventual coma.⁷⁵ Classically, this process is completely reversible. It has been typically associated with hypertensive episodes but has also been described in patients with severe electrolyte abnormalities. In the postoperative liver transplant patient, it has also been associated with calcineurin-inhibitor and sirolimus toxicity.⁷⁶ Cessation or reduction in calcineurin dose can have dramatic improvement with the co-administration of ongoing supportive care including antiepileptics.⁷⁷ There is no other specific treatment to date.

CPM, on the other hand, is a neuropathologic process of osmotic demyelination secondary to correction of hyponatremia, first described in 1959.⁷⁶ Classically, it is presented as a tetraplegic, malnourished liver failure patient or postoperative OLT patient. The definition has evolved to include other causes of severe metabolic and electrolyte derangements including septic shock, burns, and HIV. Because liver transplantation is frequently burdened by osmotic and electrolyte imbalances, ODS deserves diligent attention. Distinction between PRES from CPM may be performed with diffusion-weighted imaging MRI and, specifically, the presence of increased T2 signaling in the posterior white matter. However, unless there is acute cytotoxic edema associated with PRES, the radiographic findings of delayed-diagnosis PRES and active ODS may look very similar. Aggressive replacement or reduction in the calcineurin inhibitor must be undertaken as well as judicious fluid management and nutritional support.

Calcineurin inhibitors, cyclosporine, and tacrolimus are commonly used in liver transplantation immunosuppression regimens. Their toxic effects have been associated with multiple neurologic complications that can manifest at any time during the posttransplant course. In the early postoperative period, calcineurin inhibitors are often used in higher "induction" doses resulting in dose-dependent neurotoxicity.^{78,79} The manifestation of these effects is typically tremors, headaches, and encephalopathy, and, in severe cases, PRES can develop. Reduction of these neurotoxic immunosuppressants or replacing them with less toxic medications will often resolve the clinical manifestations.

Critical illness weakness may affect up to 7% of liver transplant recipients.⁷⁷ It is characterized by symmetric weakness in the limbs preferentially affecting the more proximal muscles; it can even involve the respiratory muscles as described by Osler in 1915. One can distinguish between the critical illness myopathy (CIM, which is a primary myopathy secondary to loss of myosin heavy chains) from critical illness polyneuropathy (CIP) by means of a simple sensory examination. However, because OLT patients are often sedated or have other reasons for altered mentation, this can prove to be difficult. Advanced electrophysiologic testing is likely to be required with a concomitant neurology consultation. If these studies prove to be equivocal or normal, a muscle biopsy may be required. CIM is more common and is associated with higher rates of recovery. A primary risk factor for development of critical illness myopathy is the catabolic nature of the post-liver transplant state with subsequent skeletal muscle wasting.⁷⁷

CIP, on the other hand, is speculated to be secondary to derangements in microcirculation resulting in neuronal injury and axonal degeneration. Hyperglycemia can exacerbate the problem. Diligent glucose control can reduce the rates of critical illness polyneuropathy and reduce ventilator days.^{78,79} Other risk factors include a higher illness severity, requirement for hemodialysis, and higher doses of steroid use in the postoperative period. It is important to understand that both of these conditions can coexist as the risk factors overlap significantly (Tables 159-4 and 159-5).

Alterations in consciousness, such as encephalopathy, may carry over from the patient's pretransplant condition.⁷⁹ A protracted pretransplant course of encephalopathy portends a much higher risk of posttransplant neurologic complications. With either delayed allograft function or primary allograft failure, hepatic encephalopathy can precipitously appear. In addition, liver dysfunction will alter the pharmacokinetics of many medications, worsening the clinical picture. Many causes of ESLD can directly affect the nervous system (e.g., Wilson's disease, primary biliary cirrhosis, and amyloidosis). With recovering allograft function, these neurologic manifestations will often improve and occasionally completely resolve. To minimize the risk of medication-induced confusion, avoidance of benzodiazepines,

narcotics with active metabolites, and medications that require hepatic metabolism or clearance should be undertaken.⁷⁸ A more thorough review of delirium can be found in a previous chapter, understanding that in the OLT population, akinetic delirium is more common.⁸⁰

Early Infectious Complications

Evidence of sepsis should invoke a workup of the patient for infectious causes common to all ICU patients, including pneumonia, urosepsis, and line infections.⁸¹ The most common cause of in-hospital death of liver transplant patients is infection. Nearly 80% of solid organ transplant patients will develop infections, mostly from bacteria, and the overall infection rate within the first 30 days remains at about 25%.⁸² There are many factors that increase the risk of bacterial infections following OLT, including ischemia-reperfusion injury of the graft, large-volume blood transfusions, and causes of cholangitis including hepatic artery thrombosis and biliary strictures.⁸³ This discussion will not include information found in previous chapters regarding sepsis, pneumonia, and the need for adequate nutrition.

Because immunosuppression is necessary to allow for symbiosis of the graft, patients must be protected prophylactically against opportunistic infections.^{55,82} Liver transplant patients are given trimethoprim-sulfa prophylactically for life to protect against *Pneumocystis jirovecii*. Occurrences of *P. jirovecii* are now usually only found during times of withdrawal of prophylaxis and are treated with resumption of trimethoprim-sulfa. As with all opportunistic infections following OLT, reductions in immunosuppression may be required.

There are specific issues that pertain to liver transplant patients that may be different from those of other critically ill ICU patients. The liver transplant patient is susceptible to recurrence of the inciting hepatitis virus that resulted in liver failure or HCC.^{2,84} They are also at risk of other viral infections that would be uncommon in the general ICU population such as CMV and EBV that may occur as a result of induction immunosuppression therapy. These comprise nearly 20% of infections and can also include Epstein-Barr virus (EBV), cytomegalovirus (CMV), and recurrent hepatitis B (HBV) or hepatitis C virus (HCV).

CMV is a member of the human herpesvirus group. Infection by CMV is defined as detection of viral proteins in any body fluid or tissue specimen, fever greater than 38°C for 2 to 4 days, and neutropenia or thrombocytopenia.⁸⁵ When CMV infects and causes end organ disease, this can be particularly devastating in an immunosuppressed and metabolically stressed liver transplantation host. Two common CMV infection syndromes are hepatitis and pneumonia. When the lungs are affected by CMV infection, the ensuing pneumonia is often superinfected with bacteria, resulting in one of the most life-threatening complications of immunosuppression. Other noninfectious consequences of CMV include an increased risk of allograft rejection, invasive fungal or bacterial infections, and even activation or acceleration of other viruses such as HCV and EBV. It is noteworthy that even "successful" antiviral treatment may still result in persistence of CMV within hepatocytes and biliary epithelium rendering the patient with a lifetime risk of reactivation, chronic inflammation, and rejection.⁸⁶

The risk of acquiring CMV infection or disease is determined by the pretransplant serologic status of both the donor and the recipient, with the highest risk assigned to the seronegative recipient of an organ from a seropositive donor.⁸⁵ Most of these recipients will seroconvert, and most will eventually develop symptoms. Even those that are seropositive prior to transplantation can become superinfected with donor CMV from the allograft. Other risk factors include specific immunosuppressive medications including prednisone, calcineurin inhibitors, and thymoglobulin.⁸⁷

Prevention and treatment of CMV begins at the time of induction immunosuppression with administration of antiviral agents prophylactically. Prophylactic antiviral therapy does not protect the patient from primary infection with CMV, but it delays the onset of viral replication. Primary CMV infections are often observed upon cessation of prophylactic antivirals.^{83,86} Patients are then monitored carefully for any signs of infection, tested immediately with PCR, and antiviral

| TABLE 159-4 Surgical Vascular Complications | |
|--|---|
| COMPLICATION | TIME AFTER TRANSPLANTATION |
| Hepatic artery thrombosis | First two weeks; late occurrence less devastating |
| Hepatic artery stenosis | Few weeks to months |
| Portal vein thrombosis | 1-4 weeks |
| Portal vein stenosis | >6 months |
| Hepatic vein stenosis | >6 months |

| TABLE 159-5 EMG Findings in Critical Illness Weakness | | |
|--|---------------------------------|---------------------------|
| | CRITICAL ILLNESS POLYNEUROPATHY | CRITICAL ILLNESS MYOPATHY |
| Nerve conduction velocity | Normal, minimally reduced | Normal, minimally reduced |
| CMAP amplitude | Reduced | Reduced |
| CMAP duration | Normal | Prolonged |
| SNAP amplitude | Reduced | Normal |
| Muscle excitability (direct) | Normal | Reduced |

CMAP, compound muscle action potential; SNAP, sensory nerve action potential.

therapy initiated immediately upon detection. There is no specific threshold value for seropositive recipients, and treatment is determined based on the clinical suspicion. Any instance of CMV DNA detection warrants immediate treatment with antiviral medications. When CMV disease occurs, valgancyclovir is the most effective therapy.

Acute EBV infection presents with fever, malaise, leukopenia, lymphocytosis, and thrombocytopenia. Nearly 90% of adults are EBV seropositive, but most occur as subclinical infections.⁸² It is presumed that in the liver transplant patient, EBV infections are a result of reactivation rather than primary infection. Other risk factors for EBV infection in liver transplant patients are CMV donor-recipient mismatch, CMV disease, and high-dose immunosuppression.⁸³ There is an association between EBV and posttransplant lymphoproliferative disease (PTLD). However, it is relatively uncommon in adult liver transplantations. EBV viremia by PCR is not diagnostic of EBV PTLD. The initial treatment for PTLD is reduction of immunosuppression. Escalation to rituximab and cytotoxic chemotherapy is done only if a clinical response fails to occur within 2 to 4 weeks of withholding immunosuppression.

Hepatitis B core antibody (HBcAb)-positive and hepatitis B surface antigen (HBsAg)-negative donors are routinely utilized throughout the world. Careful prophylaxis with hepatitis B immunoglobulin (HBIG) and an antiviral at the time of transplantation has resulted in a reduced incidence of HBV infection even with HBcAb-positive grafts.⁸⁸ Some centers are using potent antivirals without HBIG with success in selected patients. Unrecognized reactivation of HBV can lead to graft failure and recipient death.

Hepatitis C virus-related liver disease has become one of the world's leading OLT indications.⁸⁹ It is well known that if HCV RNA is present at the time of OLT, not only does it persist, but also it can result in a chronic active hepatitis in up to 60% of patients. A smaller proportion of patients will experience an aggressive decline with fulminant fibrosing hepatitis and an accelerated development of cirrhosis. For these few patients, early retransplantation is their only option for survival. Identified risk factors for HCV recurrence after OLT include co-infection with HBV, rejection therapy, female recipient, recipient age greater than or equal to 50 years, ECD, and no HCV antiviral treatment.^{14,90} There does not appear to be any difference in the recurrence rate with different induction therapies.⁵⁵ Ideally, eradication of HCV takes place prior to transplantation; however, the treatment cannot be tolerated by all recipients. It is estimated that approximately 20% of patients achieve long-term viral clearance after OLT with completed therapy.⁹⁰ After OLT, recurrence can be treated with peginterferon, ribavirin, and HCV protease inhibitors. HCV protease inhibitors can lead to extreme elevations of tacrolimus and cyclosporine.

Aspergillus infections will affect 1% to 3% of liver transplant patients.⁹¹ These infections occur early in the posttransplant period with a median time of onset post transplantation of 16 to 17 days, although *Candida* infections are more common. Invasive fungal infections used to be a fatal consequence of extreme immunosuppression.^{81,92} Modern, more targeted immunosuppression regimens and better tolerated antifungal therapy have resulted in fewer *Aspergillus* infections and better recovery. Common prophylaxis agents include triazole antifungals (itraconazole, voriconazole, posaconazole), polyene antifungals (amphotericin B products), or echinocandins (caspofungin, anidulafungin, micafungin). Caution must be used with these drugs as they can alter the levels of the immunosuppression drugs as well as interact with the P450 enzyme system. Common antiviral drugs will also induce drug clearance and lower the effective dose of antifungals.

PRIMARY GRAFT DYSFUNCTION AND RETRANSPLANTATION

Primary graft dysfunction (PGD) leading to graft failure is a rare but devastating occurrence and is the leading cause of retransplantation in

TABLE 159-6

Risk Factors for Retransplantation Mortality

| |
|---|
| Age > 55 years |
| MELD > 27 |
| >1 prior OLT |
| Mechanical ventilation |
| Albumin < 2.5 g/dL |
| Donor age > 45 years |
| >30 U PRBC transfusion |
| Need for transplant 15-180 days from primary transplant |

liver recipients.⁹³ PGD is the inadequate metabolic function of the liver graft at any point following liver transplantation. There are many risk factors for PGD, including higher risk donors, increased need for blood transfusion, and perioperative vasopressor requirement (which may be a surrogate for tissue bed hypoperfusion). The etiology of PGD and subsequent graft failure is thought to be due partially to the development of ischemic cholangiopathy, which is 10 times higher in DCD as compared to brain death donation. Other studies report marked cellular energy depletion with the increased warm and cold ischemia time as experienced in circulatory death.

Although the exact mechanisms are complex and multifactorial, it is clear that early graft dysfunction in the early posttransplant period is negatively predictive of both graft and patient survival.^{50,67,68} Clinical symptoms of PGD or failure are altered mental status, failure to awake from anesthesia, clearance of bilirubin, and ongoing hyperdynamic cardiovascular physiology. Several diagnostic criteria have been proposed for identification of primary graft dysfunction at 7 days after transplantation including INR greater than 1.6, bilirubin greater than 10 mg/dL, and ALT or AST greater than 2000 IU/L.⁹⁴

Up to 23% of liver allografts are predicted to fail over the lifetime of the recipient, and up to 19% of patients who experience early graft failure will go on to retransplantation.⁹⁵ During the first 7 days following primary transplantation, the risks of primary graft failure (PGF) are prolonged warm and cold ischemia time, ongoing life support, early variceal bleeding, and younger recipient age.⁹⁶ It is thought that younger patients are more likely to have a more robust immune response resulting in early aggressive graft damage as has been found in other solid organ studies. PGF is the leading cause of retransplantation within the first week (>40%) followed by hepatic artery thrombosis (approximately 25%).⁹⁷ Interestingly, the cause for graft failure at 1 month is reversed secondary to the potential for collateral perfusion with progressive loss of the hepatic artery (Table 159-6).^{98,99}

CONCLUSION

The postoperative care of the liver transplant recipient patient is complicated by the slow resolution of the derangements of ESLD: hyperdynamic, vasodilated, hyperaldosteronism with PPHTN, PHTN, and renal dysfunction. These patients can be some of the most physiologically challenging to manage. They are also at risk for early, invasive infections and reinfection with hepatitis viruses. Rarely, they can develop complications or infections resulting in fulminant hepatic failure and will require retransplantation. However, when successful, the long-term benefits of transplantation make this endeavor rewarding.

KEY POINTS

1. Transplant recipients with cirrhotic ESLD will exhibit postoperative hemodynamics similar to their preoperative state. They may require medications to lower their pulmonary artery pressures for weeks in order to prevent hepatic allograft venous congestion.
2. Initial postoperative hypotension may be a result of PHTN, PPHTN, hemorrhagic shock, or cardiomyopathy. Invasive monitors can help discern the etiology.
3. Initiation of immunosuppression beginning with induction therapy will be comprised of steroids, calcineurin inhibitors, and MMF initially.
4. Viral and fungal prophylaxis is necessary and is likely not to be weaned during the first weeks following transplantation.
5. Steroid exposure increases the risk of recurrence of hepatitis C after liver transplantation. MMF exposure can reduce the risk of reinfection with HCV.
6. Many medications will be metabolized more slowly in liver transplant recipients as well as have significant interaction with each other; frequent measurements of drug levels and adjustments should be made.
7. Fever, leukopenia, or mental status changes should illicit a prompt evaluation of opportunistic infections, hepatic artery thrombosis, as well as the potential for rejection.

ANNOTATED REFERENCES

Klouche K, Amigues L, Massanet P, et al. Outcome of renal transplant recipients admitted to an intensive care unit: a 10-year cohort study. *Transplantation* 2009;87:889–895.

This single-center study reports a retrospective analysis of all renal transplant patients admitted to their ICU over the 10-year period 1997 to 2007 to evaluate outcome and determine predictive factors of outcome. Of their patient population, 57 were admitted over this time period, equaling a rate of 17 per 1000 patient-years. Mortality was twice the mortality of an unselected population of ICU patients (40% vs. 20%). Predictors of mortality included need for mechanical ventilation and mean arterial pressure.

Jeloka TK, Ross H, Smith R, et al. Renal transplant outcome in high-cardiovascular risk recipients. *Clin Transplant* 2007;21:609–614.

The authors report their experience with patients undergoing renal transplant who have risk factors for cardiac morbidity. They included 429 patients with roughly 10% suffering posttransplant cardiac events. Patients who were high risk (pretransplant angina, myocardial infarct, or angiogram history) were more likely to die post transplant. Intervention with stenting or bypass grafting did not reduce the risk of postoperative cardiac events.

Thomas MC, Mathew TH, Russ GR, et al. Perioperative blood pressure control, delayed graft function, and acute rejection after renal transplantation. *Transplantation* 2003;75:189–195.

This single-center study evaluated the relationship of perioperative blood pressure control to delayed graft function and acute rejection, and identified a significant relationship between better blood pressure control, reduced rejection, and improved graft function.

Matas AJ, Humar A, Gillingham KJ, et al. Five preventable causes of kidney graft loss in the 1990s: a single-center analysis. *Kidney Int* 2002;62:704–714.

This large, single-center review identified five major causes of renal graft loss over 10 years (1990–1999) in the 1467 primary renal transplants performed at this institution. These causes included thrombosis, acute rejection, chronic rejection, death with function, and non-compliance. Death with function and thrombosis were the most common causes of graft loss in the first year after transplant.

Catena F, Ansaloni L, Gazzotti F, Bertelli R, et al. Gastrointestinal perforations following kidney transplantation. *Transplant Proc* 2008;40:1895–1896.

The authors of this single-center study report their experience with GI complications in 1611 patients following kidney transplantation. Perforations of the colon (n = 21), small bowel (n = 15), duodenum (n = 6), and stomach (n = 4) were noted. GI perforation was associated with a 24% mortality rate, and nearly 50% of the perforations were associated with a period of high-dose immunosuppression.

Evens AM, David KA, Helenowski I, et al. Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era. *J Clin Oncol* 2010;28:1038–1046.

This multicenter analysis included patients from four transplant centers over a decade who developed posttransplant lymphoproliferative disease. In this cohort of patients (n = 80), mean time to development of PTLN was 48 months post transplant. Three-year survival rate was 62%, and survival with rituximab was significantly improved compared to without (73% vs. 33%). Poor prognostic indicators for outcome included CNS involvement, bone marrow involvement, and hypoalbuminemia.

■ References for this chapter can be found at expertconsult.com.

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Intestinal and Multivisceral Transplantation: The Ultimate Treatment for Intestinal Failure

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Intestinal and multivisceral transplantation remains a dynamic process, moved forward by advances in the multidisciplinary care of intestinal failure, surgical techniques, innovative immunosuppressive strategies, and an improved understanding of intestinal transplantation immunology. More recently, great strides have been made in the medical and surgical management of patients with intestinal failure so that the number of patients undergoing intestinal transplantation has decreased.¹ However, no matter how good the nontransplant management of intestinal failure becomes, there will inevitably remain a group of patients in whom transplantation is the ultimate and final component of their intestinal care. Recognition of intestinal transplantation as an established modality for select intestinal failure patients combined with improved outcomes since the early 2000s had previously led to an increasing number of candidates referred for intestinal transplantation each year (Fig. 160-1). This coincided with the development of multidisciplinary units, where patients could be managed the most appropriately, with medicine, surgery, or transplantation and often a combination of these. The goal is that patients likely to require transplantation will be listed, followed, and transplanted at the optimum time after weighing the risks and benefits and complications of each of these modalities. In the United States alone, nearly 1000 patients were alive with a functioning intestinal allograft as of December 2013.² Although the time interval between listing and intestinal transplant has decreased over the past decade (Fig. 160-2), wait list mortality remains high, particularly for infants and adults with concomitant liver failure.³ Immunosuppression for intestinal and multivisceral transplantation commonly involves some form of perioperative antibody induction, although many centers now tailor induction and management protocols to individualize strategies based on each patient's situation, often by employing immunologic testing, in particular cross-matching and donor-specific antibody reactions, to help determine optimum strategies. The future of intestinal transplantation depends on the prevention and treatment of chronic rejection in isolated intestinal allografts, which continues to be a fundamental barrier to achieving successful long-term outcomes and is the ongoing subject of rigorous investigation. Long-term data on nutritional outcomes and transplantation morbidity help further determine the optimal timing and role of intestinal and multivisceral transplantation in patients with intestinal failure.

MANAGEMENT OF INTESTINAL FAILURE

Intestinal failure is clinically defined as the loss of nutritional autonomy secondary to bowel dysfunction and the need for parenteral nutrition (PN) for more than 28 days. Patients with intestinal failure are initially managed by administration of PN through central venous access. The duration of intestinal failure is variable and, in certain patients, unpredictable, from short-term to lifelong, and depends largely on the adaptation capacity of the remaining viable intestine, which in itself is dependent on variable factors such as patient age and underlying diagnosis. Improved long-term outcomes in PN-dependent pediatric patients have been reported recently by single centers.^{4,5,6} Nonetheless, there remains a significant subset of patients who develop irreversible

intestinal failure and require indefinite PN therapy with its attendant complications. Intestinal transplantation has proved to be lifesaving in this later group of patients with irreversible intestinal failure who suffer complications from administration of PN.⁷

Optimal management of patients with intestinal failure is achieved after a detailed multidisciplinary evaluation.^{8,9} Obtaining a comprehensive history is critical and must include birth details (such as prematurity) and disease history, complicating comorbid medical history, past surgical procedures, infections, number and location of previous central venous lines, presence of central venous thrombosis, a detailed nutrition history including duration of PN, details of PN prescriptions, and maximal enteral feeding tolerance and its trajectory (still advancing or static) as well as medication history and frequency/volume of stools. A careful history obtained and physical examination performed by the intestine rehabilitation team is critical to the process of achieving a complete pretransplant workup. Further investigations include blood tests, upper gastrointestinal (GI) contrast study with small bowel follow-through, contrast enema if indicated, abdominal sonogram to assess for hepatosplenomegaly, and an ultrasound exam of central venous anatomy. Occasionally, endoscopy with small intestinal aspiration for quantitative microbial culture and mucosal biopsy is recommended. In equivocal cases, liver biopsy is recommended if there is evidence of liver dysfunction or portal hypertension to determine if concomitant liver containing transplantation is required.

Management of patients with intestinal failure focuses on optimization of gut adaptation and recovery of intestinal function to achieve enteral autonomy. With improved management of PN and minimization of complications, longer duration of PN can be achieved to allow for gut adaptation. There has been renewed interest in enterocyte trophic factors, including growth hormone and more recently glucagon-like peptide (GLP2),^{10,11} which has shown some benefit in adults, with a pediatric trial ongoing. Surgical therapies that have a role in adaptation after intestinal failure include autologous reconstructive surgeries (repair enterocutaneous fistulae and disconnected bowel) and bowel lengthening procedures,¹² such as the Bianchi procedure¹³ and serial transverse enteroplasty (STEP).^{14,15} Alternatively, if gut dysfunction is considered irreversible, management of these patients concentrates on maintaining optimal growth in children and nutritional repletion in adults to prepare them for likely intestinal transplantation. Recently, there has been a shift in timing of intestinal transplantation, focused more on the individualized risks and complications of PN versus intestinal transplantation. In other words, if patients, especially children where there still may be hope for further adaptation, are stable on PN, with no significant complications, then continuing on this line and deferring transplant is quite reasonable.

Small bowel bacterial overgrowth (SBBO) is a common clinical problem in patients with intestinal failure and is treated with a variety of antibiotic regimens. To date, no comparative studies are available to enable an evidence-based approach to treat SBBO. The use of metronidazole for anaerobic overgrowth, combined with trimethoprim and sulfamethoxazole or an oral aminoglycoside for gram-negative organisms, is a common theme. Metronidazole monotherapy is used if the

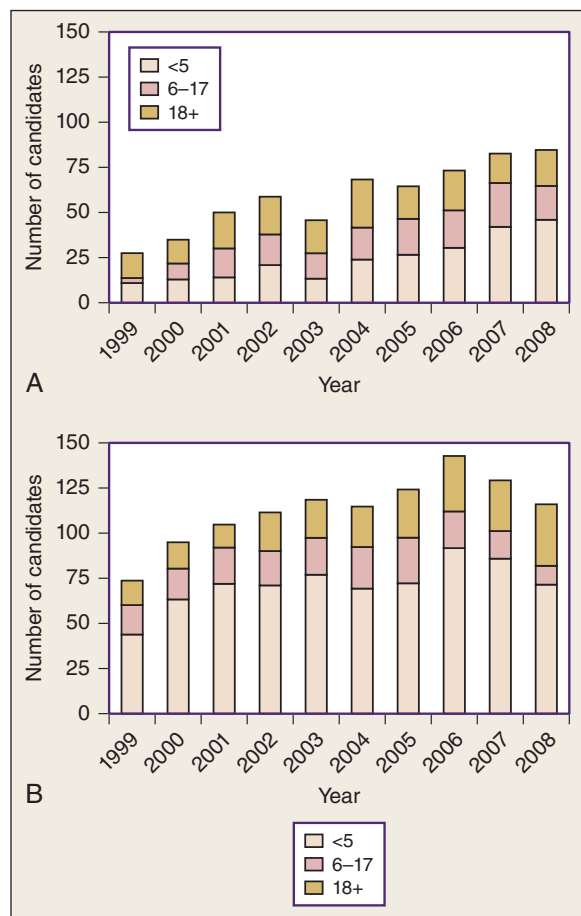


FIGURE 160-1 ■ **A**, Number of candidates on the isolated intestine waiting list by age, 1999-2008. **B**, Number of candidates on the combined liver and intestine waiting list by age, 1999-2008. (Adapted from Mazariegos GV, Steffick DE, Horslen S, et al. Intestine transplantation in the United States, 1999-2008. *Am J Transplant* 2010;10:1020-1034.)

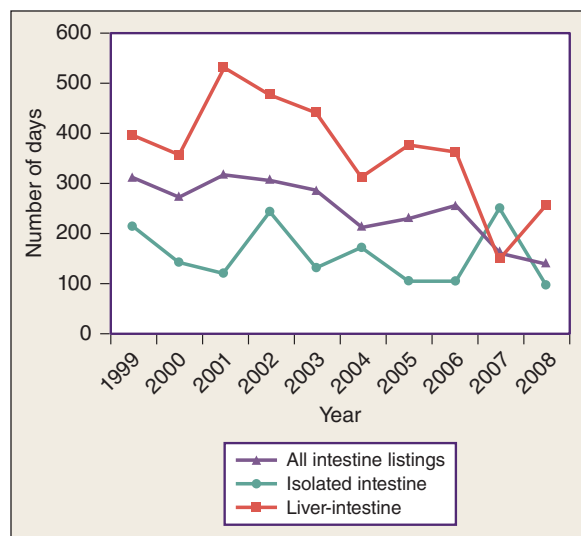


FIGURE 160-2 ■ **Median time to transplant for intestine waiting list registrants, 1999-2008.** (Adapted from Mazariegos GV, Steffick DE, Horslen S, et al. Intestine transplantation in the United States, 1999-2008. *Am J Transplant* 2010;10:1020-1034.)

dominant symptoms suggest predominantly anaerobic overgrowth (such as bloating, increasing diarrhea, and D-lactic acidemia). The extreme sensitivity of anaerobes to oxygen makes the use of small bowel aspirate cultures relatively unreliable as a means of microbial surveillance or indication to treat SBBO. Probiotics such as *Lactobacillus* and *Saccharomyces* have been used in an attempt to limit SBBO. Given the absence of randomized evidence to support the efficacy of probiotics, coupled with reasonable concerns about impurities and possible contamination with other bacteria (e.g., *Leuconostoc*), the use of probiotics is controversial and mostly discouraged in patients with central venous catheter access and intestinal failure and especially after transplantation due to increased immunosuppression.

Parenteral nutrition-associated liver disease (PNALD), also referred to as *intestinal failure-associated liver disease* (IFALD), remains a critical problem in this patient population, affecting infants disproportionately. The 1-year mortality of patients with PNALD exceeds 80% in the absence of PN weaning or transplantation. Although not always feasible, the best strategy to prevent and treat PNALD involves a commitment to the advancement of enteral nutrition. Despite a conscientious approach to PN therapy, many children and adults still develop cholestasis relatively early in their clinical course. Prevention and timely treatment of infection, minimizing SBBO, preventing overfeeding with dextrose, providing adequate amino acids, cycling PN, or providing PN-free days when possible are probably important measures to slow the progression of PNALD.¹⁶ Stasis of bile in the nonstimulated biliary system and gallbladder can lead to sludge buildup and cholelithiasis. In the authors' experience, cholecystectomy may be beneficial to minimize the risks of developing biliary obstructive episodes and pancreatitis and should be considered early in any operative course as part of a combined procedure. If long-term use of PN is to be expected, then cholecystectomy on its own is rarely done as it rarely improves liver function and is not indicated for PNALD alone. Bowel reconnection, even in patients with very short guts, may relieve some of the high pressure in the upper GI tract and issues of reflux cholangitis. This, in association with the cholecystectomy, may allow for long-term improvements in liver function. None of the components of standard PN solutions have been conclusively shown to cause or contribute to PNALD, but excess glucose and improper ratios of glucose to amino acid have been associated with hepatic steatosis. Interest in the manipulation of the lipid component of PN has led to lipid minimization protocols with the reduction of soy-based lipid solutions and even their eventual removal by substituting with Omegaven (a fish oil-based, intravenous [IV] lipid solution rich in omega-3 fatty acids). Omegaven is, as yet, not FDA approved and is currently available as a study drug under an IRB-approved compassionate use protocol. Substantive evidence that these measures retard or reverse the progression of liver disease has not yet been definitively demonstrated, and although bilirubin levels are lowered, it is not known if improvement in hepatic fibrosis occurs at the molecular level.^{17,18,19} Other options, such as SMOF (soybean oil, medium-chain triglycerides, olive oil, fish oil), which has been utilized for many years in Europe, is currently in trial in the United States and may offer another improved alternative in patients with PN dependence. In some circumstances, either due to poor weight gain and need for increased calories or concerns for essential fatty acid deficiencies, it may be necessary to add, but not entirely substitute, fish oil-based lipids for soy-based solutions. However, this is administered to patients in whom liver function tests demonstrate abnormalities.

In addition to PNALD, patients on long-term PN are at risk of developing metabolic bone disease (MBD). Associated with an insidious onset of bone pain that can become quite severe, patients with MBD will present with normal serum calcium, phosphorus, vitamin D, and parathyroid hormone, but with hypercalciuria. Nontraumatic spinal and rib fractures have been reported in these patients. To optimize bone maintenance in patients on PN, it is important to include calcium in parenteral formulations, prevent metabolic acidosis, and minimize aluminum contamination. Symptoms of MBD tend to resolve only after stopping PN.

Many intestinal transplant recipients will require intensive care unit (ICU) management during the pretransplant period, although the number of patients being transplanted from home (outside of a hospital setting) has increased with improved medical management and resulted in improved outcomes in this subset of patients.¹ Sepsis and GI hemorrhage are common reasons for ICU admission in patients with intestinal failure. Blood products, though necessary in the resuscitation of GI hemorrhage, should be used judiciously in the absence of acute bleeding. Pretransplant exposure to blood products, particularly platelets, can predispose intestinal transplant recipients to developing antibodies and can place them at a higher risk of developing antibody-mediated rejection after transplantation. Leukoreduced blood products may be preferable in patients awaiting transplant.

Central line–associated bloodstream infections (CLABSI) unfortunately are common in PN-dependent patients. All attempts should be made to avoid this event, with fastidious central line care at the core of the matter, with strategies like antibiotic and ethanol locks²⁰ playing an important role. As the incidence and degree of liver dysfunction lessens with improved PN management, long-term therapy is still required. One of the determining factors to move forward with transplantation is loss of venous access. Hence, although infection (especially fungal and life-threatening gram-negative infections) may necessitate removal of a tunneled central venous catheter, all attempts at salvaging the line, or at least the venous site, should be considered. In particular, smaller pediatric patients and patients with a history of thrombosis may have limited venous access, necessitating preservation and treatment through an infected line. Percutaneous lines should be placed with caution in these patients as great vessels may no longer be patent, and the trauma to the remaining vessels may have serious consequences. Many surgeons, anesthesiologists and intensivists now place central lines under ultrasound guidance, although the more difficult and chronic issue lines are best served in interventional radiology with their vast cadre of specialized techniques. Ultrasound evaluation of deep veins to assess for patency is notoriously variable and often unreliable, and in difficult or concerning cases venography remains the gold standard. Mapping should be considered before excessive loss of venous access occurs.

Nutritionally deplete patients are relatively immune suppressed and prone to severe community-acquired infections. Pediatric patients with intestinal failure and IFALD are at increased risk of respiratory failure even with common viral infections. Since children have a compliant chest wall, increased abdominal girth creates a mechanical disadvantage even during normal tidal volume breathing. In the setting of pulmonary infection, volume overload, or decreased cardiac output, the work of breathing can lead to fatigue.

■ INDICATIONS FOR TRANSPLANT

The goals of the transplant team are to determine whether the patient may benefit from transplantation, assess alternatives to transplant, evaluate any contraindications to transplantation, and provide education to the patient about the complex process of undergoing transplantation. After evaluation by the multidisciplinary team and open and frank discussion among all the team members, the usual result is one of three choices: (1) patient may be followed closely as an intestinal care patient and listing status deferred depending on progress, (2) listed as a status 2 recipient to accrue time on the list while awaiting possible medical improvement or bowel adaptation but realizing that transplantation is still quite likely, or (3) as a status 1 intestinal recipient if the patient has met criteria for complications of irreversible intestinal failure or as a liver intestine recipient if the patient is deemed to have irreversible intestinal failure and associated irreversible significant liver dysfunction for immediate consideration where criteria make transplantation inevitable.

In October 2000, the Center for Medicare and Medicaid Services approved intestinal, combined liver-intestine, and multivisceral transplantation as a standard of care for patients with irreversible intestinal failure who could no longer be maintained with PN. Intestinal and

TABLE 160-1

Indications for Intestinal and Multivisceral Transplantation

| PEDIATRIC PATIENTS | ADULT PATIENTS |
|--------------------------------|---|
| Volvulus | Superior mesenteric artery thrombosis |
| Gastroschisis | Crohn's disease/irritable bowel disease (IBD) |
| Necrotizing enterocolitis | Desmoid tumor |
| Pseudo-obstruction | Volvulus |
| Intestinal atresia | Trauma |
| Microvillous inclusion disease | Familial polyposis |
| Hirschsprung's disease | Budd-Chiari disease |
| Trauma | Intestinal adhesions |
| | Pseudo-obstruction |
| | Radiation enteritis |

multivisceral transplantation are considered for patients with irreversible intestinal failure who fail PN therapy due to complications, such as recurrent life-threatening catheter infections, multiple venous thrombosis limiting line access, and impending liver failure. Other criteria include those who cannot tolerate quality-of-life limitations associated with PN therapy or who have no chance of intestinal rehabilitation either due to extreme gut loss or no hope of restoration of function of the gut that exists. Subsequently, there has been discussion within the intestinal transplant community as to whether the above criteria and timing of these events need to be reconsidered or modified. The myriad causes of bowel dysfunction can be subcategorized into acute and chronic pathophysiologies. Common causes of acute dysfunction include necrotizing enterocolitis, volvulus, and mesenteric thrombosis. Common causes of chronic dysfunction include Crohn's disease and radiation enteritis. These disease processes can alternatively be classified as either surgical due to resection leading to short bowel syndrome (SBS) or nonsurgical due to congenital enterocyte disorders leading to dysmotility or malabsorption. Unlike patients with SBS, patients with nonsurgical causes of intestinal failure may have native intestines with normal gross morphology and anatomic length. [Table 160-1](#) lists the already well-described clinical indications for intestinal and multivisceral transplantation.

Owing to the particularly high morbidity and mortality of children with IFALD, increasing efforts have been made by the pediatric medical community to optimize timing of referral of these patients to specialized intestine failure rehabilitation centers and transplant centers to improve overall outcomes. A recent expert consensus panel²¹ recommended the following pediatric criteria for consultation or referral for small bowel transplant assessment: (1) children with massive small bowel resection, (2) children with severely diseased bowel and unacceptable morbidity, (3) continuing prognostic or diagnostic uncertainty, (4) microvillous inclusion disease or intestinal epithelial dysplasia, (5) persistent hyperbilirubinemia (>6 g/dL), (6) thrombosis of two of four upper body central veins, and (7) the request of the patient or family. This initiative, to a large extent, has been relatively successful in breaking down previously held prejudices and allowed for prompt and, at times, very early evaluation. This in turn has allowed for more coordinated expert multidisciplinary management of these patients, and with fewer patients now heading into liver failure with improved preservation of the liver, it gives the medical and surgical teams more time to let the native bowel grow, so that more patients, even after 5 or more years of PN therapy with ultrashort guts are eventually able to wean off of PN that previously would never have been given this chance.

Transplantation is unlike any other surgical procedure in that it is rarely an isolated event, unlike general surgical procedures, and has significant short- and long-term medical and surgical issues that need to be considered. Nowadays, as the overall management of PN improves, the indication and timing of transplantation become a

balancing act, trying to weigh the risks and complications of PN versus the potential short- and long-term risks of intestinal transplant.

EVALUATION FOR TRANSPLANT

For both children and adults, the evaluation of intestinal and multivisceral candidates usually begins as an inpatient process due to the complexity of the case and the need for many different services to see the patients and investigations that may be required. Most intestinal failure units utilize multidisciplinary teams that assess patients during evaluations. This comprises the GI team, other medical teams as indicated (cardiac, renal, genetic, immunology, pulmonology, etc.) general surgery (especially pediatric surgery), transplantation, and many allied services including psychology, social work, pharmacy, and others as indicated in each case. Transplant teaching is a vital component, as is determining fiscal ability and supportive structures for potential recipients. Each team provides recommendations, and in particular the GI team may make recommendations with the PN and IV medications that may be quite beneficial to the patient and the referring team. At times, especially in a multidisciplinary center with both good pediatric surgical and transplant skills, these patients may undergo surgical exploration and attempts at reconstruction and/or bowel lengthening procedures prior to transplantation. These are done with an attempt to either avoid transplantation, or at least minimize the need for PN and delay the need for transplantation, or to make the conditions at transplant better (i.e., obtain colonic growth and health in previously disconnected patients or resecting enteric fistulae/intraabdominal abscesses that may be contributing to sepsis).

Having a surgeon well versed in medical management strategies, able to operate as a general surgeon to try to help restore enteral autonomy by surgical means, and be able to put the patient up for transplant is advantageous for both the patient and intestinal failure unit, allowing for more aggressive surgical interventions to try to avoid or delay transplantation.

Determining which type of allograft to use in patients with intestinal failure involves a comprehensive evaluation of the function and anatomy of the remaining bowel along with other abdominal organs. Intestinal failure patients are considered candidates for isolated intestinal transplant (with or without colon), combined liver and intestine transplant, multivisceral transplant (including liver, stomach, duodenum, pancreas, and small bowel with or without colon), or modified multivisceral transplant that excludes the liver. There has been ongoing debate in the transplant community regarding the above nomenclature; however, from a practical and immunologic point of view the major differentiation is the inclusion of the allograft liver as part of the transplant bloc. Whether to perform simultaneous hepatic replacement remains a challenging decision even to experienced transplant surgeons, particularly for patients with borderline liver dysfunction and a biopsy that shows fibrosis (Ishak level 3-4 and above) and some degree of synthetic dysfunction suggestive of portal hypertension. Nevertheless, it must be realized that the classic symptoms and signs of impending liver failure may not be the same in patients with no intestine, and the use of Omegaven may make the bilirubin at least look relatively normal. This also impacts the MELD and PELD score in these potential recipients, hence the “supplemental” points added to their total when the intestine is added to the liver transplant listing. This has been allowed in the pediatric population for some time now but remains a vexed issue in the adult population. The key factors in determining whether to perform liver transplant in patients with intestinal failure are the extent of portal hypertension and the severity of parenchymal liver disease. In general, patients with mild portal hypertension should be cautiously considered for isolated intestinal transplant. Under these circumstances, it is mostly recommended that venous outflow from the intestinal allograft bypass the portal circulation and be drained to the recipient systemic circulation through the inferior vena cava. This is especially relevant as there has been no documented proof that portal drainage is more beneficial or that relative portal and mesenteric hypertension may have deleterious effects

on intestinal allograft function. The other predicament is the patient with marginal intestinal length who may, under ideal circumstances and more time, be able to adapt and come off of PN but the liver has undergone such considerable damage that it needs to be replaced. In this circumstance, liver transplantation in the face of short gut syndrome can and has been done but is fraught with potential dramatic consequences and the potential need for liver and intestine retransplantation if it is not successful.

TRANSPLANTATION PROCEDURES

Brief descriptions of recipient operations are provided below. The multivisceral donor procurement operation has previously been well described.²² It is important to note that to a large extent, the future course post transplant is significantly determined by the quality of the donor and success of the donor recovery and back table preparation. The intestine is perhaps the most sensitive donor organ and prone to ischemic events either by nature of the cause of death or due to pharmacologic agents (pressors) that are used to support the donor leading up to and after brain death. It is thought that damage to the bowel sets up an inflammatory cascade that in turn makes the organ more immunogenic, or at least more susceptible to a rejection episode once it is reperfused in the recipient. Hence, the recipient surgeon is extremely judicious in the selection of a suitable donor and the number of acceptable donors is restricted. Other factors that play into this decision include blood group (generally identical), size-matching issues due to restricted abdominal domain (reduced grafts have been shown to have short- and long-term issues) and, some potential crossmatch issues (especially in retransplant patients). Thus, it is clear why the intestinal allograft is one of the more infrequently recovered allografts.

Isolated Intestinal Transplant

For isolated intestinal transplants (Fig. 160-3), the donor intestinal graft (jejunum and ileum) is procured along with donor vascular conduits, including an artery (iliac and/or carotid) and a vein (iliac, occasionally jugular). The donor superior mesenteric vessels are occasionally anastomosed directly to the recipient superior mesenteric artery and vein if adequate length is achieved. More commonly,

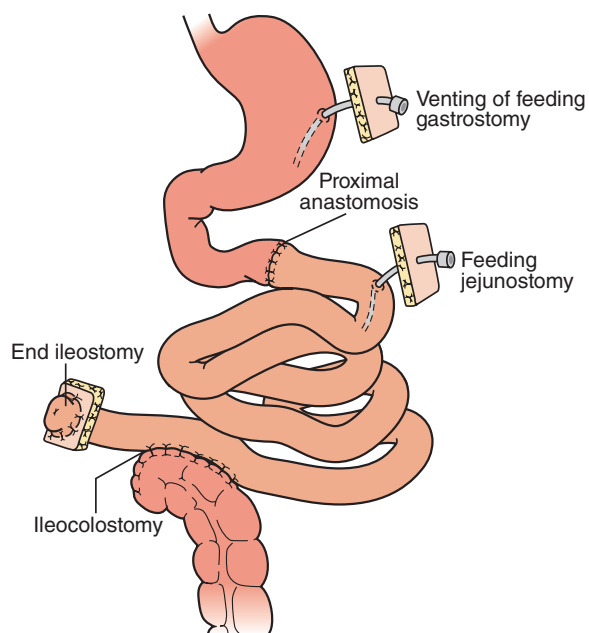


FIGURE 160-3 ■ Isolated intestinal transplant.

interposition vascular conduits are anastomosed to the recipient infrarenal aorta and recipient superior mesenteric vein (portal drainage) or inferior vena cava (systemic drainage) to provide sufficient length and proper orientation for the allograft.

The intestinal reconstruction involves a proximal duodeno- or jejunojunction, depending on individual recipient considerations of remnant bowel viability and anatomy. The distal end of the intestinal allograft may be used as a permanent end ileostomy if the recipient has no remaining viable colon or may be anastomosed to the remnant colon, leaving a short portion of allograft distal to the enterocolic anastomosis to bring out as a temporary end ileostomy (Brooks-type ileostomy) that allows access to the bowel for endoscopic surveillance and mucosal biopsies. Colonic transplantation with the small bowel has been utilized in some centers with good results, especially in situations where the native colon is very short or nonfunctional (such as Hirschsprung's disease or pseudo-obstruction). In this case, a loop ileostomy is formed so that the small bowel can be biopsied and the colon normally brought out as an end colostomy, or if anastomosed to the remaining colon, a loop colostomy may be formed as well. In patients with gastric dysmotility, although a stomach inclusive allograft may be ideal, due to donor availability (size and/or anatomic vascular aberrations) it may not be recoverable; hence a gastrojejunostomy may also need to be performed as an alternative to drain the stomach. Single or multiple feeding tubes (gastrostomy tube, jejunostomy tube, and combined gastrojejunostomy tube) may be placed based on multiple considerations including recipient pretransplant oral intake capacity and dysmotility issues.

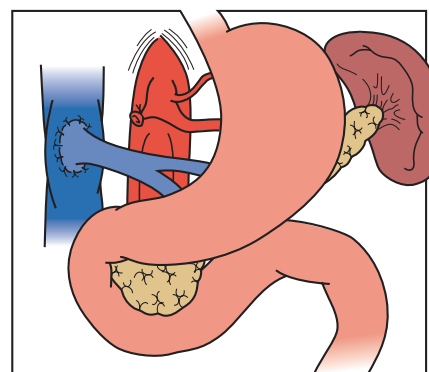
Combined Small Bowel and Liver Transplant

For combined small bowel and liver transplants (Fig. 160-4), the recipient hepatectomy is routinely performed with preservation of the native retrohepatic inferior vena cava. The recipient foregut including stomach, native pancreas, and proximal duodenum is also preserved and its outflow maintained with a permanent end-to-side portocaval shunt. The composite donor allograft includes the primary organs (liver and small bowel) as well as the donor duodenum and pancreas, allowing for maintenance of donor hepatobiliary continuity. Arterial inflow to the composite donor allograft is achieved using an arterial interposition conduit from the recipient infrarenal aorta to the reconstructed donor aorta placed onto the Carrel patch of donor celiac artery and superior mesenteric artery. Allograft venous outflow via the suprahepatic inferior vena cava commonly involves the well-described "piggyback" technique, anastomosing donor suprahepatic inferior vena cava to the confluence of the recipient hepatic veins and cava. Occasionally, a "standard" bicaval anastomosis is performed. Intestinal reconstruction is performed in a similar fashion to an isolated intestinal transplant, mostly with the upper anastomosis being a jejunojunction. Feeding tubes are placed as indicated.

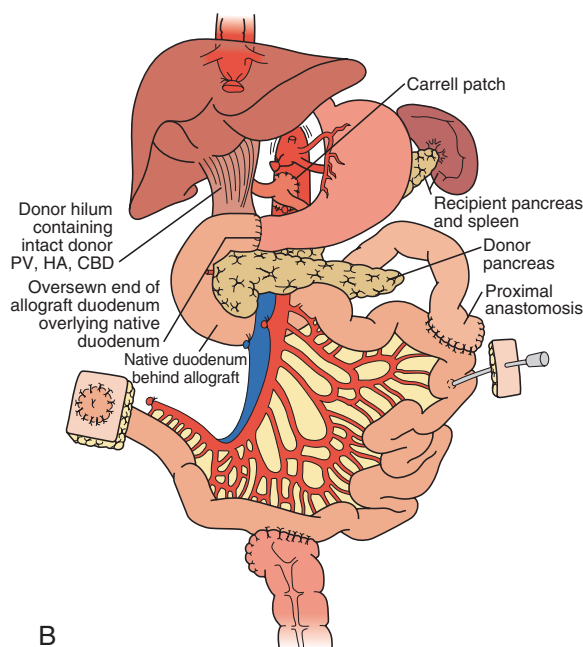
Full Multivisceral Transplant

In the majority of cases of full multivisceral transplant procedures (Fig. 160-5), prior to implantation the recipient distal stomach, duodenum, pancreas, liver, and remaining small bowel are resected. The recipient inferior vena is routinely meticulously preserved. The absence of remaining foregut or midgut precludes the need for portocaval shunt. Vascular inflow is similar to composite liver-bowel transplant but now includes celiac inflow to the stomach as well. Vascular outflow is identical to composite liver-bowel transplant. The donor spleen is removed from the composite allograft on the back table prior to reperfusion.

Intestinal reconstruction is performed proximally with a gastrogastrostomy anastomosis, and the distal anastomosis is similar to previously described intestinal transplants. To avoid gastric outlet obstruction due to vagal denervation, a Heineke-Mikulicz pyloroplasty is routinely performed after reperfusion. Feeding tubes are placed as indicated.



A Native portocaval shunt draining native foregut into recipient vena cava



B

FIGURE 160-4 ■ Combined liver and intestinal transplant. A, Portocaval shunt draining native foregut. **B,** Combined liver and intestinal transplant with feeding jejunostomy.

Modified Multivisceral Transplant

A "modified" multivisceral transplant (Fig. 160-6) involves transplantation of a full composite allograft without a liver. The recipient liver is preserved along with its vasculature and the extrahepatic biliary system with duodenum, pancreas, and spleen. Vascular conduits are used routinely (Fig. 160-7). If the native enterohepatic biliary system is intact, the native duodenum or jejunum is drained into the allograft duodenum or jejunum. If, however, the procedure involves disruption of hepatobiliary continuity, the native bile duct can be drained via Roux-en-Y hepaticojejunostomy constructed from donor intestinal allograft (often the case in children where the donor bile duct is very small), or in adults and older children via a choledochoduodenostomy (duct-to-duct) anastomosis.

POSTOPERATIVE MANAGEMENT

Advances in the technical aspects of intestinal and multivisceral transplantation have occurred in parallel with improvements in intraoperative monitoring and postoperative critical care management of these challenging patients.

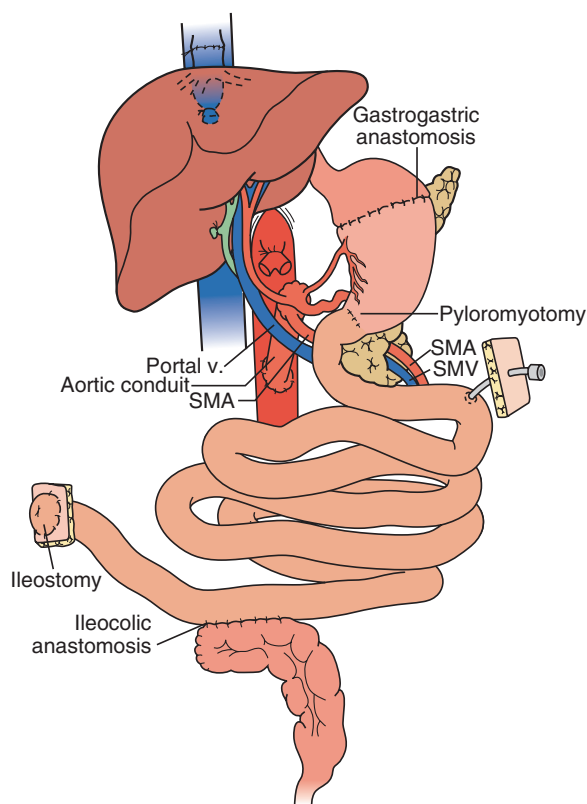


FIGURE 160-5 ■ Full multivisceral transplant.

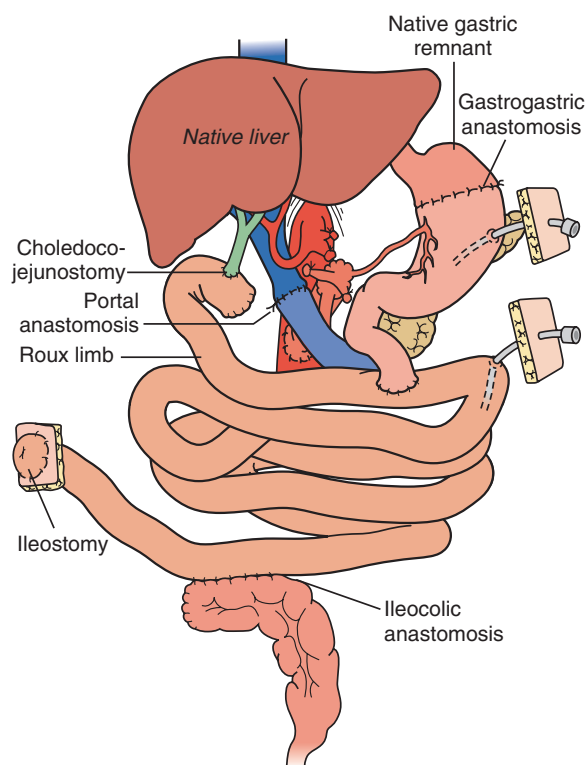


FIGURE 160-6 ■ Modified multivisceral transplant.

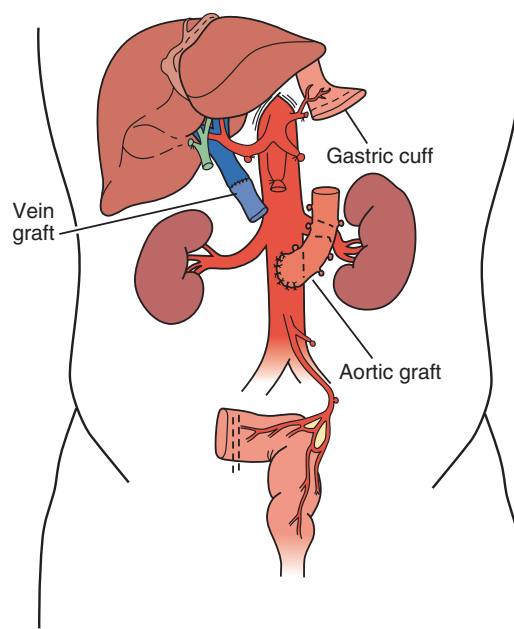


FIGURE 160-7 ■ Vascular conduit extensions for modified multivisceral transplant.

Ventilatory Management

Extubation is commonly achieved within 48 hours of the transplant operation in adult patients. Mitigating factors that might delay extubation include graft malfunction, delayed abdominal wall closure, volume overload, sepsis, organ failure, and surgical complications such as bleeding. In children, delayed abdominal wall closure is commonly necessary due to allograft size constraints and swelling post reperfusion and requires continued neuromuscular blockade and mechanical ventilation while diuresis is performed. Given that recipients tend to be nutritionally compromised preoperatively and that intestinal and multivisceral transplant operations are relatively long in duration (8 to 18 hours), a careful assessment of weaning parameters prior to extubation is essential. Changes in intraabdominal pressure and abdominal girth may adversely affect respiratory mechanics, leading to rapid, shallow breathing. These problems are most common in children, in small adults who receive large allografts, and in patients whose course is complicated by large-volume ascites. Pleural effusions are common due to nutritional depletion with hypoalbuminemia and intraoperative manipulation of the diaphragm. Although attempts to overcome them by diuretics may be attempted, thoracentesis and placement of pleural tubes often are necessary.

Renal Function

It is common for intestinal transplant recipients to demonstrate some degree of renal dysfunction pretransplant, owing to multiple episodes of sepsis with hypotension, the side effects of antibiotics, chronic dehydration, and hepatic dysfunction. Although patients receive significant volumes of fluid during the long course of the transplant operation, intravascular volume depletion can be a problem in the immediate posttransplant period. Significant fluid volume may accumulate in the intestinal allograft secondary to preservation injury (peaking at 48 to 72 hours), and large-volume ascites production due to mesenteric lymphatic leakage may occur. Either of these processes can lead to profound and sometimes underappreciated intravascular volume depletion and can worsen the nephrotoxicity of immunosuppressive agents and antibiotics.

Maintenance of ideal volume status is challenging in these patients, and interventions should be directed at optimizing cardiac output and organ perfusion. Extravascular volume overload is common and should be interpreted with caution, particularly in the immediate posttransplant period. In patients with impaired renal function or high tacrolimus drug levels, urine output may not be an accurate indicator of perfusion. Skin perfusion, mixed venous oxygen concentration, and serum lactate are useful surrogates. Since intestinal transplant recipients are commonly nutritionally deplete, use of 5% albumin as a volume expander may be preferable to larger volumes of crystalloid solution. In patients with large-volume stoma output or ascites drainage, standing orders for fluid replacement may be necessary. Balancing adequate volume resuscitation with the avoidance of volume overload in the setting of baseline renal dysfunction can be a significant challenge that requires considerable clinical experience and meticulous attention to detail.

Infection Control

Recipients of intestinal or multivisceral transplants will routinely receive prophylactic broad-spectrum antibiotics intra- and post transplant. Any history of nosocomial infections before transplant should be addressed with administration of the appropriate specific antibiotics. Colonizing organisms growing from enterocutaneous fistula tracts should also be covered appropriately. Selective bowel decontamination with nonabsorbable oral antibiotics is performed routinely in the donor and in some intestinal transplant recipients. Some centers also perform surveillance stool cultures on a regular basis post transplant.

Translocation of bacteria or bacterial toxins from the intestine into the bloodstream can cause sepsis or systemic inflammatory response syndrome (SIRS). A history of repeated exposure to broad-spectrum antibiotics leads to colonization with multiple resistant organisms in many intestinal transplant recipients. Empiric antibiotic therapy for sepsis should include coverage for common enteric organisms and should take into account a history of antimicrobial resistance. Episodes of translocation occur most commonly during acute rejection, when the mucosal barrier of the allograft has been compromised but can also be demonstrated with enteritis associated with Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infection. In the absence of positive blood cultures to direct antibiotic therapy, organisms growing from quantitative stool cultures in significant numbers ($>10^8$ colony-forming units [CFU]/mL) in patients with sepsis or acute cellular rejection may be considered potential causes of bacteremia and may be treated with IV antibiotics. The high incidence of renal dysfunction in intestinal transplant recipients should prompt use of nonnephrotoxic antibiotics when possible and careful monitoring of antibiotic levels when necessary.

One of the major complications post transplantation is opportunistic infections, be they viral or fungal. Fungal infections must always be considered in recipients with fevers and negative cultures, and often appropriate antifungal treatment is commenced empirically pending extended culture results and imaging studies.

Antiviral Prophylaxis

Opportunistic viral infections play a significant factor in postoperative complications. Antiviral prophylactic strategies have evolved with intestinal transplantation. Viral infections can cause significant morbidity, especially in pediatric recipients in the early postoperative period. Common pathogens include CMV, EBV, herpes simplex virus (HSV), adenovirus, and influenza viruses. Many pediatric recipients have no prior protective exposure to these viruses, so primary infection occurs in these patients while they are highly immunosuppressed. Recent advances in prophylaxis and preemptive therapy have significantly decreased early morbidity associated with EBV, CMV, and HSV, lowering the incidence of clinically significant infections to less than 5%. Lack of definitive treatment for infections with respiratory viruses such as influenza and adenovirus in the early postoperative period

can be catastrophic because of clinical sequelae including disseminated viremia, necrotizing pneumonitis, and bacterial superinfection. The currently recommended anti-CMV prophylaxis includes a 2-week course of IV ganciclovir with concomitant administration of cytomegalovirus-specific hyperimmune globulin (Cytogam). The IV dose for ganciclovir is 5 mg/kg twice daily. The dose for Cytogam is 150 mg/kg, administered 2, 4, 6, and 8 weeks after transplant, and 100 mg/kg/d at 12 and 16 weeks after transplant, except in the case of donor CMV negative to recipient CMV donor negative. Close monitoring of CMV and EBV polymerase chain reaction (PCR) is performed frequently post transplant and spaced out moving away from the time of transplant and as indicated.

Nutritional Support

Immediate posttransplant nutritional support is administered using standard PN, which is tapered gradually as enteral feeding is advanced. Tube feedings with isotonic formula are started based on clinical determination of intestinal allograft function. In the authors' experience, most intestinal transplant patients especially children, do not voluntarily ingest adequate amounts of nutrition in the early postoperative period. To achieve maximal nutritional repletion, tube feeding is usually required once the intestinal tract becomes functional. Resistance to oral feedings is a particular clinical challenge in younger pediatric recipients, many of whom demonstrate oral aversion. This should be assessed and attempts should be made pretransplant to avoid or overcome this issue.

Immunosuppression

Although a variety of combinations of immunosuppressive drugs have been used in intestinal transplant recipients, most patients are maintained on tacrolimus (Prograf [Astellas, Tokyo, Japan]) therapy along with other adjunctive medications. Organ Procurement and Transplantation Network (OPTN) data show that 99% of intestinal transplant recipients receive tacrolimus as part of their maintenance immunosuppression at the time of posttransplant discharge. Moreover, during the first posttransplant year, only a select number of patients are taken off of tacrolimus (mostly for complications perceived to be related to tacrolimus), with nearly 97% remaining on tacrolimus-based therapy. Recent International Intestinal Transplant Registry data suggest that rapamycin may have some improved outcomes and could be used as an alternative or in combination with tacrolimus. However, further research is needed to validate these data. Currently, the most common regimen at 1 year post transplant is tacrolimus in combination with steroids, with tacrolimus monotherapy being the second most common. In some patients who have had significant rejection, a third agent may be employed, in addition to tacrolimus and steroids, like mycophenolate mofetil (MMF) or Imuran.

Two classes of immunomodulatory drugs have been introduced for intestinal transplantation and have been associated with improvements in 1-year patient and graft survival. Depleting antilymphocyte antibody therapies include rabbit antithymocyte globulin (rATG, Thymoglobulin [Genzyme Corp., Cambridge, Massachusetts]) and rarely now alemtuzumab (Campath-1H [Genzyme Corp.]). The individual use of these agents by high-volume single centers has demonstrated improved short-term survival and decreased rejection rates as well as severity.^{23,24,25} Associated with similar improvements in survival and decreased incidence of acute rejection and severity, induction with the nondepleting interleukin (IL)-2 receptor antagonists, daclizumab (Zenapax) and basiliximab (Simulect), has also gained increasing acceptance by many intestinal transplant programs. In select cases of suspected antibody-mediated rejection (class II DSA and evidence of histologic injury), other agents such as rituximab or bortezomib may also be utilized (often in addition to pheresis and intravenous immunoglobulin [IVIG]). Immunosuppression for intestinal and multivisceral transplantation now involves perioperative antibody induction in over 60% of cases.

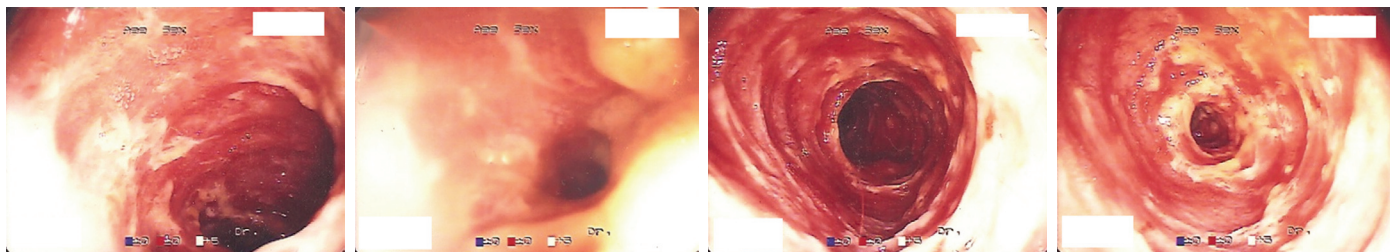


FIGURE 160-8 ■ Enteroscopic findings consistent with acute cellular rejection of intestinal allograft. (Courtesy Kareem Abu-Elmagd, MD.)

Immunologic Monitoring

The gold standard for monitoring and diagnosing rejection in intestinal and multivisceral transplant recipients to date remains routine ileoscopy and proximal enteroscopy with histopathologic examination of multiple random mucosal biopsies. Significant investigation is under way into the development of tools to guide and monitor the immunologic state of intestinal transplant recipients. Ideally, noninvasive markers such as serologic, proteomic, or genomic markers may identify those patients who are at increased risk of rejection and, conversely, those who might benefit from decreased levels of immunosuppression.^{26,27} A recently developed Pleximmune test²⁸ may be helpful, in conjunction with other studies, to determine both those who seem to be at risk for or are currently undergoing rejection, and warrant augmented levels of immunosuppression, or conversely maintain or lower immunosuppression in those who appear to be at lower risk of rejection. Further validation in a larger cohort of patients is needed. Preformed antibody and de novo antidonor-specific antibody measurements may be of assistance in determining the risk of rejection.^{29,30} When technically feasible, the presence of circulating donor cells in the recipient peripheral blood should be serially evaluated after transplantation by either flow cytometry or PCR. Monoclonal antibodies specific for donor HLA class I and II molecules are used for single-color immunofluorescence analysis. The presence of donor-specific antibodies, especially class II, in intestinal transplant recipients may prompt aggressive therapy with augmentation of immunosuppression and addition of other agents and in some circumstances serial plasmapheresis and IVIG until clearance of antibodies has been confirmed. The use of fecal calprotectin or serum citrulline as noninvasive biochemical markers of allograft rejection has certain restrictions in timing of the test and sensitivity issues especially in the initial post-transplant phase and does not appear to be warranted based upon currently available data.^{31,32}

As mentioned, to date the gold standard for detection of rejection is histologic evaluation. Hence, in recipients of intestinal or multivisceral transplants, surveillance endoscopy and biopsy (esophagogastroduodenoscopy [EGD], ileoscopy, colonoscopy) are performed biweekly for the first 4 to 6 weeks post transplant and then weekly for an additional 4 to 6 weeks to monitor for rejection. After the first 3 months post transplant, the frequency of surveillance endoscopies performed in recipients is based upon individual clinical assessments. More frequent scopes and biopsies are performed where clinically or histologically indicated.

ASSESSMENT OF INTESTINAL ALLOGRAFT

The process of examining the anatomic and functional integrity of the intestinal allograft begins in the operating room. The normal intestinal allograft after reperfusion appears pink and nonedematous, with occasional contractions. Altered appearance can be observed in the operating room, especially in the mucosa when the bowel is opened for the anastomosis, and in the proximal jejunal and distal ileal segments using endoscopy postoperatively.

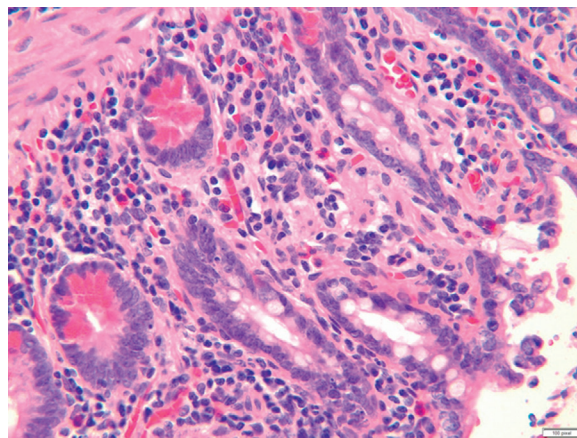


FIGURE 160-9 ■ Ischemia-reperfusion injury. Reperfusion injury is characterized by extensive loss of villi, followed by pronounced regenerative changes of crypt epithelium with conspicuous mitosis, capillary congestion, shortening of villi, and variable degrees of neutrophil-rich inflammatory infiltration.

Surveillance for intestinal allograft rejection in the early postoperative period focuses on clinical evaluation and gross morphologic examination of the stoma and distal ileum. Frequent routine endoscopic surveillance is the most reliable method for achieving an early diagnosis of intestinal rejection (Fig. 160-8). Endoscopic evaluations are performed initially twice a week through the allograft ileostomy. Upper endoscopy is reserved for occasions where clinical changes are not well explained by distal allograft evaluation and biopsy. Common physical changes to the normal appearance of an intestinal allograft include edema, cyanosis, congestion, and increased stomal output. These changes should prompt an immediate workup, with a differential diagnosis that includes preservation injury (Fig. 160-9), sepsis, rejection, enteritis, and vascular compromise (such as thrombosis).

The allograft stomal output is assessed for volume and consistency. Normal stomal output during the early postoperative period is characteristically clear and thin. During the first week post transplant, normal stomal output is 1 to 2 L/d and 40 to 60 mL/kg/d for adult and pediatric recipients, respectively. If these stomal volumes are exceeded in the absence of significant pathology, agents to control volume of output can be started, including loperamide, lomotil, paregoric (tincture of opium), pectin, rarely somatostatin, or oral antibiotics. The presence of blood in the stomal output is an ominous sign and a concern for acute rejection, until proven otherwise. Other causes, however, include anastomotic bleeds in the early posttransplant period, perianastomotic ulcers in the later period, or post biopsy bleeding, which is often seen initially or 5 to 7 days after the biopsy.

Intestinal allograft absorption of nutrients and medications develops gradually and commonly requires several weeks post transplant to improve. Abnormal absorption after approximately 1 month should

prompt an aggressive search for underlying pathology, especially rejection. The ability to maintain whole blood tacrolimus trough levels above 15 ng/mL on oral therapy alone is a good indicator of adequate absorption. In the authors' experience, intestinal transplant recipients demonstrate evidence of sufficient absorptive function at a mean of 28 days after transplantation. Recipients of multivisceral transplants can demonstrate even longer delays until intestinal allograft absorption is well established.

MANAGEMENT OF ALLOGRAFT REJECTION

Allograft rejection (Fig. 160-10) is strongly associated with graft loss and mortality and remains a significant obstacle to achieving successful long-term outcomes for intestinal and multivisceral transplant recipients. Historically, acute cellular rejection was reported in 70% to 90% of intestinal allografts, within 90 days post transplant. In contrast, rejection rates of 30% to 40% are currently reported by large centers due to advances in allograft histopathologic surveillance, immunosuppression, and immunologic monitoring. There does appear to be disparity between some centers where reported rejection rates may be very low (less than 10%) while others still have higher rates (greater than 50%), depending on induction therapies. Unlike liver allograft rejections, the natural history of rejection of intestinal allografts is unforgiving, making early diagnosis and treatment critical for successful reversal of the rejection process.

Until proven otherwise by culture and allograft biopsy, each episode of allograft dysfunction should prompt an expeditious evaluation for acute rejection. No laboratory tests are currently available to warn of allograft dysfunction or rejection for intestinal transplantation although the Pleximmune assay is showing good sensitivity and specificity when utilized in certain criteria, but more assessment is required. Clinical

features of intestinal allograft rejection include nonspecific signs and symptoms such as diarrhea (increased stomal output), nausea/vomiting, fever and abdominal pain. Infectious enteritis and medication-related loose bowel movements are common etiologies of allograft dysfunction that present with a clinical picture similar to allograft rejection. The stoma may become edematous, erythematous, and friable. Endoscopy may demonstrate normal mucosa despite mild to moderate grades of ongoing acute cellular rejection. Moderate to severe rejection of the intestinal allograft usually leads to mucosal inflammation beginning with erythema and friability, progressing to mucosal slough and exudates overlying ulcers, with eventual loss of the mucosal layer. Histologically, there is variable presence of edema in the lamina propria and villous blunting. However, mononuclear cell infiltrates and intestinal crypt apoptosis with regeneration and eventual crypt loss are the hallmark signs of intestinal allograft rejection that establish the diagnosis.

Treatment of intestinal acute cellular rejection initially involves steroids. At the Children's Hospital of Pittsburgh of UPMC, a total dose of approximately 30 mg/kg of methylprednisolone is usually given, either by three boluses of 10 mg/kg/d over 3 days or more routinely by a single bolus and subsequent cycle of tapering doses over a more extended duration. Antilymphocyte antibodies for steroid-resistant rejection include antithymocyte globulin (rATG [rabbit-derived], Thymoglobulin) and rarely nowadays alemtuzumab (Campath-1H [Genzyme Corp.]). Unfortunately, the discontinuation of muromonab CD3 (OKT3, a murine monoclonal anti-CD3 antibody) has been detrimental to the field. Adverse immune-mediated drug reactions to immunomodulatory antibodies can be life threatening. These agents are usually administered to patients with cardiopulmonary monitoring following premedication with steroids, antipyretics, and histamine blockers. In many cases, it is appropriate to initiate therapy in an ICU setting. During and after the treatment of acute rejection, tacrolimus

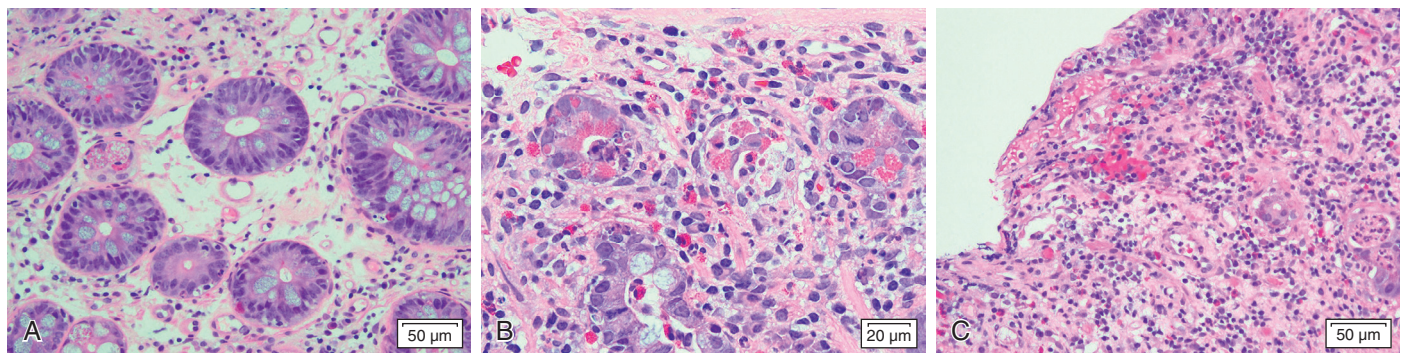


FIGURE 160-10 ■ Acute cellular rejection of intestinal allograft: mild (A), moderate (B), and severe (C). **A,** Mild acute rejection is characterized by a generally mild and localized inflammatory infiltrate, which tends to be concentrated around small venules in the lamina propria. Mucosa is intact, but crypt epithelium displays evidence of injury: mucin depletion, cytoplasmic basophilia, decreased cell height, nuclear enlargement with hyperchromasia, and inflammatory infiltration. Crypt epithelial apoptosis is increased, usually with more than six apoptotic bodies/10 crypts. If sampled by biopsy specimen, preexisting lymphoid aggregates (Peyer's patches) demonstrate an intense accumulation of activated lymphocytes. Villi are variably shortened, and architecture may be slightly distorted owing to expansion of lamina propria by inflammatory infiltration. **B,** In moderate acute rejection, inflammatory infiltrate is widely dispersed within the lamina propria. Crypt injury and cryptitis are distributed more diffusely than in mild acute rejection, and villi tend to have a greater degree of flattening. Number of apoptotic bodies is greater than in mild acute rejection, usually with focal "confluent apoptosis." Mild to moderate intimal arteritis may be seen. Mucosa remains intact without ulceration, although focal superficial erosions can be present. **C,** Severe acute rejection is distinguished by a marked degree of crypt damage and mucosal ulceration, with lymphocytic infiltration extending deep into allograft wall and involving nerves and ganglia. As a consequence of mucosal destruction, luminal contents gain access to submucosa, prompting a neutrophil-rich infiltrate and an overlying fibropurulent (pseudomembranous) exudate with widespread mucosal sloughing as the final result. Adjacent viable epithelium usually shows rejection-associated changes such as crypt epithelial damage and abundant apoptosis. Severe intimal arteritis or transmural arteritis may be seen.

whole blood levels are maintained around 15 to 20 ng/mL in intestinal and multivisceral allograft recipients. Maintenance steroid therapy usually consists of 1 to 2 mg/kg/d of intravenous methyl prednisolone prednisone converted to oral prednisone, tapered over several weeks to months based on individual clinical assessments. Addition of a third agent such as mycophenolate mofetil (MMF; CellCept [Roche]) or sirolimus (Rapamune) or azathioprine (Imuran) may be indicated if rejection is refractory or recurrent.

A fundamental principle that guides treatment of allograft rejection is the preservation of as much intestinal function as possible. Each episode of rejection likely shortens the longevity of intestinal graft function, so the diagnosis of steroid-resistant rejection in intestinal allografts must be made in a more timely fashion than in a regenerating organ such as the liver. Antilymphocyte therapy in response to a diagnosis of steroid resistance will rapidly reduce the overall number of immunocompetent cells and is usually a highly effective treatment for steroid-resistant rejection. Antilymphocyte therapy must be used cautiously in refractory rejection, since sequential biopsies separated by reasonable time intervals allow for objective confirmation of steroid treatment failure. In isolated cases of intestine recipients with preexisting immune debilitation or a predisposition to a life-threatening illness such as posttransplant lymphoproliferative disorder (PTLD), allograft enterectomy may be safer than escalation of immune suppression and this can potentially be lifesaving.

Antibody-mediated rejection (AMR) of the intestinal allograft (Fig. 160-11) is characterized by intestinal dysfunction, diffuse C4d staining on allograft biopsy, and usually identification of donor-specific antibodies. Treatment of AMR, in addition to thymoglobulin and campath, may consist of plasmapheresis in combination with IVIG and steroids. Rituximab or bortezomib can be used in select recipients.

Chronic rejection remains the most significant complication affecting long-term graft survival. Chronic rejection (Fig. 160-12) is observed in 10% to 15% of pediatric and adult intestinal allografts but occurs more commonly in isolated intestinal allografts. In adult recipients at the University of Pittsburgh, multivisceral transplants including a liver allograft demonstrated a significantly better chronic rejection-free survival compared to the liver-free intestinal and other multivisceral transplant recipients.³³ Risk factors for chronic rejection include type

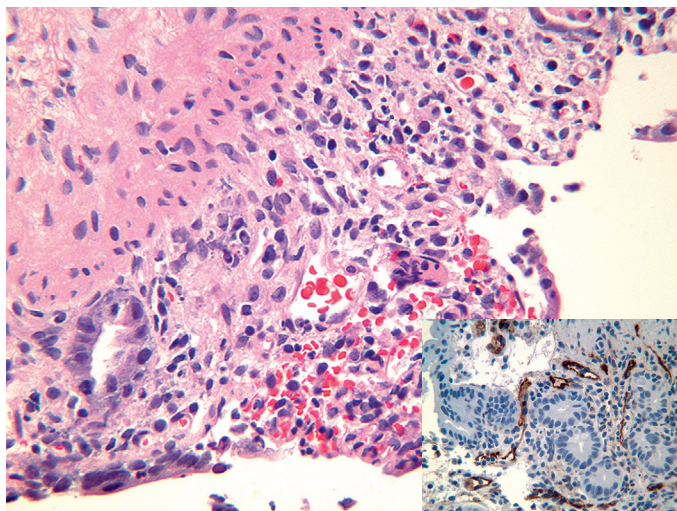


FIGURE 160-11 ■ Antibody-mediated rejection of intestinal allograft. Humoral rejection is characterized by a grossly cyanotic small intestine allograft. Histologic findings include severe congestion, neutrophilic margination, and fibrin-platelet thrombi within the lamina propria microvasculature, along with focal hemorrhage. Immunohistochemical staining to C4d confirms the diagnosis of antibody-mediated rejection with heavy and diffuse staining of the lamina propria capillaries.

of allograft and loss of previous intestinal allograft. The clinical presentation of chronic rejection may include weight loss, chronic diarrhea, intermittent fevers, recurrent subacute bowel obstruction and distal intestinal allograft obstruction, or GI bleeding. Histologically, chronic rejection is characterized by villous blunting, focal ulcerations, epithelial metaplasia, and scant cellular infiltrates on endoscopic mucosal biopsies but can be difficult to diagnose based on just a mucosal biopsy as larger vessels need to be ascertained. Full-thickness biopsies of intestinal allografts with chronic rejection demonstrate the classical obliterative thickening of not only intestinal arterioles but also even bigger vessels.

■ MANAGEMENT OF COMPLICATIONS

Postoperative Hemorrhage

Recipients of intestinal and multivisceral transplants will commonly demonstrate varying degrees of liver dysfunction, qualitative and quantitative platelet abnormalities, and fibrinolysis that can lead to profound intraoperative coagulopathy. Induction intraoperatively with thymoglobulin may also lead to hematologic and clotting diathesis and warrant cessation or slowing down/delay of the infusion. Intraoperative bleeding can also develop from lysis of vascularized adhesions due to previous surgeries and portal hypertension. Transient graft reperfusion coagulopathy mediated by plasminogen activators from the graft may also occur. Every effort is made to address these factors in the operating room, and usually whatever coagulopathy persists postoperatively is mild. Postoperative hemorrhage is most often a technical problem arising from vascular anastomoses or extensive raw peritoneal surfaces. Even mild coagulopathy should be completely corrected if bleeding is suspected in the posttransplant recipients although caution has to be taken to avoid issues with thrombosis of the allograft. Any bleeding that causes hemodynamic alteration should be managed by early exploration.

Vascular Complications

Superior mesenteric artery thrombosis is a catastrophic complication that leads to rapid and massive necrosis of the intestinal allograft. Elevation of hepatic enzymes (with liver allografts) and pallor of the intestinal stoma are accompanied by clinical deterioration, usually fulminant sepsis, and hepatic coma (with liver allografts). Isolated small bowel allografts can be explanted with a reasonable expectation of patient survival, but in patients with composite allografts removal for arterial thrombosis leads to almost certain death in the absence of immediate retransplant. Clinical suspicion of arterial thrombosis in the immediate postoperative period should be definitively evaluated in the operating room and not delayed by performance of Doppler ultrasound examination. In cases of delayed presentation, arteriography in interventional radiology can often be useful diagnostically and therapeutically.

Acute venous thrombosis also leads to loss of the intestinal allograft without timely surgical intervention. Clinical signs of venous thrombosis include acute massive ascites and stomal congestion. Mesenteric infarction is the ultimate outcome of unresolved venous thrombosis, necessitating explant of the intestinal allograft.

Incomplete obstruction of major inflow or outflow vessels may be suspected based on allograft biopsies or on clinical and laboratory signs of graft dysfunction. Contrast vascular radiographic studies are confirmatory, and the correction is either surgical or endovascular based upon individual assessments and available clinical expertise.

Gastrointestinal Complications

Gastrointestinal bleeding after intestinal transplantation is an ominous sign that requires timely evaluation. Acute rejection and infectious enteritis are the most likely etiologies and should be diagnosed or excluded based upon endoscopic biopsy results, although arterioenteric fistulae must also be considered, as this can be catastrophic. The

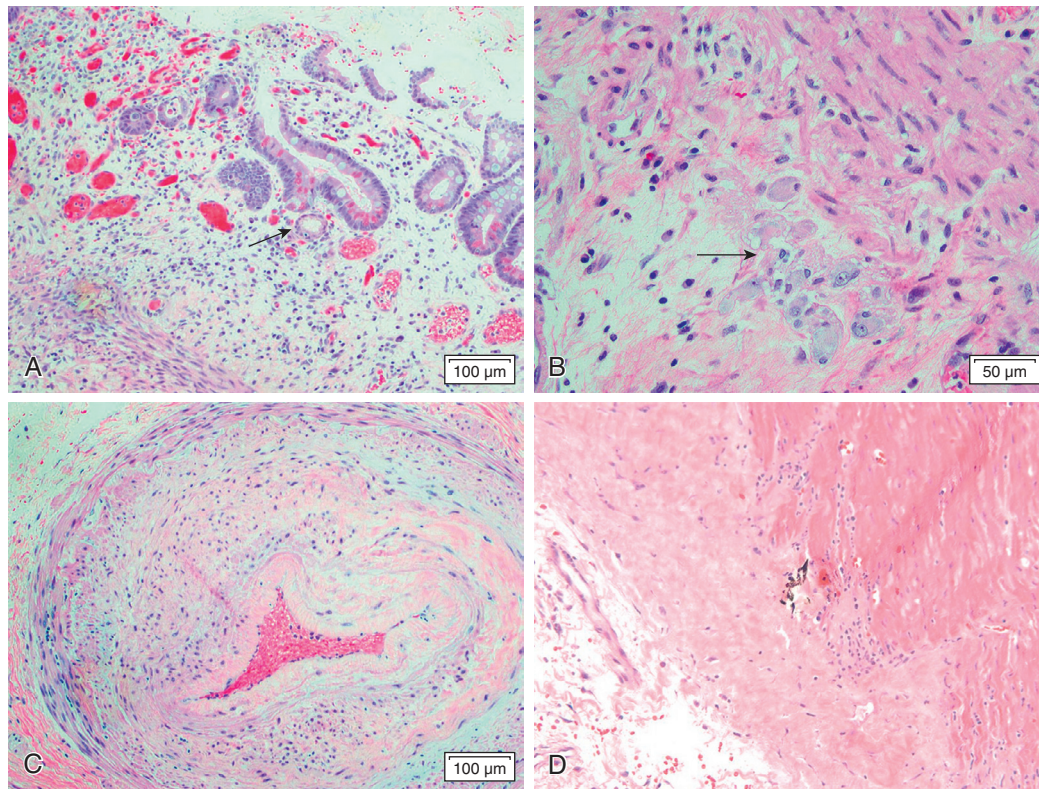


FIGURE 160-12 ■ Chronic rejection of intestinal allograft. Mucosa shows loss of villous architecture, chronic ulcers with exudate and granulation tissue, widespread loss of the crypts of Lieberkühn, crypts of Lieberkühn with pyloric gland metaplasia (**A**, arrow), neuronal hyperplasia (**B**, arrow) and mucosal fibrosis. Histologic findings in resection specimens are obliterative arteriopathy (**C**), lymphoid deletion, and mesenteric sclerosis (**D**).

diagnosis of rejection relies primarily on histologic evidence but also on the endoscopic appearance of the mucosa. Bleeding from ulcerated EBV- or CMV-induced lesions may be differentiated by gross endoscopic examination, but confirmatory stains and serum PCR testing often help validate the diagnosis. Empiric therapy for rejection of intestinal allografts is rarely indicated except when suspicion on clinical and/or endoscopic evaluation is high and infectious parameters have been low and obtaining pathologic confirmation is delayed.

Anastomotic leaks may occur in all intestinal transplant recipients but are more common in pediatric patients. Clinical presentation commonly involves florid sepsis, drainage via abdominal drain, or wound drainage and infection. Confirmation is achieved with oral contrast imaging. Owing to immunosuppression, almost all bowel leaks require surgical revision, evacuation of any peritoneal contamination, and often second-look laparotomy to confirm resolution. Diagnostic laparotomy is indicated in the setting of sepsis and equivocal imaging studies.

The progression of motility patterns in the denervated intestinal allograft is still not fully understood. High allograft stomal output occurs early after transplant, and in the absence of infection or rejection, it can be regulated with agents such as loperamide, lomotil, pargoric, or pectin. Conversely, often poor upper motility may exist between the native and allograft bowel, and promotility agents may be required.

Renal Complications

Deterioration of renal function in intestinal transplant recipients remains a significant clinical challenge. Pretransplant renal dysfunc-

tion is exacerbated by overall higher target levels of immunosuppression in intestinal transplant recipients compared to other types of transplants, as well as repeated exposure to nephrotoxic antibiotics, and episodes of dehydration with intestinal allograft dysfunction. The incidence of chronic renal failure for intestinal transplant recipients at 5 years post transplant exceeds 15%.³⁴ Overall, a review of the Scientific Registry of Transplant Recipients (SRTTR) data shows that patients without severe pretransplant renal dysfunction who do not receive a kidney as part of the composite allograft will generally demonstrate a 50% increase in serum creatinine at their 5-year follow-up.

Posttransplant Lymphoproliferative Disorder

The development of PTLD is almost always associated with EBV infection. Posttransplant infection with EBV results in a spectrum of diseases, from mononucleosis syndromes and plasma cell hyperplasia to neoplastic PTLD (Fig. 160-13). In a series of 500 intestinal and multivisceral transplants at the University of Pittsburgh, all but two of 57 recipients with PTLD developed the disorder as a consequence of confirmed EBV infection. Early studies found that primary tacrolimus use in pediatric patients was associated with a 15% long-term risk of PTLD, with almost 80% of these cases occurring within the first 2 years after transplant. Achieving an optimal immunosuppression steady state and avoiding excessive therapy intervals appears to be key to minimizing EBV/PTLD complications. Cumulative PTLD-free survival for intestinal transplant recipients undergoing induction immunosuppression has improved to nearly 90%, possibly attributable to a lower incidence of acute rejection (and thus decreased need for escalation of immunosuppression) as well as improved EBV viral load monitoring.

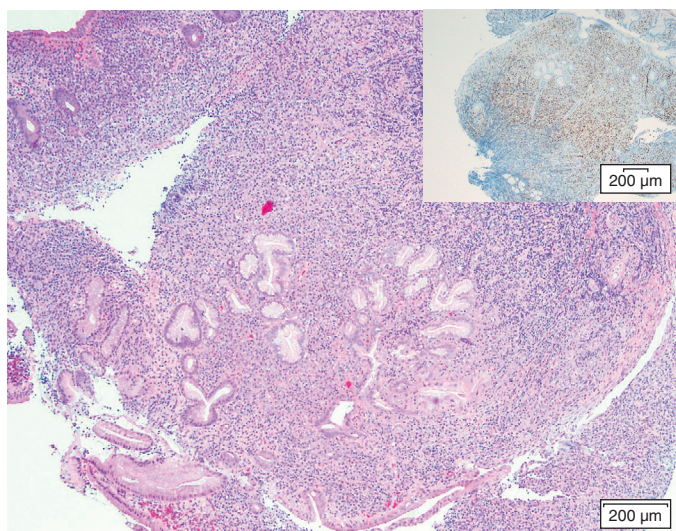


FIGURE 160-13 ■ Epstein-Barr virus posttransplant lymphoproliferative disorder (EBV/PTLD). At the early phase of EBV infection, tissue is expanded by scattered EBV encapsulated RNA (EBER)-positive lymphocytes. With disease progression, the number of positive cells increases, lymphocytes become activated and transformed, and ultimately, tissue architecture is effaced by a malignant lymphoproliferative process that replaces the duodenal mucosa seen in this example. The EBER in situ probe is shown in the inset.

Patients presenting with PTLD complain of sporadic fever, lethargy, and malaise. Weight loss, diarrhea, and GI complaints are common, as are signs of graft dysfunction. Standard laboratory evaluation may demonstrate neutropenia, atypical lymphocytosis, anemia, and thrombocytopenia. Further evaluation of PTLD is guided by findings on contrast-enhanced computed tomography (CT) scanning of the head, neck, chest, abdomen, and pelvis, with or without endoscopy, based on results of noninvasive imaging. Histologic examination of the tissue is optimal, and specimens should be promptly submitted for fresh staining with the EBER-1 probe by experienced pathologists. An evaluation for CD20 staining should also be performed.

Ideally, the treatment of PTLD involves stopping immunosuppression completely, as can be done in most other types of allografts, but with the intestine this may not be possible. The goal, however, is to lower the level of immunosuppression as much as possible (holding steroids and third agents and lower primary agent) and follow very closely with repeat scopes and biopsies. PTLD that is unresponsive to lowering/discontinuation of immunosuppression should be treated with monoclonal antibody, usually rituximab, if shown to be CD20 positive by biopsy. Complete remission rates of 60% to 70% have been reported in children. The antibody therapy is relatively well tolerated, and for the 20% of patients who have recurrence, retreatment with rituximab can be curative. For PTLD refractory to monoclonal antibody, low-dose cytotoxic chemotherapy and steroids have been used effectively (Gross protocol).

Graft-Versus-Host Disease

Acute graft-versus-host disease (GVHD) results from immunocompetent donor T cells causing damage to recipient tissues after transplantation. The incidence of GVHD (Fig. 160-14) after intestinal transplantation ranges between 5% and 10% and usually occurs within the first 6 months post transplant.³⁵ The major targets of GVHD intestinal transplant recipients are epithelial cells of skin, bone marrow, the native GI tract and the native liver. Cardiac muscle involvement is not common but has been described. A recipient with GVHD commonly presents with fever and a maculopapular rash on the upper

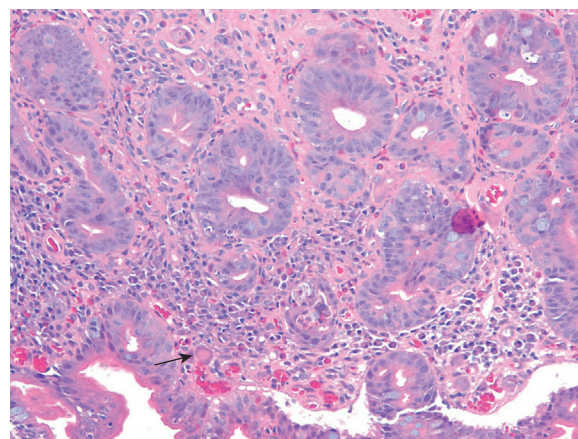


FIGURE 160-14 ■ Intestinal allograft graft-versus-host disease (GVHD). Mucosal biopsy of native small intestine showing crypt epithelial apoptosis and lamina propria inflammation. An incidental CMV inclusion is also noted in this biopsy (arrow).

torso, neck, or palms of hands and feet, which may coalesce to form blisters or more diffuse erythema. Other clinical signs and symptoms include oral lesions, diarrhea, intestinal mucosal ulceration, native liver dysfunction, lymphadenopathy,³⁶ and bone marrow suppression with pancytopenia. The variability of GVHD focality and severity leads to a wide spectrum of disease, from mild GVHD presenting with fevers and self-limiting rash to more severe forms leading to end-organ damage.

The diagnosis of GVHD is based on clinical presentation and confirmed histologically, when possible. Corticosteroids are the first-line therapy to control epithelial damage caused by GVHD and are effective in around 50% of the cases, overall. If unresponsive to steroids, GVHD can usually be controlled by reduction of calcineurin-based immunosuppression, although in some cases the level of immunosuppression needs to be augmented. Other forms of refractory GVHD have been treated successfully using antilymphocytic therapy (e.g., Thymoglobulin), as well as antiinterleukin therapy (e.g., Zenapax and Simulect) and anti-tumor necrosis factor (TNF) antibody therapy (e.g., Remicade).

OUTCOMES

Patient and Graft Survival

From January 1985 to January 2015, according to the latest update of the Intestinal Transplant Registry, there have been 3067 intestinal transplants performed in 84 centers around the world, with 30 centers still currently active. Small bowel transplants alone account for 45% of the total, liver/intestine 31%, and multivisceral/modified multivisceral the remainder. Currently there are 1631 survivors. The leading cause of recipient death is sepsis (65%), followed by graft failure (10%), lymphoma (5%), technical issues (4%), and then cardiovascular, renal, and liver failure. The retransplantation rate is approximately 10%, with most being liver inclusive.

A significant improvement in early patient and graft survival after intestinal transplantation has been achieved over the past decade and a half, with 1-year patient and graft survival (Fig. 160-15) reaching 89% and 79% for intestine-only recipients and 72% and 69% for liver-intestine recipients, respectively. In 1998, the 1-year adjusted graft and patient survival after intestinal transplantation were only 52% and 69%, respectively. Data from the Children's Hospital of Pittsburgh on 262 intestinal transplants between 1990 and 2015 show 1- and 5-year survival of 84% and 63%, respectively, with about half the recipients currently alive. Survival of both patient and graft has improved over

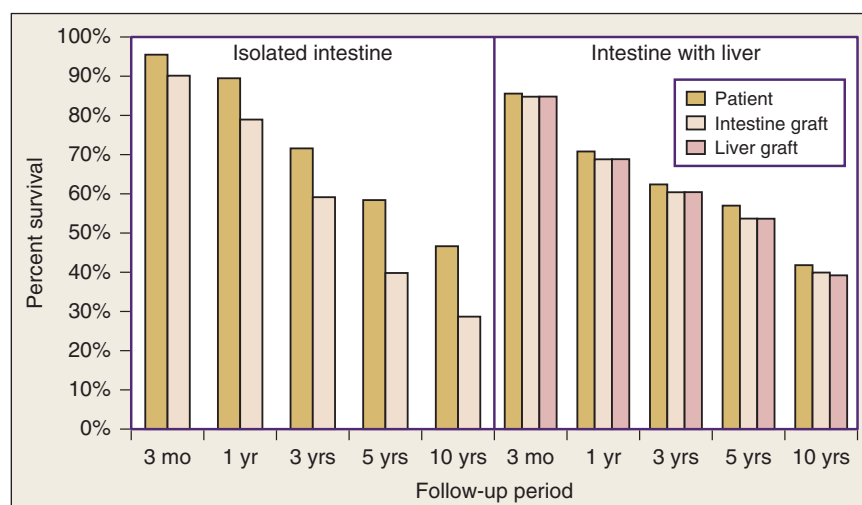


FIGURE 160-15 ■ Unadjusted patient and graft survival for isolated intestine and combined liver and intestine recipients. (Adapted from Mazariegos GV, Steffick DE, Horslen S, et al. Intestine transplantation in the United States, 1999–2008. *Am J Transplant* 2010;10:1020–1034.)

time for multifactorial reasons, with the most recent patients undergoing Thymoglobulin induction doing the best.

Updated outcomes for intestinal transplant recipients are now comparable to outcomes following pancreas and lung transplantation. Contributing factors to this marked improvement in outcomes after intestinal transplantation include increased experience among intestinal transplant teams, improvements in anesthesia and critical care, advances in immunosuppression, and advances in the detection and treatment of rejection. The hospitalization status of the recipient at the time of transplantation also remains a strongly predictive factor for patient survival, with an unadjusted 1-year survival rate of 83% for recipients not waiting in the hospital, 73% for recipients waiting in the hospital, and only 50% for recipients waiting in the ICU. In 1999, almost one-third of intestinal and multivisceral recipients were in intensive care at the time of transplantation, whereas in 2008, 70% were not in the hospital, and only 12% were in intensive care.

In contrast to recent achievements in short-term outcomes, long-term survival after isolated intestinal transplantation has not significantly improved. Ten-year patient and graft survival remains 46% and 29%, respectively, for isolated intestinal transplantation and 42% and 39%, respectively, for intestine-with-liver grafts. These results are similar to those reported for lung and combined heart-lung transplantation but compare unfavorably to kidney, liver, and heart transplantations, where 10-year patient and graft survival exceeds 50%.

The conclusion from the most recent Intestine Transplant Registry is that there have been no major advances in intestinal transplant graft survival rates for the past 5 years. Short-term outcomes are excellent, but longer term outcomes remain suboptimal. Factors associated with a better graft survival include being a pediatric recipient, being called in from home for transplant, having a liver allograft as part of the transplant, and early maintenance of rapamycin (although the last finding is being reanalyzed because of supporting evidence).

Long-Term Rehabilitation and Quality of Life

There are only a few reports pertaining to long-term outcomes, especially pertaining to quality of life, partly as the field is still relatively new and only a few centers have significant numbers to make a useful assessment. A small preliminary study³⁷ in pediatric recipients with functioning intestinal allografts more than 1 year post transplant found that quality of life was perceived by recipients to be comparable to that of their peers, while parental proxy assessments compared less favorably in terms of physical functioning, general health, and family

activities. Younger recipients (5–10 years of age) demonstrated significantly worse outcomes than older recipients (11–18 years of age) in terms of global health assessments, general health perception, and family activities. There have been reports demonstrating significant improvement in certain aspects of psychiatric health after transition from PN to posttransplant PN independence.³⁸ In these reports, long-term physical and psychiatric rehabilitation was achieved in over 80% of intestinal transplant recipients who survived beyond the sixth postoperative month.

The most robust recent paper details 227 adult and pediatric recipients who survived beyond the 5-year milestone.³⁹ Conditional survival was 75% at 10 years and 61% at 15 years. Nutritional autonomy was achieved in 90% of the survivors. Morbidities with impact on global health included dysmotility (59%), hypertension (37%), osteoporosis (22%), and diabetes (11%) and were observed more in the adult population. Survivors in general were reintegrated into society with self-sustained socioeconomic states. It is also vital to note that nonfunctional social support was one of the most significant survival risk factors. This evidence ties back to the original evaluation process, and the importance of teaching and assessing social support. No matter how good the medical, surgical, and transplant management may be, for continued long-term success adequate and appropriate social resources are essential. The intestinal and multivisceral transplant process is demanding and forever ongoing for the recipient, the family, and the healthcare professional team. Hence, picking the right recipient for transplantation is vital and conversely one of the reasons why all efforts are made to rehabilitate patients without transplantation, if at all possible, given these long-term concerns.

CONCLUSION

The field of intestinal failure has undergone ebbs and flows, based on medical, surgical, and transplantation advances and outcomes. Intestinal and multivisceral transplantation remains the ultimate therapy, but with improved medical and surgical management the timing and utility of transplantation have shifted.

Significant improvements in outcomes from intestinal and multivisceral transplantation have been achieved through advances in the multidisciplinary care of intestinal failure, surgical techniques, innovative immunosuppressive strategies, and an improved understanding of intestinal transplantation immunology. These accomplishments, however, remain overshadowed by the remaining fundamental challenge of preventing or minimizing chronic allograft rejections. The

relatively high waiting list mortality, particularly for infants and adults with concomitant liver failure, requires an ongoing reexamination of national guidelines for multivisceral procurement to maximize the usage of acceptable donor allografts. Limited long-term data on nutritional outcomes and transplantation morbidity indicate good allograft survival and quality of life for those who get through the early period, however, not without some significant morbidity. Once again, ongoing continual loss of the nonliver-containing intestinal allograft hampers wider acceptance of intestinal transplantation failure. More so, the

recent dramatic improvements in the provision of exemplary care in the multidisciplinary intestinal care clinics have significantly altered the need, timing and type of intestinal allograft needed. With no substantial advancement in the field of intestinal transplantation over the past decade, the pendulum of transplantation versus delaying/avoiding transplantation has swung once again. Still intestinal transplantation, until successful tissue engineering evolves or some other new modality of treatment is developed, remains the ultimate and definitive form of intestinal failure salvage.

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Aortic dissection remains a highly lethal condition, and the incidence may be on the rise.¹ Diagnosis remains difficult, and over one-third of the cases are missed at initial presentation.² In the absence of treatment, patients die at a rate of 1% to 2% per hour during the first 24 hours, and nearly 50% die within 1 week.^{3,4} Herein, we will discuss the optimal diagnostic and treatment strategies for thoracic aortic dissection including preoperative, operative, and postoperative care.

DEFINITION AND EPIDEMIOLOGY

The aorta is comprised of three layers, the endothelial-lined intima, the media composed of muscular and connective tissues, and the adventitia. When the intimal layer is disrupted, blood ejected under pressure enters the medial layer, thereby creating two lumens in the aorta—an aortic dissection. The true lumen can become compressed or even obliterated by the false lumen. The dissection can propagate proximally (retrograde) toward the aortic valve or distally (antegrade). Morbidity and mortality occur due to a host of complications. The disruption of myocardial blood flow from coronary ostial involvement can result in myocardial infarction, acute heart failure can occur from acute aortic valve regurgitation due to commissural dehiscence, and pericardial tamponade can develop from bleeding into the pericardial space. Aortic dissection can compromise blood flow through almost any major artery, resulting in stroke, spinal ischemia/paralysis, mesenteric ischemia, renal failure, or limb ischemia. Aortic rupture can occur, leading to catastrophic hemorrhage.

The incidence of acute aortic dissection ranges from 3 to 6 per 100,000/yr.^{1,5} There is a male predominance, with a male:female ratio ranging from 2 to 3:1.⁶ The mean age of presentation is 63 years (range 50–63). The majority of aortic dissections involve the ascending aorta (70%–80%), whereas the remaining 20% to 30% involve the descending thoracic aorta and less frequently the aortic arch.

CLASSIFICATION

Classification Systems: DeBakey and Stanford

The two most widely used classification systems for aortic dissection are the DeBakey and Stanford (Fig. 161-1). DeBakey and colleagues developed the first widely used classification system for categorizing aortic dissections.⁷ It divides dissections into types I, II, and III based on the site of the originating tear. A DeBakey type I dissection originates in the ascending aorta and extends through the descending thoracic aorta. A type II dissection involves only the ascending aorta. The tear in a type III dissection originates in the descending thoracic aorta distal to the ligamentum arteriosum. The DeBakey type III dissections are further subdivided into IIIA, originating distal to the left subclavian artery and extending to the diaphragm, and IIIB, involving the aorta below the diaphragm. The Stanford classification system reported by Daily and colleagues⁸ divides dissections into two groups: Stanford type A aortic dissections, involving the ascending aorta, and type B dissections, “limited to the descending aorta with primary intimal tear usually within 2 to 5 cm of the left subclavian artery.”⁸ This is a key area of importance, as there is controversy regarding classification and management of arch aneurysms. On the basis of the

initial description of the Stanford system, many consider dissections involving the aortic arch without ascending involvement to be type B dissections.

The aforementioned classification systems provide a framework for managing patients with aortic dissection. We use the Stanford system, as it provides a simple approach for separating patients who should be considered for immediate surgery versus medical management. The primary lethality of dissection results from coronary ostial involvement and subsequent myocardial infarction, severe aortic valve insufficiency from commissural detachment, or pericardial tamponade, all of which can occur in the setting of ascending aortic involvement or type A dissections. Although complications involving the abdominal viscera can occur with type B dissections, these are not as common. Therefore, speaking in broad terms, type A aortic dissections are managed with surgery and type B medically (unless they are complicated by bleeding or malperfusion).

In addition to determining the dissection type (A vs. B, I vs. II vs. III), dividing dissections based on duration from symptom onset is essential for management, as chronic dissections can be managed on a more elective basis. Traditionally, dissections are termed *acute* if symptoms have been present for less than 2 weeks and *chronic* if present for greater than 2 weeks. Booher and colleagues have developed a new classification system that classifies dissections as hyperacute (<24 hours from symptom onset), acute (2–7 days), subacute (8–30 days), and chronic (>30 days), as survival differs significantly by category.⁹

PRESENTATION

History and Risk Factors

The most typical complaint at presentation in patients with aortic dissection is abrupt and severe chest pain, followed by back pain. Classically described as tearing, the pain can also be sharp, ripping, or knife-like. Some degree of chest pain is present in three-fourths of patients, followed by back pain in 40% and abdominal pain in 25%.^{3,10,11} Ten percent of patients may present with no complaints of pain at all.² Additional neurologic complaints may include syncope, complaints of weakness or paresis, or rarely hoarseness from left recurrent laryngeal nerve compression. Abdominal pain may be the result of pain from the dissection itself or mesenteric ischemia. Key elements of the history that should be queried in the setting of chest or back pain and should raise the index of suspicion for aortic dissection are outlined in Box 161-1.

Physical Examination

Physical examination may not be diagnostic but in conjunction with the history, can aid in raising the suspicion for acute aortic dissection. Tachycardia may occur due to pain or hypovolemia if rupture has occurred. Bradycardia or heart block may occur with root involvement of the dissection. Blood pressure measurements should be taken in both arms, and a 20-mm Hg differential should raise the suspicion for dissection. Neurologic examination should assess the overall mental status and for findings of stroke or spinal cord ischemia. Paresthesias and motor deficits may be seen in the absence of stroke when arterial insufficiency and limb ischemia are present. Absent breath sounds in

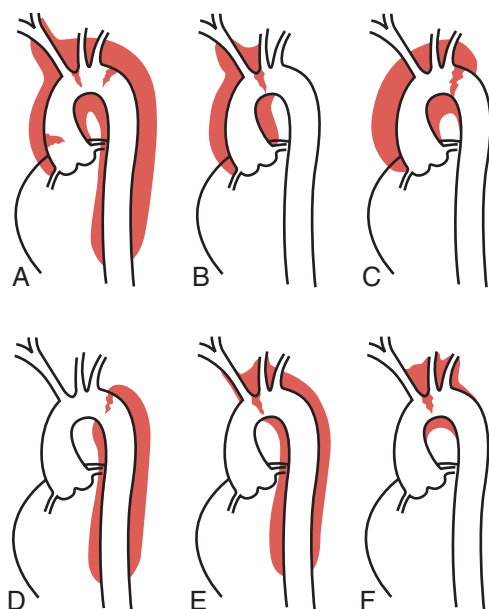


FIGURE 161-1 ■ Schematic illustration of Stanford classification system of aortic dissections. Examples in the top row (**A, B, C**) are all type A aortic dissections involving the ascending aorta. Examples in the bottom row (**D, E, F**) are all examples of type B dissections in which the ascending aorta is not involved. Note that the aortic arch can be involved in a type B dissection. (From Miller DC. Surgical management of aortic dissections: indications, perioperative management, and long-term results. In: Doroghazi RM, Slater EE, editors. Aortic dissection. New York: McGraw-Hill; 1983, p. 196.)

BOX 161-1 Risk Factors for Aortic Dissection

GENETIC/HEREDITARY/CONGENITAL CONDITIONS

Marfan syndrome
 Loeys-Dietz syndrome
 Ehlers-Danlos syndrome
 Turner's syndrome
 Bicuspid aortic valve
 Familial thoracic aortic aneurysm/dissection syndrome
 Aortic coarctation

INFLAMMATORY/AUTOIMMUNE CONDITIONS

Takayasu arteritis
 Giant cell arteritis
 Syphilitic aortitis

ACQUIRED CONDITIONS

Hypertension
 Smoking
 Cocaine
 Amphetamines
 Pregnancy
 Trauma
 Postprocedural
 Cardiac catheterization
 Intraaortic balloon pump placement
 Cardiac surgery

the left hemithorax can be seen with rupture. Cardiac examination should focus on the presence of an early diastolic murmur with a loud P2 component as seen with acute aortic regurgitation. Muffled heart sounds in conjunction with hypotension should alert for tamponade and the presence of a type A dissection. A thorough pulse examination is essential, as acute limb ischemia will not be seen in the setting of

other causes of chest pain such as pulmonary embolism. Abdominal tenderness should raise a concern for the involvement of the descending thoracic or abdominal aorta and the possibility of mesenteric ischemia. Examination of the extremities should assess for ischemia and also for the presence of connective tissue disorders such as Marfan syndrome.^{11,14}

■ DIAGNOSTIC TESTING

Laboratory Testing and Electrocardiogram

Routine laboratory analysis is generally unhelpful in diagnosing aortic dissection. Standard complete blood count may demonstrate anemia if there has been significant blood loss as in the case of dissection complicated by rupture. Chemistry panels may demonstrate low serum bicarbonate or elevated lactic acid levels if hypotension has been present for a prolonged duration with systemic hypoperfusion. Significantly elevated lactic acid levels should raise concern for compromise of perfusion to the abdominal viscera, particularly compromise of the mesenteric circulation to the bowel, which is ominous in terms of survival. Cardiac enzymes (creatinine kinase [CK], CK-myocardial band, and troponin) may be elevated in the setting of demand ischemia or if there is involvement of the aortic root and compromise of the coronary ostia. Extensive investigation has been performed to identify blood markers of dissection to aid in early diagnosis, but at this time, no sole lab value or combination of values is in routine clinical use for diagnosis. Testing for D-dimer, soluble elastin fragments, and smooth muscle myosin heavy chain have thus far yielded the most promising results, but none is routinely used in the clinical setting.¹⁵⁻²⁰

Electrocardiograms (ECGs/EKGs) should be obtained in all patients presenting with chest pain or concern for aortic dissection. Acute EKG changes can be present in nearly half of the patients and chronic changes in one-third of the patients. ST elevation is often associated with coronary ostial involvement of the dissection flap. These findings should be taken into particular consideration prior to initiating systemic anticoagulation or thrombolytics, which may be catastrophic in the setting of acute aortic dissection.²¹

Imaging

Historically, invasive angiography has been used but has since been replaced with echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI). For diagnosis, whichever modality is used will need to visualize a dissection flap within the aorta and visualize the site of the entry tear. Additional information will aid in management.

Standard chest radiograph (CXR) findings are neither sensitive nor specific for diagnosing aortic dissection but can be useful to identify other diagnoses and raise an index of suspicion for dissection. A widened mediastinum is present in 62% of the cases, and a blunted aortic knob may be seen. Additional findings suggestive of intrathoracic dissection include an irregular or double aortic contour or inward displacement of atherosclerotic calcification. The presence of a large left pleural effusion should raise concern for hemothorax. The CXR may be normal in 10% to 15% of patients.³

Contrast-enhanced CT scanning is the most widely used. Ideally a contrast-enhanced study should be obtained. If dissection is suspected before the imaging, imaging should be obtained from the base of the neck through the pelvis to delineate the extent of dissection and distal involvement. Helical scanning and ECG gating limit motion artifact and have been shown to have sensitivity and specificity rates of 95% to 98%.²² Contrast-enhanced CT imaging allows for distinction between type A and type B aortic dissections and allows for surgical planning (Figs. 161-2 and 161-3). Limitations of CT scanning include motion artifact in patients who are unable to remain still during image acquisition, the need for iodinated contrast dye, and the use of ionizing radiation.²³

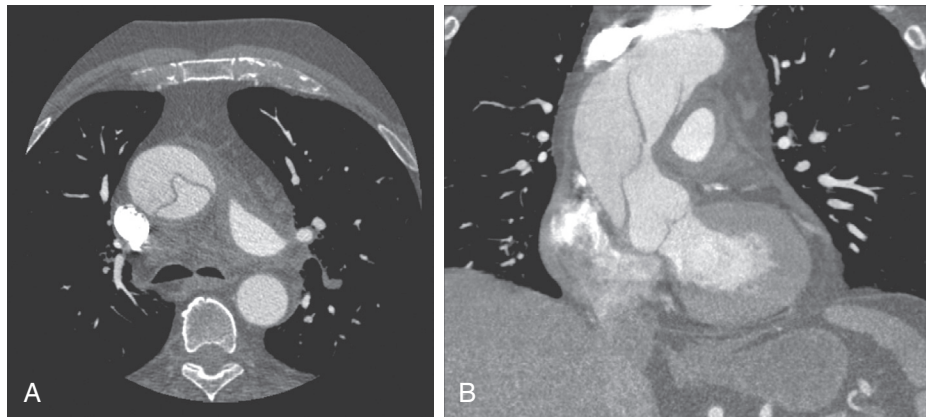


FIGURE 161-2 ■ Acute type A aortic dissection. Axial (A) and coronal (B) views.

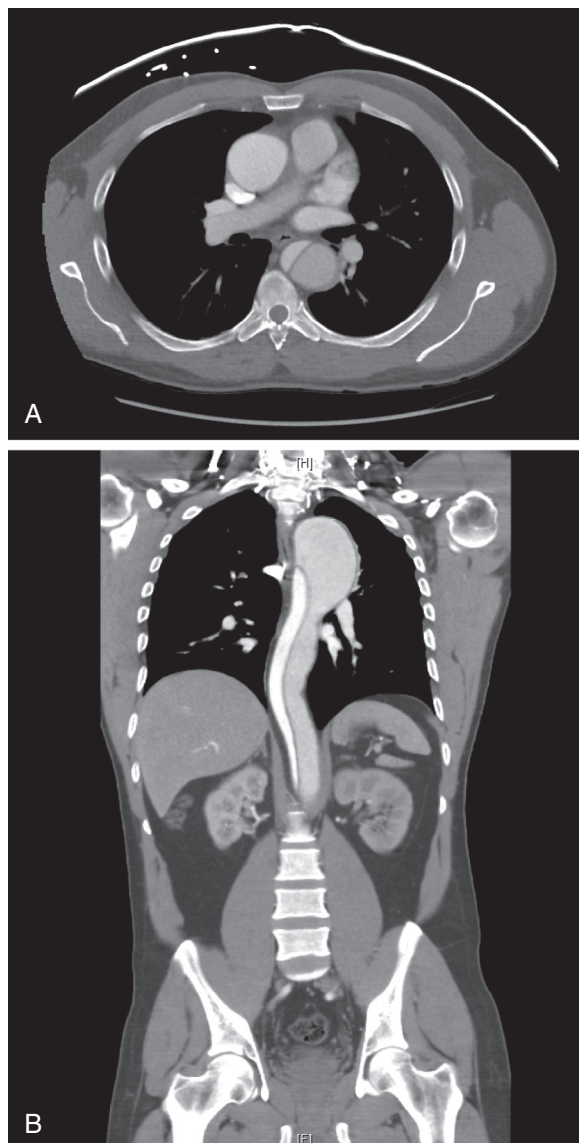


FIGURE 161-3 ■ Acute type B aortic dissection. Axial (A) and coronal (B) views.

Magnetic resonance imaging/angiography is not widely used for diagnosing dissection because of limited availability and the time required for image acquisition relative to CT scanning. From an imaging perspective, MR imaging provides the best sensitivity and diagnostic odds ratio relative to CT or transesophageal echocardiography (TEE) with sensitivity and specificity rates greater than 98%, and is the best imaging modality to confirm the presence of dissection if other imaging is equivocal.²⁴

Coronary angiography is rarely performed unless there is clear compromise of myocardial perfusion. Coronary angiography may delay definitive treatment and rarely improves the management. However, when the patient has a clear history of coronary artery disease and is hemodynamically stable, consideration may be given to performing coronary angiography if the patient presents with a *chronic* type A aortic dissection.

Transthoracic echocardiography (TTE) can be useful for diagnosing aortic dissection but is limited primarily by poor sensitivity. TTE images, which can be obtained rapidly at the bedside in an unstable patient, have the advantage of being noninvasive and the ability to identify aortic valve insufficiency, pericardial effusion or tamponade, and presence of a dissection flap in the ascending aorta or root. The significant limitations of TTE include limited diagnostic accuracy (80% sensitivity and 90% specificity if dissection involves ascending aorta) and difficulty imaging the ascending aorta and arch. Ranges for TTE sensitivity have been reported anywhere between 78% and 100% for diagnosing type A aortic dissection and 31% and 55% for type B aortic dissections.^{22,25}

TEE is significantly more sensitive and specific than TTE but has the limitation of being an invasive procedure, which can have complications such as aspiration, arrhythmia, or esophageal injury. The proximity of the aorta to the esophagus allows for excellent diagnostic accuracy for types A and type B dissections when TEE is used, but depending on the patient's anatomy, visualization of the distal ascending aorta or proximal arch may be limited as a result of air within the trachea or bronchus. Sensitivity of TEE has been reported between 97% and 99%, with specificity rates of 97% and 100%.^{22,26}

For patients who are transferred from a referring institution with an aortic pathology as the diagnosis, reconfirmation of the diagnosis must be performed. Imaging studies should be requested with the transfer of the patient for review and to avoid repeating studies. A study by Beaver and colleagues reviewed a series of patients transferred to their tertiary care center with a referring diagnosis of aortic dissection or aneurysm. Approximately 25% of the referring diagnoses were incorrect. Most commonly, aortic dissections were misdiagnosed as aortic aneurysms or aneurysms as dissections. Less frequently, the dissection type (A vs. B) was incorrect, or there was no aortic

pathology present at all.²⁷ Given the differences in the management for aneurysms versus dissections and types of dissections, personal image review is essential.

MEDICAL MANAGEMENT OF TYPE A AND TYPE B AORTIC DISSECTIONS

Once the diagnosis has been established, care should immediately focus on blood pressure management and need for surgical intervention.^{28,29} Sufficient intravenous access should be obtained with central venous line placement for administering vasoactive drugs. Arterial blood pressure should be monitored with an arterial line placed preferably in the radial artery, as the femoral artery may be needed for cannulation during surgery or may be involved in the dissection. Care should be taken when selecting the site of arterial catheterization based on the extent of dissection, as when there is subclavian arterial involvement, blood pressure readings may be artificially low because of compromised flow in the true lumen. Pain should be aggressively controlled with narcotics as necessary and during any procedures such as line placement to avoid sudden exacerbation of hypertension and to minimize endogenous catecholamine release from discomfort and anxiety. The primary tenet of medical management centers on anti-impulse therapy, which aims to limit propagation of the dissection by reducing the change in pressure over the change in time (dp/dt). If the patient is hypertensive, the initial treatment of choice is intravenous beta-blockade if the heart rate allows. Labetalol, esmolol, and metoprolol are all reasonable choices with doses as outlined in Table 161-1. If the heart rate is less than 70 at baseline or the blood pressure remains greater than 120 mm Hg systolic after the initiation of beta-blockers, afterload reduction with vasodilators such as sodium nitroprusside or nicardipine should be initiated. Pure vasodilators should be avoided as the initial treatment, as reflex tachycardia and increased cardiac contractility may increase dp/dt and theoretically propagate the dissection. Goal heart rates should be between 60 and 70 beats/min with goal systolic blood pressure between 100 and 120 mm Hg.³⁰ If pericardial tamponade is present or develops, pericardiocentesis should be avoided because there are high rates of cardiac arrest postprocedurally when performed in the setting of dissection.³¹ These events may occur due to abrupt increases in blood pressure after release of intrapericardial pressure with subsequent exacerbation of hemorrhage. If tamponade is encountered, aggressive volume resuscitation should be undertaken to optimize intracardiac filling, and definitive drainage can occur during surgery.

Patients may present with a range of neurologic deficits ranging from paresthesias to stroke. In patients with a delayed diagnosis and completion of a significant stroke, the use of high doses of heparin required for cardiopulmonary bypass and the restoration of blood flow to the brain may result in intracranial hemorrhage or catastrophic cerebral edema. Preoperative CT scanning of the brain may aid in determining the extent and severity of infarction. In patients present-

ing with recent onset of stroke, stroke-like symptoms, or fluctuating neurologic exam, surgical outcomes are acceptable provided restoration of perfusion to the brain can be obtained with dissection repair.³² Advanced age above 80 years remains an area of debate. Rates of mortality for emergency surgery for type A dissection in patients aged 80 years and older have been reported at nearly 50% to 60%, and survival with a nonoperative approach may be similar in patients beyond the age of 80 years.³³⁻³⁵ Decision to operate on patients older than 80 years remains at the surgeon's discretion, as reasonable survival may be obtained in these patients with medical management.³⁶ In addition to patients presenting with extensive stroke or advanced age, those with underlying comorbidities such as advanced malignancy, cirrhosis, or extensive mesenteric ischemia/bowel infarction may not be considered surgical candidates.³⁷ Certain patients may be diagnosed after the acute phase (2 weeks) with a chronic type A aortic dissection. These most commonly will be patients in whom the diagnosis is made incidentally during imaging for other complaints, or those who present weeks after symptom onset. In surviving the acute period, these patients have self-selected for medical management, and indications for surgery in the asymptomatic patient would electively be based on aortic size from aneurysmal change rather than the presence of dissection.

For patients with acute type B aortic dissection that is uncomplicated, medical management as detailed earlier is the primary treatment strategy, with acute surgical intervention reserved for those who present with or develop complications (see "Surgical Management of Type B Aortic Dissection") and possible delayed (weeks to months later) surgical intervention for potentially improved aortic remodeling. Once blood pressure and pain have been normalized for 24 to 48 hours, intravenous medications can be converted to oral agents, and transfer out of the critical care setting is reasonable. Imaging should be obtained prior to discharge with CT scanning or MRI to ensure there has been no progression of dissection and for baseline assessment.

SURGICAL MANAGEMENT OF TYPE A AORTIC DISSECTION

The primary goal of surgery for acute type A aortic dissection is to immediately treat the life-threatening pathology and then to prevent future complications. Thus, the extent of surgical procedure required will take into account the origin of the dissection, involvement of the aortic root/valve, arch and descending aorta, and, importantly, the overall condition of patients, as extensive reconstructions may not be well tolerated in the elderly or patients with major comorbidities or ongoing visceral or extremity ischemia.

Ascending Aortic Replacement

In cases where the dissection is limited to the ascending aorta or the intimal tear is clearly identified in the ascending aorta, aortic replacement with a polyester graft from the level of the sinotubular junction to the distal ascending aorta is performed. If the aortic valve is normal but acute aortic insufficiency has resulted from detachment of the aortic valve commissures, valve competency can be restored by resuspension of the commissural posts. The aortic root and coronary arteries are left in situ. Depending on a patient's anatomy and a surgeon's preference, the operation can be performed without deep hypothermic circulatory arrest.

Ascending Aortic Replacement with Aortic Valve Replacement

Similarly, in cases where the dissection is limited to the ascending aorta or the intimal tear is clearly identified in the ascending aorta, aortic replacement with a polyester graft from the level of the sinotubular junction to the distal ascending aorta is performed. If the aortic valve is incompetent but the coronary ostia are otherwise uninvolved and the sinuses of Valsalva are not aneurysmal, the aortic valve may be

TABLE 161-1 Medical Management for Patients with Acute Aortic Dissection

| DRUG | DOSAGE |
|----------------------|--|
| Labetalol | 0.25 mg/kg IV over 2 minutes; 40-80 mg q 10 min up to 300 mg; 1-2 mg/min IV infusion |
| Esmolol | 50-200 µg/kg per minute IV infusion |
| Metoprolol | 5 mg IV slow bolus up to 4 doses 15 minutes apart |
| Nicardipine | 5-15 mg/h IV infusion |
| Diltiazem | 0.25 mg/kg IV over 2 minutes; 5-10 mg/h IV infusion |
| Sodium nitroprusside | 0.2-0.3 µg/kg per minute up to 300 µg/min IV infusion |

IV, intravenous.

replaced with a tissue or mechanical prosthesis and the remainder of the aortic root left intact. As mentioned earlier, depending on a patient's anatomy and a surgeon's preference, the operation can be performed without deep hypothermic circulatory arrest.

Aortic Root Replacement

When there is extensive destruction of the aortic root, complex reconstruction must be undertaken. In this setting, there is usually extensive coronary ostial involvement, the native aortic valve is unsalvageable, or there is aneurysmal degeneration or destruction of the sinuses of Valsalva. To address the aortic valve, the valve may be replaced with a mechanical prosthesis attached to a polyester aortic graft (Bentall procedure), a tissue prosthesis attached to a polyester aortic graft (bio-Bentall procedure), or the valve leaflets may be preserved and the native valve reconstructed (valve-sparing aortic root replacement or David procedure). In addition to addressing the valve, the sinuses of Valsalva are replaced with the graft conduit, and the native coronary arteries are reimplanted into the graft.

Aortic Hemiarch Replacement

When the dissection extends beyond the distal ascending aorta and the flap or site of intimal tear is visualized in the proximal underside of the aortic arch, hemiarch replacement may be considered. In hemiarch replacement, the ascending aortic graft is beveled, or, alternatively, two separate grafts may be used and the underside of the arch is replaced. The innominate artery, right common carotid, and left subclavian artery are left in situ. This will require deep hypothermic circulatory arrest to provide adequate visualization and the ability to resect an adequate amount of diseased tissue.

Aortic Arch Replacement

If there is extensive dissection involvement of the aortic arch or branch vessels originating from the aortic arch or there is aneurysmal disease of the arch, complete aortic arch replacement is undertaken. Complete reconstruction of the aortic arch requires deep hypothermic circulatory arrest. The diseased aorta is excised or excluded distally to beyond the left subclavian artery. The innominate artery, right common carotid artery, and left subclavian artery are isolated individually, or as an "island" with a common cuff of aortic tissue, and implanted onto the synthetic graft after the graft has been anastomosed distally to the descending thoracic aorta. The proximal portion of the graft is then anastomosed directly to the ascending aortic graft or the sinotubular junction. At times, the left subclavian artery may be sacrificed if reimplantation is not technically feasible. If significant aneurysmal disease exists beyond the left subclavian artery and there is consideration for future open replacement or stent grafting of the descending thoracic aorta, an "elephant trunk" procedure may be performed. In this setting, the synthetic aortic graft is anastomosed distal to the left subclavian artery, but approximately 10 cm of the graft unfolds distally into the descending thoracic aorta. These operations are technically demanding and require extended periods of circulatory arrest, increasing the risk of neurologic complications.

Thoracic Endovascular Aortic Repair

Conventional surgery remains the standard of care for managing acute type A aortic dissection, but as detailed earlier, certain patients may not be operative candidates or tolerate extensive surgery. Thoracic endovascular aortic repair (TEVAR) is an area of active investigation for managing ascending aortic pathology, and early reports indicate future promise for patients without extensive root involvement. The largest series thus far reported on 22 patients undergoing TEVAR of the ascending aorta, 9 of whom had acute type A dissection, 2 with chronic type A dissection, and 2 with intramural hematoma. The early mortality was 13.6%, and major complications were not uncommon.

As development of device technology continues, outcomes should improve.³⁸

SURGICAL MANAGEMENT OF TYPE B AORTIC DISSECTION

Approximately 25% of acute type B aortic dissections will present with or progress to complications that may be an indication for surgical intervention. Indications for intervention in the setting of acute type B dissection include significant visceral or extremity malperfusion, persistent pain, saccular aneurysm, hemothorax, or evidence of impending rupture. In the setting of a chronic type B dissection, primary indications for intervention include recurrent pain, growth, or aneurysmal degeneration. These indications are evolving as surgeons are more aggressively pursuing TEVAR in the absence of complication to improve aortic remodeling.^{39,40}

Descending Thoracic Aortic Replacement

Open replacement of the descending thoracic aorta is approached via a left posterolateral thoracotomy. Single-lung ventilation is used to provide exposure in the operative field. Commonly, partial left heart bypass obtaining drainage from the left atrium with arterial inflow returned to the femoral artery is used. Alternatively, complete cardiopulmonary bypass can be performed via femoral arterial and venous cannulation. As with type A aortic dissection, a primary goal of the operation is to resect the initial entry tear. As this often occurs near the left subclavian artery, deep hypothermic circulatory arrest may be needed to perform the proximal anastomosis. The descending aorta is then replaced with a polyester-based graft with reimplantation of intercostal islands as needed. The distal anastomosis aims to restore continuity of the true lumen and obliterate the false lumen, thereby restoring perfusion distally. Spinal drainage catheters may be placed preoperatively to optimize the spinal perfusion pressure.

Thoracic Endovascular Aortic Repair

TEVAR is the preferred treatment modality for patients requiring intervention on a type B aortic dissection. Its primary goal is to close the entry tear, stabilize the dissected aorta, and prevent later complications by inducing remodeling. It is performed using a catheter-based approach, generally from the femoral arteries, or at times the iliac arteries, to deploy a covered stent graft across the primary dissection tear. Anatomic requirements for safe deployment of a stent graft include a proximal and distal aortic landing zone diameter of less than 40 mm and at least 20 mm of length. In certain cases, severe peripheral vascular disease or arterial tortuosity may preclude, and an endovascular approach and open repair may be required.

POSTOPERATIVE MANAGEMENT

Immediate postoperative care centers on the management of blood pressure, as during preoperative management, and early detection of complications. The critical care provider should be given a detailed report on operative findings, procedure performed, and areas of potential complications for which to be vigilant. Early and serial neurologic assessment is essential to determine if an intraoperative stroke has occurred (may occur with persistent dissection in the carotid artery as a result of particulate or gaseous embolization during or after surgery or as a result of prolonged deep hypothermic circulatory arrest). In the setting of type B dissection repair, spinal cord ischemia may occur with fluctuations in blood pressure and result in paresthesias or paralysis. As noted earlier, spinal drainage catheters for draining cerebrospinal fluid (CSF) may be placed preoperatively to allow for intervention if this occurs. Goal CSF pressures are 10 mm Hg or less and can be manipulated with additional drainage or increasing mean arterial pressure to greater than 90 mm Hg with vasopressors. Nonfocal neurologic deficits such as delirium or impaired cognition

may be encountered, especially with the use of circulatory arrest. Pain control remains essential to minimize hypertension. Extubation can be considered once hemodynamics has been stabilized and bleeding is controlled. From a hemodynamic perspective, blood pressure control remains critical to prevent suture line bleeding and propagation of residual dissection (if present) within the distal aorta. The extremities should be examined for pulses as ischemia may develop from residual distal dissection or persistence of a false lumen. Compartment syndrome can arise from reperfusion and in the sedated patient may be difficult to diagnose as they will not be able to complain of pain or paresthesias. Abdominal examination should focus on distention or tenderness that can develop from reperfusion or persistent ischemia due to residual dissection in the abdominal aorta. Early abdominal duplex ultrasonography should be considered for complex dissections involving the descending thoracic and abdominal aorta to ensure restoration of adequate perfusion to the liver, kidneys, and bowel after more proximal aortic replacement. Malperfusion may warrant endovascular approaches for fenestration of residual dissection flaps. Urine output should be monitored for volume and color. A significant coagulopathy may be present postoperatively from consumption of coagulation factors during cardiopulmonary bypass, hypothermia, and continued endogenous fibrinolysis occurring within the thrombosed false lumen of the dissection. If a mechanical prosthesis has been used to replace the aortic valve, anticoagulation can generally be safely initiated 48 hours postoperatively. We routinely obtain a transthoracic echocardiogram prior to discharge to ensure no significant aortic valve insufficiency (for preserved, resuspended, or repaired valves) or paravalvular leak exists (for replaced valves). A contrast-enhanced CT scan is also obtained prior to discharge to assess the repair, extent of any residual dissection, and for the presence of pseudoaneurysm.

CONCLUSION

As discussed earlier, the optimal management strategy for acute type A aortic dissection is surgical treatment. Medical management of acute type A dissection results in in-hospital mortality rates of nearly 55% to 60%.⁴¹ Despite advances in surgical technique and perioperative care, operative mortality for acute type A dissection ranges from 7% to 36%, and in-hospital mortality is 27%. For patients surviving the initial hospitalization, the 5-year survival rate is 68% and the 10-year survival rate is 52%.^{33,42}

For patients with uncomplicated type B aortic dissection, hospital mortality is 10% with medical management,⁴³ and 5- and 10-year survival rates range between 60% and 80% and 40% and 45%, respectively.⁴⁴⁻⁴⁶ When managed surgically, the in-hospital mortality with open repair is approximately 32%⁴³ and 9% with TEVAR.⁴⁷

KEY POINTS

1. **Definition:** Aortic dissection occurs when there is disruption of the intima of the aorta. When the intimal layer is disrupted, blood ejected under pressure from the left ventricle enters the medial layer, thereby creating two lumens in the aorta. The true lumen, lined by intima, can become compressed or even obliterated by the false lumen in the medial layer. From the site of the initial intimal entry tear, the dissection can propagate proximally (retrograde) toward the aortic valve or distally (antegrade).
2. **Classification:** Aortic dissections are classified using either the DeBakey or the Stanford classification systems. Stanford type A aortic dissections involve the ascending aorta, and type B dissections are defined as those "limited to the descending aorta with primary intimal tear usually within 2 to 5 cm of the left subclavian artery."
3. **Clinical findings:** History and physical examination may raise an index of suspicion for aortic dissection, but imaging is required for diagnosis. History is most often notable for acute onset of chest or back pain. Key exam findings include differential blood pressures among limbs, diastolic murmurs, pulse deficits, and paresthesias.
4. **Diagnosis:** CT angiography is the most widely used and available modality and allows for anatomic classification and operative planning. Magnetic resonance imaging and TEE may be useful in patients unable to undergo CT imaging or in patients in whom the diagnosis remains in question.
5. **Management:** Optimal heart rate and blood pressure control is essential for the immediate management of all acute aortic dissections, regardless of type. Acute type A aortic dissections are generally managed surgically with replacement of the aorta with a synthetic graft. More complex surgical reconstruction may be undertaken depending on the extent of the dissection. Acute type B aortic dissections, when uncomplicated, are generally managed medically with optimal rate and blood pressure control. Complicated acute type B aortic dissections may require surgical intervention, commonly using an endovascular approach.

ANNOTATED REFERENCES

Daily PO, Trueblood HW, Stinson EB, et al. Management of acute aortic dissections. *Ann Thorac Surg* 1970;10:237-247.

The most frequently used classification system for aortic dissections was developed by Daily and associates at Stanford University. This system of classification, now known as the Stanford classification, involves only two groups. Type A dissections involve the ascending aorta, and type B involve the more distal aorta, from the innominate artery to more distal regions.

David TE, Feindel CM. An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta. *J Thorac Cardiovasc Surg* 1992;103:617-621.

This paper discusses treatment of aortic dissection involving the aortic root. If the aortic root is severely damaged by the dissection process, the patient has Marfan syndrome or another connective tissue disorder, or severe annuloaortic ectasia is present, or the valve has to be replaced for other reasons (e.g., aortic stenosis). A valve-sparing technique may be appropriate.

Gillinov AM, Lytle BW, Kaplon RJ, et al. Dissection of the ascending aorta after previous cardiac surgery: differences in presentation and management. *J Thorac Cardiovasc Surg* 1999;117:252-260.

The risk of perioperative and late postoperative dissection is discussed in this paper, as well as many other associated pathologic findings such as bicuspid aortic valve, aortic coarctation, and Turner's syndrome. Aortic dissection as a rare complication of cardiac catheterization and other percutaneous diagnostic and therapeutic interventional techniques are also examined.

Miller DC. Surgical management of aortic dissections: indications, perioperative management, and long-term results. In: Doroghazi RM, Slater EE, editors. *Aortic dissection*. New York: McGraw-Hill; 1983. p. 193-243.

This chapter provides an excellent overview of the clinical features, surgical and medical management, and outcomes after aortic dissection.

Yacoub MH, Gehle P, Chandrasekaran V, et al. Late results of a valve-preserving operation in patients with aneurysms of the ascending aorta and root. *J Thorac Cardiovasc Surg* 1998;115:1080-1090.

This paper presents the late results of a valve-preserving operation in patients with aneurysms of the ascending aorta and root.

Coady MA, Ilkumidis JS, Cheung AT, et al. Surgical management of descending thoracic aortic disease: open and endovascular approaches. *Circulation* 2010;121:2780-2804.

This paper presents a contemporary review of various pathologic processes affecting the descending thoracic aorta, including aortic dissections, intramural hematomas, and penetrating ulcers, discussed in this chapter. Cutting-edge technology for treatment (endovascular approach) is compared to gold-standard open techniques.

References for this chapter can be found at expertconsult.com.

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Most stenoses in the splanchnic vessels remain asymptomatic, but some cause symptoms, and catastrophic complications can develop. Furthermore, there is much confusion regarding the terminology for describing these stenoses. In this chapter, we have used “splanchnic ischemia,” but for all practical purposes the terms *splanchnic ischemia* and *mesenteric ischemia* are interchangeable. This chapter conveys three main messages. First, gastrointestinal (GI) ischemia is an underestimated disorder that may have grave implications in patients. Second, nonocclusive mesenteric ischemia (NOMI) is a common phenomenon in patients in the intensive care unit (ICU), and its diagnosis can prevent overfeeding, provide improved treatment, and achieve better outcomes. Third, the conventional approach for treating bowel infarction (i.e., bowel resection, followed by revascularization) has been replaced by an approach involving endovascular revascularization, followed by inspection of bowel viability and resection of irreversible damage.

PHYSIOLOGY, ANATOMY, AND PATHOPHYSIOLOGY

The Main Vessels: Celiac Artery, Superior Mesenteric Artery, and Inferior Mesenteric Artery

Blood is supplied to the GI tract by three arteries, namely, the celiac artery (CA), superior mesenteric artery (SMA), and inferior mesenteric artery (IMA). Large anatomic variations exist in these vessels. The CA supplies blood to the stomach, the liver, a part of the pancreas, and the proximal part of the duodenum. The SMA supplies blood to the distal part of the duodenum, entire small bowel, ascending colon, and proximal part of the transverse colon. The IMA supplies blood to the distal colon. Branches of these arteries enter the bowel wall to form two plexuses within the serosa and submucosa. Arterioles penetrate the muscular layer toward the mucosa and branch into an extensive network of capillaries and venules that allow the diffusional shunting of oxygen through a countercurrent mechanism. Several collaterals may exist, including Buhler's arc between the CA and SMA and Riolan's artery between the SMA and IMA. The superficial mucosal layer of the bowel is the most susceptible to ischemia because of its high metabolic demand¹ and countercurrent arteriovenous exchange of oxygen.² Blood from the bowel enters the mesenteric veins and finally into the portal vein. The liver receives blood supply from two sources: (1) the portal vein, which provides venous blood, and (2) the hepatic artery, which provides arterial blood. This dual blood supply protects the liver from ischemia.

Regulation of Blood Flow

During fasting, 20% of the cardiac output passes through the splanchnic vasculature. Blood flow doubles after a meal and decreases with an increase in systemic circulatory demands like exercise and shock.

The three main vasoconstrictors are catecholamines, angiotensin II, and endothelin. Catecholamines exert different effects on splanchnic blood flow. Stimulation of α -1 adrenergic receptors leads to vasoconstriction, whereas that of β -2 adrenergic receptors leads to

vasodilatation. Angiotensin II is a key splanchnic vasoconstrictor during low blood flow.³ The main splanchnic vasoconstrictor is endothelin-1.^{4,5} Endothelin-1 activation induces long-lasting vasoconstriction and plays an important and early role in mediating the effects of shock on the integrity of the GI tract.⁶

The main splanchnic vasodilators are nitric oxide (NO) and prostaglandins. Under normal conditions, the endothelium produces NO to sustain perfusion by promoting local vasodilatation. Locally formed prostaglandins act as mucosal vasodilators, especially during low blood flow or after a mucosal injury. Inhibition of cyclooxygenase by nonsteroidal antiinflammatory drugs (NSAIDs) decreases this vasodilatory response and increases the susceptibility of the GI mucosa to the effects of circulatory shock.⁷

Low Flow Conditions

All the previously mentioned receptors and messengers act to balance perfusion with metabolic demands on a moment-to-moment basis. When circulating volume is decreased splanchnic vasoconstriction occurs early and profoundly,⁸ even before the onset of systemic hemodynamic instability.⁹ Splanchnic vasoconstriction is also induced by vasoactive medications, nicotine, and cocaine abuse. GI ischemia occurs only when blood flow is decreased to below 50% of the basal rate.^{10,11}

During splanchnic hypoperfusion, blood flow within the bowel wall is unevenly distributed among its different layers. The mucosa is relatively protected compared with the serosal layer.¹² However, superficial mucosal layers are susceptible to ischemia because of the high metabolic demand¹ and countercurrent diffusion of oxygen. Blood flow is unevenly distributed within the mucosal layer, with patchy distribution in ischemic and nonischemic areas because of microcirculatory shunting.¹³⁻¹⁵ This patchy distribution may be the reason for normal mucosal blood flow measurements despite the presence of mucosal ischemia. Therefore ischemia cannot be detected only based on blood flow measurements. This ischemia associated with a normal vessel anatomy is called *NOMI*.

Ischemic Damage

Mild ischemia does not induce any histologic damage.¹⁶ After the complete cessation of splanchnic blood flow, extensive damage occurs within 30 minutes after the disappearance of villi and exposure of subepithelial spaces. Upon reperfusion, the remaining epithelial layers retract and are shed into the lumen.¹⁷ Three phases are typically distinguished and often occur simultaneously and remittently.

Ischemic Phase

The immediate effect of decreased oxygen utilization is ATP depletion. This leads to rapid derangement of tight junctions between enterocytes and malfunctioning of membrane-bound pumps. Increased mucosal permeability and damage decrease intestinal epithelial barrier function and bacterial translocation, thus allowing bacteria to enter the circulation.¹⁸ Another effect of cellular hypoxia is the conversion of xanthine dehydrogenase into xanthine oxidase (XO), which is harmless at this stage. Subsequent tissue necrosis triggers an inflammatory response, resulting in cytokine release. Most effects of the ischemic phase are localized and remain clinically undetected for many hours. These

conditions may persist until the initiation of a systemic inflammatory response or transmural gangrene by reperfusion.

Local Effects of Reperfusion

Once the blood flow is restored, oxygen enters the ischemic tissue after the dissolution of emboli or after the improvement of general circulation. At this stage, XO converts oxygen into various reactive oxygen species (ROS) that induce protein and DNA damage.¹⁹ The damage to mucosa, blood vessels, and submucosal tissues is not only intensified but also spreads to adjacent regions by the diffusion of the small ROS molecules. Physiologically present ROS scavengers like glutathione, catalase, and superoxide dismutase limit these ROS-induced effects; however, their efficacy is limited because they soon undergo depletion.

Systemic Effects of Reperfusion

Reperfusion releases toxic products, XO, proinflammatory cytokines, and activated neutrophils into systemic circulation.²⁰ In animal studies, liver and lung damage has been attributed to activated neutrophils released from a reperfused ischemic bowel induce liver and lung damage.¹⁹ Thus, reperfusion leads to the amplification and diffusion of ischemic damage.

■ DIAGNOSTIC METHODS

Introduction

For a diagnosis of GI ischemia three parameters should be considered: the clinical presentation (complaints), vessel anatomy, and proof of ischemia.

Clinical Presentation

Most patients with nonocclusive ischemia are critically ill, and their medical history is of limited value. Typical complaints of patients with occlusive mesenteric ischemia include postprandial pain, weight loss, fear of eating, adjusted meals, and unexplained diarrhea.²¹⁻²³

Duplex Ultrasonography

Duplex ultrasonography of the splanchnic arteries provides accurate results in 80% to 90% of cases when performed by experienced professionals. Measurement of flow velocity at the origin of the CA and SMA by considering the respiratory cycle allows the assessment of stenoses.^{24,25} However, duplex ultrasonography is unsuitable for most critically ill patients because it is very operator dependent; moreover, vessels cannot be visualized in 10% to 15% of patients because of the presence of GI gas.

Computed Tomography Angiography

Computed tomography (CT) angiography (CTA) during the arterial and venous phases after the intravenous injection of a contrast by using a slice thickness of 1 mm, followed by 3D reconstruction of the vessel, is increasingly being performed in patients admitted to ICUs. CTA is accurate for detecting acute mesenteric ischemia.²⁶ A meta-analysis showed that CTA is the most reliable diagnostic tool.²⁷ Advantages of CTA include minimal invasiveness, short scan time, high-resolution vessel visualization and provision of additional information on bowel pathology or perfusion. It has recently been reported as accurate diagnostic test for NOMI as well, characterized by a reduced SMA diameter. It was suggested that incorporation of CTA in the workup for suspected NOMI might improve the mortality.²⁸

Magnetic Resonance Angiography

MRA has largely replaced CT angiography, despite its potential for 360° view of the vessels, quantitative blood flow measurement, and

oxygen content. The faster scan times and higher spatial resolution resulted in superior results for CTA in comparative studies, using angiography as the gold standard.²⁹

Digital Subtraction Angiography

Digital subtraction angiography (DSA) of splanchnic vessels, which was previously used as the diagnostic gold standard, is now used only in endovascular procedures and is usually preceded by diagnostic CTA. When a state-of-the-art CT scan is not available, multiplane aortal and selective angiography is performed for accurate diagnosis.

Endoscopy and Surgery: Inspection of the Mucosa and Serosa

Endoscopy allows the examination of mucosal layers. In contrast, abdominal inspection during surgery only allows the examination of the serosal side of the bowel. Because the mucosa is affected by ischemic changes at an early stage, when the serosa is still completely normal, endoscopy will show ischemia at stages where laparotomy yields normal findings.³⁰ The following three points should be considered: (1) Endoscopy is more sensitive for diagnosing early ischemia and often does not detect transient or mild ischemia; therefore one cannot exclude ischemia despite obtaining normal findings during endoscopic examination.¹⁶ (2) Endoscopy cannot distinguish between mucosal and transmural ischemia, even when endoscopy shows deep ulcerations or gangrenous-appearing mucosa and the serosa can be spared. (3) Transmural ischemia can only be detected surgically. Therefore laparoscopy or laparotomy is indicated when transmural ischemia is suspected and when bowel resection is indicated. On the other hand, endoscopy is performed to rule out moderate to severe ischemia.

Laboratory Tests

Serologic tests are of limited use for detecting ischemia. Classical markers like leukocyte count and arterial lactate level are not sensitive and specific for detecting ischemia. Intestinal fatty acid-binding protein and D-lactate are the most promising serologic markers^{31,32}; however, clinical data on these markers are sparse.³³⁻³⁵

Measurement of PCO₂ (Tonometry)

Measurement of intraluminal PCO₂ levels can detect ischemia irrespective of blood flow or metabolism. This extra CO₂ is released during ischemia and results from buffering by local bicarbonate of large amounts of tissue (lactic) acids produced during anaerobic metabolism. Because CO₂ diffuses readily from the mucosa to the lumen, intraluminal PCO₂ levels reflect mucosal CO₂ levels. The relation between CO₂ and ischemia was first described in the heart and skeletal muscles and in the stomach.^{36,37,38} Measurement of intraluminal PCO₂ levels was first published by Boda in 1959.³⁹ This technique was subsequently popularized by Fiddian-Green and was thereafter marketed as tonometry (Fig. 162-1A). Alternative PCO₂ measurement techniques have been recently validated by Boda almost 50 years after his first publication.⁴⁰⁻⁴¹ Tonometry is an important technique for detecting splanchnic ischemia in critical care patients. Moreover, tonometry allows the selection of patients who can benefit from the treatment of splanchnic stenoses.⁴²⁻⁴⁴ Measurement of PCO₂ levels is the only valid test for detecting GI ischemia. Increased intraluminal to arterial PCO₂ gradient is an indicator of ischemia. Normal gastric-arterial PCO₂ gradient in the stomach is below 0.9 kPa (7 mm Hg),⁴⁵ and that in the jejunum is 1.4 kPa.⁴⁶ The relation between PCO₂ gradient and blood flow is characterized by an unchanged gradient, with an increase starting when the splanchnic blood flow falls below 30% to 40% of baseline values (Fig. 162-2).^{30,45}

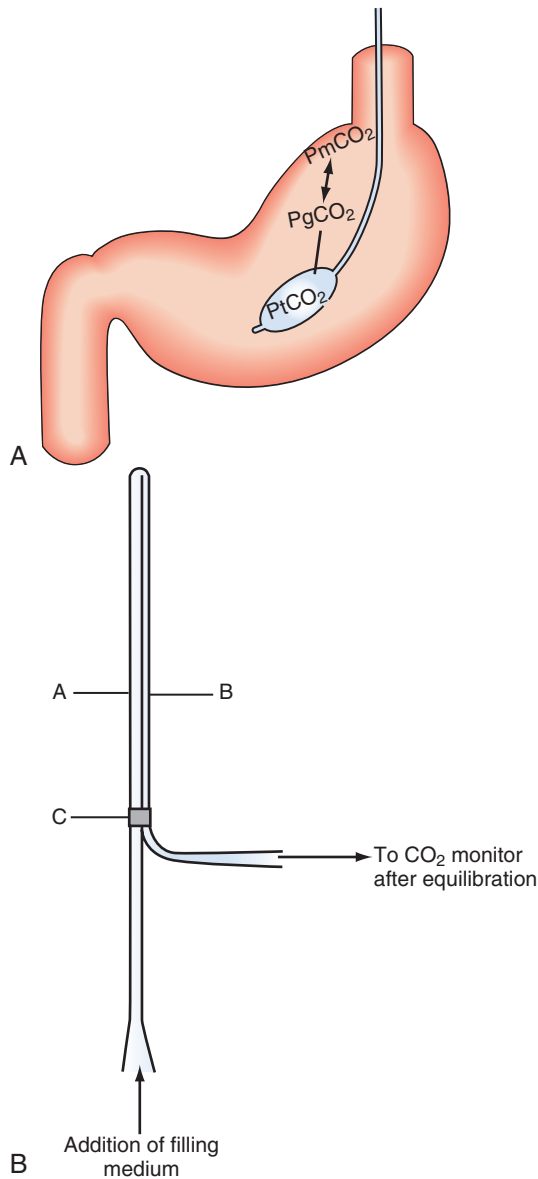


FIGURE 162-1 ■ Techniques for measuring intraluminal PCO_2 levels. **(A)** Tonometry.¹¹ PCO_2 levels can be measured using a specialized balloon-tipped catheter placed in the stomach and the small or large bowel. Because CO_2 diffuses rapidly through different membranes, mucosal PCO_2 (PmPCO_2) levels will be equal to gastric lumen PCO_2 levels. Because CO_2 permeates into the balloon, balloon PCO_2 levels reflect PmPCO_2 levels. Balloon PCO_2 levels are measured from the air that is aspirated and inflated automatically into the balloon by using a modified capnograph called Tonocap (Datex-Engström). **(B)** Balloonless intraluminal PCO_2 measurement.⁴³ In this, PCO_2 levels are measured using a balloonless catheter in which air flows through a tube that is CO_2 permeable only at the intragastric tip and that is connected to the capnograph on the sampling side.

Clinical Application of PCO_2 Tonometry

Because splanchnic ischemia is one of the earliest events during circulatory stress and typically begins when all other systemic parameters are within a normal range, it is called “the canary of the body.”⁴⁷ Like a canary, which was once used in coal mines to detect toxic levels of

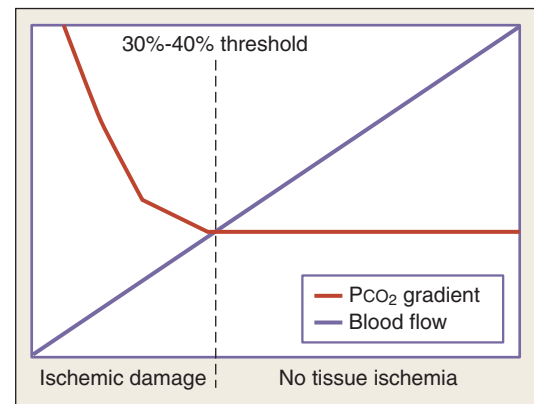


FIGURE 162-2 ■ Blood flow, ischemia, and luminal PCO_2 levels.¹¹ Reduction in splanchnic blood flow to approximately 50% does not increase luminal PCO_2 levels and does not induce tissue damage. Further reduction below approximately 30% of the basal blood flow results in a gradual increase in luminal PCO_2 levels and characteristic ischemic tissue damage. Blood flow is indicated by the blue line, and intraluminal PCO_2 is indicated by the red line. The dotted lines indicate anaerobic threshold of the tissue.

mine gas, measurement of PCO_2 levels may be a good, inexpensive, and relatively early indicator of an impending problem.⁴⁸

Although measurement of PCO_2 levels is a promising method for detecting ischemia, it is rarely used. This is mainly because first-generation tonometers involving saline and blood gas analyzers are difficult to use, time-consuming, and error prone. In addition, there is uncertainty regarding the effects of and need for acid suppression and food ingestion. These issues have now been resolved by using air-based PCO_2 measurement devices (Tonocap device), by inducing potent acid suppression, and by ensuring standardized meal consumption during testing.

Different tonometry data were obtained from non-ICU patients with occlusive ischemia. Tonometry during a 10-minute exercise test measured PCO_2 during submaximal exercise allowed to detect ischemia in the stomach and small bowel with a 78% sensitivity and 92% specificity.⁴² This test has been successfully used to select patients with single-vessel stenosis for treatment and follow-up.⁴ Using strict testing conditions, including acid suppression and standard meal consumption, provided similar accuracy with more physiologic 24-hour tonometry.⁴⁹⁻⁵⁰ This was based on an initial observation in a study performed in 1991,⁵¹ followed by studies with conflicting results.⁵²⁻⁵⁴ An imminent bowel infarction is characterized by an increased PCO_2 level (often above 15 kPa) for several hours. We detected an entire spectrum of splanchnic ischemic disorders ranging from asymptomatic stenoses to single- and multivessel stenoses and imminent bowel infarction by using this test.⁵⁵

CLINICAL PRESENTATIONS OF SPLANCHNIC ISCHEMIA

Introduction

Splanchnic vascular disorders encompass various acute and chronic (non)occlusive and aneurysmal disorders that affect the vessels in the abdominal viscera. Ischemic disorders are classified based on vessel anatomy and ischemia (Fig. 162-3). Acute splanchnic ischemia is caused by arterial embolism, arterial and venous thrombosis, arterial stenosis, or NOMI. For an intensivist, NOMI is the most common problem and hence will be discussed first. Discussion on occlusive ischemia will focus on different and often underappreciated clinical presentations, diagnostic problems, and treatment issues, with a special emphasis on ICU care.

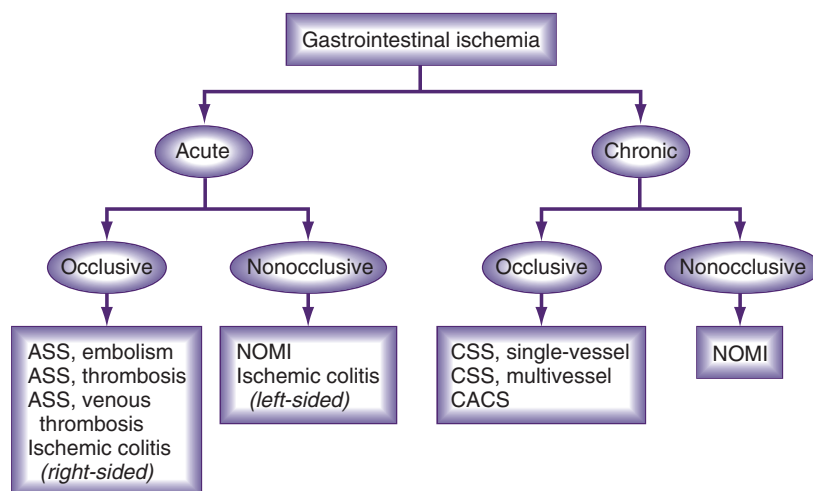


FIGURE 162-3 ■ Classification of gastrointestinal vascular diseases and ischemia.⁵³

Nonocclusive Mesenteric Ischemia

Critically Ill Patients and Major Operations

In gastroenterology and surgery, NOMI is probably a rare disorder that can cause ischemic colitis⁵⁶ or acute splanchnic infarction.⁵⁷ It can also lead to chronic complaints related to vascular spasm that are comparable to those associated with chronic splanchnic ischemia. Treatment with vasodilators is successful in the majority of patients and referred to as *abdominal migraine*.⁵⁸

NOMI is caused by physiologic responses to decreased intravascular blood volume. Early and profound splanchnic vasoconstriction that accompanies major operations may lead to splanchnic ischemia and eventually adverse prognosis.^{59,60} Similarly, in patients with acute pancreatitis, gastric mucosal ischemia is associated with a worse outcome.⁶¹ The relevance of this finding was reinforced by a recent randomized study that examined the effects of probiotics on acute pancreatitis. This study, which investigated the potential beneficial effects of probiotics supplemented with early feeding on acute pancreatitis, showed that mortality was significantly higher in patients receiving probiotics and was associated with bowel infarction.⁶²

NOMI may play a key role in the pathogenesis of multiple organ dysfunction syndrome (MODS). Although endotoxemia directly causes mucosal microcirculatory disturbances⁶³ and increases gut-derived cytokine and endotoxin levels in patients with MODS,^{64,65} there is no definite proof that NOMI is associated with the pathogenesis of MODS.

Hemodialysis Patients

NOMI is common in hemodialysis patients⁶⁶ and may lead to bowel infarction, with a 45% mortality rate.⁶⁷ This complication has been reported in 0.5% to 0.9% of hemodialysis patients.⁶⁷⁻⁶⁹ The main risk factor for NOMI is hypotension. Therefore close monitoring and prevention of hypotension during hemodialysis are crucial to prevent NOMI.⁶⁷

Medications

Many drugs, including digoxin and NSAIDs, may induce or aggravate NOMI. NSAIDs affect the integrity of the GI mucus and bicarbonate layer and decrease mucosal perfusion. Alpha-adrenergic agents like epinephrine and dopamine decrease GI perfusion, and beta-adrenergic agents like dobutamine and dopexamine maintain mucosal perfusion.⁷⁰⁻⁷² The clinical importance of these differences is probably very small because recent comparative studies have failed to show differences in mortality between patients using norepinephrine plus

dobutamine and those using epinephrine⁷³ or norepinephrine versus dopamine.⁷⁴

Occlusive Mesenteric Ischemia

The incidence of asymptomatic splanchnic stenoses (also called *chronic splanchnic disease*) ranges between 8% and 70% in populations with other manifestations of atherosclerotic diseases. Three causes of vascular obstruction can be distinguished in chronic mesenteric ischemia: atherosclerosis, external compression by the diaphragm (celiac artery compression syndrome), and vasculitis. The largest group consists of patients with atherosclerosis. Coronary artery disease, cerebrovascular disease, peripheral arterial disease, and atherosclerotic disease of splanchnic vessels have many overlapping symptoms. The incidence of symptomatic occlusive splanchnic ischemia or chronic splanchnic syndrome is relatively low, with 4 to 5 cases per 100,000 persons yearly.⁷⁵ The incidence of acute splanchnic ischemia is low but increases sharply with age. A recent autopsy study showed that 1.2% of all deaths in patients over 80 years were caused by acute splanchnic ischemia.⁷⁶ The diagnosis was suspected in the minority of patients.⁷⁷

Risk factors of splanchnic atherosclerosis are comparable to those of other atherosclerotic diseases.⁷⁸ However, patients with splanchnic stenoses are less overweight, less diabetic, and less dyslipidemic and are often women.²³ Serial duplex ultrasonography showed progression of atherosclerotic stenoses in the visceral artery in approximately 20% of patients. This progression of lesions may be especially important in multivessel chronic splanchnic disease that carries a considerable risk for acute splanchnic infarction.⁷⁹

External compression by the arcuate ligament of the diaphragm is the predominant cause of single-vessel CA stenosis in young adults. Because they are otherwise healthy, these patients rarely will be seen at the intensive care.^{44,80}

Splanchnic vasculitis is a rare cause of ischemia and is usually an unexpected finding in patients operated for bowel perforation or bleeding. The main causes include periarteritis nodosa, systemic lupus erythematosus, and rheumatoid arthritis.

Multivessel Involvement

Most patients with significant stenoses in two or three of the main splanchnic vessels experience ischemic complaints.⁷⁵ Often, the typical presentation is no longer postprandial pain, altered eating habits, or weight loss. Although most patients experience typical complaints for many years, these complaints become less typical over time because the patients grow accustomed to the pain, and it becomes part of their

lives. Moreover, in the end stage of the disease, the pattern of complaints can become extremely atypical, with abdominal fullness or loss of appetite being the main complaint. Consequently, these patients may become severely cachectic and have a high risk of bowel infarction. A study reported bowel infarction in 30% and 60% patients with severe multivessel involvement after 1 and 4 years, respectively.⁷⁹ Prognosis is poor after the development of acute ischemia, and mortality rate increases to 80% after the development of bowel infarction.^{57,81} Therefore patients with unexplained pain, malaise, and/or weight loss who develop multivessel stenosis should be suspected of having end-stage ischemia.

Acute Mesenteric Ischemia

Acute splanchnic ischemia is defined as the sudden cessation of splanchnic mucosal perfusion. It should be suspected in patients with acute severe abdominal pain without any obvious diagnosis. Classically, the severity of pain is out of proportion to the (almost normal) physical findings. In elderly patients, acute splanchnic ischemia is accompanied with unexplained confusion. If left untreated, acute splanchnic ischemia results in bowel necrosis within 8 hours. This necrosis may remain clinically silent for several hours or days as long as the necrotic segment remains nonperfused and isolated from circulation.³⁰ Subsequently, MODS develops rapidly, followed by death, after reperfusion or perforation of the gangrenous bowel. Prognosis also depends on the cause of the infarction and ranges from approximately 32% in patients with venous thrombosis and 54% in patients with arterial embolism to 70% to 80% in patients with acute arterial thrombosis and nonocclusive ischemia. Overall survival after acute splanchnic ischemia has improved over the past four decades.⁸¹

Unexpected Splanchnic Ischemia in ICU Patients

As mentioned above, many patients with splanchnic stenoses either remain undiagnosed or experience no complaints. However, increased metabolic demand during major abdominal surgery or in inflammatory disorders like pancreatitis or cholecystitis may easily cause ischemia in patients with vascular stenoses. This is also observed in critically ill patients who are fed enterally and in patients in whom the burden of enteral feeding cannot be matched with adequate perfusion.⁸² Therefore ischemia should be considered in patients with a prolonged and complicated course of cholecystitis or pancreatitis. In these patients, CTA may detect a multivessel disease, and endovascular treatment may dramatically improve the clinical course within days.

Ischemic Colitis

Left-sided ischemic colitis is a well-defined, nonocclusive disorder in most patients and is associated with normal findings on an angiogram.^{56,57} Most cases of spontaneous ischemic colitis are not preceded by shock states and are diagnosed because of unexpected findings during endoscopy for unexplained abdominal cramps, diarrhea, or blood loss. Most patients with spontaneous left-sided ischemic colitis recover within days or weeks and rarely come to the attention of the intensivist.

Ischemic colitis after aortic surgery frequently develops in ICU patients (20%-27%) who undergo an open repair of a ruptured abdominal aneurysm and is associated with an average mortality rate of 48%.⁸³⁻⁸⁶ Sigmoid ischemia after elective aortic surgery has been reported in less than 2% of patients.⁸⁷ Risk factors of sigmoid ischemia include preoperative shock, significant blood loss, and persistent hemodynamic instability. The role of IMA ligation in the development of sigmoid ischemia is debatable.⁸⁴ Increased use of endovascular stent placement for both acute and elective treatment of abdominal aortic aneurysms has sharply decreased mortality rate, duration of ICU stay, and incidence of ischemic colitis after abdominal aortic aneurysm repair.⁸⁸ However, sigmoidoscopy should be performed when patients remain unstable for over 48 hours after aortic repair.

Left-sided ischemic colitis (discussed above) should be differentiated from right-sided ischemic colitis.^{89,90} The latter is associated with

significant impairment of SMA inflow, which in turn is associated with adverse prognosis, increased surgery rates, and increased mortality.⁹⁰ Right-sided ischemic colitis should be treated immediately to improve prognosis. We recommend urgent CTA to establish or rule out vessel stenoses, to rule out other pathologies, and to prevent a "blind" laparotomy.

TREATMENT

Nonocclusive Mesenteric Ischemia

Detection and Restoration of Regional Blood Flow

Rapid optimization of intravascular volume can be achieved by measuring gastric PCO₂ levels as the end point for fluid resuscitation.⁹¹⁻⁹³ However, results of small resuscitation trials involving tonometry have provided conflicting results.⁹⁴⁻⁹⁶ A recent meta-analysis involving 816 patients indicated that tonometry-guided treatment decreased mortality by 26%.⁹⁷ However, the different types of patients included in these studies (patients undergoing surgery, patients with trauma, and patients admitted to ICUs) and the small number of patients included per study may have limited the clinical significance of this conclusion.⁹⁸ An alternative might be to perform CTA to detect mesenteric vasoconstriction; however, data on experience with CTA are sparse.^{99,100}

Prevention of Reperfusion Damage

Treatment of reperfusion damage is a promising but clinically unproven approach. Some studies involving patients with early sepsis have shown that *N*-acetylcysteine is the best ROS scavenger that increases intracellular glutathione levels and NO release¹⁰¹ and improves hemodynamics¹⁰² and splanchnic ischemia.¹⁰³

Medication

Although avoidance of treatment with the splanchnic vasoconstrictors epinephrine and dopamine in patients with NOMI is appealing,^{104,105} recent studies have failed to show a difference between different catecholamines for resuscitation after fluid correction.^{73,74} Treatment with angiotensin-converting enzyme inhibitors to reduce angiotensin II levels was effective in animal studies¹⁰⁶ and only in one out of two clinical studies.^{107,108}

Feeding

Early institution of enteral nutrition may improve perfusion in addition to exerting salutary immunologic and nutritional effects. Mechanisms underlying mucosal vasodilatation due to enteric nutrition include autoregulatory responses driven by metabolic demands associated with food absorption in the lumen.¹⁰⁹ However, in extremely low or no-flow states, enteral nutrition can be very harmful and may induce infarction and therefore should be administered cautiously.^{82,110} This may explain the high rate of bowel infarction in the previously mentioned study on probiotic pancreatitis where rapid high-volume feeding was used as a standard procedure.⁶²

Chronic Occlusive Mesenteric Ischemia

Workup: Preoperative Feeding?

Patients with occlusive splanchnic ischemia and severe weight loss should not be fed preoperatively, enterally, or parenterally. Theoretically, increased body weight could improve immune status and postoperative recovery in patients with occlusive splanchnic ischemia. However, in patients with critically narrowed vessels, bowel blood flow cannot be increased to process nutrients. This may lead to increased ischemia or bowel infarction. Parenteral feeding should also be avoided in patients with severe CA and SMA stenoses. Double vascularization of the liver is compromised because both the portal vein and hepatic artery arise from these vessels. Parenteral feeding may lead to hepatic ischemia or bowel infarction because of intramesenteric shunting.⁵⁵ Patients with multivessel critical stenoses should be treated by

performing urgent revascularization, and feeding should be avoided until the blood flow is restored.

Treatment

Treatment of chronic mesenteric ischemia is based on the restoration of vascularization and is outside the scope of this chapter.

Acute and Acute-on-Chronic Mesenteric Ischemia

Patients with severe and/or progressive complaints and with multivessel stenoses should be treated urgently (Table 162-1). Immediate treatment should be indicated when signs of bowel infarction, including peritoneal symptoms, progressive leukocytosis, and elevated lactate or C-reactive protein level, are observed. These biomarkers have limited diagnostic value. However, in patients with established multivessel stenoses, an increase in the levels of these biomarkers is a potent indicator of ischemic damage. The treatment can be divided in six chronological steps.

TABLE 162-1 Summary of Treatment Options for Acute Splanchnic Ischemia

NONOCCLUSIVE MESENTERIC ISCHEMIA (NOMI)

- Exclude vascular occlusions by performing computed tomography angiography (CTA)
- Perform aggressive volume resuscitation, with normalized PCO_2 level as the end point
- Avoid alpha-adrenergic drugs when possible
- Administer intraarterial [superior mesenteric artery (SMA)] papaverine or prostaglandin E_1 in severe cases

ACUTE AND ACUTE-ON-CHRONIC SPLANCHNIC ISCHEMIA

- Administer intravenous fluids to restore intravascular volume
- Induce acid suppression (proton pump inhibitors)
- Avoid oral food intake
- Perform urgent CTA for diagnosis and revascularization planning
- Use heparins
- Induce revascularization within hours or days

Acute and Acute-on-Chronic Splanchnic Ischemia with Possible Bowel Infarction

- Assess bowel viability (after revascularization) and resect necrotic bowel; consider a second look

Postoperative Treatment

- Maintain optimal fluid status, and avoid alpha-adrenergic drugs when possible
- If abdominal complaints recur, perform CTA to rule out vascular occlusion; if vessels are patent, suspect reperfusion syndrome
- Initiate treatment with warfarin or thrombocyte aggregation inhibitors after the recovery of bowel mucosa

Treatment of Reperfusion Syndrome

- Stop oral food intake
- Initiate total parenteral nutrition for 2-5 weeks

ISCHEMIC COLITIS

Right-Sided (Ascending Colon) Ischemic Colitis

- Perform urgent CTA
 - a. In the presence of superior mesenteric artery (SMA) occlusion or stenosis, initiate a treatment similar to that for acute splanchnic syndrome
 - b. In the presence of a normal vasculature, initiate a treatment similar to that for left-sided ischemic colitis

Left-Sided Ischemic Colitis

- Initiate aggressive volume replacement, and avoid alpha-adrenergic drugs
- Consider performing bowel decompression
- Consider laparotomy and partial colectomy in the presence of
 - a. persistent sepsis, fever, and hemodynamic instability
 - b. proven ischemic colitis (by endoscopy) despite administering treatment for NOMI
 - c. diarrhea and protein loss for >14 days after surgery

1. Fluid Resuscitation and Metabolic Demand Reduction

Restoration of intravascular volume should be the first treatment because most patients show poor food and fluid intake before admission. Usually, 2000 to 4000 mL of crystalloid is infused every 24 hours depending on the age and clinical condition of patients. Reduction of metabolic demand can be achieved by avoiding enteral and parenteral feeding and by administering proton pump inhibitors that suppress acid secretion.

2. Assessment of Vessel Anatomy and Ischemic Damage

Urgent CTA should be performed in patients with suspected bowel infarction. CTA provides information on vessel anatomy, calcifications, and end organ damage such as portal gas, mucosal ischemia, bowel wall edema, or pneumatosis.²⁶ Results of CTA are essential for determining treatment options and strategies.

3. Revascularization

Angiography serves as technique for stenting of the CA or SMA or to remove SMA emboli. In patients with NOMI, papaverine (30-60 mg/h for a maximum of 4 hours) or prostaglandin E_1 (bolus 0.020 mg, 0.060 mg/h for up to 72 hours) should be administered by performing selective SMA catheterization to decrease arterial spasms.¹¹¹

Endovascular treatment is the preferred next step in patients with occlusive ischemia preferably before laparotomy.^{112,113} Various options are available for treating these patients partly because of the lack of solid clinical evidence for preferring one treatment over the other.¹¹⁴ The order of preferred options for treating patients with acute ischemia is as follows: (1) antegrade endovascular treatment, (2) retrograde operative mesenteric stenting (ROMS), (3) operative retrograde revascularization, and (4) operative antegrade revascularization.

Antegrade endovascular treatment by performing percutaneous transluminal angioplasty (PTA) with stent placement can be performed through the femoral artery in the groin or through the brachial artery. Presence of occlusions in the splanchnic vessels is not a contraindication for performing antegrade endovascular treatment as the first-line strategy.¹¹⁵ In our institution, 5-year secondary patency for both the CA and SMA is 95% (Fig. 162-4).¹¹⁶

ROMS is performed in patients who cannot undergo antegrade endovascular treatment. It involves performing a small laparotomy to identify and cannulate the outflow of the SMA. A catheter is then advanced into the aorta under manual and fluoroscopic control, and PTA and stenting of the occluded SMA tract are then performed.¹¹²

Operative retrograde revascularization can be performed with long bypasses from the iliac arteries or the distal aorta to either the common hepatic artery or the SMA outflow. The main disadvantage of this procedure is that the long meandering bypasses are associated with higher risk of kinking and thrombosis or stenoses, thus increasing the likelihood of occlusion. However, the operative burden associated with operative retrograde revascularization is lower than that associated with operative antegrade revascularization.

Operative antegrade multivessel autologous revascularization provides excellent long-term results with respect to patency and clinical response.^{21,117} The downside is that the operative burden is very high because of aortic clamping. Therefore it is only suitable for relatively young patients with a good clinical condition and life expectancy.

4. Assessment of Bowel Viability and Resection

Bowel viability should be assessed only after restoring blood flow. Only irreversibly damaged bowel should be resected. A routine "second look" procedure, which is performed 24 hours after the original operation, should be performed. This approach spares most of the bowel length, thus providing the patient with a better quality of life. Patients should be administered parenteral nutrition immediately after the procedure. Complete but adjusted¹¹⁸ enteral nutrition can be restored in patients with small bowel length of greater than 50 cm and with an

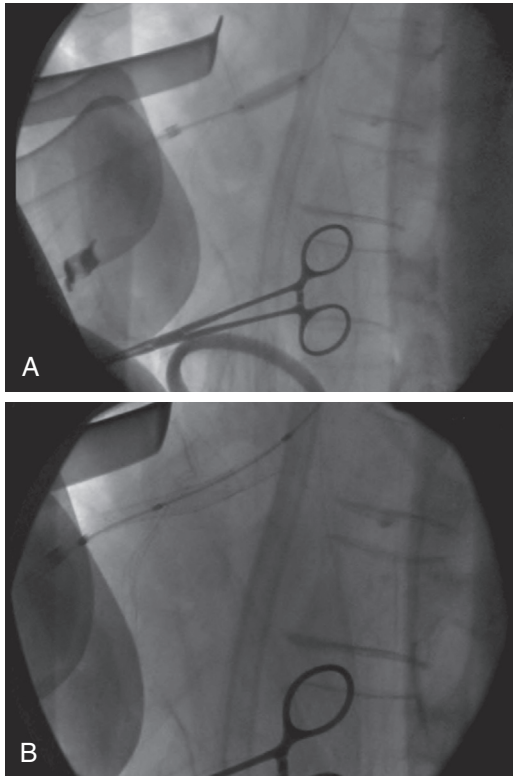


FIGURE 162-4 ■ Retrograde open mesenteric stent placement: the hybrid procedure. A superior mesenteric artery (SMA) and CA celiac artery (CA) occlusion was detected in a patient with imminent splanchnic infarction. Therefore standard endovascular stenting could not be performed. **(A)** After performing a small supraumbilical laparotomy, the outflow of the SMA was controlled. Retrogradely, a 5 French sheath was introduced into the SMA, and endovascular connection between the SMA outflow and the aorta was established under manual and fluoroscopic visualization. **(B)** Subsequently, PTA and stenting of the occluded trajectory of the SMA was performed. (From Blauw et al.¹¹²) PTA, percutaneous transluminal angioplasty; SMA, superior mesenteric artery

intact ileocecal valve or in patients with small bowel length between 50 and 100 cm and without ileocecal valve.¹¹⁹ The quality of life of these patients is relatively good and is comparable to that of hemodialysis patients.¹²⁰ Therefore revascularization and resection should be considered in patients who have relatively good health but with almost completely necrotic bowel and without the clear involvement of the stomach, duodenum, liver, and pancreas.

5. Treatment of Reperfusion Damage

Risk factors of reperfusion damage after revascularization include severe and long-standing multivessel disease, end-organ damage (mucosal ulceration), and continuous abdominal pain not associated with feeding. The typical course of events in reperfusion damage during splanchnic ischemia includes initial uneventful recovery, followed by sudden deterioration 2 to 5 days after the intervention. Recurrence of abdominal pain is the most common clinical presentation; however, gastric ulceration, massive ascites, and sometimes severe hypoalbuminemia and leukocytosis may also occur.

The first action should be to exclude stent or bypass occlusion by performing CTA or duplex ultrasonography. Four measures can be considered to limit reperfusion damage: (1) stop oral food intake, (2) initiate total parenteral nutrition, (3) induce acid suppression, and (4) provide sufficient intravenous fluids. Most patients recover within 2 to 6 weeks without any lasting complications.

6. Prevention of Reocclusion and Rethrombosis

Aggressive anticoagulation treatment is essential in all patients with bypasses of stents in critical areas. Heparin treatment is recommended until the patient becomes completely anabolic. Subsequently, heparin can be switched to acetylsalicylic acid (100 mg) and clopidogrel (75 mg) once daily or to warfarin if they are indicated for other reasons. Starting warfarin early may be hazardous as its absorption may be unpredictable, resulting in severe anticoagulation and severe GI bleeding events.

Ischemic Colitis

In most cases, left-sided ischemic colitis resolves spontaneously with only fluid resuscitation. Endoscopic bowel decompression should be considered if the colon is markedly dilated. Surgery is restricted to patients with transmural irreversible ischemia. Sigmoidoscopy should be considered after aortic surgery in patients with persistent hemodynamic instability lasting for over 48 hours. Right-sided ischemic colitis is an indicator of main vessel inflow stenosis.¹²¹ CTA should be considered in patients with right-sided ischemic colitis.

KEY POINTS

1. Nonocclusive mucosal or mesenteric ischemia (NOMI) is the result of blood flow redistribution following adaptation of the blood flow distribution in all types of circulatory stresses. It is a common disorder in patients admitted to intensive care units.
2. The first-line treatment of NOMI involves aggressive volume resuscitation and avoidance of alpha-adrenergic drugs. In severe cases of imminent bowel infarction, the second-line treatment should include intraarterial papaverine or intravenous prostaglandin E1.
3. In patients with severe NOMI and with imminent bowel infarction, computed tomography angiography (CTA) with 1-mm slices should be performed to exclude vascular stenoses and alternative pathology.
4. Splanchnic vessel stenoses are common but remain asymptomatic in most patients. In critically ill patients, endovascular reconstruction can be achieved in most cases even if asymptomatic stenoses may be the root cause of unimproved abdominal complaints.
5. Retrograde mesenteric stenting should be considered in patients who cannot undergo antegrade stenting before surgical revascularization.
6. Enteral and parenteral nutrition increases splanchnic perfusion and can exert detrimental effects. In addition, enteral and parenteral nutrition induces infarction in patients with highly decreased splanchnic blood flow because of splanchnic stenosis or severe shock syndrome. In these patients, nutrition should be withheld or should be initiated with utmost caution until the improvement of splanchnic perfusion through revascularization or improved hemodynamics.
7. Colonoscopy is the gold standard for diagnosing early mucosal ischemic colitis, and laparotomy is the gold standard for diagnosing transmural or gangrenous ischemic colitis.
8. Right-sided ischemic colitis is an indicator of significant large vessel inflow stenosis.

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DEFINITIONS

To date, the most common method to measure intraabdominal pressure (IAP) is the intravesical technique via a urinary catheter (often referred to as *urinary bladder pressure*).¹⁻³ The mean value of IAP in hospitalized patients is 6.5 mm Hg (range, 0.2-16.2 mm Hg).⁴ In critically ill patients, IAP is typically higher (12-16 mm Hg).⁵

Intraabdominal hypertension (IAH) is graded from I to IV based on IAP (grade I: 12-15 mm Hg; grade II: 16-20 mm Hg; grade III: 21-25 mm Hg; and grade IV: above 25 mm Hg).

Abdominal compartment syndrome (ACS) is defined as the presence of sustained IAP of greater than 20 mm Hg associated with attributable organ dysfunction.

Primary ACS is a condition associated with injuries or diseases in the abdominopelvic region.

Secondary ACS refers to a condition that does not originate from injuries or diseases in the abdominopelvic region.

DAMAGE CONTROL

Patients undergoing surgery for major bleeding are at risk for entering the "bloody vicious circle" of acidosis, hypothermia, and coagulopathy and, as a result, exsanguination. Prevention of this scenario is the rationale of damage control.^{6,7} Damage control has two goals: (1) quick control of bleeding and (2) prevention of further contamination from hollow viscous perforations. In this, the abdomen is temporarily closed without fascial approximation, and the patient is triaged to the intensive care unit (ICU) for resuscitation and correction of abnormal bloody vicious circle physiology. However, damage control has resulted in new challenges, including diagnosis and management of ACS and management of open abdomen and early multiple organ failure (MOF).

Abdominal Decompression

Traditionally, abdominal decompression has been achieved through a full midline laparotomy. Recently, other techniques such as transverse laparotomy, percutaneous drainage, and minimally invasive linea alba fasciotomy have been described as potentially useful methods in selected cases. Decompressive laparotomy can be performed in ICUs in extreme cases. However, it is generally preferred to be performed in operating rooms, especially when further intraabdominal procedures are anticipated.

HISTORICAL PERSPECTIVE

Studies on IAH have been performed for over 150 years.^{8,9,10} Results of these studies had little impact until pediatric surgeons in the 1950s recognized the fatal consequences of acutely closing large congenital abdominal defects. Silo closure with gradual reduction of abdominal defect was recommended to prevent fulminant organ failure.¹¹ In the 1980s, vascular surgeons described ACS after abdominal aortic aneurysm surgery and popularized the use high IAP as a criterion for re-exploration.¹ However, it was not until the 1990s, when trauma surgeons adopted the liberal use of the damage-control strategy, that sufficient number of patients survived to allow the characterization of this elusive complication.¹²⁻¹⁵ In addition, it was recognized in the

1990s that ACS occurred in a variety of scenarios such as extreme constipation,¹⁶ ovarian hyperstimulation,¹⁷ noninvasive ventilation,¹⁸ pancreatitis,¹⁹ and severe burns.²⁰

INTRAABDOMINAL PRESSURE MEASUREMENT

Clinical examination of the abdomen for monitoring IAP can provide inaccurate results.^{21,22} The intravesical technique involving the use of a standard urinary catheter is the most reliable and least invasive method for monitoring IAP.²³ The intravesical technique has been shown to correlate well with IAP measured directly using a laparoscopic insufflator.²⁴ The vesical route is more accurate for monitoring IAP than rectal and gastric routes.²⁴ Animal studies have shown that the pressure in the inferior vena cava correlates well with the vesical pressure but is more invasive.^{25,26} Several proprietary devices are available to intermittently monitor urinary bladder pressure. Unfortunately, IAP measurements are rarely obtained more often than every 4 hours because of logistic problems. These shortcomings have been overcome by developing and validating a continuous IAP measurement technique.²⁷

PATHOPHYSIOLOGY

The volume of the abdominal cavity is limited by its least tensile component, the fascia. Increased pressure can be due to an increase in the volume of abdominal contents or because of a decrease in the volume of the "container" (Table 163-1). After IAP increases to greater than 20 mm Hg, the abdominal cavity is on the steep portion of its pressure-volume curve, and as a result, small increases in content volume or decreases in cavity volume can cause dramatic increases in IAP. This is when close monitoring of IAP (preferably continuously) and organ dysfunction is essential for timely intervention.

PATHOPHYSIOLOGIC RESPONSE OF SPECIFIC ORGANS

Cerebral Perfusion

Increased IAP forces the diaphragm cephalad, thus increasing the intrathoracic pressure, which impedes venous return from the brain. This increases intracranial pressure (ICP) and consequently decreases the cerebral blood flow.²⁸⁻³⁰

Cardiac Function

Increased IAP impedes venous return to the heart, thus decreasing preload. Simultaneously, left ventricular afterload increases because of increased systemic vascular resistance. Increased intrathoracic pressure also increases right ventricular afterload, leading to right dilation with leftward displacement of the ventricular septum and impairment of left ventricular filling.³¹⁻³⁴ Low cardiac index (CI) is a typical finding associated with ACS. Low CI usually does not respond to fluid challenges; moreover, ongoing volume loading can lead to the "futile crystalloid cycle" (described below, see Fig. 163-1). An increase in CI in response to decompression is a predictor of outcome.⁵

Respiratory Function

Increased IAP pushes the diaphragm into the thoracic cavity, thus decreasing thoracic compliance. Therefore, increased airway pressure is required to restore the functional residual lung volume for oxygenation during mechanical ventilation.^{34,35} Airway pressure promptly decreases in response to abdominal decompression. However, this cannot be used to differentiate between survivors and nonsurvivors.⁵

| TABLE 163-1 Causes of Intraabdominal Hypertension and Abdominal Compartment Syndrome | |
|---|--|
| INCREASED ABDOMINAL CONTENTS | DECREASED ABDOMINAL VOLUME |
| Ascites | Reduction of large long-standing hernia |
| Hemoperitoneum | Direct closure of large, long-standing abdominal wall defect |
| Visceral edema | Circumferential abdominal wall burn |
| Abdominal packs | Continuous positive-pressure ventilation |
| Peritonitis | |
| Retroperitoneal edema (pancreatitis) | Retroperitoneal edema (pancreatitis) |
| Large pelvic and retroperitoneal hematoma | Large pelvic and retroperitoneal hematoma |
| Intestinal obstruction | |
| Ileus | |
| Gastric distention (esophageal ventilation) | |
| Abdominal aortic aneurysm | |
| Severe constipation | |
| Large abdominal tumor (chronic) | |
| Morbid obesity (chronic) | |
| Pregnancy (chronic) | |

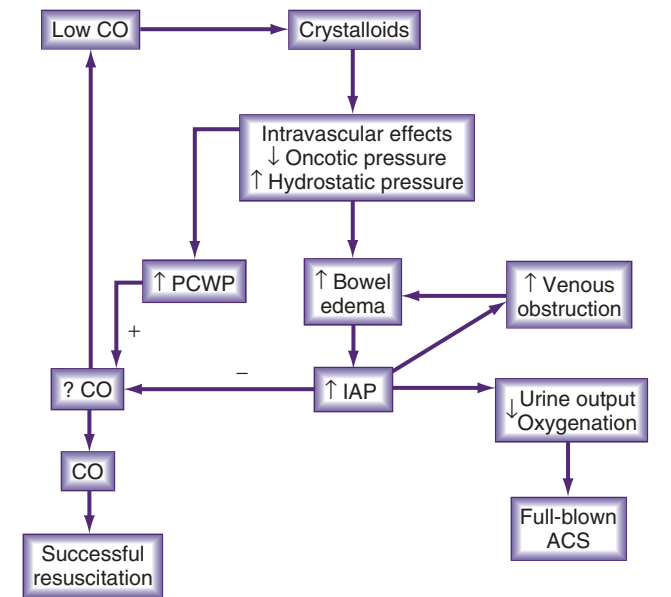


FIGURE 163-1 ■ Futile crystalloid preloading. ACS, abdominal compartment syndrome; CO, cardiac output; IAP, intraabdominal pressure; PCWP, pulmonary capillary wedge pressure; ↑, increased; ↓, decreased; +, positive effect; −, negative effect.

Monitoring of airway pressure is important during attempted primary fascial closure after laparotomy when ACS is a possible complication.

Renal Function

Oliguria or anuria is a typical sign of ACS. Mechanisms responsible for decreased renal function include direct compression of the renal parenchyma, decreased perfusion of the kidneys, and increased water and sodium retention due to the activation of renin-angiotensin system.³⁶⁻³⁸

Gut Function

Increased IAP impairs splanchnic perfusion by decreasing CI and by increasing splanchnic vascular resistance. Tissue ischemia can occur in severe cases.³⁹⁻⁴² Intestinal perfusion can be assessed objectively by performing gastric tonometry. Increased gastric regional partial pressure of carbon dioxide (PrCO₂) is an indicator of impaired abdominal visceral perfusion. Combined with IAP measurements, tonometry to identify increasing PrCO₂ is an excellent adjunct for identifying impending ACS.³ Moreover, the physiologic response to effective decompression is a prompt decrease in PrCO₂, reflecting gut reperfusion.⁵ Laboratory studies have shown that ACS induces gut ischemia and that decompression-induced reperfusion primes circulating neutrophils and releases cytokines into portal circulation. This causes acute lung injury, which is similar to that induced after hemorrhagic shock and resuscitation.^{43,44} Therefore, ACS decompression can serve as a “second hit” for MOF.⁴⁵

Extremity Perfusion

Increased IAP increases femoral venous pressure, increases peripheral vascular resistance, and decreases femoral artery blood flow by as much as 65%.⁴⁶

■ CLASSIFICATION

ACS can be classified based on its duration, presence or absence of intraperitoneal pathology, and cause of increased IAP (Table 163-2).

Acute Versus Chronic

The pathophysiologic responses described above are acute phenomena in critically ill patients. However, ACS can be present in certain clinical conditions with chronic IAH, such as morbid obesity, chronic constipation, and pregnancy.⁴⁷

| TABLE 163-2 Classification of Abdominal Compartments | |
|---|--|
| SYNDROME | |
| BASIS OF CLASSIFICATION | SUBCATEGORIES |
| Time frame | Acute Chronic |
| Relation to peritoneal cavity | Primary Secondary |
| Etiology | Trauma Burn Postoperative Pancreatitis Bowel obstruction Ileus Abdominal aortic aneurysm Oncologic Gynecologic |

Primary Versus Secondary

Primary ACS typically develops after a damage-control surgery with temporary abdominal closure.⁴⁸ As time progressed, intraabdominal bleeding and bowel edema (secondary to resuscitation) caused the volume of the intraabdominal contents to increase IAP, thus precipitating ACS. Primary ACS can also occur in patients who do not respond to nonoperative management of abdominal organ injuries because of bleeding.⁴⁹

Secondary ACS typically occurs in the setting of severe shock requiring massive resuscitation in the absence of intraperitoneal pathology or injury.³ Secondary ACS is more elusive, which delays its diagnosis.⁵⁰ Typical causes of secondary ACS are hypovolemic shock associated with multiple open extremity fractures, unstable pelvic fractures, penetrating chest injuries,⁵¹ and severe burns.^{52,53}

■ EPIDEMIOLOGY

Incidence

Because of variable definitions and patient populations, the reported incidence of ACS among high-risk patients with trauma who are undergoing laparotomy varies from 2% to 36%.^{15,54} A prospective study by Malbrain showed that the incidence of ACS in medical ICU patients was 2%.⁵⁵ Changes in treatment strategies also affect the incidence of ACS. For example, Meldrum et al.⁵⁶ and Balogh et al.³ studied similar traumatic shock populations, and both reported that the incidence of ACS was 14%. These two studies were performed 6 years apart. The earlier series by Meldrum only considered primary ACS; moreover, this series was performed when liberal use of the open abdomen was just initiated. The later series by Balogh reported that the abdomen was left open initially in almost all patients undergoing damage-control laparotomy and suggested that this was associated with decreased incidence of primary ACS. However, the previously unrecognized secondary ACS is now an equally prevalent clinical entity.

If IAH is used as a surrogate for ACS, the incidence is higher but similarly inconsistent. In surgical patients with different IAP cutoff points for defining IAH, the incidence varies from 33% to 81%.^{23,38} In medical patients, the incidence of IAH (IAH > 12 mm Hg) is only 18%.⁵⁵ Using a cutoff value of 20 mm Hg, Balogh and coworkers reported a 39% incidence in a cohort of patients who experienced severe traumatic shock.⁵⁷

Outcome

Full-blown ACS emerged in the mid-1990s as an epidemic in trauma centers worldwide and was closely linked to deaths associated with early fulminant MOF. With more timely diagnosis and treatment, more than 50% afflicted patients are now surviving this chronic critical illness.^{3,53}

■ PREDICTION AND DIAGNOSIS

Potential risk factors of ACS include severe hemorrhagic shock, high-volume crystalloid resuscitation, damage-control laparotomy, high injury severity score, and markedly elevated PrCO₂ level.^{42,58,59} Studies on secondary ACS have identified resuscitation fluid volume thresholds that warrant IAP monitoring. Maxwell et al. recommended that IAP should be monitored when resuscitation volume exceeds 10 L of crystalloid fluid or 10 units of packed red blood cells.⁶⁰ Ivy et al. suggested that the trigger to initiate IAP monitoring should be greater than 0.25 L/kg of crystalloid resuscitation.^{20,52} Biffl et al. reported that both these cutoffs are ineffective and recommended the following thresholds: 6 L of crystalloid fluid or ≥6 units of packed red blood cells in a 6-hour period in patients with a base deficit of greater than 10 mEq/L, especially when a vasopressor agent is required.⁵³

Multiple logistic regression analysis was performed using a prospective database of patients who experienced a major torso trauma

TABLE 163-3

Independent Predictors of Postinjury Primary and Secondary Abdominal Compartment Syndrome

| | ED MODEL | ICU MODEL |
|---------------|---|--|
| | INDEPENDENT PREDICTORS | INDEPENDENT PREDICTORS |
| Primary ACS | To OR < 75 min Crystalloids ≥ 3 L | Temp ≤ 34°C GAPCO ₂ ≥ 16 Hb ≤ 8/dL BD ≥ 12 mEq/L |
| Secondary ACS | Crystalloids ≥ 3 L No urgent surgery PRBC ≥ 3 units | GAPCO ₂ ≥ 16 Crystalloids ≥ 7.5 L UO ≤ 150 mL |

ACS, abdominal compartment syndrome; BD, arterial base deficit; CI, confidence interval; ED, emergency department; GAPCO₂, carbon dioxide gap; Hb, hemoglobin concentration; ICU, intensive care unit; OR, operating room; PRBC, packed red blood cells; Temp, temperature; UO, urine output.

and who underwent standardized shock resuscitation.⁵ An emergency department (ED) model (at 3 hours in patients discharged from the ED) and an ICU model (at 6 hours in patients admitted to the ICU) were developed. Table 163-3 lists independent risk factors of primary and secondary ACS that were determined using the ED and ICU models. A receiver operator characteristic curve of 0.88 was a predictor of ACS in the ED model and of 0.99 was a predictor of ACS in the ICU model.⁵⁶

■ TREATMENT

Nonsurgical Methods

Treatment of early organ dysfunction by traditional ICU interventions is often necessary in patients with impending ACS; however, these interventions may aggravate underlying pathophysiologies. For example, ventilator strategies for increasing mean airway pressure to improve oxygenation directly increase IAH by pushing down the diaphragm. In addition, increased intrathoracic pressure impedes venous outflow from the abdominal cavity. This promotes gut edema with ongoing crystalloid resuscitation. Seminal studies performed in the mid-1990s advocated volume loading to improve low urine output in patients with moderately high IAP. Increased IAP falsely elevates central venous pressure, resulting in the underestimation of ventricular end-diastolic volume. Thus volume loading was recommended to increase preload for improving CI and for increasing renal perfusion.⁶¹ Although this makes physiologic sense, close monitoring in a standardized resuscitation protocol identified this to be ineffective in increasing CI, and if volume loading continued, it would precipitate full-blown ACS. This is referred to as the *futile crystalloid cycle* (Fig. 163-1).^{57,62}

Theoretically, other nonsurgical interventions may exert beneficial effects; however, the efficacy of these interventions is unproven.⁶³ Use of colloids and albumin may mobilize interstitial fluids into the vascular space, and use of muscle relaxants might exert a salutary effect by decreasing the tension in the abdominal wall.^{52,64}

Percutaneous Methods

If ACS is caused by acute or chronic fluid collection, its symptoms can be relieved by initiating percutaneous drainage. Case reports have described successful drainage of abdominal fluid in burn patients with secondary ACS and drainage of blood in patients with nonoperatively managed liver injuries.⁶⁴⁻⁶⁷

Surgical Decompression

Surgical decompression by opening the midline fascia along its full length remains the primary recommended intervention. Almost all reports have described a very good physiologic response to decompression. However, this does not necessarily translate into better outcomes. The best predictors of survival are postdecompression improvement in CI and urine output.^{5,51} The decision to perform surgical decompression is a difficult one because it results in an open abdomen that is associated with numerous complications. Case series have shown that early decompression is associated with better outcomes. However, patients with ACS are critically ill, and their intrahospital transfer can exert detrimental effects. Thus, if no other intraabdominal surgical intervention is anticipated, bedside decompression can be performed in the ICU. More recently, alternatives to midline laparotomy, such as transverse laparotomy and linea alba fasciotomy, were described. These approaches were popularized in cases of severe acute pancreatitis.⁶⁷ The (subcutaneous) linea alba fasciotomy can prevent peritoneal contamination in selected pancreatitis cases where laparotomy is not required, only reduction of IAP.^{68,69}

MANAGEMENT OF THE OPEN ABDOMEN

Decompressive laparotomy results in an open abdomen, and temporary abdominal closure is performed to keep the fascia open. Several methods (towel clips, Bogota bag, synthetic mesh, vacuum-assisted closure, Velcro patch, and zipper) are available. The key goals are to prevent evisceration, allow swelling of abdominal contents, control peritoneal fluids, prevent contamination, and preserve the fascia for a possible later closure. Ongoing experience with a vacuum-assisted closure technique has provided very promising results. Moreover, use of the vacuum-assisted closure technique has dramatically improved the management of the open abdomen.^{70,71,72}

ANNOTATED REFERENCES

Balogh Z, McKinley BA, Cox CS Jr, et al. Abdominal compartment syndrome: the cause or effect of postinjury multiple organ failure. *Shock* 2003;20:483-92.

This article summarizes present knowledge on postinjury ACS including epidemiology, prediction, pathophysiology, individual organ responses, response decompression, and ongoing research.

Balogh Z, McKinley BA, Holcomb JB, et al. Both primary and secondary abdominal compartment syndrome can be predicted early and are harbingers of multiple organ failure. *J Trauma* 2003;54:848-61.

This is a comprehensive epidemiologic paper describing postinjury primary and secondary ACS that occurred in major torso trauma patient arriving with severe bleeding and subjected to standardized state-of-the-art resuscitation.

References for this chapter can be found at expertconsult.com.

KEY POINTS

1. It is essential to distinguish between intraabdominal hypertension (IAH) and abdominal compartment syndrome (ACS) through the early identification of organ dysfunctions.
2. Intraabdominal pressure (IAP) should be monitored during shock resuscitation requiring ongoing volume loading regardless of the cause of the shock (e.g., burn, sepsis, and trauma).
3. At present, the safest and most feasible method to monitor IAP is the intravesical technique.
4. ACS can occur without abdominal pathology or injury (secondary ACS).
5. To date, the best characterized types of ACS are postinjury ACS, burn-associated ACS, and pancreatitis-associated ACS.
6. Outcomes associated with ACS are very poor even after performing early decompression. Prevention, prediction, and surveillance are the keys to achieve successful management of ACS.
7. Postinjury primary and secondary ACS can be accurately predicted 3-6 hours after hospital admission through adequate monitoring.
8. Awareness of the use of excessive crystalloids during shock resuscitation has decreased the incidence of ACS.
9. Outcomes with open abdomen are improving with the use of vacuum-assisted closure techniques.

Ivy ME, Atweh NA, Palmer J, et al. Intra-abdominal hypertension and abdominal compartment syndrome in burn patients. *J Trauma* 2000;49:387-91.

This is a prospective evaluation of patients with large burns, in whom secondary ACS is a frequent complication. The authors recommend IAP measurements after 0.25 L/kg crystalloid resuscitation and report a high success rate using conservative management of ACS in burn patients.

Malbrain ML. Abdominal pressure in the critically ill: measurement and clinical relevance. *Intensive Care Med* 1999;25:1453-8.

This prospective clinical study describes the incidence of intraabdominal hypertension and ACS in a general medical ICU.

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■ EPIDEMIOLOGY

Compartment syndrome occurs whenever the tissue pressure within a limited space of the body reaches the point where the circulation, nerve function, and muscle function of that space are compromised. For compartment syndrome to occur, the body compartment should be enveloped by fascia that prevents inner tissue expansion, and there should be at least one cause of increased tissue pressure present, either externally or internally.

The German physician Dr. Richard Von Volkmann first described the late sequelae of compartment syndrome in 1881.¹ He wrote: “The paralyzes and contractures that follow tightly applied bandages, chiefly in the forearm and hand, and less often in the lower extremity, are to be viewed as ischemic. They arise from the arterial supply being interrupted for too long.” Volkmann’s ischemic muscle contractures of untreated forearm compartment syndrome are named after him (Fig. 164-1). Later, in 1912, Wilson first described exertional compartment syndrome,^{1a} and Mayor, in 1956, first reported chronic exertional compartment syndrome in a football player.^{1b} Since then, various cases of compartment syndrome have been reported in the literature, and the pathophysiology and treatment options have been discussed. Compartment syndrome has been reported in a wide variety of clinical conditions including tetanus, meningococcemia, malignant hyperthermia, frostbite, horseback riding, and childbirth.²⁻⁶ Typically, it occurs after traumatic events, most commonly those involving fractures or vascular trauma with subsequent ischemia-reperfusion injuries. The most commonly affected body compartments are lower extremity compartments. Recent literature describes an increasing incidence of around 2% in severely injured patients.⁷⁻⁹ This occurs with developments in shock resuscitation in a population of patients with otherwise noninjured extremities. The incidence of compartment syndrome varies depending on the patient population studied and the etiology of the syndrome. In a group of patients with leg pain, according to Qvarfordt and colleagues, 14% were noted to have anterior compartment syndrome.¹⁰ Compartment syndrome was also seen in 1% to 9% of leg fractures.¹¹

Common locations of compartment syndromes are in the upper and lower limbs. The most commonly affected are the four compartments of the lower extremity (anterior, lateral, superficial posterior, and deep posterior), followed by two compartments of the forearm (volar and dorsal). Other compartments that may be affected are the deltoid and biceps compartments of the arm, interosseous compartments of the hand, gluteal compartment of the buttock, quadriceps compartment of the thigh, and interosseous, medial, central, and lateral compartments of the foot.¹²⁻¹⁵

The etiology of compartment syndrome varies and can be divided into three major groups: decreased compartmental volume, increased compartmental content and therefore pressure, and externally applied pressure. There are probably more than 40 causes that fit into one of these groups. Common causes in critical care surgical cases are presented in Table 164-1.¹⁶

The most common causes of compartment syndrome are categorized based on increased compartmental content. The pathophysiologic mechanism of bleeding is easy to understand. Most commonly, bleeding is caused by trauma, but recently, more reports of atraumatic bleeding due to wide use of warfarin, low-molecular weight heparins, or recombinant tissue plasminogen activator (rtPA) have been reported.¹⁷⁻¹⁹

Increasing volume of blood in a space limited by noncompliant fascia results in an exponential rise in intracompartmental pressure. Postischemic swelling or reperfusion injury is more complex since it causes the so-called double ischemic insult. Initial ischemic insult from any cause leads to abnormal function of all tissues including nerves, muscles, and capillaries. This results in abnormalities of neuromuscular function; this is the *first insult*. Increased permeability after the relief of initial ischemia leads to postischemic swelling and subsequently increased compartmental volume and pressure. This leads to the development of compartment syndrome, which causes additional injury to neuromuscular function; this is the *second insult*. This process has clinical consequences. The classic physical examination in patients with reperfusion injury can be unreliable due to loss of motor and nerve function.^{16,20,21}

■ CLINICAL PRESENTATION

Most compartment syndromes in patients who are able to cooperate can be diagnosed by a clinical examination. The most common clinical signs found in the literature are the classic 5 P’s: pain (out of proportion), pulselessness (or weak pulse), pallor, paralysis (numbness and loss of motor function), and pressure (swelling and tenseness of compartment). Occasionally, poikilothermy (cold extremity) is also included (Fig. 164-2, A). These signs are a consequence of increased intracompartmental pressure and loss of various tissue functions. Other signs include skin edema and blisters, swelling, and subcutaneous blood suffusions (see Fig. 164-2, B).

To make the diagnosis, there must first be evidence of increased intracompartmental pressure. If so, these signs do not occur simultaneously but develop with time. One of the first signs is a swollen or tight compartment in combination with severe pain that is out of proportion to the injury and is not relieved by typical analgesia. Other signs present late and often, when present, represent irreversible damage to soft tissues. There are numerous other pathophysiologic events that can cause a similar clinical picture. In fact, a large meta-analysis of studies comparing clinical signs with the development of acute lower extremity compartment syndrome showed a sensitivity of 13% to 19%, specificity of 97%, positive predictive value of 11% to 15%, and negative predictive value of 98%.²² Thus, the absence of this sign rules out compartment syndrome, but the presence rarely confirms the correct diagnosis.

Nevertheless, clinical observation of the suspected compartment is what is recommended since the progress of the symptoms over hours is what should be noted first before making a definitive diagnosis and initiating definitive treatment. In traumatic cases, careful observation is required in open fractures as well. Although early surgery is usually indicated in this group of patients, they can still present with compartment syndrome. One recent animal study has confirmed the necessity of careful monitoring of both open and closed tibial fractures.²³ A useful tool for such monitoring could be a simple sheet with notes about date, time, location, pain level, and motor and sensory testing. To do this, one must know the anatomic position of various compartments and their vascular and nerve content. An example of a simple screening form of the most commonly observed acute lower extremity compartment is shown in Figure 164-3.²⁴ To focus on this relatively rare syndrome and prevent missed diagnoses, more complex systems for monitoring and recognition have been developed in some institutions,



FIGURE 164-1 ■ Dr. Richard Volkmann. (Courtesy of the United States National Library of Medicine, Portrait no. 6859.)

| TABLE 164-1 | Most Common Etiology of Increased Compartment Pressure in Critical Care Surgery |
|---------------------------------|--|
| Decreased compartmental volume | Application of excessive traction due to fracture immobilization Closure of fascial defects after trauma |
| Increased compartmental content | Intracompartmental bleeding due to fractures, vascular injury or bleeding disorders Increased capillary filtration in reperfusion after ischemia, embolectomy, soft tissue trauma, burns, fracture fixation |
| Externally applied pressure | Tight immobilization of fractures Lying on limb |

Adapted from Matsen FA. Compartmental syndromes. New York: Grune & Stratton, 1980.

with better recognition and outcomes.²⁵ In order to improve screening in special groups of patients with various etiology are described, where this condition occurs more often. In a large review study, stepwise logistic regression identified the presence of vascular injury, need for PRBC transfusion, male gender, open fracture, elbow or knee dislocation, GSW, ISS greater than or equal to 16, and age less than 55 years as independent predictors for the need for extremity fasciotomy.²⁶ Several statistically significant predictors of relevant compartment syndromes following surgical reperfusion were found, including lactate, uric acid, transcutaneous oxygen pressure, bilirubin, intrafascial pressure, and serum myoglobin.²⁷

■ **DIAGNOSIS**

To make a diagnosis of compartment syndrome, we must have evidence of increased tissue pressure, inadequate tissue perfusion, and loss of tissue function. When all three factors are present, the diagnosis may be made with assurance; when one or more of these factors are absent,



FIGURE 164-2 ■ A, A patient with right lower extremity compartment syndrome due to isolated tibial fracture. On clinical presentation, pain, swelling, and inability of dorsal flexion of the toe were noted. **B,** Another patient with left lower extremity compartment syndrome after popliteal artery tear and revascularization in combination with proximal tibial fracture, was treated with external fixation. A few hours later after initial treatment there are obvious signs of developing compartment syndrome with swelling, skin discoloration, function loss, and fracture blisters.

the diagnosis is less accurate. Evidence of increased tissue pressure may include patient complaints of tightness or pressure in the involved area. By palpation, a physician may perceive tenseness of the compartmental envelope.²⁸

Evidence of inadequate perfusion of local tissue pressure may include the symptom of pain out of proportion to what would be anticipated from the clinical situation. Increasing analgesia requirements in a properly immobilized leg should raise suspicion. Pain on a passive stretch of the intracompartmental muscles is another useful indication of increased pressure, especially if the muscles have not been injured. Reduced peripheral pulses are very late signs of compartment syndrome; in fact, studies have shown normal pulses with Doppler signals in otherwise severely elevated intracompartmental pressures.

| Acute Lower Extremity Compartment Syndrome Screening Form | | | | | | | | | | | | | | |
|---|--------------|--|---------|----------|----------|----------|--------------|----------|----------|----------|----------|----------|----------|--|
| Start Date: ____/____/____ Start Time: _____ | | CLINICAL DIAGNOSES | | | | | | | | | | | | |
| Increased tissue pressure / swelling | | YES / NO | | | | | | | | | | | | |
| Pain | | Assess according to scale from 1 to 10 | | | | | | | | | | | | |
| | | Calf Pain - Calf pain at rest PPSF - Pain with passive stretch, foot in plantarflexion PPSE - Pain with passive stretch, foot in extension/dorsiflexion | | | | | | | | | | | | |
| Neurologic Exam - Motor | | Strength | | | | | Scale | | | | | | | |
| | | DPN - Deep Peroneal Nerve Movement against gravity with full resistance | | | | | 6 | | | | | | | |
| | | DPN-M Foot dorsiflexion Movement against gravity with some resistance | | | | | 5 | | | | | | | |
| | | TN - Tibial Nerve Movement against gravity only | | | | | 4 | | | | | | | |
| | | TN-M Foot plantar flexion Movement with gravity eliminated | | | | | 3 | | | | | | | |
| | | Visible/palpable muscle contraction | | | | | 2 | | | | | | | |
| | | Without movement, no contraction | | | | | 1 | | | | | | | |
| Neurologic Exam - Sensory | | Scale | | | | | | | | | | | | |
| | | DPN Deep Peroneal Nerve Touch Sensation | | | | | 3 | | | | | | | |
| | | DPN-S 1 st to 2 nd toe web space Normal | | | | | 2 | | | | | | | |
| | | TN Tibial Nerve Diminished | | | | | 1 | | | | | | | |
| | | TN-S Sole Absent | | | | | | | | | | | | |
| <i>If unable to assess – write N/A</i> | | | | | | | | | | | | | | |
| Left Right | Initial exam | Exam 4h | Exam 8h | Exam 12h | Exam 16h | Exam 20h | Exam 24h | Exam 28h | Exam 32h | Exam 36h | Exam 40h | Exam 44h | Exam 48h | |
| Date | | | | | | | | | | | | | | |
| Time | | | | | | | | | | | | | | |
| Swelling | | | | | | | | | | | | | | |
| Calf Pain | | | | | | | | | | | | | | |
| PPSF | | | | | | | | | | | | | | |
| PPSE | | | | | | | | | | | | | | |
| DPA | | | | | | | | | | | | | | |
| PTA | | | | | | | | | | | | | | |
| DPN-M | | | | | | | | | | | | | | |
| DPN-S | | | | | | | | | | | | | | |
| TN-M | | | | | | | | | | | | | | |
| TN-S | | | | | | | | | | | | | | |
| YOUR Hospital Name | | | | | | | | | | | | | | |
| Your Department Name | | | | | | | | | | | | | | |
| Acute Lower Extremity Compartment Syndrome Screening | | | | | | | | | | | | | | |
| Patient Sticker | | | | | | | | | | | | | | |

FIGURE 164-3 ■ An example of a screening form for acute lower extremity compartment syndrome observation. (Kosir R, Morre FA, Selby LH, et al. Acute lower extremity compartment syndrome (ALECS) screening protocol in critically ill trauma patients. J Trauma. 2007;63:268–275.)

Arterial flow is rarely compromised in elevated tissue compartment pressures. On the other hand, diminished pulses could be a result of other causes (e.g., vascular lesions), and, in combination with reperfusion injury, could also lead to the development of compartment syndrome.²⁸

Evidence of abnormal tissue function includes weakness of the intracompartmental muscles and nerves, including sensory branches, leading to hypoesthesia. Both nerve and muscle function may be altered by direct injury; therefore, evidence of progressive loss of function over time may be a more reliable sign.²⁸

To summarize, in awake and cooperative patients who can be reexamined frequently, the diagnosis of compartment syndrome is associated with the following findings:

1. Pain out of proportion to what is anticipated from the clinical situation
2. Weakness of the muscles in the compartment
3. Pain on a passive stretch of the muscles in the compartment
4. Hypoesthesia in the distribution of the nerves coursing through the compartment
5. Tenseness of the compartmental envelope

Since some clinical signs progress over time, the clinical decision making can be challenging.^{12,30-32} Especially in critically ill patients who are unable to cooperate due to head trauma, sedation, or even neuromuscular blocking drugs, the diagnosis cannot be made based on the clinical examination alone.²⁴ In the pediatric population, compartment syndrome does not always present classically, making clinical diagnosis uniquely challenging.³²

Although the clinical examination should be a cornerstone of the diagnosis of compartment syndrome, it has the disadvantage of being subjective and requiring patient cooperation.^{12,22,33} Therefore, tissue pressure measurement should be performed to assist in establishing a diagnosis so that immediate treatment can be initiated. The normal compartmental interstitial tissue pressure is around 5 mm Hg. Capillary blood flow becomes compromised at 20 mm Hg, and pain develops at pressures between 20 and 30 mm Hg. A tissue pressure of more than 45 mm Hg has been reported to be usually associated with compartment syndrome, and a pressure of more than 60 mm Hg can confirm the diagnosis.³⁴⁻³⁶ However, the tolerance of tissues for increased pressure may be reduced by other factors, such as arterial occlusion, limb elevation, and shock.^{35,37} In these conditions, compartment syndrome may occur at significantly lower interstitial pressures. According to the arteriovenous gradient theory, the local blood flow (LBF) depends on the pressure gradient between arteries (Pa) and veins (Pv) and local vascular resistance to flow (R).

This is described by the formula:

$$\text{LBF} = (\text{Pa} - \text{Pv}) / \text{R}^{38}$$

LBF should be maintained to deliver enough oxygen to the tissues. According to the above relationship, increased resistance that correlates with interstitial pressure is not the only factor that reduces local blood flow. The arterial pressure is also important, whereas venous pressure is somehow related to interstitial pressure. Increasing interstitial pressure also increases venous pressure and furthermore decreases blood flow.

Because tolerance of tissues to increased intracompartmental pressure varies among different individuals and as there are more factors that influence LBF, only one isolated measurement of interstitial pressure may not be enough to diagnose compartment syndrome.³⁹ For example, higher compartment pressures may be necessary before injury occurs to peripheral nerves in patients with systemic hypertension,³⁵ while compartment syndrome may develop at lower pressures in those with hypotension and/or peripheral vascular disease.^{37,40} It has been proposed that the difference between diastolic pressure and intracompartmental pressure is a better marker for compartment syndrome. ΔP is calculated as follows: $\Delta P = \text{DBP (diastolic blood pressure)} - \text{IP (interstitial pressure)}$, and values greater than 30-35 mm Hg suggest compartment syndrome, but a specific threshold does not exist.⁴²⁻⁴⁵

There are numerous methods of tissue pressure measurement.⁴⁶⁻⁴⁹ The most commonly used are commercial handheld pressure monitors (e.g., the Stryker™ device), a simple needle manometer system (Whitesides' technique), and the needle, wick, or slit catheter techniques. The question is accuracy since there are reports that an arterial line manometer is the most accurate device.⁵⁰ The slit catheter, side-ported bevel-tipped needle, or an 18-gauge needle, when appropriately used with current electronic transducer monitoring, may be used clinically with confidence.⁵¹ The arterial line manometer device has an additional advantage of being able to monitor pressure continuously. This is

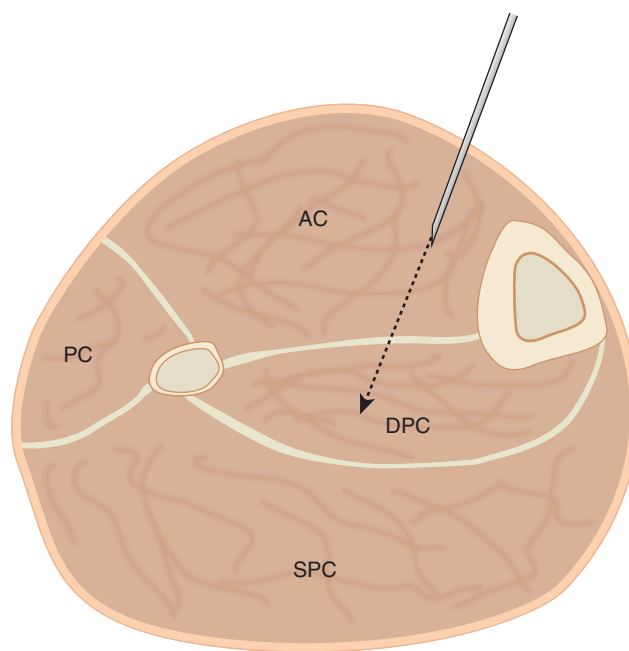


FIGURE 164-4 ■ Example of pressure measurement in the lower leg. Cross-section shows anatomic compartments and needle placement first in the anterior compartment and then proceeding into the deep posterior compartment. AC, anterior compartment; DPC, deep posterior compartment; PC, peroneal compartment; SPC, superficial posterior compartment.

reported to be useful in tibial diaphyseal fractures, where the estimated sensitivity and specificity of continuous pressure monitoring is high and continuous monitoring should be considered.⁵² Independent of the method used to measure compartment pressures, accuracy depends upon proper calibration of the measuring device and placement of the needle or pressure sensor at the level of the injured compartment. The principle of tissue pressure measurement in the case of acute lower extremity compartment syndrome is shown in Figure 164-4.

Use of near-infrared spectroscopy for detection of low tissue oxygenation and, therefore, the development of compartment syndrome is controversial. It has been reported as a useful noninvasive tool in diagnosing compartment syndrome after surgical revascularization of lower limb ischemia and also in traumatically injured patients; subsequent studies did not prove its utility in injuries due to severe edema of the soft tissues, and it cannot measure Sto_2 inside the muscle compartment.^{30,44,53-60}

In recent animal research, the role of intramuscular glucose and partial pressure of oxygen for detecting compartment syndrome has been evaluated. Intramuscular glucose concentration and partial pressure of oxygen measured with commercially available probes rapidly identified muscle ischemia with a high sensitivity and specificity after an experimentally induced compartment syndrome in an animal model.⁶²

In establishing a diagnosis of compartment syndrome, other causes of pain-producing symptoms have to be ruled out or confirmed, or a cause of elevated intracompartmental pressure should be determined. When facing traumatic injuries, a workup for rhabdomyolysis (creatinine phosphokinase [CPK], renal functions, urinalysis, and urine myoglobin) should be considered. In a group of patients with tibial fractures with or without compartment syndrome, a model combining maximal CPK level greater than 4000 U/L, maximal chloride level greater than 104 mg/dL, and minimal BUN level less than 10 mg/dL had a 100% association with compartment syndrome (CS).⁶³ Extremity x-ray or CT scans can confirm the presence of a fracture. MRI or

ultrasonography can show muscle tears. Doppler ultrasonography or arteriography can detect vascular abnormalities.

MANAGEMENT

The objective of treatment of compartment syndrome is to minimize deficits in muscular and neurologic function by promptly restoring LBF. Certain nonoperative measures may be effective, such as eliminating external pressure and maintaining local arterial pressure. When there is external pressure that causes compartment syndrome, such as tight casts, it is essential to release the envelope immediately (remove and exchange for a noncircular splint) when there is only one symptom or sign present. Usually, this is pain and is most often observed in patients with fracture splints several hours after treatment. Restoration of normal limb perfusion has priority over closed fracture treatment, and this can be postponed until perfusion returns to normal. Prior to resorting to operative methods for reducing tissue pressure, it is important to consider improvement of LBF if it has been reduced by shock, peripheral vascular disease, or elevation of the limb above the heart. All causes of systemic hypotension should be treated. Limb elevation should be avoided because it lowers local arterial pressure and does not help in reducing swelling.⁶⁴ Use of vasodilating drugs or sympathetic blockade appears to be ineffective because, in this condition, local maximal vasodilatation is already present. The use of phosphodiesterase inhibitors in experimental animal models caused modulation of compartmental pressures.⁶⁵ In a large study on trauma patients with isolated arterial injury, early anticoagulation with heparin was found to reduce the incidence of compartment syndrome without significant bleeding as a consequence.⁶⁶ Carbon monoxide-releasing molecule-3 displays a potent protective/antiinflammatory action in an experimental model of compartment syndrome, suggesting a potential therapeutic application for patients at risk of developing compartment syndrome.⁶⁷

The primary goal of treating compartment syndrome is to decrease intracompartmental pressures. Surgical decompression of all limiting envelopes is the gold standard of treatment, indicated in the presence of a characteristic clinical picture of compartment syndrome in a cooperative patient. When the clinical examination is unreliable or difficult to obtain, pressure measurement should be obtained, where either pressure should not exceed 45 mm Hg or ΔP should not be below 30 mm Hg.

Standard treatment involves a long skin incision and fasciotomy of all involved compartments and debridement of obvious nonviable tissue. Usually, this procedure is performed under general or spinal anesthesia. Bedside fasciotomy under local anesthesia has been described in select cases to be feasible and reliable.⁶⁸ Fasciotomy should be performed without a tourniquet to avoid prolonging ischemia and to permit the surgeon to assess the degree of viability and restoration of blood flow. The skin is incised through the entire length of the involved compartment. There is obvious muscle bulging observed in true compartment syndrome (Fig. 164-5). Only obvious necrotic muscle should be removed because the tissue may have the potential for reperfusion and recovery. The sign of contractility with electrostimulation should not be used initially. After fascial release, postischemic swelling should be anticipated; therefore, the skin should be left open and the wound temporarily closed with a patch of compliant artificial temporary skin closures. If release of the compartment is not complete, “rebound” compartment syndrome may occur.

After surgical decompression and temporary skin closure, sterile dressings are applied and the extremity is usually splinted in a functional position. In the presence of fractures, one should consider fixation with external fixators, rarely with plates or intramedullary nails. This stabilization is performed immediately after fascial decompression and greatly facilitates later care of the wound, limb, and fracture. Passive stretching exercises are performed to maintain range of joint motion. Skin closure may usually be performed 3-5 days after surgical decompression, usually by a mesh graft and rarely by direct suturing (Fig. 164-6). At that time, additional debridement of nonviable tissue can be performed. Fascial closure is not recommended because this



FIGURE 164-5 ■ The patient in Figure 164-2A after fasciotomy of the anterior and peroneal compartment and external fixation of the tibial fracture. Note obvious muscle bulging after release of fascial compartments. Direct skin closure was not possible.



FIGURE 164-6 ■ Cosmetic result of the lower extremity compartment syndrome after mesh grafting of the lateral compartment.

requires closure under tension and can lead to re-development of compartment syndrome. Muscle hernia is left behind and should be large enough to not cause additional late problems. When an optimal cosmetic result is desired, one may progressively approximate the wound edges over 7-14 days with sutures to achieve direct skin closure.

Negative pressure wound care closure devices can be useful in the management of fasciotomy wounds. Negative pressure decreases wound edema, facilitates approximation of the skin edges, enhances LBF, promotes granulation tissue, and decreases bacterial colonization. Conversely, in one animal study, negative pressure may be harmful to skeletal muscle after compartment syndrome.⁶⁹ One recent randomized study compared vacuum-assisted closure (VAC[®]) with the shoelace technique. Both techniques were safe, reliable, and effective methods for closure of leg fasciotomy wounds. VAC[®] required a longer time for definite wound closure and was reported to be far more expensive than the shoelace technique, especially when additional skin grafting was required.⁷⁰ In retrospective analyses, negative pressure led to significantly higher rates of complete skin closure and decreased time to skin closure.^{71,72} Hyperbaric oxygen as an adjunct to management following fasciotomy is reported in some case reports and animal studies, but there is a lack of evidence suggesting that this is advantageous over current practices.⁷³⁻⁷⁷

FASCIOTOMY

Fasciotomy depends on the underlying condition or mechanism that caused compartment syndrome. The length of the lower extremity skin incisions has been debated for a long time. Minimal skin incisions with more extensive fascial incisions could place the patient at risk of recurrent compartment syndrome.⁷⁸⁻⁸⁰ The degree of muscle swelling after reperfusion cannot be predicted, and peak edema occurs several hours after surgery.

Fasciotomy of the Upper Extremity

The upper extremity is anatomically divided into the brachium, antebrachium, and hand. Each of the anatomic segments has a different number of compartments with various muscle functions. Techniques for release of these compartments have to be discussed separately, and combined fasciotomy is shown in [Figure 164-7](#).

Fasciotomy of the Brachium

The arm has two compartments: anterior, which includes biceps and brachioradialis muscles, and posterior with the triceps muscle. Fasciotomy includes a lateral skin incision from the deltoid insertion to the lateral epicondyle. Care must be taken to avoid damage to the larger cutaneous nerves. At the fascial level, the intermuscular septum between the anterior and posterior compartments is identified, and fascia overlying each compartment is released with longitudinal incisions. The radial nerve should be protected as it passes through the intermuscular septum from the posterior compartment to the anterior compartment just below the fascia (see [Fig. 164-7](#)).

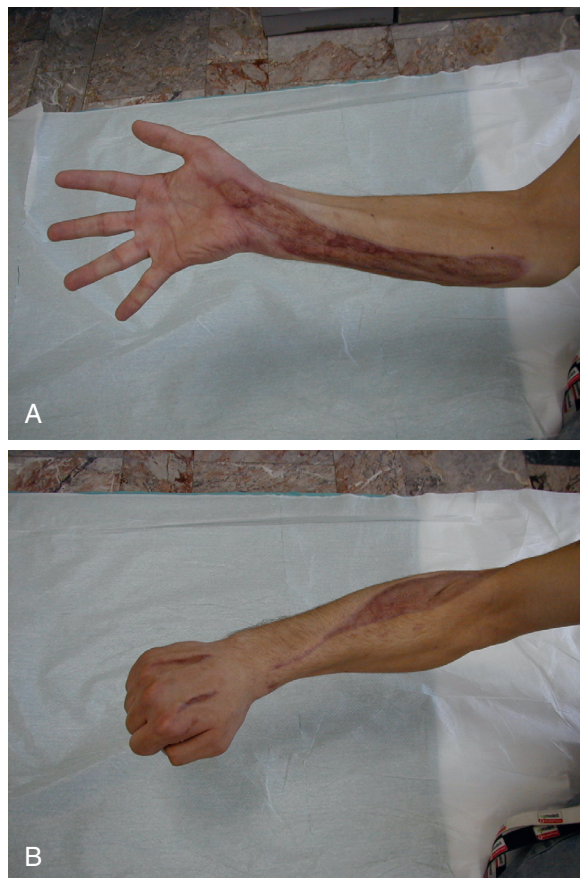


FIGURE 164-7 ■ Clinical photographs of combined fasciotomy of the upper extremity. Dorsal and volar aspects.

Fasciotomy of the Antebrachium

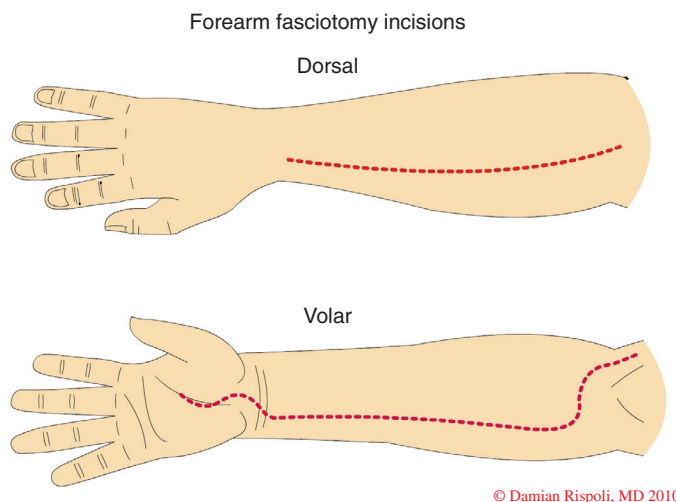
The antebrachium has three muscular compartments: mobile wad proximally, volar compartment, and dorsal compartment. Fasciotomy consists of a longitudinal, centrally placed incision over the extensor compartment and a curvilinear incision on the flexor aspect beginning at the antecubital fossa ([Fig. 164-8](#)). A palmar incision is made between the thenar and hypothenar muscles in the palm, where the carpal tunnel can be released if needed. The incision is extended transversely across the wrist flexion crease to the ulnar side of the wrist and then arched across the volar forearm back to the ulnar side at the elbow. At the elbow, the incision is curved just radially to the medial epicondyle across the elbow flexion crease, and the deep fascia is released. At the antecubital fossa, a fibrous band overlying the brachial artery and median nerve is carefully released. This incision allows for soft tissue coverage of underlying neurovascular structures at the wrist and elbow and prevents soft tissue contractures from developing at flexion creases. A second straight dorsal incision can be made to release the mobile wad if necessary.

Fasciotomy of the Hand

The hand has a unique anatomy with 10 separate fascial compartments: 4 dorsal and 3 volar interossei, thenar muscles, hypothenar muscles, and the adductor pollicis muscle. Fasciotomy consists of four incisions ([Fig. 164-9](#)). One incision on the radial side of the thumb metacarpal releases the thenar compartment. A dorsal incision over the index finger metacarpal is used to release the first and second dorsal interossei, to reach the ulnar-to-index finger metacarpal, and to release the volar interossei and adductor pollicis muscle. A dorsal incision over the ring finger metacarpal is used to release the third and fourth dorsal interossei and to reach down along the radial aspect of the ring finger and small finger metatarsal to release volar interossei. An incision placed at the ulnar aspect of the small finger is used to release the hypothenar muscles.

Fasciotomy of the Lower Extremity

The lower extremity is anatomically divided into three parts: thigh, lower leg, and foot. As in the upper extremity, each anatomic segment has a different number of compartments with various muscle functions. Techniques for release of these compartments are discussed separately as well.



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FIGURE 164-8 ■ Fasciotomy of antebrachium. Dorsal and volar aspects. (From Wheelless CR. *Wheelless' Textbook of Orthopaedics*. Towson, MD: Data Trace; 2014. © 2010, Damian Rispoli, MD.)

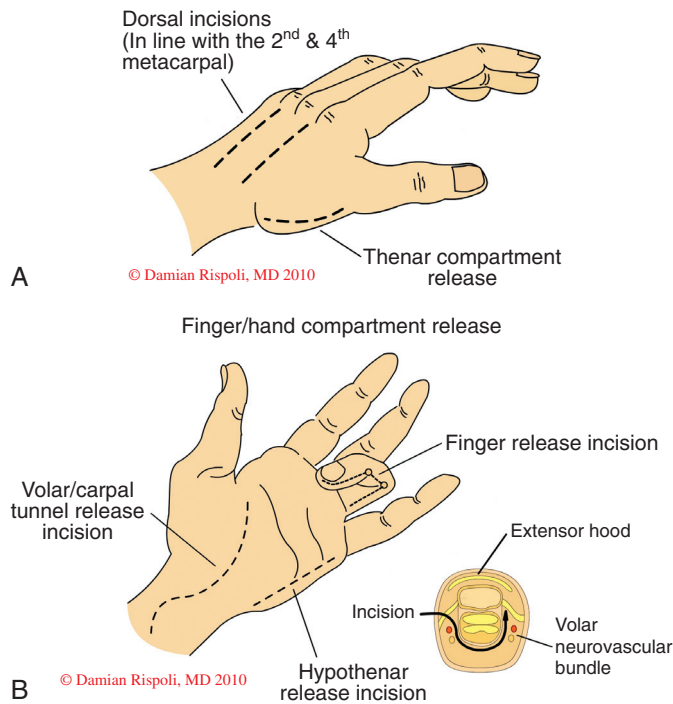


FIGURE 164-9 ■ Fasciotomy of the hand. Dorsal (A) and volar (B) aspects. (From Wheeless CR. Wheeless' Textbook of Orthopaedics. Towson, MD: Data Trace, 2014. © 2010, Damian Rispoli, MD.)

Fasciotomy of the Thigh

The thigh has three compartments: anterior (quadriceps), medial (adductors), and posterior (hamstrings) (Fig. 164-10). Because of the large potential volume, compartment syndrome and blending of fascial compartments with the hip (allows extravasation of blood outside compartments) in the thigh are less likely to occur but can be seen especially in patients with high-energy femoral fractures or hip fractures. Fasciotomy consists of lateral incisions made from the greater trochanter to the lateral condyle of the femur. The iliotibial band is incised, and the vastus lateralis is reflected off the intermuscular septum bluntly, thereby releasing the anterior compartment. The intermuscular septum is then incised over the length of the incision, releasing the posterior compartment. This release should not be done close to the femur since a series of perforating vessels pass through the septum posteriorly to anteriorly near the bone. The medial compartment is released through separate anteromedial incisions (Fig. 164-11).

Fasciotomy of the Lower Leg

Lower extremity compartment syndrome is the most common due to the unique anatomy of compartments. Most of the studies on compartment syndrome have been conducted on this part of the body, and most of the current knowledge about epidemiology and treatment is based on lower extremity compartment syndrome studies. The lower leg has four compartments: lateral (peroneal brevis and longus), anterior (extensor hallucis longus muscle, extensor digitorum longus muscle, tibialis anterior muscle, and peroneus tertius), superficial posterior (gastrocnemius and soleus), and deep posterior (flexor hallucis longus muscle, flexor digitorum longus muscle, and tibialis posterior muscle) (Fig. 164-12). The anterior compartment is the most commonly involved, followed by the deep posterior compartment. In the case of compartment syndrome of any of the compartments, release of all four is recommended.

There are two surgical techniques for release of all four compartments in the lower leg: one-incision technique (Fig. 164-13) and

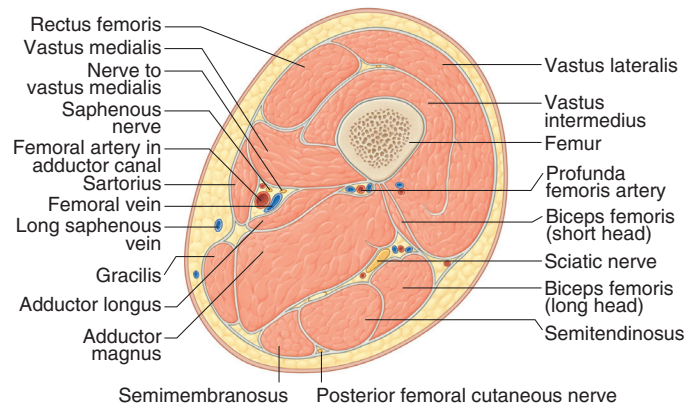


FIGURE 164-10 ■ Anatomy of the compartments of the thigh. (From Standing S, et al., editors, Gray's Anatomy, 40th ed. Edinburgh, Churchill Livingstone, 2008.)

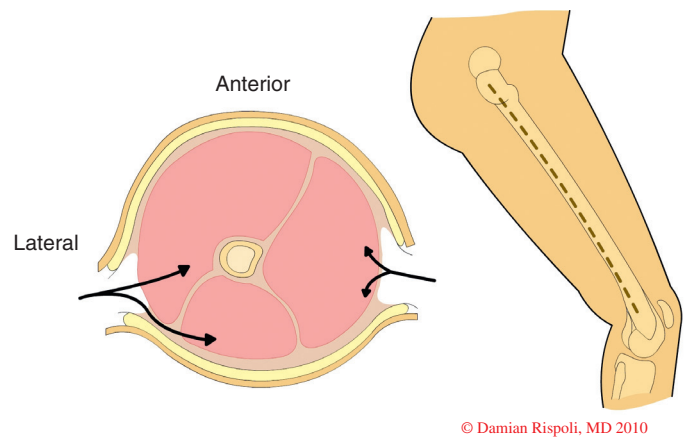


FIGURE 164-11 ■ Schematic presentation of fasciotomy of the thigh. (From Wheeless CR. Wheeless' Textbook of Orthopaedics. Towson, MD: Data Trace, 2014. © 2010, Damian Rispoli, MD.)

two-incision technique (Fig. 164-14). There is no strong evidence on which technique has an advantage over the other. The only retrospective study in the setting of tibial fractures comparing the two methods found similar infection and nonunion rates.⁸¹ The one-incision technique resulted in only one surgical wound and fewer related complications in one study.⁸² It seems that the choice for fasciotomy can be based on surgeon experience, and, due to simplicity, the two-incision technique is more often used.

One-Incision Technique

The one-incision technique is technically more difficult as it is difficult to visualize the deep posterior compartment, and therefore, there is an increased risk of injury to the peroneal artery and nerve. The technique starts with a skin incision 1 to 2 cm anterior and parallel to the fibula, just inferior to the fibular head and 3 to 4 cm proximal to the lateral malleolus. An anterior flap enables exposure of the anterior and lateral compartments. Longitudinal incisions are made in the fascia, and care must be taken to avoid damage to the common, superficial, and deep peroneal nerves at the fibular head. A lateral flap is exposed more posteriorly to visualize the superficial posterior compartment. The gastrocnemius muscle should be identified, and the fascia is incised longitudinally. The deep posterior compartment is identified later,

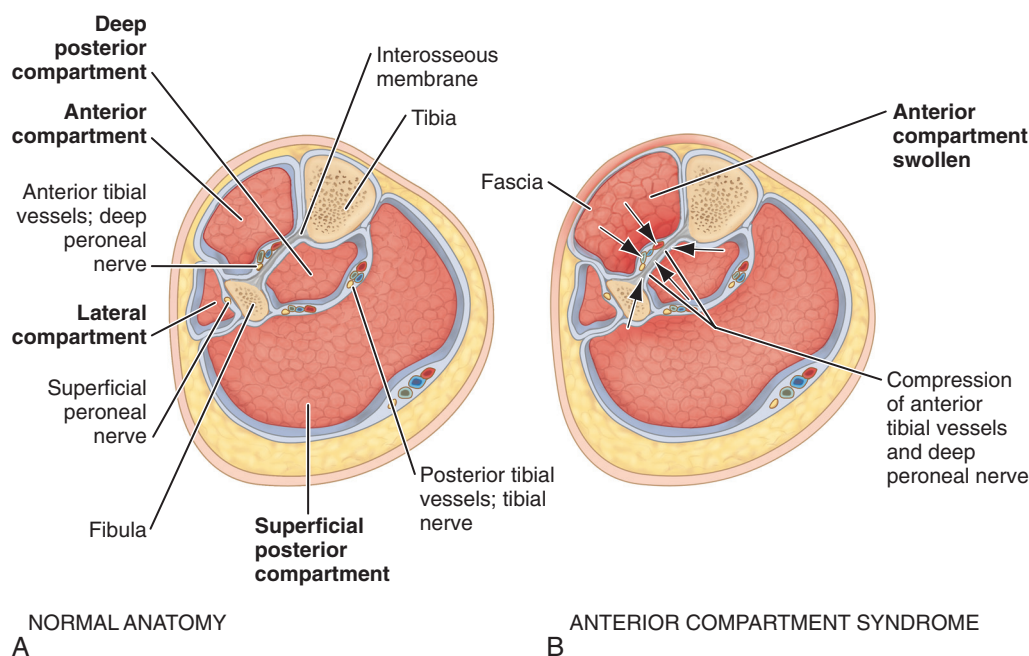


FIGURE 164-12 ■ Anatomy of the compartments of the lower leg. (From Black JM, Hawks JH. Medical-Surgical Nursing, 8th ed. Philadelphia: Saunders, 2009.)

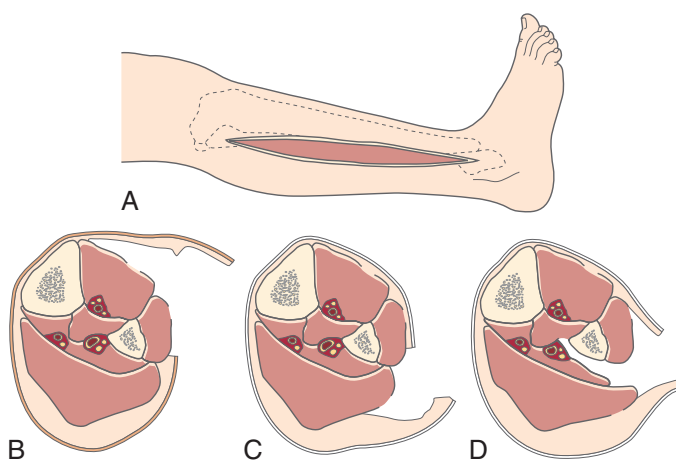


FIGURE 164-13 ■ Single-incision fasciotomy of the lower leg.

A, Lateral skin incision from the fibular neck to 3 to 4 cm proximal to the lateral malleolus. **B,** The skin is undermined anteriorly, and a fasciotomy of the anterior and lateral compartments is performed. **C,** The skin is undermined posteriorly, and a fasciotomy of the superficial posterior compartment is performed. **D,** An interval between the superficial posterior and lateral compartments is developed. The flexor hallucis longus muscle is dissected subperiosteally off the fibula and retracted posteromedially. The fascial attachment of the posterior tibial muscle to the fibula is incised to decompress the muscle. (From Davey JR, Rorabeck CH, Fowler PJ. The tibialis posterior muscle compartment: an unrecognized cause of exertional compartment syndrome. *Am J Sports Med* 1984;12:391–397.)

after exposure of the posterior side of the fibula with dissection of the soleus muscle. Fasciotomy of the deep posterior compartment is performed at the medial border of the fibula. Here, peroneal vessels should be retracted and protected posteriorly to avoid injury (see Fig. 164-13).

Two-Incision Technique

This technique uses medial and lateral longitudinal incisions that should be long enough to completely release all four compartments. In adults, incisions can be up to 30 cm long. The lateral incision starts about 5 cm lateral to the anterior border of the tibia. Underlying the incision are the fascial tissues of the anterior and peroneal compartments; these are identified and released. The intermuscular septum should be identified to ensure that both compartments are released. Care must be taken to not damage the common peroneal nerve proximally as it passes around the fibular head; therefore, skin incisions should not reach the fibular head level. Distally, the skin incision ends about 5 cm above the lateral malleolus. The medial incision of the two-incision technique starts 2 cm medial to the tibial margin. It is used to release both posterior compartments. Care must be taken to avoid saphenous nerve and vein damage, and these structures should be identified prior to fasciotomy of these compartments. The superficial posterior compartment is decompressed by incising the gastrocnemius fascia in a longitudinal direction proximally to distally. The posterior compartment is decompressed by dividing the attachments of the soleus muscle to the tibia (see Fig. 164-14).

Fasciotomy of the Foot

Acute compartment syndrome of the foot most commonly occurs due to crush injury, and fasciotomy is rarely needed. There are four major compartments of the foot: intraosseous, lateral, central (calcaneal), and medial (Fig. 164-15). They are further divided into smaller muscle groups, so there are nine compartments in the foot, but this number is controversial (Fig. 164-16). Whereas each of the compartments should generally be released, some debate exists whether the superficial compartment of the dorsal central compartment, which contains the flexor digitorum brevis muscle, should be included. A dorsal approach is most commonly used and requires less dissection than the other two. It begins with dual dorsal longitudinal incisions over the medial side of the second metatarsal bone and the lateral side of the fourth metatarsal bone. Each of the four interosseous compartments is released first between the metatarsal bones. The medial compartment may be released by accessing a space medial to the second metatarsal; the

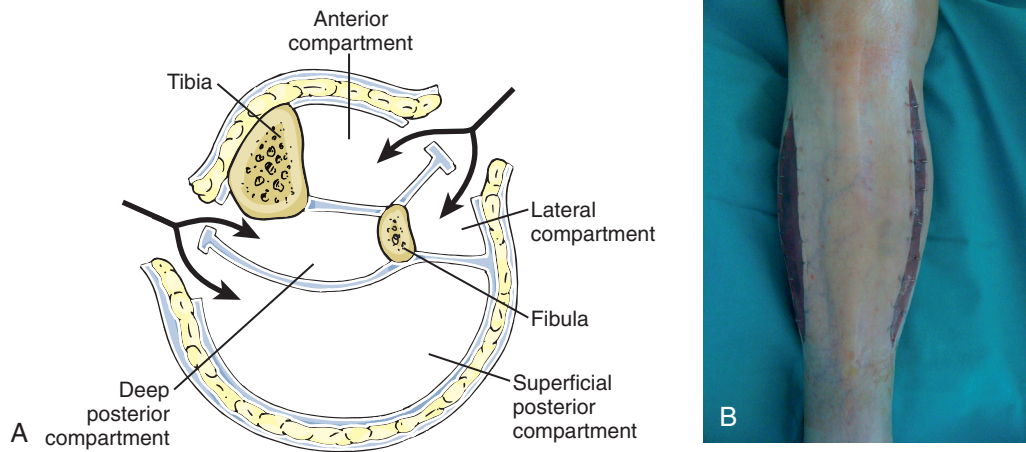


FIGURE 164-14 ■ Two-incision technique for fasciotomy of the lower leg. (A) A cross-sectional view and (B) position of skin incisions. Both wounds have been temporarily covered with an artificial skin graft. (A, from Cameron JL, Cameron AM. *Current Surgical Therapy*, 10th ed. Philadelphia: Saunders, 2011.)

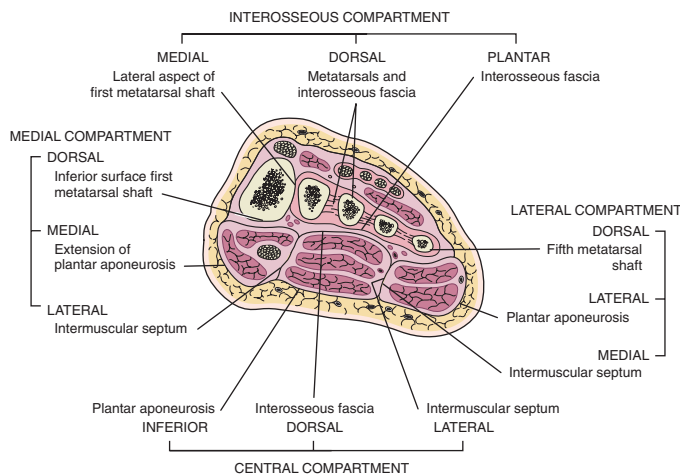


FIGURE 164-15 ■ Compartments of the foot. (From Twaddle BC, Amendola A. *Compartment syndromes*. In: Browner BD, Jupiter JB, Levine AM, et al., editors. *Skeletal Trauma*, 4th ed. Philadelphia: Saunders, 2009.)

lateral compartment is released by accessing a space lateral to the fourth metatarsal bone. The calcaneal compartment lies underneath the second interosseous space and can be released through a medial incision. The superficial compartment is accessed through the calcaneal compartment by blunt dissection of the adductor hallucis muscle. Sometimes release of this compartment is not required, since it contains predominantly tendons of the finger flexors and is not a “true” muscular compartment.

POTENTIAL COMPLICATIONS

Delay of treatment of compartment syndrome can lead to irreversible complications and, left untreated, can lead to death. The initial management should be focused not only on preservation of tissue viability in the compartment but also on the initial management of systemic complications of reperfusion injury. This requires restoration of intravascular volume, prevention of hyperkalemia, and treatment of metabolic acidosis and myoglobinuria, which may lead to acute

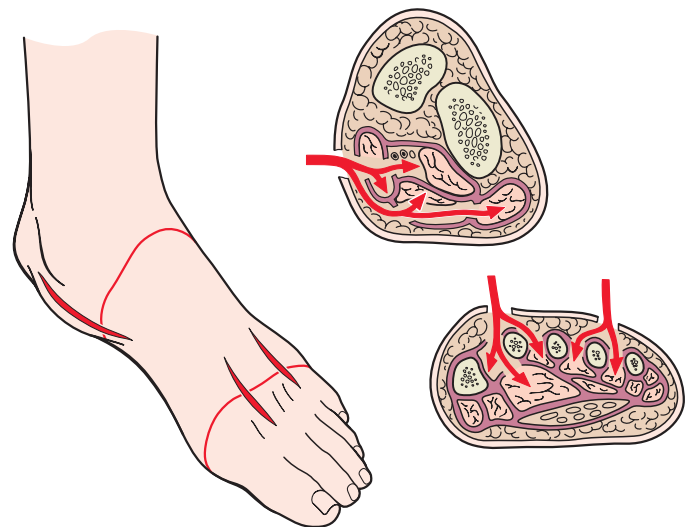


FIGURE 164-16 ■ Fasciotomy of the foot. Medial and dorsal approaches. (From Banerjee R, Nickisch F, Easley ME, DiGiovanni CW. *Foot injuries*. In: Browner BD, Jupiter JB, Levine AM, et al., editors. *Skeletal Trauma*, 4th ed. Philadelphia: Saunders, 2009.)

kidney injury. Complications may also occur as a sequela of surgical procedures performed and wound management. Late sequelae of compartment syndrome include persistent hypoesthesia, dysesthesia, persistent motor weakness, infection, myoglobinuric renal failure, contractures, amputation, and death. In one study, persistent sequelae are reported to be associated with a higher number of operations, post-fasciotomy complications, closures with skin grafting, and increased time to closure.⁸³

Technical complications of fasciotomy are preventable when considering the anatomy of important structures. Persistent or recurrent compartment syndrome can occur if fascial incisions are not adequate to permit complete decompression of the compartment or if selective fasciotomy has been performed.⁷⁸

Persistent neurologic deficits following fasciotomy are common. Nerve injury can occur due to the initial traumatic event, prolonged ischemia, or as a consequence of fasciotomy dissection and tissue

débridement. The most common neuropathic syndrome is altered sensation at the margins of the incision; chronic pain syndromes are also described.⁸⁴ Impaired neurologic function after lower extremity fasciotomy is described in 7% to 36% of injured limbs.⁸⁵⁻⁸⁷

Wound complications after fasciotomy may occur immediately or be delayed for months to years. Early wound complications occur in up to 40% of patients following lower extremity fasciotomy.^{85,88,89} Risk factors are related to the presence of vascular injury, lower extremity site, and premature or delayed closure of the wound.⁸⁹ Wound infection occurs in 4% to 7% of extremity fasciotomies.^{85,88} Prophylactic antibiotics should be given at the time of fasciotomy and discontinued after 24 hours. Repeated débridement of devitalized tissue may protect from severe wound infections and sepsis. Late wound complications are reported in 4% to 38% of limbs.^{84,85,88,89} Delayed wound complications include tethered scars and tendons, muscle hernias, and poor healing and ulceration, especially in patients with underlying vascular diseases. Venous insufficiency can predispose patients to chronic venous disease after fasciotomy. Tibial diaphyseal fracture healing in patients with compartment syndrome has been found to be delayed, and the rates of nonunion are reported to be higher compared with patients without compartment syndrome.⁹⁰

Acute extremity compartment syndrome is associated with significant risk of limb loss.⁹¹ Major amputation will be required in 5% to 21% of limbs treated with fasciotomy.^{85,86,88,89,91} Combined orthopedic and vascular injury, other severe injuries, and systemic factors may contribute to the need for amputation in severely injured patients. The highest amputation rate occurs in patients with severe vascular injuries with occlusion.⁸⁵ A large review of the National Trauma Data Bank for lower extremity vascular injury comparing early versus late fasciotomy findings suggests that appropriate implementation of early fasciotomy may reduce amputation rates.⁹² Amputation of the upper extremity following fasciotomy is rare.

The most severe cases of compartment syndrome left untreated may cause death. Reported mortality ranges from 11% to 25% and depends on the epidemiology of the compartment syndrome.^{78,86,88,93} Mortality is most often due to massive trauma, severe hypovolemic shock, and multisystem organ failure and cannot be attributed only to the need for fasciotomy. This is especially true in severely injured patients with massive shock resuscitation where the mortality after fasciotomy in one study reached 67%.²⁴

CONCLUSION

The patient who undergoes fasciotomy requires a physical therapy program to regain function. Postoperative care and rehabilitation

are just as important as the procedure itself. During the immediate postoperative period, weight bearing is limited, and assistive devices (e.g., crutches) are needed. Within a few days, and with adequate pain control, the use of crutches can be discontinued. The rehabilitation program then involves range of motion (ROM) and flexibility exercises involving the muscles of the affected compartment. Adjacent joints need to be exercised to maintain their normal ROM.

Once the patient is able to ambulate with a normalized gait pattern, a program of graduated resistive exercises (depending on the patient's regular activities or work) is initiated. In the case of athletes, sports-specific exercises are started with the intention of returning to a regular athletic schedule. Cross training is also beneficial for these athletes. Activities such as swimming, pedal exercises, water jogging, or running help athletes regain muscle strength and flexibility without loading the affected compartment.

With surgical intervention for decompression, occupational therapy consultation should be considered early in the postoperative period. Appropriate treatment and assessment of the patient's deficits with regard to activities of daily living, as well as for instruction in the use of any necessary assisted devices should be assessed.

KEY POINTS

1. Compartment syndrome is a life-threatening condition and should be treated as soon as it is diagnosed.¹⁶
2. One of the first signs of compartment syndrome is a swollen extremity with pain out of proportion and increasing requirements for analgesia.^{12,28,30-32}
3. Critically ill patients, especially after severe trauma with massive fluid resuscitation, require special attention and frequent evaluation.²⁴
4. Diagnosis of compartment syndrome is very likely when intracompartmental pressure reaches 45 mm Hg or the difference between diastolic blood pressure and intracompartmental pressure is less than 30 mm Hg.^{34-36,38,42-45}
5. Treatment of compartment syndrome is primarily surgical with prompt release of muscle compartments by fasciotomy.⁶⁴⁻⁶⁸

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Thrombolytic agents comprise a diverse group of compounds that indirectly initiate the lysis of a thrombus. After the initiation of a coagulation cascade, fibrinolytic mechanisms are concomitantly activated to prevent unconstrained thrombosis. Fibrinolysis begins with the cleavage of proenzyme plasminogen to plasmin, which hydrolyzes key bonds within a fibrin clot matrix, resulting in clot lysis (Fig. 165-1). Thrombolytic agents function by converting plasminogen to plasmin. Different thrombolytic agents vary in their specificity for plasminogen, metabolic half-life, and antigenicity (Table 165-1).

■ DRUGS

Streptokinase

Streptokinase, a protein produced by beta-hemolytic streptococci, was identified as having fibrinolytic properties in the 1930s¹ and was the first compound to be used clinically as a thrombolytic drug.² Streptokinase complexes with plasminogen and converts it to plasmin. However, one of the major drawbacks of using streptokinase is its antigenicity because streptococcal infection may induce antibody formation. Mild allergic reactions occur in 2% to 5% patients; however, severe anaphylactic reactions may also occur.³

Urokinase

Urokinase is a thrombolytic protein that was initially isolated from human urine and has been used clinically for over 30 years. At present, it is isolated from human fetal renal tissue cultures. Unlike streptokinase, urokinase enzymatically cleaves plasminogen. In 1999, urokinase was removed from the U.S. market after concerns raised by the Food and Drug Administration (FDA) regarding its safety.⁴ It was reintroduced in the United States in 2002 after rigorous testing showed that urokinase preparations were free of human pathogens. However, at present, it is only approved for treating pulmonary embolism (PE). Prourokinase (also known as single-chain urokinase-type plasminogen activator) is a single-chain precursor of urokinase that is converted into two-chain urokinase by hydrolysis.

Tissue Plasminogen Activator

Tissue plasminogen activator (t-PA), which was first isolated in 1981,⁵ is a naturally occurring protein synthesized by human vascular endothelial cells. Several recombinant variants of t-PA are available, including alteplase (rt-PA, approved by the FDA in 1987) and duteplase. Other forms of tissue-type t-PAs include reteplase (r-PA), tenecteplase (TNK-tPA), and lanoteplase (n-PA). Recombinant t-PAs are nonantigenic and show specificity for fibrin-bound plasminogen. They also avoid the infectious risks associated with products isolated from cultured human tissues. Newer recombinant t-PAs have improved pharmacokinetics that enables their convenient administration such as bolus dosage.

Other Agents

Other compounds that have been developed and investigated include vampire bat plasminogen activator (isolated from the saliva of vampire

bat), fibrolase (isolated from the venom of southern copperhead snake), and staphylokinase (isolated from *Staphylococcus aureus*). However, data on these compounds are relatively limited; hence, they are rarely used clinically.

■ CLINICAL INDICATIONS

Myocardial Infarction

Acute myocardial infarction (AMI) is associated with a significant health care burden in industrialized countries. Modern management of AMI focuses on rapidly restoring perfusion to optimize myocardial salvage. Primary percutaneous coronary interventions are superior to thrombolytic therapy when employed as an early reperfusion strategy after AMI and are the first-line therapy.⁶ However, logistic barriers hinder the access of patients with AMI who require interventional cardiology services to early percutaneous coronary intervention (PCI). On the other hand, fibrinolytics are administered in almost all hospitals.

Lytic therapy was first used for treating AMI in the 1950s.⁷ Fibrinolytic Therapy Trialists' Collaborative Group performed a meta-analysis by using results obtained from over 58,000 patients treated with thrombolytics.⁸ This meta-analysis showed that treatment with thrombolytics resulted in approximately 25% reduction in mortality in patients with ST-segment elevation or bundle branch block. Since then, numerous studies have evaluated the efficacies, dosage strategies, administration routes of different lytic agents, and adjunctive therapies with these agents for rapidly restoring blood flow in thrombosed coronary arteries.

Early studies such as ISIS-2³ and GISSI⁹ focused on the use of streptokinase and showed 18% and 25% reduction in mortality after 3 and 5 weeks, respectively. Similar results were obtained after 1- to 10-year follow-up.¹⁰ The efficacy of t-PA was studied in the GUSTO-1 trial, which examined four dosing regimens for the treatment of MI in 41,021 patients.¹¹ This study used "accelerated" t-PA dosage in which two-thirds of the total dose was administered in the first 30 minutes rather than over a 3-hour period. This dosage regimen resulted in a modest but significant reduction in 30-day mortality (6.3%) compared with streptokinase (7.4%) or a combination of t-PA and streptokinase (7.0%). The GUSTO angiographic substudy showed that differing patency rates among patients treated with either agent accounted for this difference in clinical efficacy. However, a subsequent meta-analysis of this approach failed to validate the survival advantage.¹²

Newer generation t-PAs such as r-PA and TNK-tPA can be used to administer bolus dosage. The GUSTO III trial compared reteplase, the recombinant deletion mutant of t-PA, with accelerated t-PA in 15,059 patients. This trial did not detect any survival advantage with r-PA and showed that rates of intracranial hemorrhage (ICH) were similar after treatment with r-PA and t-PA (0.91% and 0.87%, respectively).¹³ The ASSENT-2 trial showed that 30-day mortality and ICH rates were identical in patients treated with TNK-tPA and those treated with accelerated t-PA.¹⁴ Although r-PA and TNK-tPA are not superior to t-PA in terms of safety and efficacy, their pharmacokinetics allow simplified administration compared with that of accelerated t-PA.

Adjunctive therapies such as aspirin, clopidogrel, and antithrombin agents improve the results of lytic therapy. Fibrinolysis strips fibrin

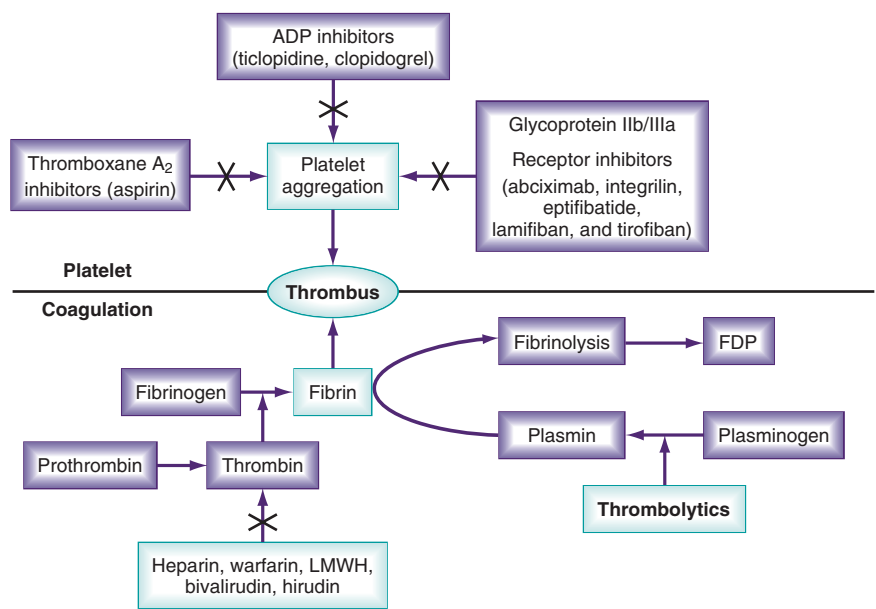


FIGURE 165-1 ■ Components of thrombus formation and effects of various antithrombotic and thrombolytic agents. FDP, fibrin degradation products; LMWH, low-molecular-weight heparin.

| TABLE 165-1 Properties of Commonly Used Thrombolytics | | | |
|---|-------------------------------|------------------------------|--|
| | STREPTOKINASE | UROKINASE | TISSUE PLASMINOGEN ACTIVATOR (T-PA) |
| Source | Group C <i>Streptococcus</i> | Human fetal kidney | Recombinant |
| Lytic | First | First (prourokinase: second) | Second (non-alteplase t-PAs: third) |
| Generation | Anistreplase | | |
| Available compounds | APSAC (half-life, 70-120 min) | Prourokinase | Alteplase, duteplase, reteplase (r-PA), tenecteplase (TNK-tPA), and lanoteplase (n-PA) |
| Molecular weight (kD) | 47 | 35-55 | 63-70 |
| Half-life (min) | 18-23 | 14-20 | 3-4 |
| Metabolism | Hepatic | Hepatic | Hepatic |
| Antigenicity | Yes | No | No |
| Fibrin specificity | Minimal | Moderate | Moderate |
| Plasminogen binding | Indirect | Direct | Direct |

from an occluding thrombus; the exposed thrombin then initiates platelet aggregation and subsequent rethrombosis.¹⁵ Heparin is typically used to maintain activated partial thromboplastin time (aPTT) between 50 and 70 seconds. If heparin-induced thrombocytopenia is suspected, then direct thrombin inhibitors such as hirudin or bivalirudin are viable options.¹⁶ Another development is the introduction of glycoprotein IIb/IIIa receptor blockers such as abciximab (ReoPro), eptifibatide (Integrilin), and tirofiban (Aggrastat).¹⁷⁻¹⁹ Despite some promising early results,²⁰ no randomized trial has yet shown the effect of these agents on mortality.²¹⁻²³ A meta-analysis of 11 randomized trials assessing thrombolytic treatment with and without abciximab suggested a significantly increased risk of major bleeding events (5.2% vs. 3.1%, $P < 0.001$) with abciximab.²⁴

The timing of diagnosis and institution of thrombolytic therapy is critical.^{25,26} Patients with AMI who are treated with thrombolytic agents at more than 4 hours after symptom onset have 2 to 3 times higher 30-day and 6-month mortality rates than patients treated within 2 hours of symptom onset.²⁷ The Late Assessment of Thrombolytic Efficacy study reported 1-year mortality rates of 17.6% and 15.8% in patients treated with rt-PA at greater than 3 hours and less than

3 hours, respectively, after symptom onset.²⁸ Therefore, prehospital administration of thrombolytics is recommended in select patients showing ST-segment elevation on electrocardiogram.^{29,30}

The currently accepted guidelines for lytic therapy of AMI are outlined by the American College of Chest Physicians in the 8th edition (2008) of Evidence-Based Clinical Practice Guidelines and by the American College of Cardiology/American Heart Association in their 2013 guidelines.^{31,32} A treatment algorithm for AMI is shown in Figure 165-2. The established guidelines indicate that patients who are most likely to benefit from fibrinolytic therapy are those with ST-segment elevation, symptoms that began within 3 hours, anticipated delay to reach PCI facility, and low bleeding risk. However, the value of thrombolytic agents for managing unstable angina remains unproven thus far. At present, lytic therapy is not used for treating acute coronary syndrome without ST-segment elevation in two or more contiguous leads or without new-onset bundle branch block. Contraindications to lytic therapy in the setting of AMI are summarized in Table 165-2.

Since the development of thrombolytics, coronary angioplasty has become the gold standard for treating MI with ST-segment elevation.

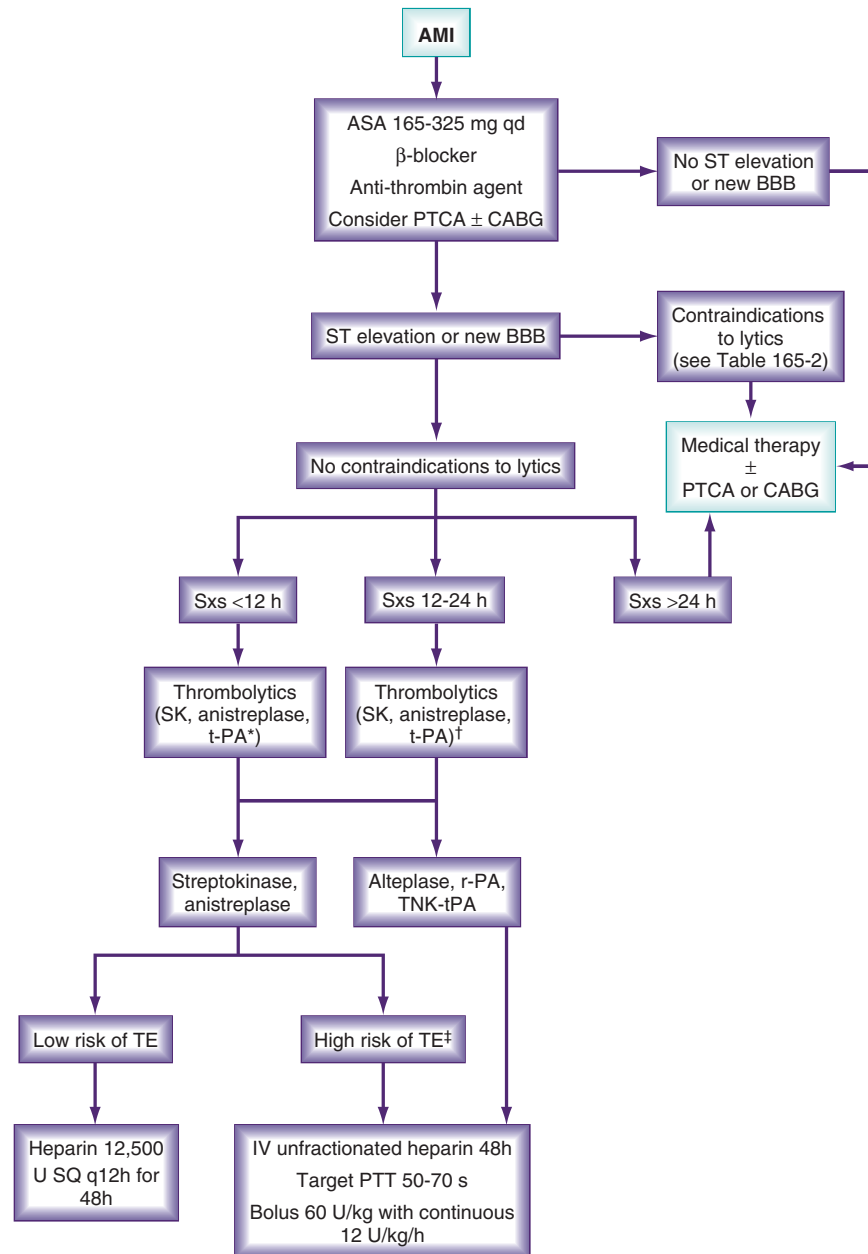


FIGURE 165-2 ■ Algorithm for treating acute myocardial infarction.*Preferred for symptom duration of <6 hours; †grade 2b data¹¹; ‡anterior myocardial infarction, existing heart failure, previous embolus, atrial fibrillation and left ventricular thrombus. AMI, acute myocardial infarction; BBB, bundle branch block; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; Sxs, signs and symptoms; PTT, partial thromboplastin time; SK, streptokinase; SQ, subcutaneous; TE, thromboembolism. (Data from 1999/2002 ACC/AHA Guideline Update and 2001 ACCP Consensus Conference.¹¹⁻¹²)

A large meta-analysis of 7739 patients with ST-segment elevation who were randomized to receive thrombolytic therapy (76% receiving fibrin-specific lytics) or primary percutaneous transluminal coronary angioplasty (PTCA)⁶ showed that short-term (4- to 6-week) mortality in patients in the PTCA group was 7% compared to 9% in patients in the lytic therapy group ($P = 0.0003$). Patients treated with primary PTCA showed lower rates of nonfatal reinfarction (3% vs. 7%) and stroke (1% vs. 2%) during follow-up in a smaller study.³³ Short-term results of this meta-analysis are summarized in Fig. 165-3.

Potential advantages of angioplasty over thrombolysis³⁴⁻³⁷ as the primary therapy for AMI are tempered by the recognition that results

of angioplasty are highly dependent on the volume of cases at a given treatment center. Moreover, many patients initially present to facilities where interventional cardiology services are not available for performing PCI, resulting in the use of thrombolytics before performing PCI. The recent Strategic Reperfusion Early After Myocardial infarction (STREAM) trial showed that fibrinolytic therapy, clopidogrel, and enoxaparin followed by PCI exerted beneficial effects compared with primary PCI in patients with MI associated with ST-segment elevation who were unable to undergo PCI within 1 hour.³⁸ Moreover, the Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) trial

TABLE 165-2

Contraindications to Thrombolytic Therapy in the Setting of Acute Myocardial Infarction (With ST-Segment Elevation and/or New Bundle Branch Block)

| ABSOLUTE CONTRAINDICATIONS | RELATIVE CONTRAINDICATIONS |
|--|---|
| >24 hours since symptom onset | 12 to 24 hours since symptom onset |
| Prior intracranial hemorrhage | Age >75 years |
| Stroke within the past year | Systolic blood pressure of >180 mm Hg or diastolic blood pressure of >110 mm Hg |
| Intracranial neoplasm | Bleeding disorder |
| Active bleeding/bleeding diathesis | Prior allergic reaction to thrombolytics |
| Suspected aortic dissection | Pregnant or lactating |
| Significant closed-head or facial trauma within 3 months | Prolonged cardiopulmonary resuscitation (>10 min) |
| | Recent internal bleeding (less than 2-4 weeks) |
| | Active peptic ulcer |

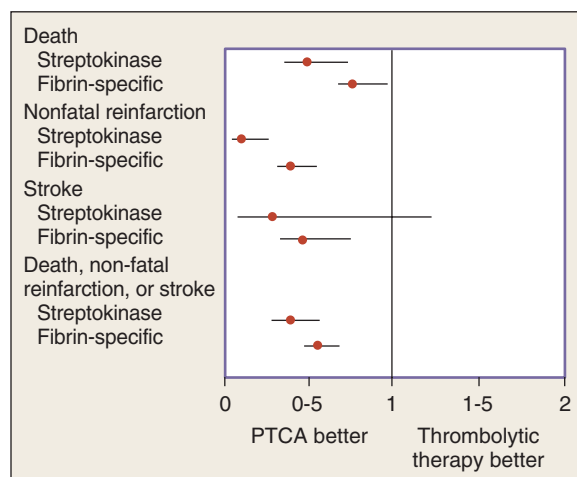


FIGURE 165-3 ■ Short-term clinical outcomes in patients treated with percutaneous transluminal coronary angioplasty and those treated with thrombolytic therapy. Odds ratios with 95% confidence intervals. (Reprinted with permission from Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;361:13-20.)

showed a reduction in the composite endpoint of death, reinfarction, recurrent ischemia, new or worsened congestive heart failure, or cardiogenic shock within 30 days (11.0% vs. 17.2%; OR, 0.64; 95% CI, 0.47-0.87) in patients treated with early (<6 hours) PCI after thrombolytic therapy compared with those treated with standard therapy.³⁹ The ideal treatment for some patients may involve a combination of thrombolytic therapy, antithrombotic agents, antiplatelet agents and PCI.

Stroke

Stroke is the third leading cause of death in the United States, affecting over 700,000 people per year. The majority of strokes are ischemic and result from sudden occlusion of arteries that deliver blood to the brain.

Traditional therapy for ischemic stroke includes anticoagulant and antiplatelet agents for medical support, followed by rehabilitation after the acute event. More recently, thrombolysis has emerged as a treatment for ischemic stroke. Similar to that for AMI, the efficacy of thrombolysis for treating stroke is highly time dependent because of the characteristics of ischemic penumbra⁴⁰ and is the highest when lytic treatment is initiated within 90 minutes after symptom onset.⁴¹

Use of clot-busting therapies for ischemic stroke dates back to 1995 when the National Institute of Neurological Disorders and Stroke (NINDS) published a study on rt-PA for treating acute ischemic stroke.⁴² The trial examined the clinical efficacy of intravenous (IV) t-PA administered within 3 hours of symptom onset. Administration of t-PA did not improve neurologic function at 24 hours compared with administration of placebo. However, in the long term, patients who received t-PA were 30% more likely to have minimal residual disability or were more likely to return to baseline functional status after 3, 6, and 12 months.⁴³ However, patients treated with t-PA showed higher incidence of intracerebral hemorrhage (6.4% vs. 0.6%, $P < 0.001$) at 36 hours. Nevertheless, mortality at 3 months was not significantly different (17% vs. 21%, $P = 0.30$). The results of this study led to the approval of IV t-PA by the FDA for treating acute ischemic stroke within 3 hours of symptom onset.

Other early randomized trials on IV t-PA for treating acute stroke were the European Cooperative Acute Stroke Study (ECASS-I),⁴⁴ ECASS-II,⁴⁵ and ATLANTIS trials.^{40,46} Although these trials did not reach significance for their primary outcome measure, they did show a significant benefit of using t-PA within 0 to 6 hours of symptom onset for improving alternative outcome measures, thus supporting its clinical use. More recently, the ECASS-III trial showed a significant but modest benefit of t-PA compared with that of placebo when administered within 3 to 4.5 hours of symptom onset, with no difference in mortality.⁴⁷ Based on the results of this trial, Lansberg et al. calculated the number of patients deriving benefit per 100 treated as 28, 23, and 17 for the 0- to 1.5-, 1.5- to 3-, and 3- to 4.5-hour windows, respectively.⁴⁸ As a result of the ECASS III trial, IV t-PA for the treatment of stroke within 3 to 4.5 hours has been supported by the Scientific Advisory from the American Heart Association Stroke Council. The European Medicines Agency has approved the use of IV t-PA within 4.5 hours of symptom onset even though the FDA has not approved it to date.⁴⁹ The third International Stroke Trial evaluated whether t-PA exerted beneficial effects in all patients within 6 hours of symptom onset and in patients older than 80 years. The 18-month follow-up showed no improvement in mortality in those treated with alteplase versus standard care alone (34.9% vs. 35.1%, $P = 0.85$) but did have a modest, statistically significant, improvement in patients with a low (0-2) Oxford handicap scale score (35.0% vs. 31.4%; OR, 1.28; 95% CI, 1.03-1.57; $P = 0.024$).⁵⁰

At present, IV t-PA is the only drug and route of administration approved by the FDA for treating ischemic stroke. However, intraarterial (IA) administration of thrombolytics for treating ischemic stroke is gaining popularity. This method requires a neurointerventionalist to place a catheter into the thrombosed vessel and directly infuse a thrombolytic. Some studies have reported the efficacy of direct IA delivery of thrombolytics. The Prolyse in Acute Cerebral Thromboembolism (PROACT II) study⁵¹ randomized 180 patients with middle cerebral artery occlusion to receive IA prourokinase plus heparin or heparin alone. The results of this study showed that over 40% of patients receiving IA prourokinase plus heparin had improved modified Rankin score of ≤ 2 compared with only 25% patients receiving heparin alone. The MELT trial (a Japanese trial) on IA urokinase was halted early and thus did not reach significance for its primary endpoint.⁵² Nevertheless, secondary analysis of this study and combined analyses with PROACT trials suggested a benefit of IA urokinase.⁵³

Interventional Management of Stroke trialists recently conducted a phase 3 trial to compare a standard dose of IV t-PA with that of IV t-PA bridge for endovascular treatment.⁵⁴ The trial was stopped early due to futility. Patients treated with t-PA and endovascular therapy did not show significant differences compared with those treated with t-PA

TABLE 165-3 Contraindications for Thrombolytic Therapy in Ischemic Stroke

| CONTRAINDICATIONS | RELATIVE CONTRAINDICATIONS |
|---|--|
| Symptom duration of >6 hours | Symptom duration of 3 to 6 hours |
| History of intracranial hemorrhage | Witnessed seizure |
| Evidence of active bleeding | Gastrointestinal or urinary |
| Platelet count of <100,000/mm ³ | Hemorrhage within 3 weeks |
| | Recent lumbar puncture, noncompressible arterial puncture site |
| Prior stroke, head trauma or intracranial surgery within 3 months | Systolic blood pressure of >185 mm Hg or diastolic blood pressure of >110 mm Hg |
| Rapidly improving or only minor symptoms | Mass effect or hypodensity of >½ middle cerebral artery distribution on head computed tomography |
| Major surgery within 14 days | |
| Known arteriovenous malformation or intracranial aneurysm | Glucose level of <50 or >400 mg/dL |
| | Elevated partial thromboplastin time or international normalized ratio (>1.7) |

alone with respect to 90-day mortality (19.1% vs. 21.6%, $P = 0.52$) or modified Rankin score of ≤ 2 (40.8% vs. 38.7%, absolute adjusted difference, 1.5 percentage points; 95% CI, -6.1 to 9.1). The 2013 American Stroke Association guidelines recommend that patients eligible for IV t-PA treatment should receive the treatment even if IA therapy is being considered.⁵⁵ Standard contraindications for IV thrombolytic therapy in patients with acute ischemic stroke are similar to exclusion criteria used in the NINDS study (Table 165-3). Several adjunctive therapies, including mechanical thrombectomy,⁵⁶ glycoprotein IIb/IIIa inhibitors⁵⁷ and ultrasonography,^{58,59} have provided promising results for improving recanalization rates.

Pulmonary Embolism

PE is a major source of morbidity and mortality in hospitalized patients, accounting for up to 15% in-hospital deaths.⁶⁰ Anticoagulation has been the mainstay of treatment for PE since it was first shown to be beneficial in 1960.⁶¹ This has been historically achieved using IV unfractionated heparin (UFH), although subcutaneous (SC) low-molecular-weight heparin (LMWH), SC fondaparinux, or monitored or fixed-dose SC UFH may also be used.⁶² Despite the proven efficacy of anticoagulation for treating acute PE, a significant proportion of patients show incomplete resolution of their occlusion, with subsequent organization of thrombus and obliteration of involved pulmonary artery.⁶³⁻⁶⁵ Therefore, thrombolytic therapy for PE may offer more rapid and complete resolution of thrombus.

The Urokinase Pulmonary Embolism Trial (UPET) was one of the initial trials to evaluate thrombolytic therapy for treating PE.⁶³ This prospective study did not show any improvement in mortality or perfusion rate after 5 days of lytic therapy. However, the UPET and subsequent Urokinase-Streptokinase Embolism Trial showed improvements in small-vessel patency at 2 weeks and 1 year after thrombolytic therapy compared to anticoagulation therapy alone.^{66,67} A 7-year follow-up of this cohort of patients suggested that the risk of pulmonary hypertension decreased after thrombolytic therapy presumably because it resulted in superior clot dissolution.⁶⁸

At present, thrombolytic therapy is used only for treating patients with massive PE resulting in hemodynamic instability. In addition, patients with right ventricular dysfunction or refractory hypoxemia in the setting of preserved systemic arterial blood pressure may benefit from thrombolytic therapy. Right heart strain is correlated with an intermediate risk of death.⁶⁹ Patients with submassive PE showed

TABLE 165-4 Food and Drug Administration–Approved Regimens for Treating Pulmonary Embolism

| DRUG | SYSTEMIC ADMINISTRATION |
|------------------|--|
| Streptokinase | 250,000 U over 30 minutes, followed by 100,000 U/h for 24 hours |
| Urokinase | 4400 U/kg over 10 minutes, followed by 4400 U/kg/h for 12-24 hours |
| t-PA (alteplase) | 100 mg over 2 hours |

improved clinical course after treatment with IV thrombolytic therapy compared to anticoagulation therapy alone; however, IV thrombolytic therapy did not improve long-term mortality.⁷⁰ Pulmonary Embolism Thrombolysis (PEITHO) investigators recently conducted a randomized trial involving 1006 patients with PE, right ventricular dysfunction, and cardiac enzyme elevation to compare TNK-tPA and heparin with placebo and heparin. The primary outcome of death or hemodynamic compromise within 7 days was less frequent in patients in the TNK-tPA group than in those in the control group (2.6% vs. 5.6%; OR, 0.44, 95% CI, 0.23-0.87; $P = 0.02$). Patients receiving thrombolytic therapy showed higher rates of stroke (2.4% vs. 0.2%, $P = 0.003$) and major bleeding (6.3% vs. 1.2%, $P < 0.001$) but similar 30-day mortality (2.4% vs. 3.2%, $P = 0.42$).⁷¹

Verstraete et al. performed the first trial to compare direct pulmonary artery infusion with IV infusion.⁷² However, this trial failed to show a benefit of pulmonary artery infusion. Other adjunctive techniques include use of ultrasound-producing catheters that may increase the permeability of t-PA within a clot. Recently, a prospective, randomized trial comparing the efficacy of ultrasound-assisted catheter-directed thrombolysis (USAT) with that of anticoagulation alone in patients with right heart strain showed the superiority in USAT in reversing the heart strain within the first 24 hours.⁷³ Although no significant differences exist among different thrombolytic regimens,⁷⁴ IV t-PA therapy is preferred because of its short infusion time.⁷⁵ FDA-approved regimens for treating acute PE are listed in Table 165-4. Major hemorrhagic complications occur in approximately 12% of patients irrespective of the lytic agent used.⁷⁶

Deep Venous Thrombosis

The formation of deep venous thrombosis (DVT) is common in acutely ill patients, occurring in as many as 30% of intensive care unit patients despite prophylaxis.⁷⁷ Acute occlusion of the deep venous system leads to severe sequelae such as venous gangrene (phlegmasia cerulea dolens) as well as long-term consequences, including recurrent DVT and post-thrombotic syndrome (PTS).⁷⁸⁻⁸¹ PTS is characterized by persistent pain, edema, discoloration, and ulceration. Patients with ilio-femoral DVT show higher postthrombotic morbidity than those with infrainguinal DVT. Traditional therapy for DVT includes anticoagulation, prevention of thrombus propagation, stabilization of thrombus, and prevention of PE. However, anticoagulation is not effective for restoring and preserving venous function. Thrombolytic therapy of DVT focuses on the dissolution of clot to prevent PTS. The 2014 Cochrane Review, which grouped both systemic and regional thrombolysis with anticoagulation versus anticoagulation alone, found that patients receiving lytic therapy showed more complete clot lysis (RR, 4.91; 95% CI, 1.66-14.53; $P = 0.004$) and lower incidence of PTS (RR, 0.64; 95% CI, 0.52-0.79; $P < 0.0001$). Thrombolysis carried a higher risk of bleeding complications (RR, 2.23; 95% CI, 1.41-3.52; $P = 0.0006$), but there was no significant difference in mortality.⁸²

More recently, catheter-directed thrombolysis (CDT) and pharmacomechanical thrombolysis have evolved as the first-line lytic therapies for DVT because they are theoretically associated with a reduced risk

of bleeding complications. CDT involves catheter-directed infusion of thrombolytic agents that decreases the total number of doses, which in turn decreases systemic side effects. A recent randomized controlled trial (CaVenT study) involving 209 patients showed that patients with first-time iliofemoral DVT who were treated with CDT within 21 days of symptom onset showed improved iliofemoral patency at 6 months (65.9% vs. 47.4%, $P = 0.012$) and reduction in PTS at 2 years (41.1% vs. 55.6%, $P = 0.047$) compared with patients treated with anticoagulation therapy alone. However, patients receiving thrombolytics also developed 20 bleeding complications.¹⁰⁹

The current guidelines put forth by the Society for Vascular Surgery and the American Venous Forum recommend CDT or pharmacomechanical thrombolysis for treating patients with iliofemoral DVT diagnosed within 14 days of symptom onset, good functional capacity, acceptable life expectancy, and low bleeding risk.⁸³ The ACCP also recommended similar guidelines and reported that CDT was a more preferable approach than systemic thrombolysis.⁸⁴ CDT is also recommended for patients with phlegmasia cerulea dolens. In addition to treating patients with lower extremity disease, CDT has been used for treating young patients with primary upper extremity DVT due to effort thrombosis (Paget-Schroetter syndrome) or idiopathic factors.⁸⁵ Results of the Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis trial will be available in the near future and will help determine the role of thrombolysis for treating DVT.⁸⁶

Acute Peripheral Arterial Occlusion

Acute peripheral arterial occlusion (APAO) is a highly fatal condition that can lead to amputation in 10% to 30% of cases and is associated with a high mortality rate of 15% at 30 days.⁸⁷ Arterial occlusions arise from dissection, trauma, local thrombosis, or emboli. Various noninvasive methods have been developed for treating thromboembolic diseases.

Thrombolysis has become a popular means of treating acute arterial occlusion in certain settings, such as for those without an immediately threatened limb. This approach has been performed since the 1950s.³ Initial attempts involved systemic delivery but were associated with high bleeding risks and poor clinical outcomes. Since the early 1970s, catheter-directed infusion has become the standard of care, which allows higher local thrombolytic concentrations while decreasing the systemic burden of drugs.⁸⁸ Various infusion methods have been developed, including low-dose infusion regimens, high-dose infusion regimens, and high-pressure infusion (pulse spray). However, none of these methods have shown genuine benefit in terms of clinical outcomes.^{89,90}

Although streptokinase was the first agent used for treating APAO, multiple studies have indicated that urokinase and t-PA are more effective for treating APAO than streptokinase, with fewer bleeding complications.⁹¹⁻⁹³ Recently, t-PA and its derivatives have supplanted urokinase as the drugs of choice for treating APAO. The safety and efficacy profiles of low-dose (<2 mg/h, usually beginning at 0.5 mg/h) t-PA regimens are similar to those of urokinase with adjunctive heparin infusion to maintain the aPTT at 1.5 times of that at baseline. With this regimen, over 60% of patients have shown complete resolution and 30% of patients have shown partial resolution of thrombus within 24 hours of treatment initiation.⁹⁴ An advisory panel on CDT recommended weight-based dosage (0.001 to 0.02 mg/kg/h) or non-weight-based dosage (0.12 to 2.0 mg/h), with total doses not exceeding 40 mg.⁹⁵

Use of thrombolytics for treating APAO is part of a multifaceted approach that often involves additional endovascular techniques and/or surgical interventions. The Rochester trial compared initial surgery with urokinase treatment in 114 patients with severely threatened limbs.⁹⁶ Limb salvage rates in the two groups were identical (82%) at 12 months; however, mortality was significantly lower in patients treated with urokinase (16% vs. 42%). The Surgery or Thrombolysis for the Ischemic Lower Extremity trial examined 393 patients randomized

to undergo surgery or one of two lytic therapies (rt-PA or urokinase).⁹⁷ At 30 days, limb loss rates (5% with lysis vs. 6% with surgery) and mortality rates (4% vs. 5%, respectively) were similar between the two groups. Subgroup analyses^{98,99} performed in this study showed higher benefit of thrombolytic therapy in patients with graft occlusion than in those with native vessel occlusion and acute ischemia of less than 2 weeks. The TOPAS trial compared recombinant urokinase therapy with surgery in 544 patients.^{100,101} Although it failed to demonstrate an amputation-free survival benefit at 1 year (68% for urokinase, 69% for surgery), it did show that over 30% of the patients treated with urokinase were not only alive without amputation but also had nothing more than a percutaneous procedure at 6 months. Thus, a significant number of patients can avoid surgery after using thrombolytic therapy. A contemporary series by Taha et al. comparing the effectiveness of endovascular (154 limbs) versus surgical (326 limbs) revascularization for acute limb ischemia also showed similar amputation rates at 1 year (13.0% vs. 19.6%, $P = 0.074$). In this study, 1-year mortality was significantly lower in patients in the endovascular group (12.9% vs. 33.8%, $P < 0.001$).¹⁰²

A 2013 Cochrane Review identified five prospective, randomized trials from the 1990s that compared surgery with thrombolytic therapy for managing acute limb ischemia. The review did not show any overall difference in limb salvage or mortality at 1 year. As expected, patients treated with thrombolytic therapy showed a higher rate of stroke (1.3% vs. 0%) and major hemorrhage (8.8% vs. 3.3%).¹⁰³ Therefore, thrombolytic therapy is still not considered as the standard of care for treating APAO. However, it may be useful for treating patients who are poor candidates for surgery. In some cases, thrombolysis can aid in recanalization of distal vessels that are not patent at treatment initiation, thus permitting subsequent revascularization through bypass surgery. Moreover, it may be the best approach for treating patients with occluded bypass grafts^{97,98} (Fig. 165-4). Use of lytic agents is contraindicated in patients with early postoperative thrombosis, thrombosis after penetrating or multiple trauma, or irreversible ischemia in the limbs.

Other Applications

In addition to the previously listed indications for thrombolytic therapy, another common application is the treatment of thrombosed dialysis grafts or central venous catheters. Although the ultimate goal is to recognize and treat a graft before its failure, thrombolytic treatment can play an important role if the graft is occluded. Several techniques have been used for treating acutely thrombosed grafts, including mechanical thrombectomy, surgical revision, and pharmacologic thrombolysis. A recent meta-analysis indicated that surgical thrombectomy remains the standard of care and is associated with superior patency¹⁰⁴ presumably because of anastomotic revision, which is performed concurrently. In patients with occluded central venous catheters, a 2-mg (1 mg/mL) aliquot of alteplase may be used for treating each occluded lumen for up to 2 hours.⁹⁵ Multiple studies have shown this regimen to be both safe ($\leq 1\%$ bleeding risk) and efficacious ($\approx 90\%$ patency after two treatments).¹⁰⁴⁻¹⁰⁶

MANAGEMENT/LABORATORY VALUES

Administration of thrombolytic agents decreases the levels of circulating plasminogen and fibrinogen. Fibrinogen is degraded during fibrinolysis, reaching nadir values between 5 and 7 hours after therapy initiation.¹⁰⁷ In most patients, these values return to baseline within 48 hours after lysis. Fibrin degradation products are a reliable indicator of fibrinolytic activity because degradation of fibrinogen or fibrin by plasmin is the only source of these products in humans.

Monitoring of fibrinogen levels every 6 to 8 hours is recommended during lytic therapy, with a decrease in dose or discontinuation of infusion if levels decrease to below 100 mg/dL. In addition, platelet counts should be monitored daily or every alternate day. Thrombocytopenia occurs in as many as 10% patients receiving rt-PA compared

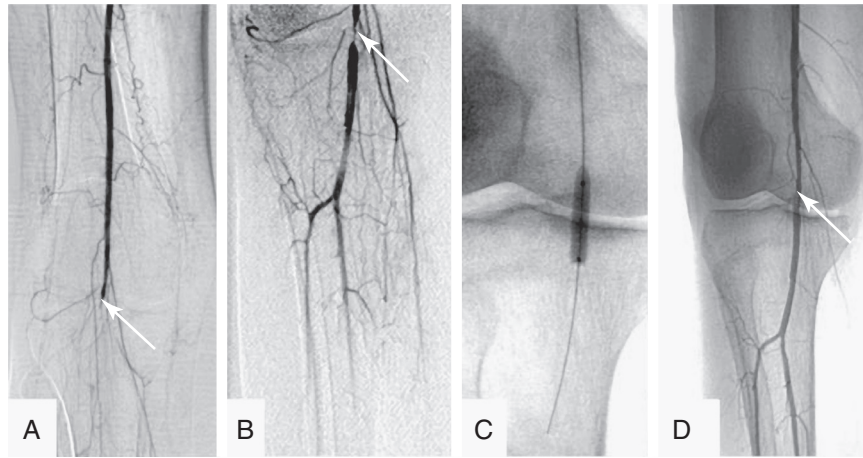


FIGURE 165-4 ■ Successive angiograms showing occluded popliteal artery (arrow, **A**) treated with thrombolytics. After thrombolysis, a focal popliteal artery stenosis is observed (arrow, **B**) along with patent distal vessels. This area was subsequently treated by performing balloon angioplasty (**C**). Thrombolysis and angioplasty resulted in a patent popliteal artery (arrow, **D**), with good distal arterial flow.

with less than 1% patients receiving streptokinase.¹⁰⁸⁻¹¹⁰ If bleeding occurs, thrombolysis should be discontinued and blood products—namely, fresh frozen plasma or cryoprecipitate—should be administered as appropriate to correct the patient's coagulopathic state.

CONCLUSION

Although evidences strongly support the use of thrombolytic agents for treating various occlusive vascular disorders, this treatment is

administered in relatively few patients. Increasing data support the safety and efficacy of thrombolytic therapy, which has substantially increased its use over the past decade. One of the challenges in the coming years will be to more clearly define patients who will benefit the most in terms of both decreased mortality and prevention of hemorrhagic complications. Evolution of technology, including diagnostic modalities, mechanical clot busters and adjuvant therapies, will expand the indications for thrombolytic therapy.

KEY POINTS

1. Thrombolytics comprise a diverse group of compounds that convert plasminogen to plasmin.
2. Thrombolytic therapy is indicated within 6 hours of the onset of acute myocardial infarction, especially in patients who are not eligible for primary angioplasty.
3. Patients with acute ischemic stroke receive the highest long-term benefit from thrombolytic therapy when performed within 4.5 hours of symptom onset.
4. The role of thrombolytic therapy in pulmonary embolism is controversial and limited largely to patients with hemodynamic instability.
5. Urokinase and tissue plasminogen activator are commonly used for managing acute peripheral occlusion. Highest benefit is observed in patients with occlusions for less than 14 days and in those with previous extremity bypasses.
6. Thrombolytic therapy requires intensive monitoring and follow-up radiography. Fibrinogen levels should be monitored every 6 to 8 hours, and patients should be closely monitored for signs of major hemorrhage.

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Atherosclerosis and its thromboembolic complications are leading causes of mortality and morbidity. This progressive disorder usually remains clinically silent until it causes end-organ damage resulting in stroke, ischemic heart disease, and peripheral vascular insufficiency. Atherosclerosis characteristically affects the aorta, with the abdominal aorta more widely involved than the thoracic aorta. Lower limb vessels are more frequently affected than upper limb vessels, while renal, pulmonary, and mesenteric vessels are the least susceptible.

Nearly half of all strokes were thought to result from cerebral vasospasm until the 1950s, when Fisher stressed the etiologic importance of emboli from carotid artery atherosclerotic plaques.¹ Although embolization from the heart and major vessels accounts for a large number of ischemic cerebrovascular accidents, the cause of a significant proportion remains undetermined² and is thought to be embolic in origin. The following account will focus on the pathophysiology, clinical consequences, detection, prevention, and management of atheromatous embolization.

■ PATHOPHYSIOLOGY

Atherosclerosis

The process of atherosclerosis may begin as early as childhood, developing slowly with effects rarely manifesting before the fourth or fifth decades of life. Traditional risk factors include hypertension, diabetes, smoking, and hypercholesterolemia.

Atherosclerosis mainly affects large and medium-sized arteries. Intravascular sites of blood turbulence favor the development of atherosclerotic lesions. Initial changes in arterial wall morphology result in the formation of fatty streaks that consist of lipid-engorged macrophages in the arterial intima. Progression of such precursor lesions occurs secondary to an inflammatory process initiated by endothelial injury and dysfunction.³ Insufficient nitric oxide production results in increased adhesion and aggregation of platelets. Upregulation of the expression of endothelial adhesion molecules and selectins leads to the accumulation of monocytes and T lymphocytes. These cells become activated and produce growth factors, cytokines, and chemokines. Smooth muscle cells migrate from the media into the intima and proliferate. In time, these lesions develop into raised, fibrous plaques consisting of a fibrous cap covering a core containing necrotic material, lipids, and cholesteryl esters. This advanced plaque forms the base onto which the complex plaque develops, consisting of fissures, erosions, or ulceration. Interest has increased in the role of monocytes and macrophages in the pathogenesis of plaque progression and rupture,⁴ processes that are related to thrombosis, embolism, and clinical manifestations.

Atheromatous Embolization

Atheromatous embolization is a descriptive term for embolization of any atheromatous material. *Atheroembolization* refers to the dislodgment of vascular plaque material that contains cholesterol crystals, red blood cells, and fibrin.⁵ This “cholesterol emboli” syndrome comprises renal failure, skin lesions, blue toes, and neurologic manifestations. It can develop spontaneously (due to plaque rupture) or following the use of thrombolytics or anticoagulants⁶ or result from arterial

manipulation (during surgical procedures, cardiac catheterization, or insertion of an intraaortic balloon pump [IABP]).⁷ Disruption of a vascular plaque results in the release of cholesterol crystals with subsequent downstream vascular obstruction and initiation of an inflammatory process with lymphocytic and mononuclear cell infiltration. Biopsy specimens of affected organs such as skin or kidneys are usually diagnostic.

Plaque Morphology and Embolic Risk

Severe atherosclerosis of the ascending aorta appears to be the most important morphologic indicator of an increased risk of atheromatous embolization. The French Aortic Plaque in Stroke group identified a plaque thickness of 4 mm or greater on transesophageal echocardiogram (TEE) as an independent predictor of recurrent embolization.^{8,9} Plaque ulceration and morphology may contribute to an increased risk of embolic events, with evidence of pedunculated, mobile plaques and the absence of calcium conferring a higher risk.^{10,11} The cerebral embolic risk is also influenced by plaque location; as complex plaques are more frequent distal to the ascending aorta, there is increased risk to the left cerebral hemisphere and the peripheral circulation.¹⁰

Macroembolization and Microembolization

Emboli can be divided into macroemboli and microemboli, also described as thromboembolism and atheroembolism. Despite sharing the same underlying pathophysiology, clinical manifestations differ. Thromboemboli affect arteries larger than 200 μ m in diameter, while atheroemboli affect smaller arteries, arterioles, and capillaries.¹² Macroemboli may cause overt clinical presentations (e.g., stroke or peripheral ischemia) while microemboli tend to be more occult in their manifestations of end-organ injury or dysfunction (e.g., renal injury, neuropsychological impairment). Embolization may arise spontaneously or be related to vascular interventions and cardiovascular surgery. The complex aortic-plaque-related 3-year mortality is reported to be as high as 20%.¹³

■ CLINICAL CONSEQUENCES OF ATHEROMATOUS EMBOLIZATION

Cerebral

As the prevalence of aortic atherosclerotic disease increases with age, so does the rate of atheromatous embolization. Postmortem studies indicate that it affects 20% of patients in their fifth decade, increasing to 80% in those in their eighth decade.¹⁴ Emboli from the atherosclerotic thoracic aorta commonly result in stroke (50%) and transient ischemic attack (35%),¹³ with the middle cerebral artery being the most frequent site of arterial embolism. Stroke has profound effects; outcomes from acute stroke are measured in terms of survival, functional independence, and financial cost. Survival after stroke is significantly poorer than after myocardial infarction (MI) or most cancers and is the leading cause of disability in developed countries.¹⁵

Cholesterol emboli (atheroembolization) are an important and frequently unrecognized cause of stroke.¹⁶ Microembolization is a recognized cause of more subtle, sometimes subclinical neurologic injury.^{17,18} This injury is manifested by subtle changes in cognitive function that

may only be evident on detailed neuropsychological testing^{19,20} and include amaurosis fugax, transient ischemic attack, and confusional state. Rarely, embolization to the spinal cord can lead to lower extremity paralysis. The importance of microembolization has increased over recent years, particularly in patients undergoing cardiac surgery.²¹

Cardiac

Atherosclerotic disease is the leading cause of death in developed countries. Every year it results in over 19 million deaths worldwide, and coronary heart disease accounts for the majority of those.²² Most acute coronary syndromes are due to plaque rupture. Distal embolization of cholesterol and atheromatous material may be important in the pathogenesis of some acute coronary syndromes.²³ The occurrence of distal coronary embolization in the setting of acute coronary syndromes has been followed using serum levels of cardiac troponins to detect small degrees of myocardial necrosis. Embolization following percutaneous coronary interventions is well recognized, and elevated troponins are seen in up to 44% of patients.^{24,25}

Peripheral

Peripheral emboli most frequently lodge in the lower extremities. Cholesterol atheroembolization may be subclinical or result in systemic effects. While renal, neurologic, and cutaneous manifestations tend to dominate the clinical picture, involvement of most organs has been reported.

Cholesterol embolization frequently manifests as acute kidney injury^{26,27} and can even lead to renal failure.^{26,27} In those cases, renal biopsy is diagnostic.²⁸ Cutaneous manifestations, including livedo reticularis and the “blue-toe” syndrome, are the most common signs of atheroembolism, occurring in up to 34% of cases.²⁹ Atheroemboli from the carotid vessels give rise to retinal emboli,³⁰ resulting in visual symptoms. The mesenteric circulation may also be affected, resulting in small bowel bleeding³¹ and intestinal infarction. The pancreas, liver, and gallbladder may also be involved.³² More rarely, involvement of transplanted viscera such as the kidney may result in renal failure.³³

■ DIAGNOSIS AND SCREENING

Full clinical assessment and screening of patients presenting with embolic complications are essential in guiding management and prevention strategies. Diagnosis of cholesterol embolization syndrome relies on clinical findings in patients with atherosclerotic disease and a history of recent vascular intervention. As different organs can be involved, a high index of clinical suspicion is vital. It is important to differentiate between atheroembolism and thromboembolism, as the treatment may be guided accordingly.

Many imaging modalities have been used to visualize atherosclerotic plaques; some in routine clinical practice and others reserved for research. Technological advances in imaging have provided tools that allow primary prevention by identifying those at highest risk, enabling appropriate disease-modifying treatment to be initiated.

X-Ray Angiography

X-ray angiography is an invasive procedure that allows assessment of the vascular lumen. However, it is not as sensitive in plaque detection as other imaging modalities and also confers an additional risk of plaque disruption secondary to instrumentation. Despite these limitations, angiography is still regarded as the gold standard for imaging coronary, carotid, and peripheral arterial disease.³⁴

Surface and Transesophageal Ultrasonography

Measurement of carotid and aortic wall thickness as well as qualitative and quantitative assessment of atherosclerotic plaques can be determined using ultrasonography. The North American Symptomatic

Carotid Endarterectomy Trial and the Asymptomatic Carotid Artery Stenosis Study have shown that the degree of stenosis and its hemodynamic consequences are important in the development of stroke.^{35,36} High-resolution, real-time B-mode ultrasound with Doppler flow imaging is currently considered the modality of choice in imaging the carotid arteries.³⁷

With respect to screening, carotid intima-medial thickness (CIMT) measured by B-mode ultrasound is assessed as a risk factor and a marker for vascular disease risk. This marker most accurately represents subclinical vascular disease but not plaque formation or atherosclerosis per se. Epidemiologic and clinical trial evidence, digitization, and standardization have made CIMT a validated and accepted marker for generalized atherosclerosis burden and vascular disease risk.³⁸ CIMT is a predictor of coronary events and stroke, as well as all-cause mortality.^{39,40} The American Society of Echocardiography Carotid Intima-Media Thickness Task Force recommends the use of CIMT measurement by ultrasound in intermediate-risk asymptomatic patients, with a goal of predicting future coronary heart disease events.⁴¹

Transesophageal echocardiography (TEE) is a quick and safe procedure with widespread use ranging from the operating theatre to the bedside.⁴² TEE is the procedure of choice for the detection, assessment, and characterization of thoracic aortic atherosclerosis. TEE can reliably detect intimal thickening, ulceration, calcification, and the presence of mobile components within the aortic plaque (Fig. 166-1). The French Aortic Plaque in Stroke investigators used TEE to assess aortic plaque thickness in patients with stroke, reporting that increased plaque thickness imparted a significant increase in stroke risk.^{8,9} Katz and colleagues used the following 5-grade ranking system to indicate the severity of aortic atherosclerosis as assessed using TEE in 130 patients undergoing cardiac surgery with cardiopulmonary bypass: grade 1, normal aorta; grade 2, flat intimal thickening; grade 3, protruding atheroma in the aortic lumen (<5 mm); grade 4, protruding atheroma (>5 mm); and grade 5, atheroma with a mobile thrombus.⁴³ Patients with grade 5 lesions were at highest risk of stroke. Logistic regression identified aortic arch atheroma as the only variable that was predictive of stroke, with an odds ratio of 5.8. Another study of 315 coronary artery bypass graft (CABG) patients undergoing intraoperative TEE also reported a significant increase in the risk of stroke in patients with aortic arch intimal thickening of greater than 5 mm.⁴⁴

It is no surprise that patients with the highest risk carotid lesions also have high-risk aortic plaques. Assessment of the carotid arteries as well as the aorta is prudent in the investigation of atherosclerotic patients who have suffered embolic events.

Intraoperative Epi-aortic Ultrasound

Epi-aortic ultrasonography involves intraoperative imaging of the ascending aorta using a sterile-sheathed transducer. This technique is

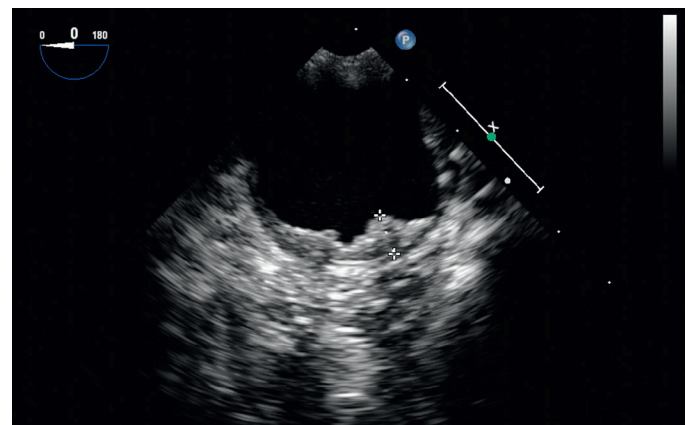


FIGURE 166-1 ■ Transesophageal echocardiogram image showing an aortic plaque measuring 57 mm.

noninvasive and has been used in the context of cardiac surgery to detect areas of ascending aortic atherosclerosis,⁴⁵ thus allowing modification of the surgical technique in an attempt to reduce potential embolic complications.⁴⁶ The main disadvantage of this technique is suboptimal imaging of the aortic arch. Intraoperative epi-aortic ultrasound can therefore be used to complement the information on the aortic arch obtained by TEE.

Transcranial Doppler

Transcranial Doppler (TCD) ultrasonography can be used to detect and quantify cerebral microemboli. Ultrasound probes are placed bilaterally on the temple, overlying the middle cerebral vessels. Emboli cause an increase in the reflected ultrasound, causing high-intensity transient signals (HITS). These HITS are the footprints of microemboli, which may consist of air, fat, atheromatous material, or platelet-fibrin emboli. In addition to detecting cerebral microemboli, TCD can be reliably used to assess cerebral vasomotor reactivity and autoregulation, to document the circle of Willis functional status, and to identify cerebral hypo- and hyperperfusion, recanalization, and reocclusion.⁴⁷

TCD can reliably detect HITS intraoperatively and has been used extensively in the context of cardiac and carotid surgery. During cardiac surgery, microemboli can be detected following intraoperative aortic manipulation (aortic cannulation and application and removal of aortic cross-clamp) as well as during cardiopulmonary bypass.⁴⁸ HITS have also been identified in patients with symptomatic carotid artery stenosis,⁴⁹ patients with prosthetic heart valves,⁵⁰ and those with aortic atherosclerosis.⁵¹ Their presence is a significant independent predictor of early recurrence of stroke.⁵²

A major limitation is an inadequate acoustic window in 5% to 20% of individuals.⁵³ With multirange, multifrequency Doppler systems, automatic artifact rejection and differentiation between solid and gaseous microemboli have become possible with high sensitivity and specificity.^{54,55} A significant reduction in intraoperative cerebral microembolism as well as a reduction in the proportion of solid microemboli has been reported with TCD, with avoidance of cardiopulmonary bypass and minimizing manipulation of the ascending aorta during cardiac surgery.^{48,56}

An exciting recent development with TCD ultrasonography is its therapeutic use in the treatment of stroke. This procedure involves the use of TCD ultrasound to augment the effect of fibrinolysis and has been shown to at least double the chance of early complete arterial recanalization.⁵⁷

Computed Tomography

Computed tomography (CT) can be used for imaging the aorta and quantifying aortic wall calcification. Contrast-enhanced CT has been proposed as a valuable method for following the progression and regression of atherosclerotic disease.⁵⁸ The main advantage over TEE is the ability to completely image the thoracic and abdominal aorta. Disadvantages include radiation and contrast exposure with potential for renal damage, limiting its use in asymptomatic populations.

Coronary multidetector CT angiography (MDCTA) can be used in identifying patients at a particularly high risk of dying suddenly or suffering a nonfatal MI. It provides information on coronary artery stenosis as well as an estimate of calcification, coronary artery calcium (CAC). The latter is related to multiple risk factors of coronary artery disease. The importance of CAC screening lies in its potential to increase the predictive power of testing for future events.^{40,59}

Magnetic Resonance Imaging Techniques

Magnetic resonance imaging (MRI) has emerged as a leading noninvasive imaging modality for atherosclerotic disease. MRI can be used to image atherosclerotic plaques in aortic, carotid, peripheral, and coronary arterial disease.^{60,61} Its major strengths rest in its ability to

determine plaque morphology. Using a range of techniques, MRI can provide valuable information on the composition of the atherosclerotic plaque by identifying the three main factors that determine plaque stability: (1) presence of a lipid core, (2) thickness of the fibrous cap, and (3) inflammation within the cap. MRI allows identification of high-risk unstable plaques and thus guides intervention and therapy⁶² as well as monitoring response to therapy with statins.⁶³ Magnetic resonance angiography has a high sensitivity and specificity and can be used to image the aorta, carotid, renal, and other peripheral vessels. Evolving magnetic resonance techniques include intravascular⁶⁴ and transesophageal⁶⁵ MRI.

Tissue Diagnosis

Cholesterol embolization can only be confirmed with biopsy, as the clinical manifestations are often subtle and nonspecific compared to those of thromboembolism. Cholesterol clefts in arterioles are evidence of cholesterol crystal emboli that have dissolved during the process of fixation of the specimen. Intimal proliferation of the arterial vascular bed following cholesterol crystal embolization may be responsible for the end-organ malperfusion.⁶⁶

VASCULAR MANIPULATION AND EMBOLIC EVENTS

Cardiac Surgery

Stroke, transient ischemic attack, and peripheral embolization are potential complications following cardiac surgery. Atheroembolism results in a variety of clinical manifestations and can be fatal in about 20% of patients.⁶⁷ Stroke affects less than 2% of CABG patients and is higher in those undergoing open-heart procedures.⁶⁸ The risk of perioperative stroke increases with advancing age, and those with concomitant cardiovascular risk factors are at highest risk.⁶⁹ Additionally, female sex is independently associated with a significantly higher risk of perioperative stroke.⁷⁰ Embolization from the atheromatous aorta is the single most important etiologic factor for stroke. This risk arises during intraoperative manipulation of the aorta, including cannulation for cardiopulmonary bypass, application, and removal of aortic cross-clamp for administration of cardioplegia, and the use of side-clamps for anastomosis of the proximal end of the graft to the aorta.⁷¹ Patients undergoing cardiac surgery with aortic plaque greater than or equal to 5 mm had a higher incidence of stroke.⁷² As previously mentioned, mobile plaques confer a greater risk of stroke. This effect was seen in an analysis of 130 patients undergoing coronary artery bypass grafting, with a higher incidence of stroke in the cohort in whom mobile plaques were identified.⁷³ Roach et al. showed that atherosclerosis of the ascending aorta is the strongest independent predictor of perioperative stroke, with an odds ratio of 4.5.⁷⁴

Cardiac Catheterization and Peripheral Vascular Intervention

Aortic manipulation during cardiac catheterization procedures or intraaortic balloon pump (IABP) insertion may cause embolization from aortic atheroma. In a report comparing 59 patients with atherosclerotic aortic debris undergoing transfemoral cardiac catheterization, an embolic event occurred in 17% of the patients with atherosclerotic aortas compared to 3% of controls.⁷⁵ In the proportion of patients requiring IABP, 5 out of 10 patients with atherosclerotic aortas had an embolic event compared with none of the 12 patients with IABP in the control group. When a transbrachial approach was used in patients with atherosclerotic aortas, none of 11 patients suffered an embolic event. Patients with mobile aortic atheromas on TEE are at highest risk of catheter-related embolization.⁷⁵ A recent study reported the rate of clinically significant distal embolization in 2.4% of patients undergoing peripheral arterial intervention.⁷⁶

Cholesterol embolization can complicate cardiac catheterization. Because it is commonly asymptomatic, the exact incidence is uncertain and mainly depends on the detection criteria used (clinical or pathologic). Cholesterol can be identified in the lumen of affected arterioles in up to 12% of patients following cardiac catheterization.⁷⁷ A prospective multicenter study reported cholesterol embolization in 1.4% of patients following cardiac catheterization based on evidence of peripheral cutaneous involvement or renal dysfunction.⁷⁸ The syndrome occurred more frequently in patients with generalized atherosclerosis.

PREVENTION AND MANAGEMENT

Treatment of atheromatous embolization depends on the clinical manifestation. However, evidence of atherosclerotic disease with plaque should be considered a cardiovascular risk factor, and preventive measures should be taken despite the symptomatic status of the individual. General measures include identification and modification of risk factors. Patients with the clinical syndrome of cholesterol embolization have a generally poor prognosis, particularly when there is evidence of visceral and renal involvement. Supportive management with blood pressure control and, if necessary, renal replacement therapy is indicated. Strategies for the general prevention and management of atheromatous embolization are discussed here.

Antiplatelet Agents and Anticoagulants

As thrombi can develop on and embolize from atherosclerotic plaques, it seems logical to use antiplatelet agents or anticoagulants to prevent these thromboembolic complications. Three studies have reported a reduction in the risk of stroke with anticoagulation.⁷⁹⁻⁸¹ These studies, however, were not randomized and did not include long-term follow-up. A randomized trial reported that in patients with stroke, large aortic plaques remain associated with an increased risk of recurrent stroke and death at 2 years despite treatment with warfarin or aspirin.⁸²

The ARCH (Aortic Arch Related Cerebral Hazard) trial was an open-label trial where patients with aortic arch atheroma (4 mm or greater) and nondisabling stroke were assigned to warfarin (target INR, 2.0-3.0) versus aspirin (75 mg/d) plus clopidogrel (75 mg/d) and followed longitudinally to determine which treatment was superior for secondary stroke prevention. Unfortunately, the trial was stopped prematurely and was underpowered to determine a difference in the primary end points of cerebral infarction, myocardial infarction, peripheral embolism, and intracranial hemorrhage, although vascular death was significantly lower in the dual antiplatelet cohort.⁸³ The main concern with anticoagulation is the risk of plaque hemorrhage and atheroembolization.⁸⁴ However, the risk of clinical atheroemboli syndrome during warfarin therapy in such patients appears to be low (only 1 episode in 134 patients according to the Stroke Prevention in Atrial Fibrillation trial).⁷⁹

In patients with atherosclerosis, acute ischemic events are usually precipitated by thrombosis, and antiplatelet agents play a fundamental role in thrombosis prevention. Routine use of aspirin in high-risk patients is universally recommended.⁸⁵ The Antithrombotic Trialists' Collaboration published a major meta-analysis with over 200,000 patients, assessing the effect of antiplatelet therapy in patients with various manifestations of atherosclerosis. This study reported a significant reduction in the rate of stroke, MI, or vascular death in those on antiplatelet therapy.⁸⁶

Aspirin is the most commonly used antiplatelet agent. It inhibits thromboxane-dependent platelet aggregation. Thienopyridines, including clopidogrel and ticlopidine, act by blocking adenosine diphosphate (ADP)-dependent activation of platelets. There is evidence that thienopyridine derivatives are modestly but significantly more effective than aspirin in preventing serious vascular events in patients at high risk, but there is uncertainty about the size of the additional benefit.⁸⁶ The thienopyridines are also associated with less

gastrointestinal hemorrhage and upper gastrointestinal upset compared to aspirin but with an excess of rash and diarrhea.⁸⁷ In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, a long-term benefit was observed with the use of clopidogrel in addition to aspirin in high-risk patients (unstable angina and non-Q-wave MI).⁸⁸

Platelet activation leads to a conformational change in glycoprotein IIb/IIIa, the major fibrinogen receptor on platelets. Intravenous glycoprotein IIb/IIIa inhibitors (e.g., abciximab) are generally reserved for the high-risk setting of percutaneous coronary intervention.

Dextran has antiplatelet and intravascular volume expansion effects. Postoperative or perioperative administration of 10% dextran 40 reduces the rate of TCD-detected microembolic signals after carotid endarterectomy.^{89,90} Dextran, however, may interfere with cross-matching blood and cause bleeding, renal failure, or (occasionally) acute allergic reactions.

The Guidelines for the Diagnosis and Management of Patients with Thoracic Aortic Disease have been published by the ACCF/AHA. Oral anticoagulation therapy with warfarin (INR, 2.0-3.0) or antiplatelet therapy in stroke patients with aortic arch atheroma 4.0 mm or greater to prevent recurrent stroke was a class IIb recommendation (level of evidence, C).⁹¹ However, ACCP guidelines from 2012 recommend that patients with aortic disease with no previous neurologic event have no indication for anticoagulation.⁹²

Statins

There is a clear association between elevated levels of plasma cholesterol and atherosclerotic disease. Statins or 3-hydroxy-3-methylglutaryl coenzyme-A (HMG Co-A) reductase inhibitors reduce the hepatocyte cholesterol content and increase expression of LDL-cholesterol receptors, resulting in a drop in serum low-density lipoprotein (LDL) cholesterol. In addition, it has become evident in recent years that statins possess cholesterol-independent or pleiotropic effects. These include improvement of endothelial function by improving the bioavailability of nitric oxide, decreasing vascular inflammation, and stabilizing plaques.⁹³ Statins are widely used in primary and secondary prevention of ischemic heart disease. A meta-analysis of randomized placebo-controlled double-blind trials with statins reported a 30% reduction in stroke risk with statin therapy.⁹⁴ Another meta-analysis of data pooled from over 49,000 patients treated with statins in 28 trials reported a relative risk of stroke of 0.76 in statin-treated patients.⁹⁵ Tunick et al. showed that statin therapy was independently and significantly protective against the occurrence of embolic events (risk ratio, 0.39) in patients with severe thoracic aortic plaque.¹³

Plaque size reduction, stabilization, and prevention of plaque thrombosis may be the mechanisms leading to a reduction in atheromatous embolization. Two randomized studies of low-dose and higher dose statins in patients with aortic and/or carotid plaques showed significant regression in plaques seen on MRI.^{96,97}

Minimal Aortic Manipulation

The use of smaller arterial catheters during cardiac catheterization may help reduce the risk of embolization.⁹⁸ Reduction of embolization during cardiac surgery is possible with modifications to the operative technique. Avoidance of aortic manipulation intraoperatively is most important.⁷¹ This can be achieved in patients undergoing CABG by avoidance of cardiopulmonary bypass, which obviates the need for aortic cannulation and cross-clamping.^{99,100} The use of composite arterial grafts (bilateral internal thoracic artery grafts with the radial artery anastomosed to the internal thoracic artery) avoids the need for proximal aortic anastomosis requiring a side-clamp.¹⁰¹ Off-pump surgery has been shown to offer a reduction in the risk of stroke in patients with atheromatous aortas.¹⁰² We have reported a significant reduction in cerebral microembolization by avoiding cardiopulmonary bypass and aortic manipulation.^{48,56} A strategy for potential prevention of embolization in cardiac surgery is summarized in [Box 166-1](#).

BOX 166-1

Prevention of Embolization During Cardiac Surgery in Patients with Atherosclerosis

- Establish the patient's preoperative risk factors.
- Image the ascending aorta and arch preoperatively.
- Assess the carotid arteries.
- Assess the ascending aorta using intraoperative epiaortic ultrasound.
- Use evidence-based decisions to reflect the operative technique.
- Decide the site and risk of cannulation.
- Avoid repeated aortic clamping.
- Consider no-touch aortic techniques.
- Perform off-pump surgery with composite arterial grafting where possible.

Surgical Treatment

Treatment of patients with symptomatic carotid atherosclerosis is well established. The European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators reported a clear benefit of carotid endarterectomy in the prevention of stroke in patients with high-grade, recently symptomatic carotid stenosis.^{35,103} This benefit is offset by the surgical risk of the procedure. The perioperative stroke and death rate for patients with high-grade stenosis was 8% at 30 days in ECST and 6% in NASCET. These rates are acceptable, given the absolute risk reduction by surgery of 10% and 17%, respectively. However, for patients with asymptomatic carotid disease, the risk-to-benefit ratio is narrower, and carotid endarterectomy is currently only recommended for high-grade carotid stenosis (70%-99%).

The international carotid stenting study looked at angioplasty and stenting of the carotid vessels as an alternative to endarterectomy. However, they reported higher rates of stroke and mortality with carotid stenting compared to endarterectomy and therefore recommended that carotid endarterectomy should remain the treatment of choice.¹⁰⁴

Management of patients with recurrent embolic events due to aortic atherosclerotic disease can be problematic. Aortic arch endarterectomy in patients with severe aortic atherosclerosis has been reported.¹⁰⁵⁻¹⁰⁷ This procedure is performed using deep hypothermic circulatory arrest and is associated with significant perioperative morbidity and

mortality. When performed during cardiac surgical procedures using cardiopulmonary bypass, it resulted in a significantly higher rate of stroke and mortality. Therefore, there is insufficient evidence to recommend this mode of treatment for stroke prevention. In the context of cardiac surgery, replacement of the ascending aorta can be performed with acceptable mortality and morbidity,¹⁰⁸ particularly in the intraoperative management of patients with so-called porcelain aorta¹⁰⁹ (severe diffuse atherosclerosis and calcification of the ascending aorta that causes an eggshell appearance on x-ray or CT).

With increasing interest in endovascular surgery, stenting as a means of preventing subsequent embolization from aortic plaque has been explored with some success. This involves the use of covered stents to exclude the plaque disease. This minimally invasive approach may offer a treatment strategy for patients who are unfit for conventional surgery despite its inherent risk of embolization secondary to instrumentation.^{110,111}

KEY POINTS

1. Atherosclerosis and its thromboembolic complications are a leading cause of death in the Western world.
2. The risk of atheromatous embolization increases significantly with increasing plaque thickness (>4 mm) and the presence of ulceration.
3. Ultrasonography (transesophageal and surface) is one of the most frequently used investigative techniques. Computed tomography provides information on coronary artery atherosclerosis and the degree of calcification. Magnetic resonance imaging provides very high resolution in imaging plaque morphology.
4. The risk of embolization increases significantly during cardiac surgery and vascular interventions.
5. The use of antiplatelet agents and statins is recommended in all patients with significant atherosclerotic disease.
6. Perioperative aortic screening allied with minimal aortic manipulation during cardiac surgery in high-risk patients may be associated with a significant reduction in the rate of atheromatous embolization.

ANNOTATED REFERENCES

Amarenco P, Cohen A, Tzourio C, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med* 1994;331:1474-9.

This French Aortic Plaque in Stroke group prospective case-control study of 250 patients with ischemic stroke reports that increased plaque thickness imparted an increased risk of stroke, especially with plaques greater than 4 mm in thickness.

Bucher HC, Griffith LE, Guyatt GH. Effect of HMG CoA reductase inhibitors on stroke. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 1998;128:89-95.

This meta-analysis of over 49,000 statin-treated participants from 28 trials reported that the risk ratio for nonfatal and fatal stroke with HMG CoA reductase inhibitors was 0.76 (95% CI, 0.62-0.92). An overall reduction in the rates of death from coronary heart disease as well as a reduction in overall mortality with HMG CoA reductase inhibitors is demonstrated.

Cohen A, Tzourio C, Bertrand B, et al. Aortic plaque morphology and vascular events: a follow-up study in patients with ischemic stroke. FAPS Investigators. French Study of Aortic Plaques in Stroke. *Circulation* 1997;96:3838-41.

This study of 334 patients aged 60 years and above reported that in patients with brain infarction, the risk associated with aortic plaque thickness (≥ 4 mm) is markedly increased by the absence of plaque calcifications.

Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.

This large meta-analysis with more than 200,000 patients reported that aspirin is protective in most patients at increased risk of occlusive vascular events, including those with an acute MI or ischemic stroke, unstable or stable angina, previous MI, stroke or cerebral ischemia, peripheral arterial disease, or atrial fibrillation.

de Groot E, van Leuven SI, Duivenvoorden R, et al. Measurement of carotid intima-media thickness to assess progression and regression of atherosclerosis. *Nat Clin Pract Cardiovasc Med* 2008;5:280-8.

This review describes the use of CIMT measurements in the assessment of atherosclerosis. CIMT is demonstrated to be a useful tool in risk evaluation of individuals and in studies of atherosclerosis progression and regression.

Evered LA, Silbert BS, Scott DA. Postoperative cognitive dysfunction and aortic atheroma. *Ann Thorac Surg* 2010;89:1091-7.

In over 300 patients undergoing cardiac surgery, the incidence of early postoperative cognitive decline was directly related to aortic atheroma burden (imaged using TEE and epiaortic ultrasound).

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■ EPIDEMIOLOGY

A *pressure ulcer* is any wound that develops in the upper and outer layers of the skin because of sustained external pressure.¹ Pressure ulcers are serious complications in hospitalized patients. They increase health care costs, decrease patients' quality of life, and often result in prolonged hospital stay. Current estimates of the prevalence of pressure ulcers in hospital patients vary between 5% and 17%. In the largest investigation to date, the incidence of hospital-acquired pressure ulcers was 4.5%, and the prevalence of pressure ulcers on admission was 5.8%. More significantly, almost 1 in 5 patients admitted with a previously acquired pressure ulcer developed an additional pressure ulcer at a different site during their hospital stay.^{2,3} The prevalence of pressure ulcers is higher (up to 30%) among residents of long-term geriatric facilities, whereas the majority of pressure ulcers (50%) in hospitalized patients are stage I ulcers, and the prevalence of stage III and IV ulcers is estimated to be as high as 4% in patients residing in long-term care facilities.

■ RISK FACTORS

Multiple risk factors associated with the development of pressure ulcers are listed in [Tables 167-1](#) and [167-2](#).³ These factors can be categorized as intrinsic, which are related to a patient's preexisting medical condition(s), and extrinsic factors, which are related to a patient's environment. Intrinsic risk factors include neurologic disease, motor impairment, cognitive impairment, sensory deficits, malnutrition, and hypoperfusion due to peripheral vascular disease or congestive heart failure. Extrinsic risk factors include inadequate mobilization by care providers, trauma, sedation, application of physical restraints, improper positioning (especially among patients under general anesthesia), moisture, and shearing forces. Of these risk factors, failure to frequently change position is thought to be the biggest contributor to pressure ulcer formation. A combination of improper positioning and moisture on the skin surface is a frequent cause of pressure ulcer formation in critically ill patients.

Because of the underlying pathophysiology of pressure ulcer formation, there are several high-risk areas for the development of pressure ulcers. Pressure ulcers are more prone to develop in bony or cartilaginous areas. These include any area of the body with limited soft tissue coverage, such as the coccyx, spinous processes, heels, elbows, and ankles. In patients who are mostly positioned on their side, the iliac crest and trochanters are considered high-risk areas. Additionally, patients with malnutrition and subsequent cachexia have significant loss of soft tissue and are more prone to the development of pressure ulcers at any location.

■ PATHOPHYSIOLOGY

Pressure ulcers develop because of hypoperfusion to an area. The principle underlying pressure ulcer development is simple. When externally applied pressure exceeds capillary perfusion pressure, blood flow becomes impaired and tissue ischemia occurs. If hypoperfusion and ischemia are not reversed, necrosis of the involved tissue layers will occur. Ischemia will initially present with erythema and induration. If this progresses to necrosis, tissue loss will occur. The duration of critical ischemia varies from patient to patient. However, it is generally

accepted that pressure injury typically occurs between 30 and 240 minutes after hypoperfusion. In patients with preexisting peripheral vascular disease, time to critical ischemia is shorter. Because of impaired arterial inflow, these patients experience significant delay in the restoration of perfusion and reversal of tissue hypoxia after the removal of external pressure. In addition, because of poor underlying tissue perfusion, these patients will experience longer healing times once pressure ulcers develop.

■ CLASSIFICATION

All pressure ulcers begin in the outer layers of the skin. With ongoing pressure, the ischemia progressively extends to deeper layers of the skin. Therefore, pressure ulcers are classified into four stages (stages I-IV) based on the depth of skin involvement, with stage I being the most superficial and stage IV being the deepest. The classification of pressure ulcers is listed in [Table 167-3](#). Having a uniform and well-defined system for pressure ulcer classification is critical for the standardization of wounds during research and for accurate communication on wound staging among health care providers. Once a pressure ulcer develops, it is important to classify the wound and monitor the progress of the wound bed. Having a standard grading system allows for continuity of care and objective monitoring of the progression of the wound.

■ PREVENTION

Prevention of pressure ulcer formation should be standard practice. This is of particular importance when caring for critically ill patients, because they often possess multiple risk factors for pressure ulcer formation.

Risk Assessment

Prevention programs should include initial risk assessment of individual patients. This assessment should include questioning patients on previous or preexisting pressure ulcers; thorough inspection of the skin; evaluation of patients' mobility/activity level, continence, and nutritional status; and a review of comorbid conditions that may contribute to the development of pressure ulcers. Assessment of these risk factors should be standardized and documented. Several tools have been developed for pressure ulcer risk assessment. The Braden Scale assesses external pressure forces and skin-related factors in a standardized manner.⁴ The Norton Scale assesses patient-specific risk factors (age, cognitive impairment, mobility, and incontinence) of pressure ulcer development.⁵ Waterlow Scale, which was initially developed for use in pediatric population, assesses both intrinsic and extrinsic risk factors.⁶ However, studies performed to date have shown limited efficacy of these tools for decreasing the incidence of pressure ulcers compared with nonstructured risk assessment.⁷

Prevention Plan

Once the individual patient risk assessment is performed, a plan for preventing pressure ulcers should be implemented. Regardless of the plan utilized, a frequent assessment of its efficacy must be performed, and any necessary adjustments should be made. The key elements for

TABLE 167-1 Participant Characteristics

| CHARACTERISTICS | TOTAL (N = 51,842) | PARTICIPANTS WITH PRESSURE ULCERS (N = 2313) | PARTICIPANTS WITHOUT PRESSURE ULCERS (N = 49,529) | P VALUE |
|--|-----------------------|---|--|---------|
| Age (mean ± standard deviation) | 73.3 ± 13.0 years | 78.0 ± 11.2 years | 73.2 ± 13.0 years | <0.001 |
| Age, n (%) | | | | |
| <65 years | 8878 (17.1) | 236 (10.2) | 8642 (17.4) | <0.001 |
| 65-74 years | 15,824 (30.5) | 494 (21.4) | 15,330 (31.0) | |
| 75-84 years | 17,621 (34.0) | 879 (38.0) | 16,742 (33.8) | |
| >84 years | 9519 (18.4) | 704 (30.4) | 8815 (17.8) | |
| Non-white, n (%) | 43,639 (84.2) | 1980 (85.6) | 41,659 (84.1) | 0.05 |
| Female, n (%) | 29,088 (56.1) | 1307 (56.5) | 27,781 (56.1) | 0.69 |
| Congestive heart failure, n (%) | 15,071 (29.1) | 1013 (43.8) | 14,058 (28.4) | <0.001 |
| Chronic obstructive pulmonary disease, n (%) | 14,716 (28.4) | 810 (35.0) | 13,906 (28.1) | <0.001 |
| Cerebrovascular disease, n (%) | 11,862 (22.9) | 785 (33.9) | 11,077 (22.4) | <0.001 |
| Diabetes mellitus, n (%) | 17,512 (33.8) | 971 (42.0) | 16,541 (33.4) | <0.001 |
| Corticosteroids, n (%) | 4154 (8.0) | 223 (9.6) | 3931 (7.9) | 0.003 |
| Obesity, n (%) | 6822 (13.2) | 343 (14.8) | 6479 (13.1) | 0.02 |
| Smoking, n (%) | 8324 (16.1) | 306 (13.2) | 8018 (16.2) | <0.001 |

Lyder CH, Wang Y, Metersky M, et al. Hospital-acquired pressure ulcers: Results from the National Medicare Patient Safety Monitoring System Study. *J Am Geriatr Soc* 2012;60(9):1603-8.

TABLE 167-2

Hierarchical Generalized Linear Model Association Between Participant Characteristics and Pressure Ulcer Development

| CHARACTERISTICS | ODDS RATIO (95% CONFIDENCE INTERVAL) | P VALUE |
|---------------------------------------|--|---------|
| Age (reference, ≥85 years) | | |
| <65 years | 0.82 (0.79-0.84) | <0.001 |
| 65-74 years | 0.82 (0.8-0.84) | <0.001 |
| 75-84 years | 0.89 (0.87-0.91) | <0.001 |
| Female | 0.99 (0.97-1.01) | 0.37 |
| White | 1.01 (0.98-1.03) | 0.56 |
| Cancer | 1.07 (1.05-1.09) | <0.001 |
| Congestive heart failure | 1.11 (1.09-1.13) | <0.001 |
| Chronic obstructive pulmonary disease | 1.05 (1.02-1.07) | <0.001 |
| Cerebrovascular disease | 1.11 (1.09-1.13) | <0.001 |
| Diabetes mellitus | 1.07 (1.05-1.09) | <0.001 |
| Corticosteroids | 1.03 (1.00-1.07) | 0.04 |
| Obesity | 1.04 (1.01-1.07) | 0.002 |
| Smoking | 1.00 (0.98-1.03) | 0.8 |

Lyder CH, Wang Y, Metersky M, et al. Hospital-acquired pressure ulcers: Results from the National Medicare Patient Safety Monitoring System Study. *J Am Geriatr Soc* 2012;60(9):1603-8.

preventing pressure ulcer formation include patient mobilization, patient positioning for preventing/removing pressure, and the use of positioning aides to redistribute pressure. In critically ill patients, particularly patients who have been sedated over prolonged periods, prevention of pressure ulcer formation requires vigilance and team effort. Prevention also includes avoidance of skin damage by shear forces and of maceration of the skin due to moisture from incontinence and heat accumulation. Various support surfaces are available for decreasing the

TABLE 167-3 Pressure Ulcer Staging

NATIONAL PRESSURE ULCER STAGING SYSTEM

| | |
|-----------|--|
| Stage I | Non-blanching erythema of the intact skin |
| Stage II | Partial-thickness skin loss involving the epidermis and/or dermis. The ulcer is superficial and presents clinically as an abrasion, blister, or shallow crater. |
| Stage III | Full-thickness skin loss, with damage and/or necrosis of the subcutaneous tissue. The wound extends farther into the skin but not through the underlying fascia. |
| Stage IV | Full-thickness skin loss, with extensive destruction and necrosis of overlying structures, including muscles, bone, or tendon. |

risk of pressure ulcer formation. These pressure-reducing surfaces include static support surfaces (mattresses and mattress overlays) and dynamic support surfaces that mechanically alter the amount of pressure applied to patients' skin. Examples of dynamic support surfaces include low-air-loss beds, air-fluidized mattresses, and alternating pressure mattresses. The use of foam mattress overlays can reduce the risk of pressure ulcer development in high-risk populations.⁸ Although associated with higher costs, dynamic mattresses have not consistently been shown to be superior to static support surfaces. However, dynamic mattresses are superior to standard hospital mattresses in preventing pressure ulcer formation.

TREATMENT

Various treatment options and products are available for managing pressure ulcers. However, very few of the currently available treatment options have been rigorously evaluated in randomized controlled trials.^{9,10} An in-depth discussion of all currently available treatment options is beyond the scope of this chapter; therefore, we have discussed general classes of these treatment options rather than specific products.

Wound Débridement

Wound débridement is a critical step in the healing of pressure ulcers. Débridement removes foreign material and devitalizes tissue from the

wound. After débridement, a wound bed of healthy tissue should be visible. Débridement of the wound bed reduces the production of inflammatory mediators that inhibit wound healing. Various techniques are available for wound débridement, such as surgical débridement, hydrotherapy, larval therapy, and topical enzymatic débridement. The choice of a débridement technique used depends on multiple factors, including size of wound, comorbid conditions, and presence of infection. Surgical débridement is often required in large-volume wounds requiring extensive tissue débridement. However, surgical débridement requires the patient be a suitable candidate for general anesthesia. The risk of subjecting a critically ill patient to general anesthesia and a trip to the operating room must be weighed against the benefits of surgical débridement of a pressure ulcer. Although hydrotherapy is commonly practiced, it has not been evaluated rigorously in large, randomized controlled trials. However, some small studies on patients with stage III or IV pressure ulcers have shown faster wound healing in patients receiving hydrotherapy compared with those not receiving hydrotherapy.^{11,12}

Larval therapy (also referred to as biosurgery) can also be used for debriding pressure ulcers. The basic concept of larval therapy is that application of larvae to wounds results in rapid débridement of necrotic tissues while avoiding potential complications associated with surgical débridement, such as pain and bleeding. Currently, there is evidence that compared to topical enzymatics, larval therapy significantly reduces the time to débridement of necrotic tissue. However, the use of larval therapy did not appear to have any effect on the time to wound healing.¹³

Various topical enzymatic débridement products are commercially available. These can be used alone or in conjunction with other débridement techniques. These agents are applied directly to the wound bed once or twice a day. Multiple randomized controlled trials have validated the efficacy of topical enzymatic débridement products for removing necrotic tissue from the wound bed.¹⁴ Before applying these agents, the wound bed should be cleansed with normal saline. Presence of any topical wound products containing metals will decrease the efficacy of topical enzymatics. Therefore, removing these agents from the wound bed is critical for the success of topical enzymatics. In the event an eschar is overlying the wound bed, it is recommended that the eschar be crosshatched using a surgical blade to allow the penetration of a topical enzymatic agent. Once applied, the wound bed should be covered with gauze. Topical enzymatic agents are a viable and valuable therapy, particularly in patients who cannot undergo alternative débridement methods.

Hydrocolloids

Hydrocolloid dressings that absorb wound exudates are widely used for managing pressure ulcers. Typical hydrocolloid dressings contain a gel-forming agent that is placed in contact with the wound bed, and this is covered with a membrane that protects the wound against external contamination but allows water evaporation.¹⁴ Hydrocolloid dress-

ings are typically applied every 3 to 5 days depending on the amount of exudates produced in the wound. Compared to standard gauze dressings, hydrocolloid dressings are more absorptive and less painful.¹⁴

Negative Pressure Therapy

The use of negative pressure therapy for wound healing has become increasingly common in the past decade. The basic concept behind this therapy is that applying negative pressure to the wound bed both removes edema fluid and increases blood flow to the area. Increased blood flow results in the delivery of oxygen and nutrients, which promote wound healing. In addition, application of negative pressure to the wound results in wound contracture. Compared to standard wet-to-dry dressings, another benefit to patients of negative pressure therapy is decreased frequency of dressing changes. The use of negative pressure therapy for treating pressure ulcers has been associated with improved wound healing and decreased hospital stay.¹⁵ Traditionally, negative pressure therapy has been applied to clean wounds with very less slough or necrotic tissue. However, some evidence indicates that the application of negative pressure therapy is a viable option for managing wounds covered with soft necrotic tissue.¹⁶

Nutritional Support

The presence of malnutrition has a significant impact on wound healing. In fact, its mere presence results in the weakening of the skin and increases the risk of pressure ulcer development. Unfortunately, nutritional assessment is often neglected, particularly in chronically institutionalized patients. Establishing nutritional assessment protocols as well as treating malnutrition is essential for preventing and healing pressure ulcers. This is best accomplished by forming a multidisciplinary team comprising physicians, dietitians, and nursing staff.¹⁷

An initial nutritional assessment should be performed. Any recent weight loss, the current weight, and the patient's dietary intake should all be evaluated. After the initial assessment is completed, a nutrition plan should be created and implemented to address any identified issues. Weekly monitoring of patients' nutritional status, including the patients' weight and functional status, should be performed to determine whether the nutritional intervention is exerting the desired effect. In addition, biochemical tests, including determination of serum prealbumin, transferrin levels, and nitrogen balance, are also helpful.

CONCLUSION

Pressure ulcers continue to be a common problem among critically ill patients. Constant vigilance and education of care providers are essential for preventing pressure ulcer formation. A multidisciplinary approach is needed to manage these debilitating wounds. Management should include objective assessment of the wound, implementation of a multimodality treatment program adapted to patients' needs, and optimization of patients' nutritional status to promote wound healing.

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Survival rates and quality have improved dramatically for victims of serious burns in recent decades. For those with smaller burns, the experience and outcome of healing have also improved and moved largely to the outpatient setting. A better understanding of injury physiology, wound healing, and the impact of early surgery for deep injuries has driven these improvements.¹ Burn critical care has evolved to be an essential embedded component of all successful burn programs. This chapter focuses on those aspects of burn critical care that are unique to the care of patients with medium to large burns.²

PHASES OF BURN CARE

Successful management of patients with serious burns requires an effective initial resuscitation and development of an overall plan for acute-phase hospitalization. This care plan can be broken down into four phases (Table 168-1).³ Phase one is the initial evaluation and resuscitation phase. This runs from approximately injury through day 3 and focuses on thorough evaluation for nonburn trauma and accurate fluid resuscitation. The second phase, initial wound excision and biological closure, occupies the first 5-7 days after injury. Major objectives of this phase are clear identification and excision of deep wounds (those unlikely to heal) with immediate permanent or temporary biological closure of generated wounds. This maneuver reduces local and systemic infection and inflammation. In unstable patients or those with large wounds, this may require a series of staged operations. Phase three, definitive wound closure, occupies the ensuing days or weeks and includes replacement of temporary wound membranes with autografts and definitive closure of small complex wounds such as those of the face and hands. Phase four is rehabilitation and reconstruction. This phase can require months or even years in patients with massive burns but is consistent with simultaneous return to work, school, and community. The priorities of this phase of care are functional independence, normalization of life, and emotional well-being.

PHYSIOLOGY OF BURN INJURY

Serious burns are associated with a stereotypical sequence of physiologic changes. Anticipation of these metabolic aberrations facilitates optimal support (see Table 168-1). During the first 1 or 2 days after a serious burn, patients require substantial fluid and hemodynamic support.⁴ If the patient is successfully resuscitated, a hyperdynamic and hypermetabolic state typically ensues. This later phase, characterized by high cardiac output, reduced afterload, fever, and muscle catabolism, must be supported by provision of adequate quantity and quality of substrates. Although this physiology is seen in most seriously injured patients, its intensity and duration are unique to those with larger burns.

Resuscitation Phase

The massive fluid resuscitation required by burn patients is unique in medicine. It is secondary to a diffuse but transient capillary leak driven by poorly characterized mediators.⁵ The clinical result is extravasation of fluids, electrolytes, and even moderate-sized colloid molecules into both burned and unburned soft tissues to a degree not seen in other disease processes. Since the 1930s, a variety of resuscitation formulas have been developed based on burn and patient size. However, this remains an area of clinical art, with no formula being reliably accurate

for all patients.² Factors contributing to varied resuscitation requirements include delay in initiation of resuscitation, inhalation injury, patient age, cardiovascular health, and the depth and vapor transmission characteristics of the wound itself.⁶

Burns under 15% generally do not require a formal fluid resuscitation program. As burn size increases, physiologic aberrations increase in intensity, explaining escalating volume requirements. Burn resuscitation is detailed below.

Hyperdynamic Phase

Typically there is a very noticeable decline in intravenous volume requirements 18 to 24 hours after injury in successfully resuscitated patients as the capillary leak abates. After this hypodynamic period, a systemic hypermetabolic state develops and is sustained in surviving patients until it slowly regresses, well after wound closure.⁷ This state is characterized by high cardiac output, low peripheral vascular resistance, fever, and increased protein flux. In patients not well supported with protein substrate, this increased protein flux will be associated with significant muscle catabolism. This postresuscitation physiology is caused by inflammatory mediators and augmented release of the counterregulatory hormones, cortisol, catecholamines, and glucagon.⁸ These hormonal changes are triggered by a combination of wound- and gut-released bacteria and their byproducts, pain, foci of infection, and some degree of evaporative heat loss.

A central component of burn critical care is to ensure adequate support of the hypermetabolic state. This is done by providing accurate fluid repletion, adequate supplies of metabolic substrates, control of environmental temperature, and competent pain and anxiety control. Early identification and excision of necrotic skin and soft tissue with immediate biological closure of the resulting wounds truncates the hypermetabolic physiologic state and is the most effective way to avoid the deleterious consequences of prolonged hypermetabolism.⁹

Burn critical care requires control of the patient's environmental temperature. Burn patients have enormous and invisible evaporative water and energy losses if they are maintained in the typical cool dry air of a general hospital.¹⁰ Burn units and burn operating rooms must be engineered to maintain high ambient temperature and humidity to avoid the difficult problem of hypothermia and excessive energy loss.

INITIAL EVALUATION AND BURN-SPECIFIC SECONDARY SURVEY

Commonly, when burn patients arrive in the intensive care unit (ICU) where definitive care will be rendered, a complete burn-specific secondary survey has not been completed.¹¹ It is essential for the intensivist to have a familiarity with these issues so burn-related pathology and coexisting injuries are not overlooked. Evaluations should follow the format taught by the Advanced Trauma Life Support course. All seriously burned patients should be approached as having potential multiple trauma.¹²

Initial Evaluation

The primary survey of the burn patient is similar to that of the trauma patient, although there are a few important differences worthy of emphasis. First among these is the progressive mucosal edema that

TABLE 168-1

The Four Phases of Burn Care, with Physiologic Changes and Objectives

| PHASE AND TIMING | PHYSIOLOGIC CHANGES | OBJECTIVES |
|---|--|--|
| 1: Initial evaluation and resuscitation, 0 to 72 h | Massive capillary leak and burn shock | Accurate fluid resuscitation and thorough evaluation |
| 2: Initial wound excision and biological closure, days 1-7 | Hyperdynamic and catabolic state with high risk of infection | Accurately identify and remove all full-thickness wounds and achieve biological closure |
| 3: Definitive wound closure, day 7 to week 6 | Continued catabolic state and risk of nonwound septic events | Replace temporary with definitive covers, and close small complex wounds |
| 4: Rehabilitation, reconstruction, and reintegration, day 1 through discharge | Waning catabolic state and recovering strength | Initially to maintain range of motion and reduce edema; subsequently to strengthen and facilitate return to home, work, school |

may compromise airway patency in the early hours after burns. This is especially true in young children because of their much smaller airway.¹³ Progressive stridor or hoarseness should prompt visualization and/or intubation of the airway. This need is ideally anticipated before the crisis stage so proper equipment and personnel can be gathered, facilitating smooth tube placement. Facial and airway edema can render the burn patient's airway challenging to control. Reintubation can be exceedingly difficult after airway edema has progressed, making unplanned extubation a potentially lethal complication. Security of the endotracheal tube should be regularly assessed. A twill-tie harness is a reliable method of securing the endotracheal tube (Fig. 168-1). Reliable vascular access is also essential for burn resuscitation. In patients with larger injuries, central venous access is often optimal. In emergencies, placing peripheral, central, or intraosseous lines though burns is entirely reasonable. These can be replaced at an unburned site in subsequent hours. Sometimes it is best to wait until volume depletion has been corrected with peripheral lines to more safely place central venous, or especially arterial, catheters.

Burn-Specific Secondary Survey

Supplementing the trauma secondary survey, a burn-specific secondary survey will identify many of the unique clinical problems associated with this type of injury. This should begin with significant past medical history and the circumstances of injury. Important points include details of the injury mechanism, neurologic status at the scene, extrication time, and tetanus immune status. Highlights of the burn-specific secondary survey are described in the following paragraphs.

The ocular and otolaryngologic examination should begin with palpation of the head and face for signs of coincident blunt or penetrating trauma. The globes should be examined prior to the development of facial and eyelid edema, which will limit examination (Fig. 168-2).¹⁴ Serious globe burns impart a clouded appearance to the cornea, and fluorescein staining will detect subtler injuries. Tarsorrhaphy is virtually never indicated acutely, because lid edema will generally provide excellent globe coverage even in the presence of serious lid burns. Pressure on the burned ear and occiput is avoided. Topical mafenide acetate is applied, as it will penetrate the relatively avascular underlying cartilage.¹⁵ Signs of inhalation injury, such as



FIGURE 168-1 ■ A twill-tie harness is a reliable way of securing the endotracheal tube. Protective pads may reduce injury to oral commissures. Tube security should be regularly assessed because reintubation can be very difficult in this setting.

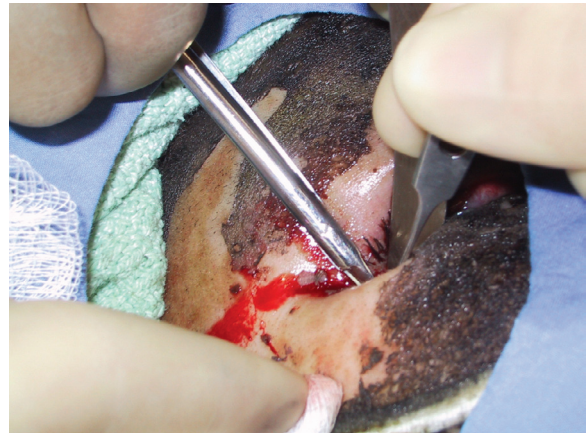


FIGURE 168-2 ■ Globes should be examined early, before development of facial and eyelid edema limits examinations. Serious globe burns impart a clouded appearance to the cornea, and fluorescein staining will detect subtler injuries. Tarsorrhaphy is virtually never indicated acutely, because lid edema will generally provide excellent globe coverage even in the presence of serious lid burns. In some patients, lateral canthotomy, pictured here, can reduce critically elevated intraocular pressures.

carbonaceous debris and singed nasal hairs, are noted on examination of the nose and throat. Ties securing endotracheal and nasogastric tubes should be checked so that pressure on the nasal septum or oral commissures is avoided.

The initial neurologic evaluation centers on exclusion of coincident neurologic injury and control of pain and anxiety. Even if they arrive alert and oriented, patients with serious burns typically become obtunded over the succeeding hours and days, if only because of the effects of pain medications and sleep deprivation. It is therefore important to exclude central nervous system trauma if the mechanism of injury is either unknown or consistent with such trauma. There should be a low threshold for ordering a computed tomographic scan of the head and spine, based on mechanism of injury. Pain and anxiety management should begin during the initial evaluation, within limits of safety.¹⁶ Good pain control may have both physiologic and

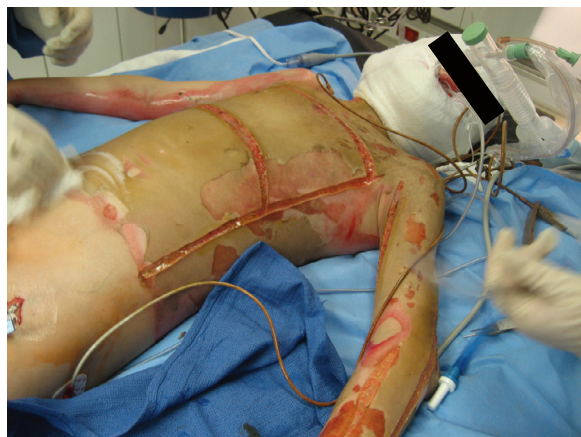


FIGURE 168-3 ■ Patients with deep near-circumferential or circumferential chest wall burns may require escharotomy to facilitate ventilation. If properly performed, escharotomy of the torso will markedly enhance compliance.

psychological benefits. In the emergency setting, this is best done with incremental administration of small doses of narcotics and benzodiazepines. When caring for paralyzed or obtunded patients, it is important to make sure there is no pressure on peripheral nerves, so that neuropathies are avoided. Finally, those burned in structural fires should be assessed for carbon monoxide (CO) exposure by history, neurologic examination, and determination of a carboxyhemoglobin level, because selected patients with significant exposure may benefit from hyperbaric oxygen treatment.¹⁷

The cervical spine and neck should be assessed for trauma, based on mechanism of injury. Extremely deep circumferential neck burns may require escharotomy to facilitate normal venous drainage of the head.

The chest wall should be assessed for compliance and symmetric air movement. Patients with deep near-circumferential or circumferential chest wall burns may require escharotomy to facilitate ventilation (Fig. 168-3). If properly performed, escharotomy of the torso markedly enhances compliance.

Most patients are hypovolemic at the time of presentation and respond promptly to volume administration. Some patients, especially the elderly, will have previously unsuspected myocardial disease that may become clinically important during the stress of resuscitation. Some data also support the existence of a myocardial depressant factor in some patients with very extensive injuries.¹⁸ Patients who do not respond as expected to calculated resuscitation volumes may benefit from invasive monitoring, pulmonary artery catheterization, cardiac ultrasonography, and inotropic support.

Genitourinary evaluation is limited in this setting. The foreskin should be reduced over the bladder catheter so paraphimosis is not the result of progressive edema during resuscitation.

Burned extremities should be examined for other trauma, based on mechanism of injury. It can sometimes be difficult to identify fractures in this setting, so liberal use of radiography is appropriate. Fractured and burned extremities are initially stabilized with external splints, prior to placement of external fixators. An essential component of the extremity evaluation is to identify limbs at risk for loss of perfusion with progressive edema during resuscitation and to develop an effective monitoring plan to allow timely decompression should it be needed. Resuscitation-associated edema can cause profound limb ischemia secondary to swelling under a circumferential eschar or within inelastic muscle compartments. This complication is seen in patients who have suffered deep extremity burns (especially if circumferential) or high-voltage electrical injuries. Low-pressure flow in the extremity should be monitored, commonly using a Doppler probe to



FIGURE 168-4 ■ Properly performed escharotomy will result in immediate improvement in extremity blood flow.

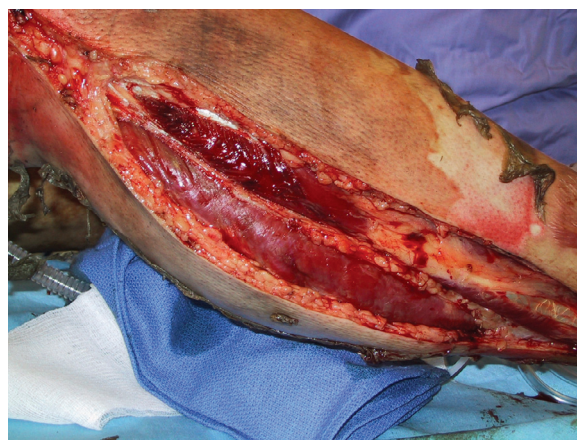


FIGURE 168-5 ■ Fasciotomy will release pressure in edematous muscle compartments.

demonstrate flow in the palmar arch or digital vessels, because capillary perfusion pressure is only one-third the mean arterial pressure monitored in larger vessels. Prompt identification of ischemic extremities is essential so that escharotomy (Fig. 168-4) or fasciotomy (Fig. 168-5) can be effected in a timely manner.¹⁹

The wound should not be allowed to interfere with complete evaluation of the patient. Wounds are assessed for extent using a Lund-Browder or other burn diagram, depth by visual examination, and the presence of circumferential components that may require decompression to ensure adequate perfusion. Typically, wounds are underestimated in depth on initial evaluation.

Carboxyhemoglobin and arterial blood gas determinations and screening baseline laboratories are part of the initial evaluation. Chest radiographs are useful to document proper placement of catheters and tubes and the absence of chest trauma. Inhalation injuries typically do not cause early radiographic changes.

Abuse or neglect should be considered when evaluating all burns, not just those in young children. Approximately 20% of burns in young children are reported to state authorities for investigation, but abuse occurs in all age groups.²⁰ Burns can also be a result of domestic violence or other interpersonal assaults. Often this determination is not made until the patient has been admitted to the ICU. Suspicious cases should be filed with appropriate state agencies. Documentation of the stated injury circumstances and of the wounds is essential. Burn diagrams should be carefully completed. Wound photography is ideal in such cases (Fig. 168-6).



FIGURE 168-6 ■ Suspicious cases should be filed with appropriate state agencies. Documentation of stated injury circumstances and of actual wounds is essential; wound photography is ideal. Note flexor-sparing pattern here.

FLUID RESUSCITATION

In the first 1 or 2 hours after a large burn, patients experience little change in intravascular volume or hemodynamics. In fact, patients are often remarkably alert during this period. However, in the hours that follow wound release mediators are released, stress-related hormones are secreted, and reactive oxygen species are formed on reperfusion of marginally perfused tissues. These and perhaps other factors trigger a diffuse loss of capillary integrity, resulting in extravasation of fluid into soft tissues, including those distant to the burn. This remarkable physiologic phenomenon abates 18 to 24 hours later and explains the unique resuscitation needs of patients who have sustained large burns. Predicting resuscitation requirements of specific patients involves multiple variables in addition to burn size, including burn depth, vapor transmission characteristics of the wound, patient age and cardiovascular health, resuscitation delay, environmental temperature and humidity, and presence or absence of concomitant inhalation injury. Numerous formulas have been promulgated to roughly guide resuscitation efforts, but none is accurate in every patient.^{6,21} A common consensus formula is the modified Brooke formula summarized in [Box 168-1](#). Consistent with the military experience of colloid-based trauma resuscitation in recent conflicts, the role of colloid is expanding in burn resuscitation, although this remains an area of ongoing controversy. It is the routine practice of this author to begin 5% albumin at a maintenance rate immediately during resuscitation of patients with larger injuries, subtracting this volume from the crystalloid recommended by formula. I find this reduces the incidence of edema-related complications, including abdominal compartment syndrome.²² Patients not responding as predicted to resuscitation efforts should have serum levels of cortisol checked, particularly if cryptic hypotension, hypernatremia, and/or hypokalemia are also in evidence. Inaccurate fluid resuscitation will cause significant morbidity. Formulas can only help determine initial volume infusion rates and roughly predict 24-hour volume requirements; however, they are so inherently inaccurate that resuscitation should be guided by hourly reevaluation of clinical endpoints. Resuscitation endpoints are summarized in [Table 168-2](#).

BURN CRITICAL CARE ISSUES

Critical care units are embedded in all successful burn programs. Indeed, this is a requirement of the American College of Surgeons–American Burn Association burn center verification program. It is absolutely essential that there is a seamless flow of information and care between critical care and wound management, as the status and

BOX 168-1 Modified Brooke Resuscitation Formula

0-24 HOURS

Adults and children >20 kg

Lactated Ringer's: 2-4 mL/kg/% burn/24 h (first half in first 8 h)

Colloid: none*

Children <20 kg

Lactated Ringer's: 2-3 mL/kg/% burn/24 h (first half in first 8 h)

Lactated Ringer's with 5% dextrose: 4 mL/kg/h

Colloid: none

24-48 HOURS

All patients

Crystalloid: to maintain urine output. If silver nitrate is used, sodium leaching will mandate continued isotonic crystalloid. If other topical is used, free water requirement is significant. Serum sodium should be monitored closely.

Nutritional support should begin, ideally by the enteral route.

Colloid (5% albumin in lactated Ringer's):

0%-30% burn: none

30%-50% burn: 0.3 mL/kg/% burn/24 h

50%-70% burn: 0.4 mL/kg/% burn/24 h

>70% burn: 0.5 mL/kg/% burn/24 h

*Increasingly, early colloid infusion (generally 5% albumin) is being used in patients with very large burns, particularly if they are young or resuscitation is not going smoothly.

Note: The Modified Brooke formula is a common consensus formula that is only useful in individual patients if adjusted to physiologic endpoints. Like all resuscitative formulas, it is a helpful starting point, but optimum-quality resuscitation requires the bedside presence of a physician capable of regularly evaluating resuscitation endpoints.

TABLE 168-2 Age-Specific Resuscitation Endpoints

| RESUSCITATION ENDPOINT | RESUSCITATION TARGET |
|-------------------------|--|
| Sensorium | Comfortable, arousable |
| Physical examination | Warm extremities, full peripheral pulses |
| Urine output | Infants: 1-2 mL/kg/h; children: 0.5-1 mL/kg/h; all others: 0.5 mL/kg/h |
| Base deficit | Less than 2 |
| Systolic blood pressure | Infants: 60-70 mm Hg Children: 70-90 + (twice age in years) mm Hg Adolescents and adults: 90-120 mm Hg |

Note: Age-specific resuscitation endpoints should be assessed regularly throughout burn resuscitation and infusions adjusted up or down in 10% to 20% increments to meet needs of the individual patient.

management of the wound drives most of the patient's systemic derangements. Organizationally, this can be done in two ways. Most commonly and perhaps most cost-effectively, the surgical team managing the wound also manages the critical care. In this schema, burn patients are typically managed in dedicated burn-trauma ICUs, giving the surgeon, nursing, rehabilitation, and support team the volume they need to work effectively. This requires surgeons to be well versed and ideally certified in critical care. The most common alternative to the surgeon-intensivist scheme is to provide critical care in a dedicated area of a general surgical ICU, taking great pains to ensure absolutely seamless flow of information between the surgical and critical care teams. Ensuring this engaged collaborative management is difficult, but it can be done effectively. Seriously burned patients present the critical care team with a set of unique but predictable issues that should be anticipated. A brief review of these follows.

Airway Issues

Although evaluation and control of the airway are part of the initial evaluation, concerns extend throughout the period of intensive care. Endotracheal tube security should be part of the regular reevaluation of every patient in the burn ICU, because facial and hypopharyngeal edema can make reintubation after unplanned extubation incredibly difficult.²³

Inhalation Injury

Inhalation injury remains a clinical diagnosis.²⁴ A history of closed-space fire, the presence of singed nasal hairs and facial burns, and carbonaceous sputum support the diagnosis of inhalation injury. Fiberoptic bronchoscopy can be useful in equivocal cases, as can technetium scanning. However, in the large majority of patients, the diagnosis is made by history and physical examination. The initial chest radiograph is almost always normal, as are gas exchange and compliance until the endobronchial mucosa sloughs several days later, occluding small airways and leading to subsegmental atelectasis and respiratory insufficiency.

Five clinical consequences commonly occur in patients with inhalation injury: acute upper airway obstruction, bronchospasm, small airway occlusion, pulmonary infection, and respiratory failure.²⁵ Airway obstruction and bronchospasm are early complications, typically appearing during the first 48 hours. Airway edema and obstruction are managed with endotracheal intubation. Bronchospasm from aerosolized irritants can be intense during this period but usually respond to nebulized β -adrenergic agonists. Infrequently, intravenous bronchodilators such as terbutaline or low-dose epinephrine infusions are needed. Ventilatory strategies should be designed to minimize “breath-stacking” from auto-PEEP (positive end-expiratory pressure) in this setting.

After 3 to 5 days, sloughing of necrotic endobronchial debris can occur, and pulmonary toilet becomes an increasing problem. Subsegmental atelectasis develops, and shunting intensifies. Frequent suctioning and toilet bronchoscopy can help maintain small distal airway patency.

As many as 50% of patients with inhalation injury will develop pulmonary infection. Differentiating between pneumonia (lobar involvement) and tracheobronchitis (purulent infection of the denuded tracheobronchial tree) is often difficult, but the difference is not really clinically important. Anyone who has fever and newly purulent sputum should be treated with antibiotics, guided by sputum cultures. Pulmonary toilet is particularly important in these patients.

Respiratory failure is unfortunately common in patients with inhalation injury but can generally be managed with a pressure-limited ventilation strategy based on permissive hypercapnia.²⁶ Patients who fail this can sometimes benefit from investigational modes of support such as inhaled nitric oxide or extracorporeal oxygenation, although the utility of the latter is quite limited in burn patients, owing to the need for anticoagulation.^{27,28}

Carbon Monoxide and Cyanide Exposure

Patients injured in structural fires are commonly exposed to high levels of carbon monoxide (CO). Although an obtunded state in this clinical setting can be due to other causes such as intoxication, trauma, or anoxia, hyperbaric oxygen (HBO) has been reported to improve the prognosis of patients who have suffered very severe CO exposure.¹⁹ There are controlled data both supporting²⁹ its use and refuting the utility of HBO,³⁰ so clinical judgment must be brought to bear in the decision whether to use this form of therapy in individual patients.

CO binds and inactivates heme-containing enzymes such as hemoglobin and the cytochromes. The binding of CO and hemoglobin forms carboxyhemoglobin, which does not deliver oxygen, resulting in acute physiologic anemia, much like an isovolemic hemodilution. A serum carboxyhemoglobin level of 50% is similar to an isovolemic

hemodilution to 50% of the baseline hemoglobin concentration. This level of carboxyhemoglobin results in unconsciousness, implying that other mechanisms are also involved in the pathophysiology of CO injury. CO binding to the cytochrome system in the mitochondria probably interferes with oxygen utilization. Approximately 10% of patients with severe CO exposure have been reported to develop severe delayed neurologic sequelae.³¹

There are two practical treatment options: 100% normobaric oxygen or HBO. There are well-designed clinical studies both supporting and refuting the utility of HBO for CO poisoning.^{29,30} Proponents cite a decreased incidence of delayed neurologic sequelae in those treated with HBO. In patients with very severe CO poisoning with either very high carboxyhemoglobin levels or neurologic impairment not otherwise explainable, HBO is probably warranted if it can be safely administered. Relative contraindications to HBO are wheezing or air trapping, which increase the risks of pneumothorax or gas embolism, and high fever, which increases the risk of seizures. Before placement in the chamber, endotracheal tube balloons should be filled with saline to avoid balloon compression–associated air leaks, and upper body central venous cannulation should be avoided if possible to avoid sudden enlargement of an occult pneumothorax during decompression.³²

Hydrogen cyanide is detected in the smoke from many structural fires and in the serum of some burn patients. At a high enough concentration, cyanide causes failure of oxygen utilization at the cytochrome level, with a secondary unexplained metabolic acidosis. Cyanide poisoning can be treated with amyl nitrate and sodium thiosulfate.³³ However, cyanide is rapidly metabolized in resuscitated patients, making specific treatment generally not necessary or useful.

Pain and Anxiety Management

Undertreatment of pain and anxiety was very common in the past, and burn intensivists need to pay particular attention to this issue. Reasons for undertreatment are related to the extraordinary drug doses required to adequately address pain in seriously burned patients and consequent fear of respiratory depression, addiction, and litigation. The opiate and benzodiazepine tolerance of patients with large open wounds is truly remarkable. Once wounds are closed, drug needs rapidly decrease, and addiction is rare. The best way to eliminate burn pain is prompt wound closure.

Unfortunately, control of pain and anxiety is very difficult in burn patients. Successful management is greatly aided by a set of guidelines. One such program addresses four clinical states: intubated acute, non-intubated acute, chronic acute, and reconstructive patients.³⁴ Within each clinical state are separate guidelines for background pain, background anxiety, procedural pain, procedural anxiety, and transition to the next clinical state. Attention to the issue has physiologic as well as obvious psychological benefits. Reduced secretion of catecholamines may decrease systemic hypermetabolism, and treatment-related acute stress is reduced. If doses of benzodiazepines and opiates are excessive, a number of alternative drugs have proven useful, particularly dexmedetomidine, which is not a respiratory depressant and has proven particularly valuable during weaning and extubation.^{35,36}

Ocular Issues

In the first 72 hours of resuscitation, rare patients will develop retrobulbar edema and intraocular hypertension that may benefit from decompression (see Fig. 168-2). Typical patients are those with large surface area burns with deep facial involvement. The diagnosis is made with tonometry. Treatment is by lateral canthotomy, a procedure that can be performed at the bedside with immediate reduction in pressure and normalization of retinal blood flow.

Contraction of burned eyelids and facial skin can cause exposure of the globe in the days or weeks after burns.¹⁵ If unchecked, this will result in exposure and then desiccation of the globe, with secondary keratitis and corneal ulceration. Infected corneal ulcers rapidly lead to

globe perforation because the cornea is almost avascular and tolerates desiccation and infection very poorly. When minimal or moderate, globe exposure can be managed with frequent ocular lubrication. Acute eyelid release should be done promptly if exposure is severe or keratitis does not resolve with lubrication over a few days.

Peripheral Neuropathies

Peripheral neuropathies are more common than is usually appreciated in burn patients.^{37,38} They can be caused by direct thermal damage to peripheral nerves or by the many metabolic disturbances seen during acute burn care. A minority of these lesions are caused by constricting eschar, compartment syndrome, or improperly filled splints. Extremities at risk should be monitored for compartment syndrome and constricting eschar. These issues are best addressed surgically as early as possible. Heavily sedated patients or those under general anesthesia in the operating room should be examined to make sure that traction and pressure injuries are avoided.

Gastrointestinal Issues

Curling's ulcers were a common cause of massive upper gastrointestinal bleeding in the past. This is now an infrequent occurrence with better resuscitation, which decreases splanchnic ischemia. Routine use of prophylactic gastric alkalization has also been important. Patients with serious burns should be treated with empiric histamine-receptor blockers, proton-pump inhibitors, and/or antacids until they are tolerating tube feedings and are at low enough risk that this therapy can reasonably be stopped. Calculous or acalculous cholecystitis in the critically ill burn patient is easily missed and can be the cause of significant illness. Fevers are often assumed to be secondary to the wound. Cholestatic blood chemistry values and modest clinical jaundice are identical to the changes that typify hepatic insufficiency. If untreated, gangrenous cholecystitis associated with peritonitis and sepsis can result. Diagnosis is easily made by bedside ultrasonography. Treatment can be either by laparoscopic or open cholecystectomy. In the critically ill patient, percutaneous transhepatic drainage is a very reasonable alternative.³⁹

Although uncommon, pancreatitis is a reported complication seen in patients with very large burns.⁴⁰ Like cholecystitis, it is easily missed until the condition is far advanced. Abdominal distention and ileus, with tenderness in those who are conscious, should prompt measurements of serum amylase and lipase concentrations as well as appropriate abdominal imaging in selected cases. Most patients can be treated with bowel rest, although pseudocysts and abscesses have been reported in this population.

Bowel ischemia and necrosis are complications generally seen in those with prolonged burn shock, often part of a delayed resuscitation syndrome. These complications present as ileus and then peritonitis. Bowel necrosis is lethal unless operated on promptly. It is a frequently reported autopsy finding in patients dying of burns.^{41,42}

Superior mesenteric artery syndrome is a rare occurrence but should be seriously considered in patients with major weight loss during the acute phase of injury, who then develop intractable vomiting in the recovery phase of their illness. It is due to compression of the duodenum in the angle between the aorta and superior mesenteric artery.⁴³ Diagnosis is by barium swallow, and treatment is a combination of parenteral nutrition and tube feedings past the point of obstruction if possible.

Finally, it is easy to miss more common abdominal pathology in the setting of burns. Appendicitis can be a lethal complication first diagnosed at autopsy. Constipation from narcotic use and inactivity is common and is ideally prevented with a bowel regimen.

Nutritional Support

Burn patients need accurate energy and protein support. Underfeeding and overfeeding have adverse sequelae. Ideally, tube feedings are begun

during resuscitation.⁴⁴ Most patients do well with continuous intragastric tube feedings, although some require postpyloric feedings.⁴⁵ Enteral nutritional support can be started through a nasogastric sump tube so that gastric residuals can be used to help determine tolerance of the feedings initially.⁴⁶ Parenteral support is useful during periods when ileus is likely, such as during septic episodes or periods when high-dose vasopressor support is needed, or during the perioperative period. Transient parenteral support can be particularly important in hypermetabolic young children who are very catabolic and do not tolerate prolonged periods of fasting.

Goals for nutritional support for burned patients are controversial. Consensus recommendations include approximately 2.5 g/kg/day of protein with a nonprotein caloric load between 1.5 and 1.7 times the calculated basal metabolic rate or 1.3 and 1.5 times the measured (by indirect calorimetry) resting energy expenditure.^{47,48} Nutritional support should be adjusted throughout the illness, based on specific endpoints. The role of anabolic agents in burn patients has been an area of controversy for two decades. Currently, many programs advise the use of anabolic steroids in particularly nutritionally depleted patients, watching carefully for hepatic complications. Serial physical examination, quality of wound healing, nitrogen balance, and indirect calorimetry can be integrated to assess the adequacy of support and help fine-tune the predictions of nutritional equations.

Infectious Disease Issues

Through loss of skin, necrosis of the endobronchial epithelium, and invasive devices, serious burns impair the host's physical barriers to bacteria while interfering with immune function. Therefore, burn patients are prone to virulent infectious complications. Anticipation of these infections will help minimize infectious morbidity and mortality.

Historically, wound sepsis has been the great killer in burn units, and burn wound infections remain surprisingly common today.⁴⁹ Diagnosis of wound sepsis is generally clinical, based on signs and symptoms of systemic infection along with changes in wound appearance. The diagnosis can be supported by wound biopsy and quantitative cultures, but both of these diagnostic techniques are infamously inaccurate, making a clinical diagnosis the most reliable.⁵⁰

The best way to prevent wound sepsis is to identify and excise deep burns within the first few days after injury and to close the resulting wounds. Topical agents are only an adjunct to this effort and cannot on their own be relied upon to prevent wound sepsis but can delay the onset of sepsis in deep wounds. They can also serve to minimize desiccation and colonization of healing wounds. There are several agents in wide general use; the most common are listed in Table 168-3. All have specific advantages and disadvantages. Use of aqueous silver nitrate commonly promotes development of hyponatremia and hypokalemia. Use of mafenide acetate, which inhibits carbonic anhydrase, leads to the development of metabolic acidosis, making it more difficult to use permissive hypercapnia for the management of patients with severe respiratory failure. Silver sulfadiazine application leads to large losses of free water across the burn wound eschar. The use of

TABLE 168-3 Topical Agents Used in Wound Management

| AGENT | CHARACTERISTICS |
|---------------------|---|
| Silver sulfadiazine | Painless on application, fair to poor eschar penetration, no metabolic side effects, broad antibacterial spectrum |
| Mafenide acetate | Painful on application, excellent eschar penetration, carbonic anhydrase inhibitor, broad antibacterial spectrum |
| 0.5% Silver nitrate | Painless on application, poor eschar penetration, leaches electrolytes, broad spectrum (including fungi) |

silver-impregnated membrane dressings has increased markedly in recent years, although primarily in the outpatient setting with smaller burns. Program-specific use in inpatients is becoming increasingly common. As with all membrane dressings, fever or other signs of potential sepsis should prompt membrane removal and wound examination.

Antibiotic use must be focused. Too-liberal empiric use will lead to development of resistant organisms. Burn physiology, in the absence of infection, includes fever and a hyperdynamic circulation. When systemic infection is suspected, a careful physical examination and wound inspection should be done and cultures taken, particularly of blood, urine, and sputum. If the patient is hypotensive or otherwise unstable, it is reasonable to start a short course of empiric antibiotic treatment while awaiting return of blood cultures. Clinical deterioration of the burn patient is most often related to infection.

Infection-control practices should be routine and relatively rigid in burn units. This patient population has a high incidence of infection in general, and resistant bacterial species are very common. Universal precautions should be practiced in all patients. The use of prophylactic antibiotics is not advised.⁵¹

Rehabilitation Therapy in the Burn Intensive Care Setting

Physical and occupational therapists should be involved from the outset and strategies implemented to avoid common contractures that will otherwise interfere with recovery later (Table 168-4). Early tasks include passive movement of all joints through an appropriate range of motion and static positioning in ways that minimize the risk of deformity. This progresses through active exercise and strengthening, which greatly speeds recovery. This is time-intensive therapy that requires many hours of therapist involvement to be successful, particularly after protracted critical illness.^{13,52}

Intraoperative Critical Care

Often, burn patients must be subjected to stressful operative procedures to excise and close wounds, even during periods of critical illness and hemodynamic instability. They can only survive these interventions if critical care efforts are continued during the operations. There must be continuous communication between the surgical and anesthesia teams during surgery. Each team must understand what the other is doing and is about to do, so it can anticipate its own next interventions.

Intrahospital transport from the protected environment of the ICU to the operating room must be carefully planned, and skilled people should accompany the patient during transport. Burn patients have huge evaporative heat losses that can rapidly render them hypothermic unless the operating room is kept warm and core temperature is continuously monitored. Hypothermia promotes development of

coagulopathy, which can complicate these operations. The intensive care team should be involved in operative events.

SPECIAL INJURY CONSIDERATIONS

Burn units have a unique set of resources: critical care expertise, complex wound care and closure skills, and strong rehabilitation programs. This resource set benefits other nonburn injuries and illnesses that are increasingly referred to burn programs for primary therapy. The most common injuries involve electrical, chemical, tar, cold, and soft-tissue trauma and infections. The most common illnesses are toxic epidermal necrolysis (Fig. 168-7) and purpura fulminans.

Electrical Injury

Electrical injuries are commonly divided into low voltage ([household] 110-220 volts), intermediate voltage (220-1000 volts), and high voltage (>1000 volts) exposures. Patients with good electrical contact to low and intermediate voltage sources can suffer severe local wounds but rarely manifest systemic consequences such as compartment syndromes or rhabdomyolysis.⁵³ Patients with good contact to high voltages commonly have compartment syndromes, myocardial injury, fractures of the long bones and spine, and free pigment in the plasma that may cause renal failure if not promptly cleared.^{54,55} These patients can also manifest deep arching wounds, flash burns, and thermal burns from clothing ignition. Such patients can also sustain blunt trauma during the incident, most commonly from falls.



FIGURE 168-7 ■ The cause of toxic epidermal necrolysis remains a mystery. This patient has both a cutaneous and a visceral wound.

TABLE 168-4 Common Contractures and Prevention Strategies Useful in the ICU

| ANATOMIC AREA | COMMON CONTRACTURE | ICU PREVENTIVE SPLINTING AND POSITIONING STRATEGY |
|----------------------------|-----------------------|---|
| Neck | Flexion | Daily range-of-motion exercises and extension splinting and conformers; split mattress |
| Shoulder | Adduction | Daily range-of-motion exercises and abduction splinting with axillary splints or troughs |
| Elbow | Flexion and extension | Daily range-of-motion exercises and alternating extension and flexion splints |
| Wrist | Flexion and extension | Daily range-of-motion exercises and splinting in functional position (20 degrees of extension) |
| Metacarpophalangeal joints | Extension | Daily range-of-motion exercises and splinting in functional position (metacarpophalangeal joints at 70 to 90 degrees of flexion, all interphalangeal joints in extension, first web space open, wrist at 20 degrees of extension) |
| Hips | Flexion | Daily range-of-motion exercises and extension splints and prone positioning (if tolerated) |
| Knees | Flexion | Daily range-of-motion exercises and knee splints and knee immobilizers |
| Ankles | Extension | Daily range-of-motion exercises and neutral splints |
| Metatarsophalangeal joints | Extension | Daily range-of-motion and splinting in functional position; rocker-bottom shoes |

After high-voltage exposures, cardiac monitoring is a good idea for 24 to 72 hours. Urine should be examined grossly for pigment after placement of a bladder catheter. Fluid resuscitation should be started based on surface burn size, but this usually does not correlate well with deep tissue injury, so resuscitation must be closely monitored and titrated to the patient's physiology. Compartment syndromes are common, and this should be considered. Compartments at risk should undergo serial reexamination and be decompressed when an evolving compartment syndrome is suspected. Wounds associated with the injury are excised and closed in the following days with a combination of skin grafts and flaps.

Cold Injury

Cold injuries often generate wounds best cared for in the burn unit; initial management is usually conservative. Early management of hypothermia is a priority. Frozen tissues are thawed with body-temperature water. Necrotic tissue is excised when demarcation is clear, and the resulting wounds are grafted or closed with flaps. If patients present with ischemic extremities with less than 24 hours of warm ischemia time, diagnostic angiography may be considered in selected stable patients. If there is no flow despite intraarterial vasodilators, thrombolytic therapy may be appropriate.⁵⁶

Chemical and Tar Injury

Chemical injuries can be associated with both local and systemic effects. Poison control centers should be consulted liberally if there is a question of systemic toxicities. It is essential to protect staff from exposure to the chemicals during removal. Most agents can be irrigated off with tap water for 30 minutes, although alkaline substances may take longer. When the "soapy feeling" alkaline substances often impart to the gloved finger is gone, or when litmus paper indicates a neutral pH, irrigation may be stopped. Hydrofluoric acid, especially in concentrated form, may result in severe acute hypocalcemia because the fluoride anion strongly binds divalent cations.⁵⁷ Subeschar injection of 10% calcium gluconate and/or immediate excision of the wound may be lifesaving. Elemental metals such as solid lithium or sodium can ignite on contact with water or air and should therefore be covered with oil. White phosphorus, a component of many munitions, will also ignite on contact with air, and wound particles are ideally covered with wet cloth or gauze. A number of road-surfacing materials are viscous and heated up to 700°F for application. They are designed to stay solid in the hot sun on dark pavement. When these materials splash road workers, the wounds should be quickly cooled by tap water irrigation. Wounds should be soaked in a lipophilic solvent after cooling and then be debrided and grafted as indicated by burn depth, which is often quite deep.

CONCLUSION

Patients with serious burns present a unique suite of challenges to the ICU team that cross multiple disciplines. Long-term outcome data support the contention that most survivors of serious burns will ultimately have a very satisfying quality of life, making the ICU efforts

worthwhile.⁵⁸ Successful outcomes require a coordinated effort by intensivists, surgical, nursing, and rehabilitation therapy professionals during what can be technically and emotionally demanding, but ultimately rewarding ICU stays.

KEY POINTS

1. Burn care can be divided into four clinical phases: initial evaluation and resuscitation, initial wound excision and biological closure, definitive wound closure, and rehabilitation and reconstruction.
2. Postresuscitation physiology is characterized by high cardiac output, reduced afterload, moderate fever, and muscle metabolism.
3. Burn units and burn operating rooms should be engineered to maintain high ambient temperatures to avoid hypothermia and energy loss.
4. The burn-specific secondary survey must often be completed in the ICU.
5. Monitoring and early identification of extremity ischemia secondary to overlying eschar or tight compartments is essential.
6. The wound should not distract examiners from a thorough and complete patient evaluation.
7. No standard resuscitation formula is accurate in an individual patient. Patients must be resuscitated using resuscitation endpoints.
8. Patients with inhalation injuries typically have normal chest radiographs and near-normal gas exchange and compliance early on. Over the 3 to 7 days after injury, significant pulmonary dysfunction may occur.
9. The best way to reduce burn wound pain is prompt wound closure.
10. Exposure of the globe must be anticipated and managed to preserve vision.
11. Early nutritional support is essential in light of postresuscitation physiologic changes. This is ideally accomplished enterally, but parenteral support is also safe when properly administered.
12. Physical and occupational therapy should begin from the outset of burn care.
13. Intensive care management of the patient should proceed throughout operations.
14. Patients with toxic epidermal necrolysis have both a cutaneous and a visceral wound.

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Thoracic trauma is responsible for approximately 20% of all trauma-related deaths and is second only to central nervous system injury as the primary cause of death at the scene. For patients arriving at the emergency department (ED) alive, rapid diagnosis and treatment of potentially life-threatening injuries are required to prevent death during the “golden hour” of initial resuscitation. However, many thoracic injuries that are not immediately life-threatening still have the potential for significant morbidity and mortality. The following is an overview of the diagnosis and management of thoracic trauma.

■ INITIAL ASSESSMENT

Primary Survey

The Advanced Trauma Life Support (ATLS) course of the American College of Surgeons Committee on Trauma¹ provides basic tenets for the management of injured patients. The process begins with the primary survey, a stepwise evaluation of the “ABCs”: Airway, Breathing, and Circulation.

Airway patency may be compromised by neurologic injury, facial injury, or obstruction (e.g., by tongue, blood, vomitus, tooth or bone fragments). Trauma to the larynx, trachea, or bronchus may also complicate or preclude airway control. Thoracic trauma may also cause life-threatening breathing (e.g., pneumothorax, pulmonary contusion) and circulation (e.g., tension pneumothorax, pericardial tamponade, massive hemothorax) problems. These must be identified and treated rapidly.

Resuscitative Thoracotomy

Resuscitative thoracotomy (RT) is indicated for traumatic cardiac arrest or persistent severe hypotension (e.g., systolic blood pressure [SBP] <60 mm Hg). The primary objectives of RT are to (1) release pericardial tamponade and repair cardiac injuries, (2) control intrathoracic hemorrhage, (3) control bronchovenous air embolism or bronchial injury, (4) perform open cardiac massage, and (5) attenuate subdiaphragmatic hemorrhage and redistribute blood flow to the brain and myocardium.² The critical determinants of survival following this procedure are the mechanism of injury and the patient's condition. The best outcomes are seen in adult patients with isolated penetrating cardiac injuries who present with detectable SBP; survival averages 35% in large series. In contrast, RT is least beneficial in the treatment of blunt injury without signs of life, with only 1% to 2% of patients surviving.

An algorithm for resuscitation of moribund trauma patients is presented in [Figure 169-1](#).² Patients arriving in extremis following blunt injury undergo thoracotomy if they have had fewer than 10 minutes of cardiopulmonary resuscitation (CPR). Penetrating trauma victims undergo thoracotomy if they have had fewer than 15 minutes (for torso injuries) or 5 minutes (nontorso injuries) of CPR. The pericardium is opened; if there is no organized cardiac activity and no blood in the pericardium, the patient is pronounced dead. Otherwise the descending thoracic aorta is occluded to limit subdiaphragmatic hemorrhage and redistribute perfusion to the myocardium and brain. Patients who do not respond with SBP >70 mm Hg are pronounced dead on the basis of futility. The value of thoracotomy in the resuscitation of a

patient in profound shock is unquestioned. Its indiscriminate use, however, is not appropriate. While the performance of RT only “costs” the price of a scalpel and sterilization of the instrument tray, it is critical to recognize futility and avoid initiating massive transfusion or transferring the patient to the operating room (OR). These resources should be reserved for potential survivors. Furthermore, while no cases have been specifically reported, there is a potential risk of transmission of blood-borne disease to the health care team. Finally, the use of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) has been proposed in this setting. Because open-chest CPR has been proven superior in the setting of hypovolemia, and REBOA placement may exacerbate thoracic hemorrhage, it is not recommended at this time.³

■ PLEURAL SPACE

Pneumothorax

Pneumothorax (PTX) is common in thoracic trauma. Decreased breath sounds and hyperresonance to percussion are not 100% accurate. Chest x-ray (CXR) has long been considered the diagnostic standard, but the extended focused assessment with sonography for trauma (E-FAST) has potentially greater sensitivity for a small PTX in the supine patient. If not relieved, a PTX may progress to a tension PTX, especially if the patient is receiving positive-pressure ventilation. In this setting, the mediastinal structures are shifted away from the affected side. Once venous return to the heart is impaired, cardiovascular collapse ensues. Immediate decompression of tension PTX can be lifesaving.

An open PTX, a.k.a. “sucking chest wound,” results from a full-thickness chest wall wound. If the wound diameter exceeds two-thirds of the tracheal diameter, negative intrapleural pressure associated with inspiratory effort results in air entering the pleural space preferentially through the wound. Because of the large hole, there is little chance of tension. However, this can be life-threatening because it prevents pulmonary gas exchange. It is managed by an occlusive dressing secured on three sides to prevent sucking of more air but allowing decompression of the pneumothorax until definitive wound closure and tube thoracostomy can be performed.

With the growing use of thoracic computed tomography (CT), small PTXs are often discovered that are not seen on CXR. These “occult PTXs” generally do not require treatment but should be monitored for progression. A recent prospective multicenter study of the American Association for the Surgery of Trauma (AAST) found that only 6% of patients with occult PTX ultimately required a chest tube. Moreover, consistent with earlier studies, fewer than 20% receiving positive-pressure ventilation required chest tubes, and none of them had tension.⁴

Tube Thoracostomy

Tube thoracostomy is the definitive treatment for PTX and hemothorax. The procedure is not difficult and can be performed rapidly, but care must be taken to avoid malpositioning. The optimal position is posterior, to facilitate dependent drainage of blood, and directed to the apex of the pleural cavity. The current trend is to place smaller diameter tubes, as they cause less discomfort for the patient and are adequate to drain most nonclotted hemothoraces.⁵

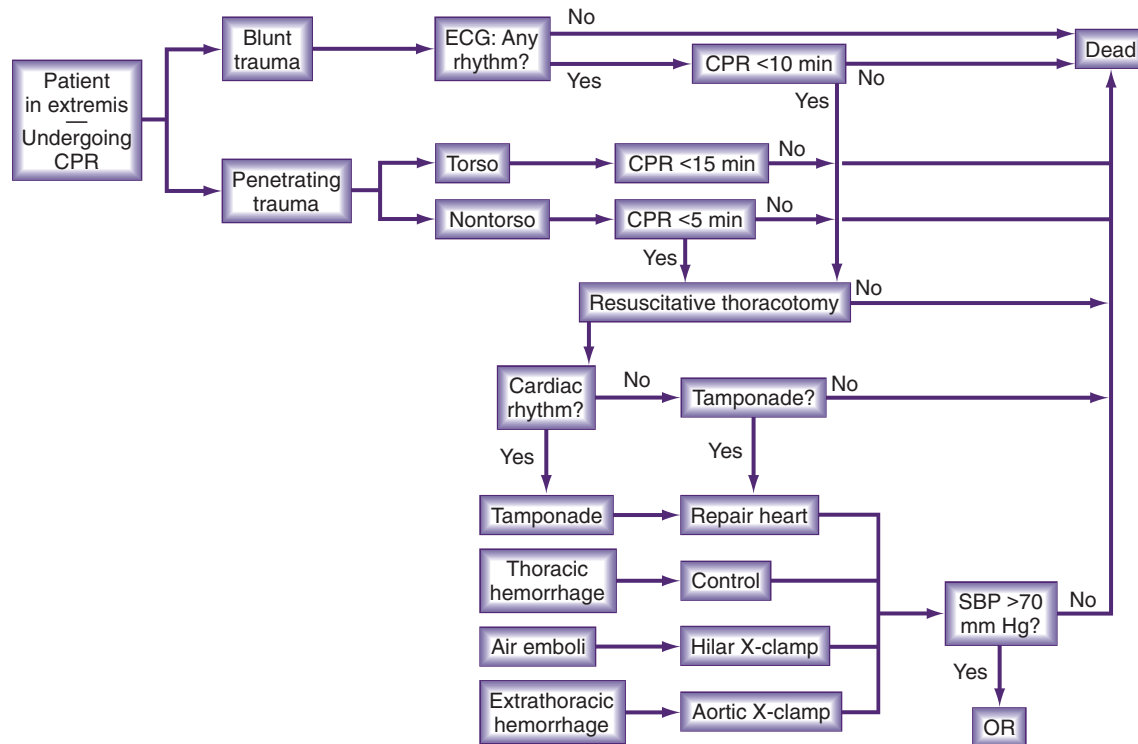


FIGURE 169-1 ■ Algorithm for resuscitative thoracotomy.

In the setting of tension PTX, if tube thoracostomy is not immediately available, the chest can be quickly decompressed with a large-bore needle. Although many authors previously promoted needle thoracostomy via the second intercostal space in the midclavicular line, it has been recognized repeatedly that catheters may be kinked in the pectoralis major muscle or breast tissue, rendering them ineffective—often unbeknownst to the clinician. Recent literature has documented that the anterior axillary line in the fifth intercostal space is, on average, 10 to 12 mm thinner. This site allows rapid, reliable, safe entry into the pleural space.⁶

In the past, some investigators proposed routine prophylactic antibiotics to prevent infections related to tube thoracostomy. However, prophylactic antibiotics do not reduce the incidence of empyema or pneumonia and may be associated with antimicrobial resistance in subsequent hospital-acquired infections.⁷

Pneumothoraces and air leaks should be resolved before removal of the tube, and ideally, drainage should be less than 2 mL/kg/d. After 12 to 24 hours without an air leak, the tube may be removed while on suction. However, a 6- to 12-hour trial of waterseal drainage is generally warranted to observe for an occult air leak.⁸ It has been recommended that tubes be removed at maximal deep inspiration with a Valsalva maneuver, but recurrent PTX may occur in 6% to 8% of patients regardless of respiratory phase. More than 20% of patients require longer than 3 days to resolve an air leak, in which case their hospital course may be expedited by the use of thoracoscopy.⁹

Hemothorax

Blunting of the costophrenic angle on upright CXR requires 200 to 250 mL of blood, and in a supine patient, there may be only subtle haziness of the affected hemithorax. Large hemothoraces should generally be drained by tube thoracostomy, but hemothoraces that are asymptomatic and seen only on CT can be managed expectantly. A massive hemothorax is usually the result of a major vascular injury and is life-threatening. Indications for thoracotomy include the immediate

return of 1500 mL of blood via tube thoracostomy, or continued output of more than 200 mL/hr for 2 to 3 consecutive hours. The clinician should be wary of an initial high-volume output that is followed by an abrupt decrease in volume. In this case, a repeat CXR should be obtained to rule out a “caked hemothorax.” If the original tube appears to be well positioned and there is significant retained hemothorax, thoracoscopy or thoracotomy is indicated. Hemothoraces associated with massive blunt chest wall trauma can pose special challenges. Ongoing bleeding suggests the need for thoracotomy, but a large incision may compound the bleeding, and diffuse bleeding from bone and soft-tissue disruption may prove difficult to control. In this setting, one might consider arteriography with embolization of intercostal vessels in a hemodynamically stable patient.

■ CHEST WALL INJURY

Rib Fracture

Rib fractures are very common. Rib fractures in elderly patients can lead to diminished pulmonary function with potentially disastrous complications. Patients over the age of 65 have two- to fivefold increases in morbidity and mortality compared with younger patients with similar injuries.^{10,11} A key factor in the management of these patients is pain control to facilitate coughing and clearance of secretions. Epidural catheters have proved to be efficacious and superior to patient-controlled analgesia in this regard and may also modify the immune response.^{12,13} Rib blocks may provide immediate relief in the ED or intensive care unit (ICU) while awaiting epidural catheter placement. A paravertebral catheter provides another alternative; current investigations are designed to determine whether this intervention may supplant epidural catheters.¹⁴

Flail Chest

Two or more ribs fractured in two or more places produce a flail segment of the chest wall. This segment may move paradoxically—

inward during inspiration, outward during expiration—and consequently impair respiratory mechanics. However, a more important cause of respiratory compromise following flail chest is the pulmonary contusion that typically accompanies it. Treatment is supportive, including supplemental oxygen, analgesia, and pulmonary toilet. Surgical stabilization of the flail segment and rib fracture repair in general has been performed for many years without clear demonstration of benefit or identification of the patient population most likely to benefit. Recent modifications in instrumentation and technique have made this potentially more efficacious¹⁵; a recent prospective study suggested benefits in terms of respiratory function, need for mechanical ventilation, and length of stay.¹⁶ However, identification of the patient most likely to benefit remains an issue.

Sternal Fracture

Early series of sternal fractures described the “steering wheel syndrome” (rapid deceleration, with impact of the sternum on the steering wheel) as the most common cause of sternal fractures. Associated blunt cardiac injury was common, so sternal fractures were thought to be harbingers of significant thoracic injury. More recently, however, sternal fractures have been reported more commonly with the “seat belt syndrome” (in conjunction with three-point or bandolier seat belts). Associated injuries are less frequent, so stable patients without ECG abnormalities can be safely discharged from the ED.

LUNG INJURY

Pulmonary Contusion

Pulmonary contusion is common following major chest trauma. The pathophysiologic changes fundamentally include hemorrhage with surrounding edema, with a broad range of severity. The clinical result is hypoxia and increased work of breathing due to ventilation/perfusion mismatching and decreased pulmonary compliance. Pulmonary contusions may not appear on initial chest radiographs, although they are usually seen by 6 hours after the injury; chest CT is more sensitive at diagnosing early pulmonary contusions. Treatment is supportive, including supplemental oxygen, pain control, pulmonary toilet, and judicious fluid management. There is no role for either routine antibiotics or steroid therapy.¹⁷ Intubation and mechanical ventilation are employed only as necessary. The degree of pulmonary dysfunction can peak at 72 hours and generally resolves within 7 days in the absence of associated nosocomial pneumonia.

Posttraumatic pulmonary pseudocysts are cavity lesions that occur in approximately 3% of lung parenchymal injuries.¹⁸ They are often noted incidentally on the chest radiograph. Most resolve spontaneously within 2 to 4 months. However, surgical intervention is indicated for infection, bleeding, and rupture. The lesion can be distinguished from an abscess by CT-guided aspiration.

Pulmonary Laceration

The typical clinical presentation is a hemopneumothorax. Bleeding is usually self-limited, and the vast majority of these injuries are definitively managed by tube thoracostomy alone. Of the 10% of patients requiring thoracotomy, approximately 20% need lung resection. Historically, this group has experienced high morbidity and mortality, with mortality following pneumonectomy approaching 100%. In 1994, Wall and colleagues introduced the concept of pulmonary tractotomy as a nonresectional means of managing penetrating lung injuries.¹⁹ It is indicated for deep through-and-through injuries that do not involve central hilar vessels or airways. The wound tract is exposed by passing clamps (as originally described) or a stapling device (our preference) through the wound and dividing the bridge of lung tissue. Air leaks and bleeding points are sutured, and the wound tract is left open. Morbidity and mortality compare favorably with anatomic resections.²⁰

Mediastinal Injuries

Pneumomediastinum

Pneumomediastinum has classically been considered a sign of aerodigestive injury, particularly when seen on CXR; however, with expanding use of chest CT, pneumomediastinum is seen with increasing frequency. Recent analyses have found that pneumomediastinum is present on approximately 5% of chest CT scans following trauma but that only 10% of these patients actually have aerodigestive injuries.²¹ In the absence of signs or symptoms or additional suspicious findings on CT scan, further investigation is not necessary.

TRACHEOBRONCHIAL INJURY

Tracheobronchial injuries are uncommon but should be excluded in the presence of cervical subcutaneous emphysema, pneumomediastinum, or pneumothorax with a persistent air leak. The definitive diagnostic test is bronchoscopy. Cervical injuries are approached via cervical incisions, with partial or complete sternotomy as needed. Blunt injuries often occur in the distal trachea or right mainstem bronchus and are approached via right thoracotomy. Tracheal injuries can usually be repaired primarily or by resection and reanastomosis without tracheostomy; late stenosis is uncommon. On the other hand, laryngotracheal injuries often require tracheostomy as an adjunct to repair, and tracheal stenosis is a common late complication. Absorbable monofilament sutures are preferred. Bronchial injuries may be repaired, but severe disruptions or associated vascular injuries may necessitate pneumonectomy or lobectomy. Positive end-expiratory pressure is avoided postoperatively.²²

ESOPHAGEAL INJURY

Esophageal perforation from blunt force trauma is a rare event caused by a sudden rise in intraluminal pressure or by the upper esophagus being crushed between the trachea and a vertebral body. More commonly, esophageal injury is the result of penetrating trauma. Early signs and symptoms of injury can be subtle. Pneumomediastinum should prompt consideration of this injury. Barium esophagography is considered the diagnostic study of choice and can be readily obtained in a stable, awake patient. However, videoendoscopy can be done at the bedside virtually anywhere in the hospital and has excellent accuracy. Thus, it is preferred in critically ill or unstable patients in the ICU or operating room.²³

If the injury is identified within 24 hours, it can usually be treated with débridement, primary repair, and drainage. If a tension-free repair is not possible, it is best managed with débridement and drainage, cervical esophagostomy, and feeding tube placement.²³

CARDIAC INJURY

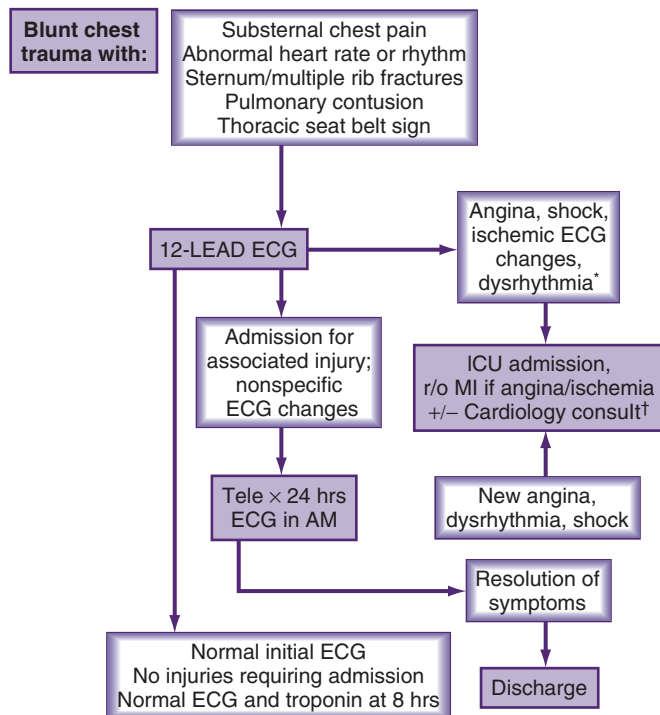
Blunt Cardiac Injury

Blunt cardiac injury (BCI) represents a wide spectrum of cardiac injuries, ranging from occult and inconsequential to lethal dysrhythmias, pump failure, or cardiac rupture. It can occur following virtually any trauma to the chest.

Diagnosis, Monitoring, and Treatment

The diagnostic criteria for BCI are not standardized; no test is 100% predictive of the uncommon but life-threatening complications of ventricular dysrhythmias and cardiac pump failure—the so-called significant BCI. The pivotal issue is to identify patients at risk and have them in a setting where the complication can be identified and treated promptly.

A guideline for monitoring patients with suspected BCI is depicted in Figure 169-2. The initial evaluation should include an ECG. Patients with shock, ischemic changes on the ECG, or significant dysrhythmias are admitted to the ICU. If angina or ischemic ECG changes are noted,



*Ischemic changes: ST elevation/depression, T wave inversion in ≥ 2 leads; Dysrhythmia: Frequent premature atrial/ventricular contractions, heart block, new atrial fibrillation/bundle branch block
 †Echocardiogram may be indicated in selected patients with unexplained or refractory shock, new murmur, or clinical suspicion of pericardial effusion/tamponade

FIGURE 169-2 ■ Evaluation for suspected blunt cardiac injury: blunt chest trauma with substernal chest pain, abnormal heart rate or rhythm, sternum or multiple rib fractures, pulmonary contusion, thoracic seat-belt sign. Ischemic changes consist of ST elevation or depression or T-wave inversion in two leads. Dysrhythmia consists of frequent premature atrial or ventricular contractions, heart block, new atrial fibrillation, or bundle branch block. Echocardiogram may be indicated in selected patients with unexplained or refractory shock, new murmur, or clinical suspicion of pericardial effusion or tamponade. ECG, electrocardiogram; MI, myocardial infarction.

the diagnosis of acute coronary syndrome should be pursued. Patients with significant blunt chest trauma and nonspecific ECG findings (e.g., sinus tachycardia) who are being admitted for associated injuries should have cardiac monitoring for 24 hours.²⁴ A subset of patients may not require admission for other injuries. These patients can be safely discharged from the ED if ECG normalizes and if a troponin-I level at 8 hours is less than 1.5 ng/mL.²⁵

Dysrhythmias are treated by pharmacologic suppression. The management of cardiogenic shock from cardiac pump failure may include early placement of a pulmonary artery catheter to optimize fluid administration and inotropic support. An echocardiogram may be indicated to exclude septal or free wall rupture, valvular disruption, or pericardial tamponade. Patients with refractory cardiogenic shock may require placement of an intraaortic balloon pump to decrease myocardial work and enhance coronary perfusion.

Comotio cordis is a distinct entity in which “virtually instantaneous cardiac arrest is produced by nonpenetrating chest blows in the absence of heart disease or identifiable morphologic injury to the chest wall or heart.”²⁶ In a series of 70 cases, Maron and colleagues reported a 90% mortality rate in a young (mean age 12 years) population of

patients.²⁵ An experimental model demonstrated that ventricular fibrillation is reproducibly triggered by a precisely timed blow during a narrow window within the repolarization phase of the cardiac cycle (15-30 msec before the peak of the T wave). Heart block may be produced by a blow during the QRS complex.²⁷

Pericardial Injury

Pericardial tears may result from direct thoracic impact or from an acute increase in intraabdominal pressure. Herniation of the heart through a large tear may be associated with significant cardiac dysfunction. A pericardial rub may be detected on physical examination. The CXR may demonstrate pneumopericardium, displacement of the heart, or bowel gas in the chest. Echocardiography or CT may be required to confirm the injury. In a stable patient, a subxiphoid pericardial window should be performed, followed by sternotomy in the presence of large hemopericardium or a visible pericardial tear. An unstable patient may require RT. Pericardial lacerations should be repaired, but large holes that cannot be closed primarily should be left widely open to prevent future cardiac herniation. A late complication is the postpericardiotomy syndrome, manifested by fever, chest pain, pericardial effusion, a pericardial rub, and ECG abnormalities; this is adequately treated with antiinflammatory agents.

Valvular Injury

Valve injuries are rare. Even in lethal cardiac trauma, the valves are injured in approximately 5% of patients. The most commonly injured valve is the aortic, followed by the mitral, tricuspid, and pulmonary. Aortic valve disruption may result in acute severe cardiac failure, but a mild injury may present with syncope or anginal symptoms. Mitral valve leaflet tears, or more commonly, rupture of papillary muscles or chordae tendineae, may also result in acute heart failure. A heart murmur will generally be present, and echocardiography and/or cardiac catheterization are used to confirm the diagnosis. Most valve injuries are amenable to supportive care until other injuries have been stabilized. Valve repair is generally preferred over valve replacement when feasible.²⁸

Septal Injury

Septal injuries are found in 5% to 7% of patients dying from blunt trauma. Ventricular septal ruptures are much more common than atrial septal injuries; they usually occur in the muscular portion near the apex. Characteristic physical findings include a systolic thrill and a harsh holosystolic murmur heard best at the left sternal edge and radiating to the right, but the symptoms may be delayed for hours or days as the defect enlarges. Atrioventricular conduction abnormalities may also be present, simulating myocardial ischemia, and severe hypoxemia may result from an acute left-to-right shunt. Prompt echocardiography is indicated to establish the diagnosis; cardiac catheterization may be needed.

Small septal defects may heal primarily, allowing expectant management with periodic follow-up. Surgical repair—either primary or with a patch graft—is indicated if the patient is hemodynamically compromised or has a left-to-right shunt with a shunt ratio of 2:1 or greater. Repair of the defect is delayed for several weeks if possible.²⁹

Coronary Artery Injury

Direct injuries to coronary arteries are rare. The left anterior descending artery is the most susceptible (76% of cases), followed by the right coronary artery (12%) and the circumflex coronary artery (6%). Surgical revascularization or repair of delayed complications related to infarction, such as ventricular pseudoaneurysms, may be indicated.

Penetrating Cardiac Injury

Cardiac penetration is rapidly lethal in 90% of gunshot wounds and up to 50% of stab wounds. All patients in shock with penetrating chest injuries between the right midclavicular line and left anterior axillary line, as well as the posterior left chest, should be considered to have a cardiac injury until proven otherwise.³⁰ The right ventricle, with its maximal anterior exposure, is at greatest risk, followed by the left ventricle, right atrium, and left atrium. Multiple cardiac structures are involved in a third of patients. Stab wounds are more commonly associated with tamponade, while gunshot wounds often result in exsanguination through a large pericardial defect.

Repair of cardiac injuries can be accomplished through either a median sternotomy or anterolateral thoracotomy incision. In a hemodynamically compromised patient, left anterior thoracotomy with transsternal extension is used for definitive repair. In a hemodynamically stable patient, sternotomy is generally preferred. A limitation of sternotomy is access to posterior mediastinal injuries. Satinsky clamps are useful in isolating atrial or caval injuries, whereas small ventricular lacerations are controlled digitally. Larger wounds may be stapled. Wounds that are very large are occasionally reparable using temporary caval inflow occlusion.³¹

Pericardial Tamponade

Potential pericardial tamponade should be suspected in all patients sustaining penetrating injuries to the anterior chest wall. Pericardial tamponade can be a two-edged sword: although it may limit initial blood loss, it can prove fatal by restricting diastolic filling of the heart.³² Because the pericardium is not acutely distensible, as blood accumulates the pressure in the pericardial sac rises to match that of the injured chamber. When the pressure approaches that of the right atrium, right atrial filling is impaired, and right ventricular preload is reduced; ultimately, this leads to decreased right ventricular output. Increased intrapericardial pressure also impedes myocardial blood flow, which leads to subendocardial and later subepicardial ischemia, with a further reduction of cardiac output. This vicious cycle may progress insidiously with injury to low-pressure conduits, or it may occur precipitously with a ventricular wound. Acute tamponade of as little as 100 mL of blood within the pericardial sac can produce life-threatening hemodynamic compromise.

Early diagnosis is key, as the ultimate cardiovascular collapse can be abrupt. Compensatory responses including tachycardia and vasoconstriction can transiently stabilize the hemodynamic status of the patient. Similarly, vigorous fluid administration may improve the patient's vital signs. The classic findings of Beck's triad (hypotension, distended neck veins, and muffled heart sounds) are present in less than 10% of patients; furthermore, Kussmaul's sign (neck vein swelling with inspiration) and pulsus paradoxus (systolic blood pressure drop with inspiration) are not reliable indicators of acute tamponade. In fact, neck veins may not become distended until hypovolemia is corrected.

In the setting of suspected pericardial tamponade, ultrasonography using subxiphoid and parasternal views (or formal echocardiography if immediately available) is extremely helpful if the findings are positive, although a negative ultrasonographic examination may be misleading if there is a pericardial laceration.³³ If pericardial fluid is demonstrated, the patient should be transported immediately to the OR for sternotomy. However, if ultrasonography is equivocal, a central venous pressure line should be inserted promptly. Persistently elevated central venous pressure in a patient with thoracic trauma should prompt consideration of subxiphoid pericardial window. If the pericardial ultrasonography is positive and there will be any delay in getting to the OR, pericardiocentesis should be done if there is any suggestion of cardiac compromise, because subclinical endocardial ischemia can lead to recalcitrant lethal dysrhythmias. The pericardial tap should be performed with a pigtail catheter to allow repeated aspiration during preparation for thoracotomy. In the setting of shock, evacuation of as

little as 15 mL of blood may dramatically improve the patient's hemodynamic profile. Pericardiocentesis is successful in decompressing tamponade in approximately 80% of cases; most failures are due to clotted blood within the pericardium. If pericardiocentesis is unsuccessful and the patient remains severely hypotensive (systolic blood pressure < 70 mm Hg), RT should be performed.

TRANSMEDIASTINAL PENETRATING TRAUMA

Transmediastinal trajectory of a bullet should be considered in the setting of (1) entry and exit wounds on opposite sides of the thorax, (2) a single entry wound with the bullet ending up on the opposite side of the thoracic cavity or in close proximity to the mediastinum, or (3) multiple gunshot wounds to the thorax. Significant injury, especially to the heart or great vessels, often results in prehospital death or hemodynamic instability. There is little controversy regarding the management of unstable patients: they should have emergent thoracotomy. However, stable patients may harbor occult injuries to critical mediastinal structures (heart, great vessels, trachea, or esophagus). Helical CT angiography (CTA) of the chest has proved useful in demonstrating the trajectory of missiles in the thorax.³⁴ In the setting of a potential transmediastinal gunshot wound, a CT scan may confirm a trajectory remote from the mediastinum, obviating further testing. A proven transmediastinal trajectory mandates further evaluation, tailored to the specific structures at risk. Our current approach to evaluating these patients is outlined in Figure 169-3.

THORACIC GREAT VESSEL INJURY

Patients with penetrating injuries to extrapericardial thoracic great vessels usually succumb in the field; however, an occasional patient arrives with a contained hematoma. Early CXR is critical to identify hemothorax, as well as a widened mediastinum or apical capping. Patients who are hemodynamically unstable should be taken directly to the OR; those in extremis should undergo RT. A reasonable approach can be inferred from the CXR and the location of the wounds. If the patient has a left hemothorax, a left anterolateral thoracotomy in the third or fourth intercostal space should be performed. Patients with a right hemothorax should likewise be approached via a right anterolateral thoracotomy. Unstable patients with injuries near the sternal notch may have large mediastinal hematomas or may have lost blood externally. These patients should be explored via a median sternotomy with cervical extension. Hemorrhage should be controlled digitally until the vascular injury is delineated. In a hemodynamically stable patient, CTA can facilitate a more directed approach. In the setting of pericardial trajectory, it must be remembered that collateral flow around the shoulder girdle can result in palpable pulses, even in the presence of a significant subclavian artery injury.

A median sternotomy, with appropriate extension, is used for exposure of the aortic arch branch vessels. In patients who have undergone RT, the left anterolateral thoracotomy incision may have to be extended to a bilateral anterolateral thoracotomy ("clamshell"). In exposing the proximal left subclavian artery, it may be necessary to create a full-thickness flap of the upper chest wall. This is accomplished with a partial sternotomy and supraclavicular extension. If necessary, the ribs can be transected laterally, allowing the flap to be folded laterally, but this is rarely required. This incision has been referred to as an *open-book* or *trapdoor thoracotomy*. The midportion of the subclavian artery is accessible via a supraclavicular skin incision.

The great vessels are rather fragile and can be easily torn during dissection or crushed with a clamp. For this reason, injuries adjacent to the aortic arch are oversewn, and a graft is inserted onto a new location on the arch. The graft is then sewn (without tension) to the distal artery. Nonoperative management of nonocclusive peripheral arterial injuries has proved successful, and there are limited data supporting similar management within the thorax for certain patients. Similarly, lesions associated with severe neurologic injuries are usually managed

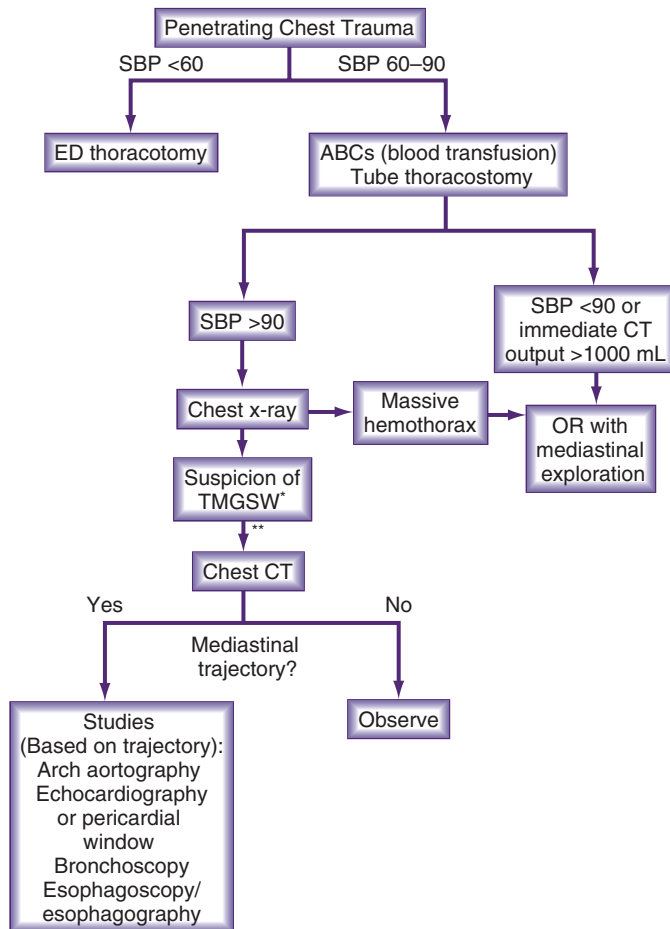


FIGURE 169-3 ■ Evaluation of suspected transmediastinal gunshot wounds (TMGSWs). ABCs, airway, breathing, circulation; CT, computed tomography; ED, emergency department; OR, operating room; SBP, systolic blood pressure.

*Suspect transmediastinal trajectory in the presence of entry and exit wounds on opposite sides of the thorax, a single entry wound with the bullet located in the contralateral hemithorax or adjacent to the mediastinum, or multiple gunshot wounds to the thorax.

**If there is evidence of mediastinal injury (pneumomediastinum, widened mediastinum on chest x-ray), consider proceeding directly to invasive diagnostic testing.

nonoperatively. Experience with intravascular stenting is growing, although long-term outcomes have not been reported.³⁵ Clearly unstable patients require operative control and repair; however, it appears that stent graft treatment of subclavian artery injuries is preferred in stable patients.³⁶

Blunt Thoracic Aortic Injury

Perhaps the most feared occult injury in trauma surgery is a blunt thoracic aortic injury (BTAI). The mechanism of aortic tears is believed to be primarily a shearing force. The tear usually occurs just distal to the left subclavian artery where the aorta is tethered by the ligamentum arteriosum. In 5% of cases, the tear occurs in the ascending aorta, in the transverse arch, or at the diaphragm. An estimated 85% of thoracic aortic injuries are fatal at the injury scene. A multicenter report from the American Association for the Surgery of Trauma (AAST) analyzed 274 accident-scene survivors of BTAI.³⁷ Motor vehicle crashes accounted for 81% of the injuries, with frontal impact in 72%, lateral

impact in 24%, and rear impact in 4%. Two additional series also documented substantial numbers of BTAI following lateral-impact crashes: 57 of 165 (35%) autopsy cases reported by Burkhart et al.³⁸ and 48 of 97 (50%) cases reviewed by Katyal et al.³⁹ Thus the surgeon should suspect this injury whenever there is significant energy transfer, regardless of directionality.

Chest x-ray is considered the initial screening tool of choice for determining whether further investigation is needed for BTAI. Commonly associated radiographic findings include mediastinal widening, obscured aortic knob, deviation of the left mainstem bronchus (downward) or nasogastric tube (rightward), and opacification of the aortopulmonary window (Fig. 169-4, A). In the AAST multicenter study,³⁷ widening of the mediastinum on the anteroposterior chest radiograph was present in 85% of cases. However, 7% of patients with torn aortas had normal chest radiographs. Dyer and colleagues⁴⁰ reported normal initial radiographs in 13% of patients. Thus, additional investigations are warranted in the setting of significant energy transfer. Thoracic aortography was previously considered the gold standard for diagnosis (see Fig. 169-4, B). However, helical CT scan is now well accepted as an excellent screening test (see Fig. 169-4, C).⁴⁰⁻⁴² When hematoma adjacent to the thoracic aorta is considered a positive finding, the sensitivity of CT for aortic injury is 100%.

There are currently a number of areas of controversy in the management of BTAI: immediate versus delayed repair, management of minimal aortic injuries (MAI), and open versus endovascular repair.

Immediate Versus Delayed Repair

Until the 1990s, BTAI was thought to require urgent repair to avoid early rupture. Recognizing significant morbidity and mortality in patients with severe associated injuries and comorbid medical conditions, the concept of immediate repair was challenged. The administration of beta-blockade to decrease systolic blood pressure (<100 mm Hg) and heart rate (<100 bpm), and therefore reduce aortic shear pressure, allowed the optimization of associated injuries and stabilization of target systolic blood pressure and heart rate.⁴¹ Numerous studies have established the safety of this approach. In fact, a recent AAST prospective multicenter trial found that delayed repair is associated with significant survival benefit.⁴³ Although patients with major associated injuries are most likely to benefit, the study supported delayed repair in all patients, irrespective of risk factors. A current practice guideline by the Eastern Association for the Surgery of Trauma (EAST) recommends delayed repair to reduce mortality and paraplegia.⁴²

Management of Minimal Aortic Injury

With increasing sensitivity of CT scans (as discussed with regard to pneumomediastinum), more MAIs are being diagnosed. These are defined as small (<1 cm) intimal lesions with minimal to no periaortic hematoma.⁴⁴ Fabian and colleagues⁴¹ identified MAI in 10% of BTAI and found that half of these lesions were missed on arteriography. Although the name suggests benign behavior, the Memphis group reported that 50% of MAIs had progressed to pseudoaneurysm formation by 8 weeks post injury.⁴⁴ MAIs are generally treated with beta-blockade and CT surveillance.⁴⁵

Open Versus Endovascular Repair

Over the past several years, open repair has been largely supplanted by thoracic endovascular aortic repair (TEVAR).⁴⁶ The weight of current evidence supports TEVAR as first-line therapy, given superior outcomes in terms of mortality, blood loss, and paraplegia.^{42,47} While long-term outcome data are still relatively sparse, they remain good, and improvements in devices will likely continue that trend.

In those patients who require open repair, a primary concern has been the occurrence of paraplegia from ischemic injury of the spinal cord. In the AAST study,³⁷ the paraplegia incidence was 1.6% in patients with cross-clamp times less than 30 minutes, but 12% if the time was greater than 30 minutes. A 20-year meta-analysis found a 19% incidence of paraplegia associated with this method and noted that average cross-clamp times were over 40 minutes.⁴⁸ The alternative

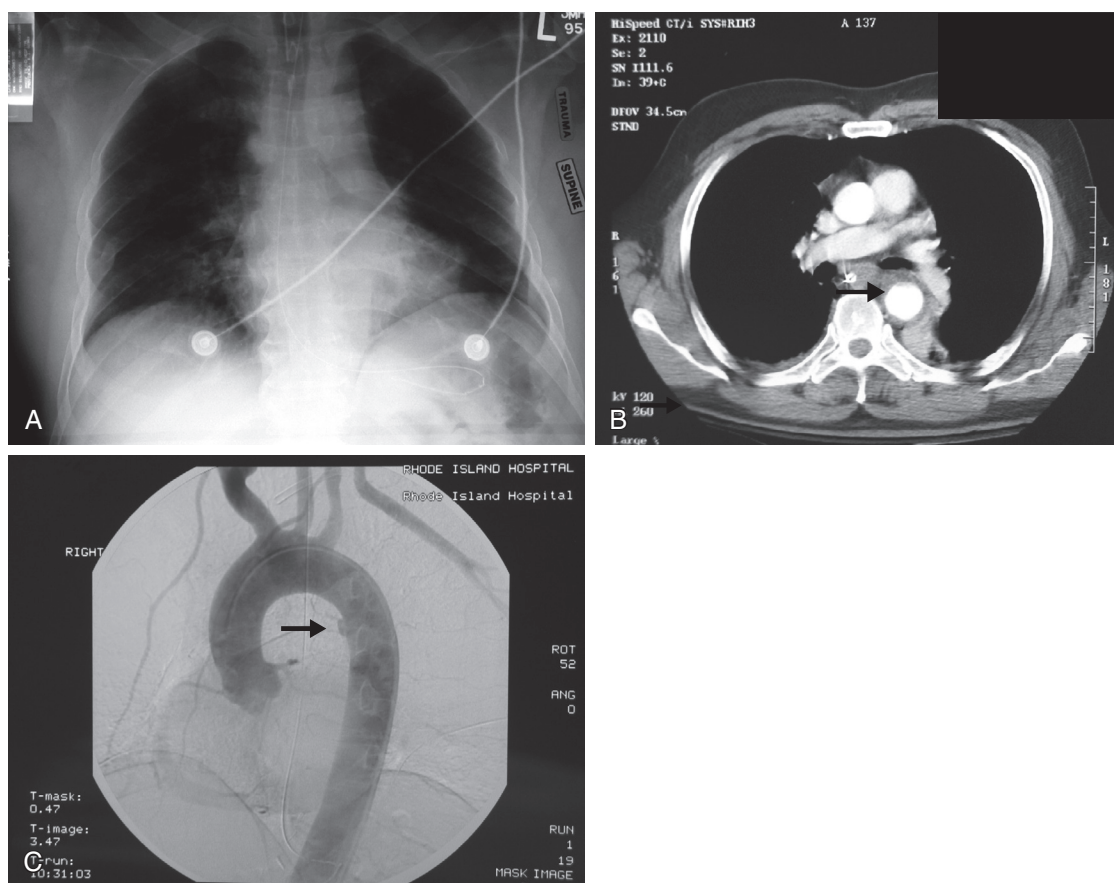


FIGURE 169-4 ■ Images from patient with descending thoracic aortic injury. **A**, Anteroposterior chest radiograph. Note widened mediastinum and widened left paratracheal stripe, indistinct aortic knob, and slight depression of left mainstem bronchus. **B**, Helical computed tomography (CT) scan of chest. Note periaortic hematoma (arrow). **C**, Digital subtraction arteriogram of aortic arch. Note pseudoaneurysm in the common location, distal to left subclavian artery (arrow).

approach is to provide some method for maintaining spinal perfusion during cross-clamping. The current preferred method is to use either active partial left heart bypass (siphoning blood from the left heart and pumping it to the distal aorta) or full bypass such as femoral-femoral bypass. The former can be a significant benefit in a patient with multiple injuries, particularly in those with intracranial hemorrhage.

However, occasional small cerebral infarcts have occurred, so heparin is administered unless contraindicated. The injury may be primarily repaired, or a graft may be inserted. A large multicenter trial suggested that polytetrafluoroethylene is the preferred graft material for aortic replacement, given its long-term patency and apparent resistance to infection.⁴⁹

KEY POINTS

Initial Assessment

1. Initial management of injured patients should follow the principles of the Advanced Trauma Life Support course.
2. Resuscitative thoracotomy will not yield productive survival when patients (1) sustain blunt trauma and require more than 10 min of prehospital CPR without response, (2) have penetrating wounds and undergo more than 15 min of prehospital CPR without response, or (3) manifest asystole without pericardial tamponade.

Pleural Space

1. Tube thoracostomy is not necessary for asymptomatic occult pneumothoraces.
2. Needle decompression should be done in the midaxillary line in the fifth intercostal space.

3. Prophylactic antibiotics do not reduce the incidence of chest tube-associated empyema or pneumonia and are associated with antimicrobial resistance.
4. Chest tube removal algorithms should include lung expansion, drainage less than 2 mL/kg/d, and a trial of 6- to 12-hour waterseal drainage.
5. High-volume chest tube output that abruptly decreases should raise the suspicion of clotted hemothorax.

Chest Wall Injury

1. Rib fractures in elderly patients are associated with significant morbidity and mortality.
2. Surgical stabilization of rib fractures should be considered for intractable pain or major chest wall deformity.

KEY POINTS—cont'd

Lung Injury

1. Treatment of pulmonary contusion is supportive, with mechanical ventilation used only when indicated.
2. Pulmonary tractotomy results in favorable morbidity and mortality rates compared with lung resection for trauma.

Tracheobronchial Injury

1. Bronchoscopy should be performed for cervical subcutaneous emphysema, pneumomediastinum, or pneumothorax with a persistent air leak.

Esophageal Injury

1. Contrast esophagography is the preferred diagnostic study, but videoendoscopy can be done at the bedside in intubated patients and is superior in the pharyngeal area.

Cardiac Injury

1. Blunt cardiac injury is commonly diagnosed, but cardiac enzymes, echocardiography, and nuclear medicine studies are not predictive of the uncommon but life-threatening complications of ventricular dysrhythmias and cardiac pump failure.
2. Echocardiography is most useful in identifying pericardial tamponade or intracardiac injuries.
3. All patients in shock who have penetrating chest injuries between the right midclavicular line and left anterior axillary line should be considered to have a cardiac injury until proved otherwise.

4. Ultrasonography and central venous pressure monitoring are critical adjuncts in diagnosing pericardial tamponade, as the classic findings of Beck's triad are present in very few patients.

Transmediastinal Penetrating Trauma

1. Helical CT scanning is useful in delineating the trajectory of potential transmediastinal gunshot wounds, allowing a truncated and cost-effective workup in stable, asymptomatic patients.

Thoracic Great Vessel Injury

1. A reasonable operative approach to unstable patients can be inferred from the chest radiograph and the location of wounds.
2. Blunt thoracic aortic injury should be suspected in any patient with severe energy transfer, regardless of mechanism.
3. Helical CT is an excellent screening test and should be considered even in the face of a normal chest radiograph if there is severe energy transfer.
4. Once aortic injury is diagnosed, the systolic blood pressure and heart rate should be controlled with a rapidly reversible beta-blocking agent.
5. TEVAR is the preferred approach for aortic repair.
6. During aortic repair, it is safest to provide distal circulation via a bypass circuit.
7. Delayed intervention is superior to immediate repair.

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A good overview of a difficult problem.

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The acutely injured patient requires a rapid, systematic, and thorough evaluation guided by the Advanced Trauma Life Support principles.¹ A high suspicion for intraabdominal pathology must also be had as delays in diagnosis and treatment increase morbidity and mortality.² When evisceration or peritonitis are absent, history and physical examination findings that suggest intraabdominal injury are often subtle.³ This chapter will focus on the diagnosis, evaluation, and management of traumatic injuries (both blunt and penetrating) to the abdominal cavity. The principles of damage control surgery and the open abdomen will also be discussed.

■ BLUNT ABDOMINAL INJURY

Operative management is the primary therapy in patients with blunt abdominal injury who present with peritonitis or hemodynamic instability, accompanied by signs of abdominal trauma or hemoperitoneum. With its bedside availability and noninvasiveness, focused abdominal sonography for trauma (FAST) should be employed in all severely injured blunt trauma patients.⁴ FAST cannot be used to detect diaphragm, hollow viscus, or retroperitoneal injuries.⁵ Diagnostic peritoneal lavage (DPL) is useful for further evaluation of the abdomen in unstable patients with a negative FAST or in patients who require an emergency operation for an injury remote from the abdomen.⁶ DPL lacks sensitivity for retroperitoneal and diaphragm injuries.

For patients who do not require an immediate laparotomy, and who are hemodynamically stable, computed tomography (CT) is the standard diagnostic tool.⁷ While it is accurate in the diagnosis of solid organ injury, it lacks sensitivity and specificity for pancreatic, hollow viscus, and diaphragm injuries.⁸

■ PENETRATING ABDOMINAL INJURY

A penetrating abdominal injury from the nipple line anteriorly or scapular tip posteriorly to the buttocks inferiorly can produce both a thoracic and abdominal injury. After a rapid primary survey, the entire body must be inspected for penetrating wounds. Radiographs are taken to identify all foreign objects and to anticipate possible structures at risk. FAST is less useful in the evaluation of penetrating abdominal trauma except for the ability to detect hemopericardium.

Indications for immediate exploration of abdominal penetrating injuries include hypotension, peritonitis, and evisceration. In the absence of these signs in a stable patient with a reliable physical exam, serial abdominal examination may be an option.⁹ The need for exploratory laparotomy is then based on a change in abdominal examination, vital signs (especially temperature or heart rate), or white blood cell count.¹⁰

■ HEPATIC TRAUMA

The liver is the most commonly injured organ in patients suffering blunt abdominal trauma.¹¹ For hemodynamically stable patients, CT is the diagnostic test of choice as it provides rapid grading of the injury and detection of active hemorrhage.¹²

The majority (80%-85%) of blunt hepatic injuries are low grade (grade 1-3), with only 15% being high-grade injuries (grade 4-5).

Patients requiring immediate laparotomy for hemodynamic instability generally have grade 4 or 5 liver injuries. Approximately 70%-80% of liver injuries can be safely managed nonoperatively.^{13,14} Predictors of failed nonoperative management (NOM) of high-grade liver injury include age, male gender, higher Injury Severity Score (ISS), lower Glasgow Coma Scale, and hypotension.¹⁵

Successful NOM requires appropriate patient selection, high-quality CT, and the availability of an effective multidisciplinary team of intensive care physicians, experienced surgeons, and interventional radiologists.¹⁶ For most liver injuries requiring surgery, the indication is related to the development of a complication, such as abscess or bile peritonitis, rather than bleeding.¹⁷ For patients who do have evidence of ongoing bleeding from the liver injury, depending on the patient's hemodynamic status, magnitude of the liver injury, and associated intraabdominal injuries, either angiography or surgery is warranted.

Angiography/embolization enhances the success of NOM but should only be utilized in patients who are hemodynamically stable without other indications for operative intervention.¹⁸ Active extravasation of contrast on CT predicts the need for embolization.¹⁹ Complications of angioembolization include hepatic necrosis, gallbladder necrosis, bile leak, and abscess formation.²⁰

While NOM has resulted in lower mortality rates, complications of NOM of hepatic injury include bleeding, bile leak, hepatic necrosis, gallbladder necrosis, abscess, fistula, and thrombosis or pseudoaneurysm of the hepatic vasculature.^{17,21} Treatment of complications after NOM may include observation of small bilomas, endoscopic retrograde cholangiopancreatography (ERCP) and stenting of large bile leaks, percutaneous drainage of bilomas or abscesses, or surgery.²² Delayed bleeding is an uncommon complication.

Although NOM of liver injury offers benefits of low mortality, reduced transfusion requirements, and reduced length of hospital stay, up to 35% of patients with complex liver injuries will require early operation.^{17,22} Postoperative hepatic angiography may also be useful.¹⁹ Definitive management of liver injuries involves not only control of bleeding but also removal of devitalized or necrotic liver, control of bile leaks, and drainage.

■ PANCREATIC TRAUMA

Pancreatic injuries are relatively uncommon due to its well-protected position in the retroperitoneum, occurring in 0.2% to 2% of all trauma.²³ Blunt pancreatic injury is often due to a crushing force compressing the pancreas against the vertebral column, with injury to the pancreatic neck.

The Western Trauma Association and the Eastern Association for the Surgery of Trauma have published guidelines for pancreatic trauma diagnosis and/or management.^{24,25} Early diagnosis remains a challenge. Signs and symptoms of pancreatic injury may be subtle and become apparent only later in the postinjury course as pancreatic secretions become activated and pancreatic and peripancreatic inflammation increases. Initial physical examination, DPL, and ultrasonography are relatively insensitive in detection of pancreatic injury.²⁶

CT is the primary imaging modality used in the diagnosis of blunt pancreatic injury despite being an imperfect test, especially for early diagnosis and detection of pancreatic ductal injury.²⁷ The sensitivity of CT scans may improve with time after injury; therefore, a repeat CT

may be warranted for patients with persistent signs or symptoms consistent with pancreatic injury.

ERCP is the most sensitive technique, short of operative exploration, for diagnosis of pancreatic ductal injury.²⁸ ERCP can define ductal anatomy in patients presenting late after injury with complications such as persistent pancreatic fistula or pseudocyst.²⁹

The use of magnetic resonance cholangiopancreatography (MRCP) is limited by a variety of factors including patient status, associated injuries, and availability of magnetic resonance imaging (MRI).³⁰ In addition, MRCP does not offer the opportunity for therapeutic intervention.

The status of the pancreatic duct, the location of injury (proximal versus distal), and the overall status of the patient determine the most appropriate management. Pancreatic injury without evidence of ductal injury (grades 1 and 2) can be managed with débridement and external drainage alone. Distal pancreatectomy and drainage should be the treatment for most distal pancreatic injuries with ductal injury (grade 3).²⁴

Proximal pancreatic ductal injuries and disruption of the pancreatic head (grade 4 and 5 injuries) are difficult to manage. Recommendations range from simple drainage alone to complex procedures such as pancreaticoduodenectomy or on-lay pancreaticojejunostomy. Pancreaticoduodenectomy should rarely be required.

Mortality from pancreatic injury ranges from 9% to 34%.²⁴ Early mortality following pancreatic trauma is due primarily to associated injuries, predominantly vascular injuries. Sepsis, multisystem organ failure, and respiratory failure account for the majority of late deaths.³¹ Unlike mortality, which is dependent predominantly on the presence of associated injuries, the pancreatic injury itself becomes a major factor in late morbidity. The presence of main pancreatic ductal injury is associated with increased morbidity. Furthermore, the incidence of pancreas-related complications correlates with the grade of injury. Pancreas-related complications include pancreatic fistula, abscess, pseudocyst, pancreatitis, and hemorrhage due to erosion of adjacent retroperitoneal vessels. This erosion is itself secondary to the presence of activated pancreatic secretions or the presence of a pancreatic abscess.^{24,32}

■ SPLENIC TRAUMA

Most splenic injuries are managed nonoperatively, with the primary indication for surgery being hemodynamic instability.^{33,34} Splenic injuries are primarily assessed through contrast-enhanced abdominal CT, which allows determination of the injury grade, as well as identification of vascular abnormalities such as contrast blush or extravasation, pseudoaneurysm, or arteriovenous fistula.

Findings that correlate with failure of NOM include high-grade injuries (grade 4 or 5), high ISS, presence of pseudoaneurysms, arteriovenous fistulae, or active extravasation.^{35,36} Most patients (90%) who fail NOM do so within the first 3 days following injury, with 60% failing within the first 24 hours.^{35,37}

Angiographic embolization is an adjunct in the management of some splenic injuries with contrast extravasation on CT. However, this strategy should not be chosen in the unstable patient or in the patient with other indications for laparotomy.^{34,38-41} Complications of angiographic embolization include femoral access issues, pleural effusions, contrast-induced acute kidney injury, splenic infarction, abscesses, or cysts; splenic-specific complications occur more frequently with distal embolization.⁴²

■ UROLOGIC TRAUMA

Hematuria is the hallmark sign of genitourinary injury. Gross hematuria mandates further evaluation. Microscopic hematuria is further evaluated in the blunt trauma patient with hypotension, lower rib fractures, flank ecchymosis or tenderness, spine fractures, or high ISS.^{43,44} Renal injuries are seen in 1% to 5% of all trauma patients, with the vast majority (approximately 90%) resulting from blunt

mechanisms.⁴⁵ Given the well-protected location of the kidneys, major force is required for significant renal injury to occur.⁴⁶

Imaging to evaluate renal trauma is usually performed with CT, which allows staging, identification of preexisting renal pathology, and documentation of the presence of an uninjured kidney.⁴⁷ A substantial injury seen on the arteriovenous phase should prompt obtaining delayed images to evaluate for urine collections, or contrast extravasation consistent with injury to the collecting system.⁴⁸

The grade of injury predicts morbidity and mortality as well as the need for interventions, with higher grade injuries more likely requiring operations, ureteral stents, or interventional angiography with embolization or vascular stenting.⁴³ NOM has become the standard in most cases of blunt renal trauma, with the goals of renal salvage and avoidance of long-term complications.⁴⁹ Complications of NOM and partial nephrectomy include bleeding, urinoma, and infection.

In a study of over 15,000 blunt trauma patients, bladder ruptures were most commonly diagnosed on CT cystogram and were commonly associated with pelvic fractures (80%) and hollow viscus injury (35%).⁵⁰ A higher risk of death is seen with intraperitoneal bladder injuries with or without a concomitant extraperitoneal injury, compared with only extraperitoneal injuries.⁵¹ A follow-up cystogram is recommended before catheter removal after complex repairs to the trigone or those requiring ureteral reimplantation. However, cystograms are not required for simple injuries.⁵²

Ureteral injuries are uncommon and occur more in penetrating than in blunt trauma.⁵³ The most commonly associated injury with blunt ureteral trauma is pelvic bone fracture, whereas penetrating ureteral trauma patients sustain more hollow viscus and vascular injuries.

A straddle injury or anterior pelvic rami fracture may be associated with a urethral injury, particularly in males. Signs of urethral injury include blood at the meatus, inability to void, perineal hematoma, or high-riding prostate gland. A retrograde urethrogram should be obtained prior to placement of a bladder catheter in these patients.

■ HOLLOW VISCUS INJURY

Hollow viscus injury (HVI) is commonly the result of penetrating abdominal injury. These injuries are generally found during routine exploration of the abdomen. Bowel injury from blunt trauma is relatively uncommon, difficult to diagnose, and carries with it a higher morbidity in the setting of delayed intervention.^{8,54,55} Moderate to large amounts of free fluid on CT after blunt abdominal trauma without evidence of solid organ injury, should raise the suspicion of an HVI and the need for exploration.^{56,57} Intestinal injury may be present despite normal findings by CT.⁵⁵ While CT may detect free air, the presence of free fluid, seatbelt sign, or radiographic signs of bowel trauma are highly predictive of injury.⁵⁸ The presence of blunt splenic and/or hepatic injuries predict a higher incidence of HVI, especially if combined.⁵⁹ Treatment of HVI requires exploration.

■ DIAPHRAGMATIC TRAUMA

Blunt diaphragmatic injury is important yet challenging to diagnose. The chest radiograph is diagnostic in 25% of cases, abnormal but not diagnostic in 50% of cases (blunting of the diaphragm, presence of haziness or infiltrates at the lung base), and normal (even in retrospect) in 25% of cases.⁶⁰ A second study evaluated the utility of CT scans. Upon retrospective review by a board-certified radiologist, only 57% of 42 patients who sustained blunt trauma and had preoperative CT scans of the torso had evidence of diaphragmatic injury on CT.⁶¹ Diaphragmatic injury is more common on the left side.⁶² Acute injury to the diaphragm is repaired through the abdomen rather than the chest because of the high likelihood of associated abdominal injury.

Diaphragmatic injuries from penetrating trauma are very difficult to diagnose, as the hole is generally small. Penetrating thoracoabdominal wounds, particularly on the left side, may result in hernias that entrap intestine years later. If the trajectory of a penetrating injury

suggests the possibility of a left-sided diaphragmatic injury, either laparoscopy or laparotomy is generally indicated.

DAMAGE CONTROL

Damage control refers to truncated surgical operations to control immediately life-threatening problems, followed by a period of vigorous ongoing resuscitation prior to subsequent return to the operating room for definitive repair of injuries.⁶³ Damage control surgery became widespread due to the recognition that prolonged efforts to completely correct anatomic abnormalities often resulted in technically adequate repairs but also resulted in patients who were physiologically exhausted and often died from irreversible shock, acidosis, hypothermia, and coagulopathy.⁶⁴

Damage control entails rapid control of hemorrhage and enteric contamination, a truncated operation, followed by temporary abdominal closure; all ideally performed in 1 hour or less.^{63,64} The patient is subsequently scheduled to return to the operating room within 24 to 48 hours, unless they require reoperation sooner due to ongoing bleeding or source control. At reoperation, packs are removed or replaced, devitalized tissue is resected, vascular repairs are performed, bowel anastomoses or stoma are created, feeding tubes are placed, and the abdominal wall is formally or again temporarily closed. Postoperative resuscitation may include angioembolization, particularly for arterial bleeding from hepatic injuries or pelvic fractures.

Care of the patient following a damage control operation focuses on resuscitation and preparation for the expected return to the operating room. The goals are rewarming, reversal of coagulopathy, and restoration of adequate perfusion. A complete reassessment with a systematic physical examination and adjunctive radiologic studies, as indicated, is essential to avoid missed injuries. It may be possible to complete radiographic assessments of the spine or extremities prior to reoperation, but the risks of transporting critically injured patients to remote diagnostic suites must be weighed against the potential benefits of finding or excluding particular injuries. Trips outside of the intensive care unit should be minimized. Correct placement of all tubes and lines should be confirmed. Laboratory parameters including acid-base status,

oxygenation, hemoglobin concentration, and coagulation profile should be monitored closely and corrected expeditiously. The inability to correct these abnormalities often suggests the need to return to the operating room. The operating surgeon must convey key information about the expected postoperative course, including critical clinical parameters that must be recognized and reported. Changes in drain output, critical laboratory values, increasing transfusion requirements, and changes in wound appearance all indicate potential deterioration. Once the patient returns to a relatively normal physiologic state, then return to the operating room for definitive repairs is undertaken.

THE OPEN ABDOMEN

A consequence of damage control is an open abdomen that refers to the unapproximated abdominal wall fascia. Massive swelling and edema of the abdominal viscera following resuscitation can result in increased intraperitoneal pressure and resultant organ dysfunction, referred to as the *abdominal compartment syndrome*.⁶⁵ Leaving the abdomen open shortens the duration of the initial operation, simplifies reexploration, and prevents abdominal compartment syndrome by creating a protected but flexible space for the enlarged viscera. Management of the open abdomen is not straightforward and carries with it significant morbidity, including enterocutaneous or enteroatmospheric fistulas and giant ventral hernias.⁶⁶ Because of these complications, multiple strategies to close the abdominal wall fascia as soon as possible have been employed.⁶⁷ However, none of these techniques has been universally successful, and optimal management of the open abdomen remains an area of active research.

CONCLUSION

Appropriate management of patients who have sustained abdominal trauma requires astute clinicians who are part of a multidisciplinary team. Significant morbidity and mortality can result, particularly from delays in diagnosis or treatment. Coordination between the surgeon and the intensivist, in particular, is essential to assure patients the best outcomes possible.

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Pelvic and long bone fractures have serious local and systemic consequences for the trauma victim. Familiarity with the sequelae of serious orthopedic injuries is essential if intensive care unit (ICU) management of these patients is to have a successful outcome. The evolution of a multidisciplinary approach using a directed clinical decision-making pathway can lead to improved patient survival, reducing early deaths from exsanguination and late deaths from shock and multiple organ failure.¹

■ PELVIC FRACTURE

Pelvic fractures are present in about 10% of patients presenting to a level I trauma center after blunt trauma.² Pelvic fractures represent approximately 3% of skeletal injuries evaluated in major trauma centers.³ The incidence of pelvic fractures is highest following a motor-cycle crash, pedestrian trauma caused by a motor vehicle, falls from heights greater than 15 feet, and motor vehicle crashes, in that order.² Overall mortality due to pelvic fractures ranges from 10% to 16%; the highest mortality (around 45%) is attributed to open pelvic fractures.^{3,4} The incidence of solid and hollow organ injury and other skeletal trauma is high in patients with pelvic fractures, owing to the powerful forces involved.^{2,5} More than 90% of these individuals have associated gastrointestinal (5%) and other abdominal injuries (16.5%).²

The transfusion requirement for patients with pelvic fractures and a mean Injury Severity Score (ISS) of 21.3 is eight units of packed red blood cells but can be much greater.⁶ Complete dissociation of the posterior pelvis has the highest degree of hemorrhage and associated mortality.^{7,8} Less than 1% of all patients with pelvic fractures have hypotension secondary to blood loss due to the fracture itself.^{6,9} Nevertheless, 12% of patients with open pelvic fractures die as a direct result of hemorrhage.¹⁰

Hemorrhage from unstable pelvic fractures can be minimized by early reapproximation and stabilization of the pelvic ring. If external pelvic fixation is unsuccessful at restoring hemodynamic stability, after initial resuscitation, angiography to evaluate and treat pelvic arterial bleeding is indicated. Pelvic arterial disruption is responsible for hemorrhage in less than 5% of all cases of pelvic fracture.^{8,11} A blush of contrast identified on pelvic computed tomography (CT) scan is evidence of arterial bleeding and is an indication for angiography. Predictors of positive angiography have been postulated to be the presence of sacroiliac joint (SIJ) disruption, female gender, and the duration of hypotension.¹¹ Early and aggressive angioembolization has been shown to improve outcomes in properly selected patients. An algorithmic team approach can provide significant benefit, helping to reduce blood loss and thereby improving the success of nonoperative management.¹² Recurrent pelvic bleeding has been found following angiography and embolization in 8% to 23% of patients.⁹ Intensive care surveillance is mandatory even after a stable response to resuscitation.

■ LONG BONE FRACTURE

The most studied and serious long bone fracture is a fracture of the femur. Approximately 15% of seriously injured motor vehicle passengers presenting to a level I trauma center have femur fractures.¹³ Some 8% to 10% of these patients have bilateral fractures.^{14,15} The mortality rate for a unilateral fracture of the femur is 10% to 12%.^{14,15} Mortality

increases to 26% to 33% with bilateral fractures and is increased by 20% in patients above the age of 65.¹⁴ The highest incidence of femur fractures in the trauma population occurs in young men, with midshaft fractures being the most common as a result of high-energy impact.¹¹ Patients with bilateral fractures have an increased incidence of head injury, requirement for laparotomy, and pelvic fractures compared to those with a unilateral femur fracture.^{14,15} As with pelvic fractures, death is more closely associated with the severity of associated injuries rather than the fracture itself.^{14,15} The American College of Surgery's Committee on Trauma continues to recommend that femur fractures in polytrauma patients be repaired within 12 hours, provided the patient is hemodynamically stable.¹⁶ In the patient who presents with a closed femoral fracture and associated hypotension, other sources of hemorrhage should be considered.

■ LOCAL COMPLICATIONS

Infection

Infection can manifest as an acute complication in the setting of both long bone and pelvic fractures with the potential for osteomyelitis. Diagnosis can be achieved using CT, magnetic resonance imaging (MRI), three-phase bone scan, or radiolabeled white blood cell scans. The most common causative organism is *Staphylococcus aureus*, but infection may also be due to *Pseudomonas aeruginosa* and Enterobacteriaceae.¹⁷ The best option in high-risk open fractures remains prophylactic antibiotics administered parenterally within 6 hours, typically consisting of a first-generation cephalosporin (Cefazolin) and an aminoglycoside (Tobramycin).

Gas gangrene or necrotizing fasciitis (*Clostridium perfringens*, *Streptococcus* sp., anaerobes, and coliform bacteria) can occur within the first 24 hours after fracture or operative repair. These fulminant, necrotizing infections usually occur in the setting of open fractures with extensive soft-tissue injury requiring débridement and are especially likely if there is a delay in treatment and/or with the presentation of shock. Tetanus prophylaxis consists of 0.5 mL of adsorbed toxoid promptly administered intramuscularly (IM) on presentation for all patients with traumatic wounds, including open fractures, who have not received a booster within the past 5 years.

Compartment Syndrome

Compartment syndrome (CS) is a potentially devastating complication that arises in the setting of either open or closed fractures. Tissue edema and bleeding raise the pressure in the fixed volume of a fascial compartment, which impedes blood flow, especially in arterioles and capillaries, resulting in tissue ischemia. Nervous tissue demonstrates functional abnormalities after 30 minutes of ischemia, with irreversible loss of function occurring after 12 to 24 hours. Muscle, on the other hand, does not exhibit functional defects for up to 2 to 4 hours, with irreversible loss of function only occurring after 4 to 12 hours. Capillary permeability also increases, resulting in further tissue edema.¹⁸

The most common location for compartment syndrome after lower extremity fracture is the anterior compartment of the leg. This complication usually results from closed tibia fractures. Up to 17% of patients with a tibia fracture secondary to a motor vehicle crash develop a

compartment syndrome.¹⁹ Compartment syndrome of the thigh can develop after open or closed fracture and may also develop after operative treatment of the fracture. Compartment syndrome of the arm, buttock, and foot are also possible after fracture. Risk factors associated with developing compartment syndrome include the severity of the fracture and associated soft tissue injury, the use of compression devices such as military antishock trousers or tourniquets, and systemic hypotension.^{18,20}

Diagnosis of compartment syndrome can be made on clinical grounds and is established when the compartment is tense on physical examination, severe pain is present with passive motion, the compartment is tender throughout, and sensory nervous function is impaired. Loss of distal pulses is often the last manifestation of compartment syndrome. The diagnosis must be made early before permanent tissue damage has occurred. Serial examinations are critical to monitor for compartment syndrome in patients at risk.¹⁸

Measurement of compartment pressure is an additional way to confirm the diagnosis; however, measurements are unnecessary when the diagnosis is evident on clinical grounds. Measurement of compartment pressure is useful when the physical examination is limited because the patient is unresponsive due to head injury or sedation. Compartment pressure values ranging from 30 to 45 mm Hg have been recommended as the threshold for triggering surgical intervention.¹⁹ Compartment pressures are measured by placement of a sterile needle connected to a pressure transducer into each compartment. Alternatively, commercial devices such as the Stryker compartment monitor (Stryker, Kalamazoo, MI) are available that accomplish the same task.

Treatment is by urgent, complete surgical fasciotomy to open all affected compartments. Fasciotomy can be performed in the ICU if the patient is too unstable to be transported to the operating room. Complete fasciotomy within 12 hours of onset results in a normal functional outcome in 68% of cases, whereas delay decreases the likelihood of successful outcome to 8%.²¹

In light of the fact that compartment syndrome can lead to irreversible neurologic and muscular damage, early diagnosis cannot rely solely on clinical findings. Hence, prophylactic fasciotomy has been advocated. Subsequent to this, a trend toward liberal use of "prophylactic fasciotomy" has been noted. According to Abouezzi et al. the most important factor influencing the need for fasciotomy is the location of the vascular injury. Popliteal vessel injuries are often associated with warm ischemia and prolonged repair time in the operating room.²² The overall incidence of neurologic damage due to a delayed, or lack of fasciotomy is difficult to determine.²²

Once the compartment has been opened, wash-out of the metabolic products of ischemia occurs. It is critical to closely monitor acid-base status, serum potassium and phosphate concentrations, serum creatinine kinase (CK) levels, fluid status, and renal function. Serum CK and creatinine measurements should be routinely done, with underlying concern for muscle injury or the development of renal failure. Serum myoglobin measurement is not necessary for the diagnosis and management of rhabdomyolysis. Since serum myoglobin is cleared more rapidly than CK, its utility is marginal, particularly when the diagnosis of rhabdomyolysis is delayed.²⁰ Urine myoglobin is not a sensitive or specific measurement for the development of acute kidney injury (AKI).

Rhabdomyolysis

Rhabdomyolysis can occur for several reasons after skeletal trauma. The disease and its pathophysiology were first described in 1941 during the "Blitz" of London. The severity of muscle necrosis depends on multiple factors including loss of arterial supply, increased compartment pressure secondary to prolonged or severe compression/injury, length of time without effective blood flow, and delayed resuscitation leading to hypovolemic shock.²³ A high index of suspicion must be maintained to facilitate early diagnosis. The most obvious cause is direct injury to muscles surrounding the fracture site. Direct injury to

skeletal muscle tissue is especially likely when the mechanism of injury results in the transfer of a great deal of energy. Second, rhabdomyolysis can occur following compression of tissues for a prolonged period after an injury. The compression causes ischemic injury to the involved muscle. Last, rhabdomyolysis can result from compartment syndrome due to a fracture. Again, the mechanism involves compression of circulation resulting in an ischemic injury. All three mechanisms of rhabdomyolysis can be exacerbated by hemorrhagic shock.²⁴

Successful treatment of rhabdomyolysis involves aggressive intravenous (IV) fluid therapy to maximize tubular flow rate, avoiding the accumulation of myoglobin in the renal tubules, and preventing the occurrence of hyperkalemia. Administration of iron-chelating agents such as desferrioxamine (standard dosage for rhabdomyolysis not established) and alkalization of urine using sodium bicarbonate as 50% of the resuscitation fluid (150 mEq dissolved in 1 L of 5% dextrose solution) or a carbonic anhydrase inhibitor such as acetazolamide are recommended by some experts. Ultimately, acute renal failure may necessitate hemofiltration or hemodialysis.^{25,26,27} In our institution, we aim to maintain a urine output greater than 1 to 2 mL/kg/h using IV fluids and follow serial serum CK and creatinine levels. We have had good success in avoiding acute renal failure without the use of urine alkalization or iron-chelating agents.

Fat Embolism Syndrome

Pathophysiology

Fat embolism syndrome occurs when marrow fat particles embolize from bone marrow to the pulmonary and systemic venous circulation via injured veins in the setting of acute fracture or fracture repair. Larger particles lodge in the pulmonary circulation, whereas smaller particles (7–10 μ m) will pass through to the systemic circulation. Estimates of the number of patients with fractures who develop pulmonary, cutaneous, and neurologic manifestations of fat embolism syndrome vary between 0.5% and 20%.^{17,28} It is estimated that 5000 deaths due to fat embolism syndrome occur annually after pathologic fractures, traumatic fractures, and orthopedic surgery.²⁹

Clinical Manifestations

Clinical diagnosis of fat embolism syndrome is based on the presence of the classic triad of respiratory compromise, mental status changes, and petechial rash in the setting of long bone fractures or orthopedic surgery involving long bone manipulation.³⁰ In patients with long bone fractures, 60% to 85% manifest symptoms within 24 to 48 hours. Therefore, in the appropriate setting, the rash is pathognomonic and presents in only 20% to 50% of cases.³¹

Severity can vary from subclinical, to subacute clinically apparent symptoms, to fulminant acute symptoms.³² The subacute course is associated with mild respiratory dysfunction and mild neurologic manifestations or cardiovascular compromise. The fulminant variety can involve any of the following: rapidly progressive acute respiratory distress syndrome (ARDS), complete cardiovascular collapse, or deep coma possibly resulting in death.³³

In trauma patients, it may be difficult to distinguish fat embolism syndrome from other causes of compromised pulmonary function. Indeed, the cause of respiratory compromise in multitrauma patients with significant long bone fractures can be multifactorial, including fat embolism syndrome, direct pulmonary/thoracic cavity trauma, and ischemia reperfusion injury with systemic activation of the inflammatory response.

The cardiovascular effects of fat embolism syndrome are mainly attributable to partial occlusion of pulmonary arterial flow resulting in acute pulmonary hypertension, and increased right ventricular afterload. These effects also vary in severity from sinus tachycardia, to reversible hypotension, to irreversible profound shock due to right heart failure resulting in death.^{17,35,29} Changes on the electrocardiogram include sinus tachycardia, bradycardia, other arrhythmias, and ST-segment changes.^{17,35,32} Treatment is supportive, with inotropic agents to increase contractility of the right ventricle so as to overcome

the adverse effects of increased afterload. Central nervous system manifestations of varying degrees are present in 70% to 80% of patients with fat embolism syndrome.³⁶ These findings can vary from mild confusion or restlessness to profound coma resulting in death.³³

Petechial rash is present in up to 50% of cases and is usually seen on the chest, neck, and axilla, although less often the rash appears on mucous membranes or the conjunctiva.^{37,28,32} Retinal changes can also be observed and include microinfarcts, cotton-wool spots, and flame-like hemorrhages.^{36,32} Petechial rash is usually a late sign of fat embolism syndrome.

Diagnosis

Many laboratory abnormalities are encountered in cases of fat embolism syndrome, but none is specific. Bronchoalveolar lavage has been advocated as a more specific test to diagnose fat embolism syndrome. Findings on chest CT scan include patchy ground-glass or nodular opacities and thickening of the interlobar septa. Because they most often occur 24 hours or more after injury, they can usually be differentiated from contusion, which should be evident earlier. CT findings in more severe cases of fat embolism syndrome include more extensive bilateral patchy airspace consolidation; similar abnormalities can also be seen on the chest radiograph.^{38,39}

Treatment

The mainstay of treatment for fat embolism syndrome is supportive. Pulmonary manifestations often respond to supplemental oxygen, but more severe cases of fat embolism syndrome develop into ARDS and multiple organ system failure, requiring prolonged mechanical ventilation. Cardiac dysfunction occurs due to increased pulmonary resistance, and shock due to fat embolism syndrome may require inotropic support.

The most important treatment of fat embolism syndrome is prevention. In the setting of traumatic fractures, prevention is achieved by providing early fixation. Multiple experimental and clinical studies clearly show that early fracture fixation (within 24 hours) decreases both the pulmonary and cardiac effects of fat embolism syndrome, as compared with delayed (>24 hours) fixation and nonoperative treatment.^{17,35,32,40-42} Intraoperative use of transesophageal echocardiography (TEE) can be a very sensitive monitor to detect fat emboli. The emboli appear as showering white flakes flowing or tumbling through the right atrium.⁴²

Thromboembolism

Pathophysiology

Venous injury, stasis, and hypercoagulability can all contribute to the risk of thromboembolism after pelvic or long bone fracture. Embolic thrombi to the pulmonary circulation or systemic circulation (paradoxical embolization) can originate in the deep veins of the thigh, pelvis, or upper extremity. Calf vein thrombosis, in general, does not embolize but extends to involve more proximal deep veins 20% to 25% of the time.

Risk Factors

A number of risk factors for thromboembolic disease including femur, tibia, and pelvic fractures, have been identified in trauma patients. Other identified risk factors include age greater than 40 years, immobility, blood transfusion, multiple trauma, head injury, spinal fracture, spinal cord injury, and high ISS.^{17,32,43-49} However, a systematic review of the literature by the Eastern Association for the Surgery of Trauma (EAST) found that only spinal fractures and spinal cord injuries were consistently shown to be associated with a higher risk of deep vein thrombosis (DVT).⁵⁰

Prophylaxis

Elevation of the affected extremity and passive motion exercises increase lower extremity venous flow rates and reduce DVT.¹⁷ Lower extremity sequential compression devices decrease the incidence of

DVT by up to 90% in orthopedic patients.¹⁷ Compression devices placed on the foot have also been shown to decrease the incidence of DVT in patients undergoing orthopedic surgery for elective indications, or trauma.¹⁷ These devices are useful when the anatomy of injury and surgery preclude placement of sequential compression devices on the leg.¹⁷ Similar improvements in the thromboembolism rate have been seen in the surgical ICU population.⁵¹ In the multitrauma population, some studies have shown sequential compression device use to be equivalent to the use of low-dose heparin, whereas other studies have shown no improvement in thromboembolic events when compared to no prophylaxis.⁴⁹ Despite conflicting data in the literature, the use of sequential compression devices continues to be a mainstay of thromboembolism prophylaxis in the skeletal trauma population because of its low cost, ease of use, and inherent safety. The salutary effects of sequential compression devices are thought to include improved venous flow, and activation of endogenous antithrombotic mechanisms. The anticoagulant effects of sequential compression devices decrease minutes after discontinuing the device, emphasizing the importance of continuous therapy.^{50,51} Because of its low cost, non-invasive nature, and high accuracy, color-flow duplex ultrasonography has become the test of choice for DVT.⁵² Aggressive screening and prophylaxis can reduce the incidence of asymptomatic venous thromboembolism (VTE) diagnosed by duplex ultrasonography.⁴⁵

Low-dose unfractionated heparin (5000 units IV, 2-3 times daily) decreases the incidence of thromboembolic events when compared with placebo in various populations of acutely ill patients. These studies have included orthopedic and nonorthopedic, critically ill and noncritically ill patients. Overall reductions in thromboembolic rates are of the order of two- to threefold.^{50,51} However, multiple studies of trauma and orthopedic patients, including two meta-analyses, have failed to show significant improvement in the rate of thromboembolic events when low-dose unfractionated heparin is compared to placebo.^{17,50}

The literature on low molecular weight heparin (LMWH) is more convincing. Several studies have shown that treatment with LMWH decreases the incidence of thromboembolism and has an excellent safety profile in patients with hip fracture or multisystem trauma.^{17,43} Moreover, studies have also shown that LMWH (enoxaparin, 30 mg subcutaneously [SQ] every 12 hours) provides superior VTE prophylaxis when compared to low-dose unfractionated heparin (5000 units SQ every 12 hours) in the trauma population.^{50,53}

Several studies have shown improved efficacy using combined sequential compression devices and low-dose unfractionated heparin or LMWH therapy when compared to either therapy alone in stroke, cardiac surgery, and neurosurgery populations.⁵² Other studies however, have shown no difference between combined and single-modality therapy.⁵¹ Further study of the fracture population is needed.

Treatment

Treatment of DVT and pulmonary embolism in patients with orthopedic injuries or multiple trauma involves a balance between the risk of bleeding and thromboembolic disease. Although virtually all pulmonary emboli arise from DVT in the thigh, pelvis, or upper extremity, calf vein thrombosis tends to propagate into the proximal veins, meaning that treatment should aim to avoid embolic phenomena.^{54,55} Treatment of DVT and pulmonary embolism usually starts with full anticoagulation using unfractionated heparin. Once therapeutic heparinization has been achieved for an average of 72 hours, treatment with sodium warfarin is begun. Patients are usually kept on bedrest for this period to prevent embolic events.^{55,56} Alternative therapy includes LMWH.

Inferior vena cava filters are generally reserved for patients who have failed anticoagulation, exhibit embolic phenomena or propagation of clots while on full anticoagulation, or are inappropriate candidates for systemic anticoagulation.^{51,57} Prophylactic use of inferior vena cava filters involves patients who have no documented pulmonary emboli or DVT but are thought to be high risk due to numerous other factors. The literature varies in attempting to ascertain what defines the "high-risk" patient. It is well recognized, however, that immobility,

venous stasis/injury, inflammatory or hypercoagulable states, and severely injured patients at risk of bleeding are contributory factors to the development of VTE and thromboprophylaxis failure.⁵⁸⁻⁶² Therefore, prophylactic use of inferior vena cava filters should be limited to those patients deemed high risk despite standard preventive measures (compression devices, anticoagulation).

Prognosis

More than 50% of deaths caused by pulmonary embolism occur within the first hour. After the first hour, patients are at a 2.5% to 10% risk of dying when treated adequately. Inadequate treatment carries a 30% risk of death.

KEY POINTS

1. Most deaths in patients with pelvic fracture are from head injury, nonpelvic hemorrhage, pulmonary injury, thromboembolic complications, and multiple organ system failure.
2. Hemorrhage from unstable pelvic fractures can be minimized by early reapproximation and stabilization of the pelvic ring. If this is unsuccessful, angioembolization can be helpful and potentially lifesaving. Angioembolization is most often used to decrease blood loss and improve success when attempting nonoperative management of hemorrhage, but it can also be used as an adjunct therapy before, during, and after an operating room (OR) visit. Direct preperitoneal pelvic packing has been suggested to help reduce transfusion requirements and the need for angiography.
3. Approximately 15% of seriously injured motor vehicle passengers presenting to a level I trauma center have femur fractures.
4. Associated injuries occur in more than 80% of patients and are responsible for more than 90% of deaths in patients with femur fracture.
5. Infection can manifest as an acute complication of open or closed fractures, with gas gangrene or necrotizing fasciitis being life-threatening infections. Treatment generally consists of débridement and antibiotic therapy.
6. Tetanus can result from any open fracture, but patients who have had farming accidents are at particularly high risk. Diagnosis relies on clinical recognition. Treatment consists of supportive care, surgical débridement, prompt passive immunization, and antibiotics.
7. Diagnosis of compartment syndrome can be made on clinical grounds when the compartment is tense on physical examination, severe pain is present with passive motion, the compartment is tender throughout, and sensory nervous function is impaired.
8. Treatment of rhabdomyolysis involves aggressive IV fluid therapy to avoid accumulation of myoglobin in the renal tubules and aid the prevention of hyperkalemia. Monitoring of urine output and serum CK and creatinine levels is mandatory.
9. An estimated 5000 deaths due to fat embolism syndrome occur annually after pathologic fracture, traumatic fracture, and orthopedic surgery combined.
10. Diagnosis of fat embolism syndrome is based on the presence of the classic triad of respiratory compromise, mental status changes, and petechial rash in the setting of long bone fractures or orthopedic surgery. Treatment is supportive, with lung protective strategies and aggressive fluid balance monitoring.
11. A number of risk factors for thromboembolic disease have been identified, including long bone and pelvic fractures, age greater than 40 years, immobility, blood transfusion, multiple trauma, head injury, spine fracture, spinal cord injury, and high ISS.
12. Signs and symptoms may be present in only 15% of patients diagnosed with DVT by venography.
13. Because of its low cost, noninvasive nature, and high accuracy, color-flow duplex ultrasonography has become the test of choice for DVT.
14. Treatment of DVT and pulmonary embolism usually starts with full anticoagulation using unfractionated heparin, transitioning to sodium warfarin or LMWH.
15. Fifty percent of deaths caused by pulmonary embolism occur within the first hour. After that, patients are at a 2.5% to 10% risk of dying when treated adequately and at a 30% risk of death when untreated.

References for this chapter can be found at expertconsult.com.

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Injury is a significant health burden in the pediatric population. It is defined as a sudden transfer of energy (thermal, electrical, mechanical, chemical, or radiation) that is physiologically intolerable or as damage that results in psychologic harm, deprivation, or maldevelopment.¹ Injuries are often classified as either intentional or unintentional. In the United States, injury remains the leading cause of mortality in children and remains a significant health burden. In 2011, more than 23 million children and young adults (age less than 24 years) were seen in an emergency department (ED) for injuries. The total cost of pediatric injury in the United States, including hospitalizations, ED visits, and permanent disability and death is estimated to be \$87 billion annually.² As children have unique anatomic and physiologic considerations, physicians caring for injured children must understand that this population is different from adult populations and that they require specialized treatment to reduce morbidity and improve survival. This chapter provides an overview of caring for critically injured pediatric patients.

TRAUMA SYSTEMS, CENTERS, AND TEAMS

The American College of Surgeons (ACS) Committee on Trauma first advocated inclusive trauma systems in 1991. This concept advocated that the trauma system be broadened to include all phases of injury and also include a multidisciplinary approach for the treatment of trauma. Trauma systems have now matured to include a network of verified trauma centers within most states and regions.³

Trauma centers work within a larger trauma system to provide specialized regional care to injured patients. In most states, trauma centers meeting stated criteria become “verified” to deliver a specified level of care based on available resources. Level 1 trauma centers are considered the highest verification level and provide comprehensive, multidisciplinary care to injured patients. Verified trauma centers also participate in regional, state, and national quality improvement initiatives by reporting their data. Trauma centers also frequently participate in research to advance the care of injured patients.

It is well recognized that trauma systems and dedicated trauma centers improve outcomes and reduce mortality secondary to injury. Trauma centers with specialized expertise in pediatric trauma continue to show advantages for injured children when compared to other centers without such expertise.⁴ For example, there is strong evidence that children with identified traumatic brain injury (TBI) should be transported directly to an available pediatric trauma center. Pediatric injury requires dedicated expertise, and children have improved outcomes with reduced mortality when admitted directly from the injury scene compared to those admitted by hospital-to-hospital transfer.⁵

The trauma team is a fundamental component to a trauma center’s mission of caring for injured patients. The trauma team refers to all who care for the trauma patient, from the initial resuscitation to hospital discharge. Members of the trauma team include trauma surgeons, ED physicians and nurses, critical care physicians and nurses, subspecialty surgeons, radiologists, social workers, and occupational, physical, and respiratory therapists. Other healthcare personnel may also be included in the trauma team, such as clergy, mental health specialists, and rehabilitation physicians. For optimal function, trauma teams

require strong hospital commitment and support. Additionally, policies and protocols that are understood and adhered to by all team members should be in place. The initial resuscitation team is usually led by a surgeon and performs best when led by an attending trauma surgeon. The prepared trauma team improves performance in resuscitation as well as outcome of the patient.⁶ The pediatric critical care physician also plays an important role in the pediatric trauma team. The pediatric critical care physician has expertise in life-support therapies including mechanical ventilation, renal replacement therapies, and treatments to prevent secondary brain injury. Together, the trauma surgeon and critical care physician should lead a multidisciplinary team with daily rounds in the pediatric intensive care unit (ICU). Such teams should include all necessary trauma team members and work to develop treatment algorithms and protocols. There is mounting evidence that this approach leads to improved outcomes in pediatric trauma and is soon becoming the standard of care.

INITIAL TRAUMA ASSESSMENT AND RESUSCITATION

Initial resuscitation begins in the field with emergency medical service personnel and continues at the trauma center with the designated trauma team. Resuscitation follows the priorities outlined in the ACS Advanced Trauma Life Support (ATLS®) protocol. While special consideration is given to anatomic and physiologic differences of children, the priorities of resuscitation remain the same as those in adults. It is recommended that all trauma team members participating in the initial assessment and resuscitation have ATLS certification. The basic principles of the initial assessment will be briefly reviewed below.

A primary survey is conducted to rapidly assess the patient and identify all potential life-threatening injuries. The primary survey is usually referred to as the ABCDEs (airway, breathing, circulation, disability, and exposure) of trauma. The first priority remains assessment of the airway for patency and maintainability and cervical spine stabilization. Patients with obvious head trauma or who have an altered level of consciousness (Glasgow Coma Scale [GCS] score ≤ 8) require airway protection. Adequate airway control must be obtained while maintaining cervical spine immobilization. When intubation is required, most trauma patients should be orally intubated with direct cricoid pressure, and the most experienced clinician should perform intubation. Many pharmacologic agents are available for rapid-sequence intubation (RSI), similar to adult resuscitation. Doses are adjusted for patient weight, and guidelines are available on the Broselow® tape. The reason for intubation as well as the types of injuries present dictate the medications used. Tracheal tube placement should be confirmed by end-tidal carbon dioxide monitoring, by auscultation of the abdomen and both sides of the chest, and by a chest radiograph. The patient’s heart rate, blood pressure, oxygen saturation, color, and perfusion should be continuously monitored. Once the airway is secure, ventilation should be evaluated. Evaluation of unequal breath sounds with a correctly positioned endotracheal tube should raise concern for a hemothorax or pneumothorax. Tracheal deviation, though rare, may help with the diagnosis of tension pneumo- or hemothorax. Breath sounds are transmitted easily in children, and a simple pneumothorax is often not apparent until a chest radiograph is obtained. Tube thoracostomies are placed as needed. Flail chest is rare

in children owing to the flexibility of the rib cage. Ventilation should be maintained with 100% oxygen during resuscitation.

After successful airway establishment and ventilation, the circulation must be assessed. Direct pressure should be applied to any site of the active hemorrhage. Pulses, perfusion, capillary refill, heart rate and rhythm, and blood pressure should be evaluated. Intravenous (IV) access, preferably two large-bore catheters, must be obtained rapidly for volume resuscitation. Intraosseous access or venous cut-down should be considered if peripheral access is difficult to obtain. Young children have vigorous compensatory mechanisms and will preserve blood pressure despite losing more than 25% of their circulating blood volume.^{7,8} For this reason, significant injury-related hemorrhage (e.g., intraabdominal) may be a life-threatening condition. The heart rate is the most sensitive indicator of hypovolemia in pediatric trauma patients. Thready pulses and altered mental status are evident with a loss of 30% to 45% of blood volume and represent a dangerous scenario as cardiovascular collapse will be imminent. Volume resuscitation begins with crystalloid at 20 mL/kg, with further volume boluses based on the patient's response. Blood products may be necessary to stabilize patients with hemorrhagic shock. Resuscitation with red blood cells, plasma, and platelets in a ratio of 1:1:1 along with appropriate use of coagulation factors such as cryoprecipitate, as well as rapid surgical control, may be necessary for ongoing hemorrhage. The attending pediatric surgeon should direct the resuscitation of a pediatric patient with active hemorrhage. All infused fluids and blood products should be warmed as pediatric patients are at high risk of hypothermia.

Hypotension contributes to secondary injury to the brain and other vital organs and must be treated aggressively. In rare cases, vasoactive agents may be necessary in the resuscitation room. Trauma victims who are pulseless at the scene have an almost uniformly fatal outcome.^{7,9} Prolonged, heroic resuscitative efforts should be avoided in these patients. Patients who have a pulse at the scene but suffer a cardiac arrest en route or in the ED have a slightly better prognosis, and resuscitation should be attempted. Most cardiac arrests associated with blunt trauma are a result of multisystem injuries, including severe brain injury.¹⁰ Open chest resuscitation should be considered only in the rare case of penetrating chest trauma as it has been shown to be of no benefit in blunt trauma.

Disability should include a brief neurologic examination focusing on the level of alertness, GCS score, pupillary response, focal signs of spinal cord injury, and signs of increased intracranial pressure (ICP). Subjects with a GCS score of 8 or less or with a waning mental status should be intubated using RSI. Patients with a suspected head injury need rapid assessment, and noncontrast head computed tomography (CT) should be performed promptly. All trauma patients are undressed and exposed for a full examination. The patient should be log rolled to inspect the spine and back and complete the assessment of obvious injuries. A rectal examination should only be performed one time when clinically appropriate as determined by the attending pediatric surgeon. Children lose heat due to their increased body surface area to volume ratio and should be warmed with lights and blankets. The resuscitation room temperature must be increased to prevent hypothermia.

Following the primary survey and stabilization, necessary laboratory studies are performed, and radiology studies including a chest x-ray and pelvic x-ray should be obtained. The secondary survey then commences with a full head-to-toe physical examination. Injuries are documented, necessary consultations are placed, and the team decides on the disposition of the patient.

Specific Injuries and Critical Care Management

Closed Head Injuries

Closed head injury or TBI is the leading cause of death in pediatric trauma, with nearly 3000 deaths annually. Childhood TBI survivors often have life-long morbidities and impairment.¹¹ Linear and inertial forces resulting in an impact injury cause the primary injury in TBI.¹² These injuries include hematomas, lacerations, and axonal shearing,

and are often described as irreparable. Secondary injury refers to the injury that occurs after impact and is considered both preventable and potentially reversible. Pathologic alterations in respiratory, hemodynamic, and cellular function occur, which may lead to secondary injury and cell death. The pathways to neuron death include inadequate oxygen and nutrient supply secondary to hypoxia and decreased cerebral blood flow. Decreased cerebral blood flow can occur secondary to hypotension, decreased cardiac output, raised ICP, cerebrovascular dysregulation including vasospasm, and microthrombus formation. Elevated ICP occurs secondary to mass lesions, cerebral edema, and increases in cerebrospinal fluid and blood volumes. Other neuronal injuries occur secondary to inflammation, oxidative stress, and apoptosis. Present TBI therapies are directed primarily at supporting oxygenation, blood pressure, and cardiac output and at controlling ICP to prevent secondary injury.¹²

Despite insufficient evidence for definitive treatment standards in TBI, a number of guidelines have been recommended.¹³ These include early admission with severe TBI to a pediatric trauma center, avoidance of hypoxia, correction of hypotension, and maintenance of cerebral perfusion pressure greater than 40 mm Hg in children. There is little evidence to support the routine use of corticosteroids or the prophylactic use of antiseizure medication. Currently, a number of National Health Institute multicenter trials are under way to better elicit treatment recommendations in pediatric TBI.

Initial stabilization and resuscitation follow the ATLS protocol. The underlying goal is airway protection and respiratory support to prevent hypoxemia and hypercarbia. Hyperoxia and brief, aggressive hyperventilation is indicated only if the clinical examination reveals signs of acute cerebral herniation. These maneuvers should be directed by neurosurgery and are usually initiated immediately before operative intervention. Normotension or mild hypertension and mild hypervolemia are indicated to support cardiac output and cerebral blood flow. Fluids, sedation, and vasoactive agents must be judiciously administered. Hypertonic saline may be advantageous in children with elevated ICP. All children with a suspected TBI, history of loss of consciousness, altered level of consciousness, focal neurologic signs, evidence of a depressed or basilar skull fracture, a bulging fontanelle, or persistent headache and vomiting should have a noncontrast head CT.¹³ Early consultation with neurosurgery is indicated in all children with significant TBI. ICP monitoring should be considered in patients with a GCS score less than 8. Even with a normal CT scan, 10% to 15% of patients with a GCS ≤ 8 have elevated ICP. ICP monitoring with a ventricular catheter, an external strain gauge transducer, or a catheter tip pressure transducer is considered accurate and reliable. Ventriculostomy allows cerebrospinal fluid drainage in addition to ICP monitoring.

ICP in children and adolescents should be kept at less than 20 mm Hg. In young infants with open fontanelles and sutures, and in older children with large diastatic skull fractures, controlling the ICP at less than 10 to 15 mm Hg may be prudent. The guidelines recommend a cerebral perfusion pressure greater than 40 mm Hg in children with TBI, although it may be better to maintain cerebral perfusion pressure according to an age-related continuum between 45 and 70 mm Hg.

Initial treatment for elevated ICP includes sedation and analgesia, ventriculostomy drainage, and muscle relaxants. Sedation can be accomplished with low-dose fentanyl, dexmedetomidine, and intermittent doses of benzodiazepines or barbiturates. If ICP is not controlled, a repeat CT should be obtained and hyperosmolar therapy begun. Osmolar agents include mannitol and hypertonic saline. Hypertonic saline appears to have several advantages over mannitol, allowing for a consistent control of osmolality and minimizing ICP spikes.^{13,14} Additionally, hypertonic saline supports mean arterial pressure and cardiac output, has beneficial vasoregulatory properties, and may have beneficial effects on inflammatory responses. Hypertonic saline (3%) is administered as a continuous infusion, and the appropriate dose is the minimum dose required to keep ICP less than 15 to 20 mm Hg. The dose may be increased provided that serum osmolality is less than 360 mOsm/L.¹⁵

Neck Injuries

Injuries to the airway in children can be rapidly life threatening. Small airway diameter combined with penetrating or blunt injury to the neck can produce rapid airway obstruction. Children are at greater risk than adults for spinal and major vascular injury from neck trauma.

Clinically, the neck is divided into three anatomic zones. Zone 1 extends from the level of the clavicles up to the cricoid cartilage. Injuries to this area may involve the apex of the lung; trachea; subclavian, carotid, and jugular vessels; thoracic duct; esophagus; vagus nerve; and thyroid gland. Patients suffering zone 1 injuries typically exhibit hypotension because the great vessels are often injured. Zone 2 encompasses the area from the cricoid cartilage to the mandible, and injuries to this area are the easiest to detect. Active bleeding can be reduced by direct pressure. Zone 2 penetrating injuries can be managed with selective surgical exploration of the wound after clinical, endoscopic, and radiographic evaluation. Zone 3 extends from the angle of the mandible to the base of the skull. The oropharynx, jaw, and teeth are located within this area. Mandibular fractures in children manifest as malocclusion of the biting surfaces of the teeth and are usually associated with dental injuries. Injury to the chin associated with tympanic membrane perforation or hemotympanum is associated with an occult fracture of the mandible. Orotracheal intubation is not usually problematic in children with mandibular fractures unless there is copious oral hemorrhage.

Penetrating neck and airway injuries occur less frequently in children than in adults, with the majority of these injuries occurring in adolescent males. Penetrating injuries can be lethal owing to the important anatomic structures injured, such as a bullet injury to the major vascular structures. As a result, penetrating wounds to the face and neck are more likely to require surgical intervention than blunt injuries. The extent of damage to deep tissues may not be apparent on examination of the wound site. Stab wounds typically produce linear tissue injury that follows a predictable path from the entrance wound into the deeper tissue, whereas ballistic injuries often produce unpredictable tissue damage as they progress through the neck. Penetrating injury to any of the major systems usually results in rapid airway compromise and shock.

Penetrating injury to the esophagus may not be immediately apparent but can produce delayed morbidity due to mediastinitis. Investigation of neck injuries that involve the trachea should always include evaluation of the esophagus for perforation. Esophageal perforation should be suspected if fever, elevated white blood cell count, and subcutaneous air in the neck occur in the days following a traumatic neck injury. Management of the perforation requires prompt surgical repair of the esophagus, drainage of the surrounding soft tissue infection, and IV antibiotics.

Blunt neck injuries are less common than penetrating injuries and can be associated with life-threatening airway disruption.^{16,17} Blunt neck trauma is also associated with injuries to the cervical spine, esophagus, lungs, and great vessels. Mortality rates of up to 30% are reported for children with these injuries, and half of these children die of tracheobronchial rupture within 1 hour of the injury.¹⁸

Blunt laryngeal trauma in children is uncommon and frequently unrecognized. The clinical presentation of laryngeal injury in children includes frank respiratory distress with hoarseness, stridor, and palpable subcutaneous emphysema.¹⁶ Radiographs of the chest and neck may show subcutaneous emphysema. The diagnosis of blunt laryngeal trauma in children is based on history, physical examination, and radiographic studies, followed by flexible or rigid bronchoscopy. CT of the neck adds little to the diagnosis of laryngeal injury. Once a laryngeal injury is suspected, rigid endoscopy in the operating suite should be used to secure the airway as well as delineate and repair the injury.

Thoracic Injuries

Thoracic trauma accounts for 5% to 10% of admissions to trauma centers and carries a 5% mortality rate. However, the mortality rate increases fivefold when there is concomitant head or abdominal injury

and can exceed 40% when a combination of head, chest, and abdominal injuries are present.¹⁹ Potentially life-threatening injuries including airway obstruction, tension pneumothorax, massive hemothorax, open pneumothorax, flail chest, and cardiac tamponade must be corrected immediately. Young children (<8 years of age) have a significantly more flexible thoracic cage compared to adults. As a result, compression of intrathoracic organs by blunt trauma may lead to significant parenchymal injuries in the absence of rib fractures. Thus, pulmonary contusions, rather than broken ribs, are far more common in children. An isolated first rib fracture, however, is a potential sign of child abuse or may be associated with significant thoracic injury.¹⁹ Multiple rib fractures should alert the clinician to look for underlying injuries in the thoracic cavity. Further radiographic evaluation directed by the attending pediatric surgeon, such as CT angiography, may be warranted to complete the diagnostic evaluation. Supportive care is the mainstay of rib fracture management. Appropriate analgesia is necessary to promote deep inspiratory effort and prevent atelectasis.

Failure of tube thoracostomy to reexpand the lung and the continued presence of a large air leak denote a tracheal or bronchial disruption. If the site of tracheal or bronchial disruption is within the chest cavity, the endotracheal tube tip should be placed distal to the disruption. This may require bronchoscopy. Selective intubation of the undisrupted main stem bronchus, followed by one-lung ventilation, is a temporizing measure until the operative repair can be performed. An experienced physician should rapidly and cautiously attempt main stem intubation to avoid extending the tracheal injury.

Pulmonary contusion may occur with or without the presence of overlying rib fractures or chest wall injury. Symptoms include tachypnea, dyspnea, cyanosis, hemoptysis, and respiratory failure. The initial chest radiograph may not demonstrate this injury, and repeat x-rays may be necessary to reveal the infiltrates. Judicious IV fluids should be administered. Acute respiratory distress syndrome (ARDS), while uncommonly associated with pulmonary contusion, may develop and require mechanical ventilation.

In children, the mediastinum is less fixed than in adults, and the physiologic consequences of tension pneumothoraces, hemothoraces, or hemopneumothoraces will be rapidly evident. In children, each hemithorax can hold 40% of a child's blood volume and may be a source of hemorrhagic shock. A chest tube large enough to drain the entire hemithorax without clotting or occluding is necessary. Surgical exploration for hemostasis may be required if the initial chest tube output is 20 mL/kg or greater than 3 to 4 mL/kg/h.²⁰ Inadequate evacuation may lead to lung entrapment and predisposes the patient to chronic atelectasis. Anterior penetrating injuries below the nipple line and posterior penetrating injuries below the tip of the scapula warrant exclusion of intraabdominal injuries. Penetrating injuries often require thoracotomy in the operating room.

Other rare thoracic injuries include traumatic asphyxia and esophageal tears. Traumatic asphyxia is caused by sudden, severe compression of the chest and upper abdomen and is characterized by craniofacial and cervical cyanosis, edema, and petechiae. Additionally, subconjunctival and thoracic wall petechiae occur, and there may be associated respiratory distress, cardiac arrest, and cerebral edema with raised ICP.²¹ Esophageal lacerations occur in less than 1% of children with blunt thoracic injuries and can be diagnosed with flexible esophagoscopy. Esophageal lacerations almost always require operative repair.²²

Cardiac and Aortic Injuries

Traumatic injury to the heart and great vessels is uncommon in pediatric patients, and most of the injuries are the result of blunt trauma. Myocardial contusion results from blunt force injury to the chest. The vast majority of pediatric patients with myocardial contusions have multisystem trauma; pulmonary contusion is the most common coexisting injury, found in 50% of patients.²³ Hemodynamically significant myocardial contusions are rare in pediatric patients and present with arrhythmia or ventricular dysfunction. Patients presenting with a normal sinus rhythm have not been shown to develop arrhythmias or cardiac failure. Diagnostic evaluation of myocardial

contusion is controversial in pediatrics, and testing may include a combination of cardiac enzyme determinations, electrocardiography, and echocardiography. Creatine kinase-MB and cardiac troponin-I elevation following blunt trauma has been used to diagnose contusion. Cardiac troponin-I is highly specific for the myocardium, and elevation of troponin-I occurs within 4 hours of injury and peaks within 24 hours. The significance of cardiac enzyme elevation in a hemodynamically stable patient is unclear, and determination may not be necessary in these patients.²⁴ An admission 12-lead electrocardiogram (ECG) is recommended in all patients. Echocardiography is useful for the diagnosis of cardiac injury in patients with hemodynamic instability who had nondiagnostic ECG.

In addition to myocardial contusion, structural damage such as traumatic ventriculoseptal defect, valve injury, ventricular rupture, or aneurysm may occur with blunt chest trauma. The management of all blunt cardiac injury is largely supportive, with operative intervention as needed for significant structural damage. Continuous ECG monitoring is recommended.

Comotio cordis is an unusual event but is much more common in pediatric patients, with 50% of victims younger than 14 years. Blunt trauma to the chest with the impact centered over the heart results in immediate cardiac arrest. It is thought that the narrow anteroposterior diameter of the chest, in conjunction with the increased compliance of the chest wall in pediatric patients, allows a chest-wall blow to be transmitted to the underlying heart. Many, but not all, cases occur during sports-related activity.²⁵ Blunt chest trauma leads to cardiovascular collapse, with ventricular tachyarrhythmia being the most common arrhythmia. Unlike myocardial contusion, there is no evidence of myocardial injury on autopsy. The survival rate is low, even with prompt resuscitation.²⁶

Blunt aortic injury is an extremely uncommon pediatric injury; however, as in adults, it is potentially lethal. The aortic arch is relatively fixed, and the descending aorta is more mobile, making it susceptible to shearing forces during horizontal and vertical deceleration. Diagnosis of thoracic aortic injury is similar in children and adults. The pattern of chest x-ray findings is similar. CT angiography is an important diagnostic tool and has sensitivity and specificity approaching that of angiography for the diagnosis of thoracic aortic injury.²⁷ Transesophageal echocardiography may also have a role in diagnosis, although it is an invasive procedure and requires additional expertise in interpretation. As in adults, successful management of potentially lethal aortic injuries depends on prompt recognition and surgical treatment.

Abdominal Injuries

More than 90% of abdominal trauma in children is the result of blunt trauma. Following initial evaluation and resuscitation as outlined by the ACS ATLS protocol (described above) the process of identifying specific injuries commences. It is critical to know the mechanism of trauma in order to appreciate patterns of potential abdominal injuries. In children with a suspected intraabdominal injury, a nasogastric or orogastric tube should be placed following the primary survey because dilatation of the stomach may lead to vomiting and potential aspiration injury. Similarly, a urinary catheter should be placed after inspection of the pelvis and perineum to monitor urine output and evaluate fluid resuscitation. Inspection of the abdomen may reveal external evidence of trauma suggestive of an underlying injury.

Evaluation of abdominal tenderness is important and, when present, is a significant finding. While a number of injuries may cause abdominal pain, including lower rib fractures, contusion or soft tissue injury to the abdominal wall, or pelvic fracture, it is imperative that intraabdominal injury be thoroughly investigated. The pelvis should be examined by compression. Rectal examination should be selectively performed in children. Rectal examination is rarely indicated in smaller children unless there is a specific concern (e.g., spinal cord injury or rectal injury). Children with pelvic fractures, bruising to the perineum, blood at the penile meatus or blood in the diaper/underwear should have a documented rectal examination performed by an

experienced pediatric specialist. Hematuria is indicative of genitourinary injury.

The gold standard for evaluation of children with blunt abdominal trauma is CT with IV contrast. It gives reliable information about solid-organ injuries, the presence of abnormal fluid, the presence of pneumoperitoneum indicating hollow viscus injury, and the retroperitoneal space. The high sensitivity and specificity of CT scanning and the successful use of nonoperative solid-organ injury have essentially replaced diagnostic peritoneal lavage (DPL) in blunt abdominal trauma. The use of DPL is rarely indicated and should only be considered in consultation with a pediatric surgeon. Penetrating injury is generally rare in pediatrics. Virtually all gunshot wounds to the abdomen and lower chest should be treated by mandatory laparotomy or thoracotomy. Stab wounds below the nipple line and above the inguinal ligament require surgical evaluation. Unlike in adults, stab wounds in pediatric patients may be amenable to nonoperative management. In general, these wounds require careful examination and local wound exploration performed by an experienced surgeon. If there are concerns for intraabdominal injury, CT scanning may be beneficial. Alternatively, diagnostic laparoscopy can be considered to evaluate for intraabdominal injury. The advantage of diagnostic laparoscopy is that many injuries are amenable to laparoscopic treatment in experienced hands.²⁸

Liver. Signs and symptoms of hepatic injury include pain and tenderness, abrasions, and contusion of the abdominal wall. Signs of peritonitis due to hemoperitoneum are frequently present. Most isolated liver injuries can be managed nonoperatively. Selective angiography and embolization may be considered to attempt control of bleeding. While angiography may be useful in older children and adolescents, it should be used with caution in younger children (less than 5 years of age). The small vessel size of smaller children may lead to unintended injury or complications. Consultation with the attending pediatric surgeon is mandatory in this decision-making process. Operation may be required for hemodynamic instability, continued transfusion requirements, or other associated injuries. The decision to operate is based on the child's physiologic status and not the graded classification of injury.²⁹ Complications of hepatic injury include hemobilia, abscess, biliary fistula, and bile peritonitis.

Spleen. The spleen is the organ most frequently injured in blunt abdominal trauma. Ecchymosis, pain, and tenderness over the left upper quadrant are suggestive of splenic injury. Left shoulder pain may be present as a result of diaphragmatic irritation. Abdominal CT is recommended to determine the extent of injury as well as the presence of hemoperitoneum and other associated injuries. Nonoperative management is preferable and is similar to the nonoperative management of liver injuries. Surgical management may be necessary in patients who are hemodynamically unstable, require continued transfusions, or have other associated abdominal injuries. A variety of surgical techniques are available to control bleeding, often without a total splenectomy.³⁰ In patients requiring total splenectomy, there is a risk of overwhelming postsplenectomy infection (OPSI). OPSI may occur at any time following splenectomy, but the risk is greatest in the first 5 years of life and carries a high mortality. All postsplenectomy patients must be immunized, and the use of prophylactic antibiotics is recommended.

Duodenum and Pancreas. The duodenum and pancreas are fixed retroperitoneal structures that are frequently injured by a blunt force trauma (e.g., handlebar injury) to the mid-epigastrium. The diagnosis of pancreaticoduodenal injuries is challenging and begins with evaluation of chemical markers and imaging studies. Serum amylase and lipase are indicators of pancreatic injury, but amylase levels may be elevated due to injuries to other organs (e.g., salivary glands). Ultrasonography and CT are the preferred imaging studies to delineate the pancreas. Recently, magnetic resonance cholangiopancreatography (MRCP) has been used to delineate pancreatic body and ductal injuries. Duodenal perforations can be diagnosed using upper GI studies with water-soluble contrast or CT scan with oral contrast. Most pancreatic injuries are mild and can be managed nonoperatively with

nasogastric decompression and parenteral nutrition.³¹ Management of patients with severe pancreatic injuries is controversial. Patients with severe pancreatic injury may require surgical repair or endoscopic placement of pancreatic duct stents. Several complications may occur after pancreatic injury, including pleural effusion, bile duct obstruction, and pancreatic pseudocyst formation. Most duodenal injuries are lacerations that can be treated by simple débridement and primary repair. Duodenal hematoma results from blunt abdominal trauma associated with rapid deceleration or from a direct blow to the upper abdomen. It may present a day or more after injury as vomiting or as a large amount of nasogastric drainage. The resultant intestinal occlusion should be treated by nasogastric decompression and parenteral nutrition until the obstruction resolves.

Small Intestine. Hollow viscus injuries are far less common than solid-organ injuries in pediatric abdominal trauma patients. The mechanism of injury is either compression or shear forces resulting from rapid deceleration. There are two points of fixation to the retroperitoneum that frequently lead to transections: the ligament of Treitz and the cecum. Handlebar blows or direct blows to the abdomen compress the bowel against the vertebral column, resulting in intestinal perforation. In the seat-belt complex, contusions or abrasions of the abdominal wall and lumbar spine injury are associated with bowel perforation. Upper lap belt loading is associated with liver, spleen, rib, stomach, small bowel, and large bowel injuries. Lower lap belt loading is associated with ribs, small bowel, large bowel, bladder, kidney, and stomach injury.³²

Identification of patients with a bowel injury is often challenging. Obtaining a detailed history of the mechanism of injury, careful physical examination, and a high degree of suspicion will often identify injuries. Detection of peritoneal signs may be difficult owing to distracting pain from the abdominal wall and back injury. There is no completely reliable imaging study available to detect intestinal injury. CT may show nonspecific findings suggestive of bowel injury. Serial clinical examinations, monitoring vital signs and fever curves, and repeat laboratory studies are often adequate for experienced clinicians to diagnose intraabdominal injury. Patients should remain NPO until a bowel injury is no longer suspected.

Diaphragm. Diaphragmatic rupture is the consequence of direct blunt trauma over the lower thorax and abdomen and is most frequent on the left side. Contusions or abrasions of the upper abdomen, bowel sounds in the chest, and respiratory distress are the classic findings of a traumatic diaphragmatic rupture. A chest radiograph is the initial study and may show bowel and/or the nasogastric tube in the thorax. The diagnosis of diaphragmatic rupture may be confirmed by ultrasonography, CT, and/or intraoperatively with thoracoscopy/laparoscopy. Laparotomy allows proper repair of the diaphragmatic defect and assessment of other organs.

Abdominal Damage Control Surgery. If the injured child remains hemodynamically unstable despite aggressive resuscitation, a laparotomy for damage control may be required.³³ Hypothermia, acidosis, and coagulopathy are considered a lethal triad, and surgical intervention may be unwarranted.³⁴ Abdominal damage control surgery has three stages. The first stage is the initial laparotomy with the goal to control hemorrhage and prevent ongoing damage. Abdominal packing and temporary closure of the wounds with loose retention sutures or an abdominal wound vacuum device can be utilized. The second stage is continued in the ICU, with the goals of continued resuscitation, active warming of the patient, correcting any coagulopathy present, and restoring acid-base balance. Intraabdominal pressure may become elevated secondary to edema, tissue swelling, ascites, and ongoing bleeding. These increased pressures are often referred to as abdominal compartment syndrome and may cause cardiorespiratory and renal deterioration. Increased abdominal pressure may also cause hypoperfusion of the abdominal contents, leading to renal failure and ischemic bowel injury. Additionally, as abdominal pressure rises, venous return may be impaired, thus impacting and reducing cardiac output. Treatment of abdominal compartment syndrome is urgent and may require a peritoneal drain or opening of the abdominal wound

and placement of a silo or suction device.³⁵ The third stage involves definitive operative repair of all injuries once the patient is stabilized.

Genitourinary Injuries

Genitourinary trauma is common and occurs in 12% of injuries in children. The unique characteristics of a child's anatomy predispose to genitourinary trauma. The kidneys are proportionally larger, the abdominal musculature underdeveloped, and the ribs less ossified compared to adults. In addition, the underdeveloped renal capsule and Gerota's fascia increase the likelihood of laceration, hemorrhage, and urine extravasation.

The majority of injuries are due to blunt force trauma and have a high association with pelvic trauma. Preexisting renal disease predisposes to renal injury and is found in 20% of cases of documented renal trauma. Findings suggestive of genitourinary trauma include flank or abdominal tenderness, perineal injury, blood at the urinary meatus, mobile or displaced prostate, and gross hematuria.

Similar to splenic and liver injuries, renal injuries are graded based on severity determined by imaging studies. Parenchymal injuries not involving the collecting system or renal vessels constitute 85% of renal injuries, whereas injuries to the collecting system or renal vessels account for 10% of renal injuries. The most severe injuries account for the remaining 5% of renal injuries and include a shattered or devascularized kidney.

Minor injuries rarely require surgery and are treated expectantly. Limited hospitalization with decreased activity until hematuria has resolved is typically all that is required, and imaging at 6 to 8 weeks following discharge is recommended.³⁶ Surgical intervention should be reserved for patients with major injuries and hemodynamic instability from persistent bleeding. The management of major injuries in patients who have normal vital signs is controversial. Even in the case of urine extravasation without urethral injury, expectant treatment with repeat imaging studies at 5 to 7 days is acceptable, and nonoperative management of pediatric renal trauma has become the preferred approach in managing blunt renal injuries.³⁷

Penetrating renal injuries secondary to gunshot wounds should be explored because of the high incidence of associated injuries. Surgical treatment for stab wounds with suspected renal involvement should be based on the severity of hemorrhage as well as clinical and imaging evidence suggesting intraabdominal injury.

Renovascular injuries generally occur in patients who have sustained life-threatening multisystem injuries. The mechanism of renovascular injury is thought to be deceleration and occurs more frequently on the left side. The diagnosis is established with contrast-enhanced CT. Successful revascularization depends on the length of renal ischemia, extent of vascular injuries, and extent of associated injuries. Repair of penetrating renal artery injuries is most successful if the ischemic time is less than 8 hours. Blunt arterial injuries are associated with the lowest rate of renal preservation and may be treated by nephrectomy when they are unilateral in a symptomatic patient.

Pelvic Fractures

Pelvic fractures are a marker of significant trauma and are often associated with other injuries. Pelvic fractures occur in approximately 2% of all blunt abdominal injuries, and 20% of those with pelvic fractures have intraabdominal injuries. Mortality varies from 10% to 50% and is often due to associated injuries. The most common mechanisms are falls, crush injuries, and motor vehicle accidents. Clinically, the diagnosis is suggested by pain with anterior or lateral compression of the pelvis, although other findings may include perineal ecchymosis, blood at the urinary meatus or on the rectal examination, disruption of the rectal wall with mass effect due to bony fragments, or displacement of the prostate.

Evaluation of pelvic trauma begins with a pelvic radiograph and should include CT. Treatment usually consists of bed rest, immobilization, and blood loss replacement. Severe injuries with significant blood loss may require prompt intervention and immobilization such as wrapping the pelvis with a bed sheet or application of an external

fixation device. Treatment is dependent on the type and severity of the injury. Orthopedic surgery should be consulted early to help define the best treatment.

Spinal Injuries

Approximately 5% of all spinal cord injuries occur in the pediatric age group. Common causes in young children include falls and motor vehicle accidents.³⁸ For older children, sports, other recreational activities (e.g., diving, horseback riding), and gunshot wounds have greater etiologic importance.

Maintaining neutral cervical alignment during transport and initial resuscitation of a child at risk of a spinal injury is critical. An appropriately sized cervical collar should be used, and often a support can be placed under the thorax to achieve elevation of the torso to maintain spinal immobilization.

Initial assessment dictates the need for imaging studies. An awake, communicative child without midline cervical tenderness, intoxication, decreased level of consciousness, focal neurologic deficit, or a painful, distracting injury does not require spinal imaging studies. Cervical spine imaging studies include lateral C-spine, anteroposterior (A-P) C-spine, open-mouth views, flexion/extension lateral C-spine radiographs, CT, and magnetic resonance imaging (MRI). For the child with symptoms of cervical spine and/or cervical cord injury, as well as for the comatose child, CT imaging and/or MRI are now recommended.³⁹

Recent studies show no benefit of high-dose methylprednisolone for complete and incomplete spinal cord injury.⁴⁰ In a child with a spinal cord injury, emphasis is placed on maintenance of optimal physiologic homeostasis. Because of loss of sympathetic tone, IV pressor agents are frequently required in addition to crystalloid and colloid solutions to maintain age-appropriate blood pressure and cardiac output. Intubation may be necessary with high cervical spine injuries because of respiratory compromise. Avoidance of unnecessary neck manipulation is mandatory.

After initial resuscitation and the identification of spinal injuries, urgent neurosurgical consultation is indicated. Closed reduction and initial stabilization of these injuries are frequently performed in the ICU. Halo rings can be placed with acceptably low morbidity in the ICU setting, even in infants; they can be attached to weighted traction mechanisms for closed reduction if necessary and converted to halo jackets to maintain alignment. The need for and timing of internal surgical stabilization should be discussed in the context of the child's concomitant multisystem issues.

Organ Failure

Respiratory Failure

Trauma can result in lung injury and respiratory failure, the most severe of which is acute respiratory distress syndrome (ARDS). Post-traumatic respiratory failure results from both direct and indirect injury to the respiratory system. Direct injuries include aspiration of gastric contents, near-drowning, smoke inhalation, and pulmonary contusion. Lung injury also occurs indirectly as a consequence of systemic insults such as hemorrhagic shock, sepsis, massive transfusion, fat embolism syndrome, or the systemic inflammatory response syndrome (SIRS). ARDS is an acute and progressive respiratory disease of a noncardiac nature associated with diffuse bilateral pulmonary infiltrates and hypoxemia. The definition includes a ratio of arterial oxygen tension (P_{aO_2}) to inspired oxygen fraction (F_{iO_2}) less than 200.

The pathologic findings in ARDS are the result of a complex sequence of cellular and biochemical changes that lead to damage of the endothelial membranes. The complex roles of leukocytes, complement activation, prostaglandin release, oxygen radicals, and other mediators of vascular damage are currently under investigation. However, neutrophils are an important mediator of lung tissue damage. Blunt trauma enhances the migratory capacity of neutrophils in response to interleukin-8, potentially increasing the risk of ARDS.⁴¹

ARDS management in the field of pediatrics has focused on minimizing iatrogenic lung injury and on adjuncts to mechanical ventilation. Both oxygen and mechanical ventilation can be injurious to the lung. Oxygen causes oxidative damage and absorptive atelectasis, with chronic exposure to high inspired concentrations of oxygen creating pathology indistinguishable from ARDS. Toxic reactions to oxygen occur commonly with the use of F_{iO_2} greater than 50%, and these effects worsen when excessive oxygen is used for longer than 24 hours. Mechanical ventilation also causes lung injury due to barotrauma as a result of shearing forces applied in the terminal airways. The higher the tidal volumes used to ventilate patients, the greater the stresses and the larger the risk of secondary lung injury. These stresses on the terminal airways and pulmonary endothelium further incite pulmonary edema, surfactant dysfunction, decreased compliance, hyaline membrane formation, and impairment of gas exchange.

Ventilation strategies focus on decreasing iatrogenic lung injury by limiting oxygen concentration and decreasing barotrauma. Permissive hypercapnia (allowing P_{CO_2} 45 to 60 mmHg or higher) is also practiced when the patient's condition allows. The strategy of "gentle" ventilation has been shown to decrease morbidity and mortality in pediatric ARDS.^{42,43} The strategy for low-volume, low-pressure ventilation comes from the National Institutes of Health ARDS Network trial comparing 6-mL/kg versus 12-mL/kg tidal volumes in patients with ARDS. Mortality in the low-tidal volume group was 31.3%, versus 39.8% in the higher tidal volume group.⁴⁴ Similar pediatric research using a high-rate, low-tidal volume (3 to 5 mL/kg) strategy in children with severe ARDS demonstrated a survival rate approaching 90%.⁴⁵ Hypercapnia is typically well tolerated, except in patients with TBI with intracranial hypertension or those with severe pulmonary hypertension. For patients who fail support with mechanical ventilation, extracorporeal membrane oxygenation (ECMO) support may be utilized if there are no contraindications (e.g., ongoing bleeding). Consultation with the pediatric ECMO team is warranted early in the course of respiratory failure. Early consultation in conjunction with the pediatric surgery and pediatric ICU teams will allow for determination of eligibility for ECMO, prepare for possible cannulation and to discuss expectations with the family. While there have been a number of adjuncts to ventilation proposed, including the use of prone positioning, inhaled nitric oxide (iNO), surfactant, steroids, immunomodulation, or antiinflammatory agents, the evidence for the use of these adjuncts is lacking and remains under investigation. For example, iNO is known to be a potent pulmonary vasodilator, and its use has been proposed for pediatric ARDS. In patients with documented pulmonary hypertension and/or right ventricular failure, the use of iNO may be attempted. Current evidence suggests that iNO increases P_{aO_2} levels, but has not been shown to confer a survival advantage. The use of inhaled NO delivered during high-frequency oscillatory ventilation (HFOV) in patients with ARDS resulted in a significant increase in arterial oxygenation.⁴⁵

Shock

Children sustaining trauma develop shock most commonly as a direct result of hemorrhage, but shock can also be the result of tension pneumothorax, spinal cord injury, cardiac tamponade, myocardial contusion, or sepsis. Direct tissue injury and hemorrhage play roles in early shock, while inflammation and altered immune function can result in SIRS, multiple organ failure, and septic shock later in the disease course.

Children have remarkable compensatory mechanisms in response to hypovolemia. Children maintain cardiac output by increasing heart rate more than the stroke volume. Hypotension is a late sign of shock in children, and, if not addressed expeditiously, will lead to cardiovascular collapse and possible death. Tachycardia and signs of end organ hypoperfusion, such as altered mental status, cool distal extremities, and decreased urine output, may be the primary clinical signs of shock in an injured child.

The focus of therapy for shock in an injured child should be on restoration and maintenance of adequate oxygen delivery and organ

perfusion. Hemodynamic monitoring of central venous pressure and direct arterial blood pressure, as well as cardiac output, may be necessary. In addition, clinical parameters such as base deficit, serum lactate, and measured creatinine clearance are useful indirect measures of adequate end organ perfusion and may have prognostic value.⁴⁶ Appropriate therapy of early shock resulting from trauma can alleviate the development of SIRS and multiple organ failure.

The tissue ischemia and hypoperfusion associated with shock result in alteration of cellular function due to oxygen and nutrient deficiency, eventually leading to activation of inflammatory mediators. A widely accepted model of SIRS and multiple organ failure in trauma patients is referred to as the “two-hit hypothesis.” The initial hit is the shock-resuscitation or ischemia-reperfusion phase, which activates neutrophils. The activated neutrophils are thought to be more susceptible to an exaggerated immune response following a secondary inflammatory stimulus (i.e., second hit).^{47,48} The immune response to trauma and shock remains the focus of active research and is discussed in greater detail throughout numerous chapters in this edition.

Renal Failure

Renal failure in pediatric trauma patients early in the hospital course is most often due to organ injury from the initial shock or from primary injury to the kidney, its vasculature, or urinary outflow tract. Anatomic reasons for renal insufficiency should be delineated by radiographic evaluation.

Renal failure that develops during the course of hospitalization is most commonly secondary to SIRS and multiple organ dysfunction syndrome. In addition, rhabdomyolysis, contrast nephropathy from imaging studies, or nephrotoxicity from medications may also contribute to renal failure. Rarely, abdominal compartment syndrome and/or renal vein thrombosis also can lead to renal failure.

Signs and symptoms of acute renal failure are due to electrolyte and acid-base derangements as well as volume overload. The first clinical features may be oliguria, hyperkalemia, and elevations in blood urea nitrogen (BUN) and creatinine. The laboratory evaluation of acute renal failure should include measurements of BUN, creatinine, electrolytes with phosphate, magnesium, and calcium, urinalysis, and urine electrolytes. Creatinine clearance should be measured to estimate glomerular filtration rate. Microscopy is necessary to differentiate hemoglobinuria or myoglobinuria from hematuria, and additional tests such as creatine phosphokinase can aid in the confirmation of crush injuries threatening renal function.

Prevention of acute renal failure includes appropriate resuscitation from shock and continued maintenance of cardiac output and organ perfusion. Additionally, minimizing and monitoring of nephrotoxic drugs is recommended. Attempts to prevent and treat acute ischemic or nephrotoxic renal injury with pharmacologic agents have mostly demonstrated no benefit. These agents include furosemide, mannitol, calcium channel blockers, and dopamine. Most of these studies have been performed in adults, and there are few dedicated studies in children.⁴⁹ While diuretic therapy may convert oliguric to nonoliguric acute renal failure, there is no evidence that patient outcome is improved. Prehydration and prophylaxis with theophylline or *N*-acetylcysteine has been shown to reduce the risk of contrast nephropathy and may be of benefit to children undergoing contrast scans who already have or are otherwise predisposed to develop renal failure.⁵⁰

Early institution of renal replacement therapy in the face of acute renal failure decreases morbidity.⁵¹ Peritoneal dialysis is a potential modality for infants and children (<10 kg), although trauma patients may have contraindications. Continuous venovenous hemofiltration dialysis (CVVHD) is a good choice in a high-acuity patient. CVVHD offers the benefit of constant and gentle manipulation and control of intravascular volume, electrolytes, dialyzable molecules, and serum osmolality.⁵² The development of regional anticoagulation with citrate-induced hypocalcemia has increased the efficacy and safety of CVVHD, especially in children at risk of bleeding from systemic anticoagulation.

Imaging

Owing to the complexities and specialized nature of pediatric radiology, an in-depth discussion is well beyond the scope of this chapter. However, there are two important points to consider in ordering radiology studies in the injured child, which will be discussed herein.

The most important issue is concern over ionizing radiation exposure. In the past 10 years, there has been a 700% increase in the number of CT scans performed, with nearly 11% of these occurring in children. The most common indications for the use of CT are evaluation of the trauma patient and diagnosing acute appendicitis.⁵³ This liberal use of CT scanning coupled with the fact that children have an estimated 10-fold increase in neoplastic potential at equivalent adult doses has led to growing concerns about the long-term deleterious effects of ionizing radiation in children. This has prompted a number of societies, including the American Pediatric Surgical Association (APSA) to issue a consensus statement regarding the use of ionizing radiation in children. These guidelines, known as ALARA (“as low as reasonably acceptable”), should be adhered to, particularly in children undergoing evaluation and treatment for traumatic injuries.^{54,55} The total amount of radiation should be reduced, repeat imaging should not routinely be used unless clinically essential, and the use of alternative imaging methods (e.g., ultrasound or MRI) should be considered. Many young children do not require the typical “trauma pan-scan” that is frequently utilized in adult trauma centers. Children should have CT imaging performed for suspected injuries based on injury mechanism and a thorough initial assessment. For example, many young children do not require chest CT following trauma. Information obtained from a routine chest x-ray is usually satisfactory, and a chest CT is rarely required to evaluate suspected great vessel injuries. There is mounting evidence that children treated in pediatric trauma centers have fewer imaging studies performed with no increase in missed injuries or mortality. In patients who require transfer to another hospital, CT scanning is often not indicated and should never result in delay of transfer to a dedicated trauma center.

Given the often subtle findings on children's x-rays studies, it is recommended that radiology studies be carefully reviewed with a pediatric radiologist. Incomplete bony ossification, open growth plates, and age-specific normal findings can often be misinterpreted as injury. Additionally, all films from transferring institutions should be re-reviewed with the pediatric radiologist to ensure all injuries are correctly cataloged. Discussion with the pediatric radiologist can be useful to determine the best methods to clearly delineate a particular injury. Finally, the pediatric radiologist can also help ensure that ALARA standards are being followed and can assist with ionizing radiation dose reduction. The pediatric radiologist is a valuable member of the pediatric trauma team.^{56,57}

Infectious Disease and Immunology

A child who sustains trauma is susceptible to infection via multiple mechanisms. The trauma itself may destroy the barriers of skin and mucosa, allowing both pathogenic and nonpathogenic organisms the opportunity to establish a clinical infection. In addition, significant immune dysfunction occurs following trauma, with abnormalities in cellular and humoral responses, as well as in macrophage and neutrophil function.⁵⁸⁻⁶⁰ Immune dysfunction can be categorized under two basic mechanisms: hyperactive, systemic, proinflammatory processes and depression of cell-mediated immunity. Hyperactive, pro-inflammatory responses may be ultimately deleterious to a child, leading to SIRS, multiple organ dysfunction syndrome, and death. Differences in the characteristics of immune dysfunction appear to be a function of the type of trauma (e.g., TBI, blunt trauma, burn injury) and appear to change over time, reflecting changes in the acute activation seen immediately after injury and subsequent evolution into immune suppression. Many of the abnormalities may be directly correlated with the severity of injury. Infections occurring within 5 to 7 days of admission are more likely to represent inoculation at the time of injury, whereas

infections occurring after the first week following trauma usually represent nosocomial pathogens.

Empiric antibiotic therapy of the pediatric trauma patient is usually reserved for open, potentially contaminated wounds. Trauma patients, in general, do not require empiric antibiotic therapy on admission to the ICU. No published data exist on the benefits or risks of empiric therapy for fungi or multiply resistant environmental bacteria in soil-contaminated injuries; therefore, extremely broad-spectrum antibiotic and antifungal agent prophylaxis is usually not recommended. Cultures obtained at the time of admission and surgical closure of open wounds can help the trauma team evaluate the child for infection later in the hospital course. Tetanus immunization should be considered in a child with devitalized, ischemic, and denervated tissues that have been inoculated by soil or with deep tissue injury by foreign objects that have been in contact with soil.

Nosocomial infections of indwelling vascular catheters, surgically implanted foreign bodies, the lung, the urinary tract, and injured tissues are all well recognized, with therapy targeted to the organisms prevalent in the ICU. Gram-stained exudates and cultures can provide information on the types and susceptibilities of the nosocomial pathogens causing infection. Providing sufficiently broad coverage empirically to achieve a high likelihood of success may both improve patient outcomes and decrease the emergence of certain antibiotic-resistant organisms. The definitive selection of antibiotics and a decision on the duration of therapy should be based on the isolated or suspected pathogens and the child's response to therapy. A poor response to broad-spectrum therapy despite the use of antimicrobial agents active against the isolated pathogens suggests either a hidden focus of infection, which may require further investigation and possible surgical intervention, or additional antibiotic-resistant pathogens not originally isolated. Lack of response to therapy may also be related to noninfectious causes of clinical instability. Therapy should not be continued indefinitely, because subsequent colonization and infection by antibiotic-resistant bacteria or yeast are likely to occur. Once antimicrobial therapy is discontinued, careful observation for relapse or recurrence of infection is essential.

Coagulopathies

Trauma is a potent activator of the inflammatory response, and a growing body of literature describes the relationship among inflammatory cytokines, endothelial function, and coagulation through cellular and molecular signaling.⁶¹ A severely injured child is at risk of impaired hemostasis as well as pathologic thrombosis.

Activation of the coagulation cascade is proportional to the stimulus. Local thrombus formation by a discrete injury is protective by inhibiting local bleeding, and pathologic thrombosis is normally impeded by anticoagulant mechanisms. Massive activation of the coagulation axis can overwhelm the counterbalancing mechanisms, leading to deep venous thrombosis locally or microvascular thrombosis systemically. The latter culminates in varying degrees of clotting factor consumption and pathologic and protective thrombolysis and may ultimately result in disseminated intravascular coagulopathy (DIC). The microangiopathic thrombosis of DIC can also contribute to hemolytic anemia, ARDS, and organ failure remote to the site of traumatic injury. The epidemiology of injuries in children puts them at increased risk of trauma-induced DIC because the brain and liver release strong procoagulant thromboplastins. Indeed, the likelihood of coagulopathy has an inverse relationship to the presenting GCS score.⁶² A recent paper showed that in children who meet clinical criteria for a head CT scan after trauma, a low plasma D-dimer strongly suggests the absence of significant brain injury.⁶³

Evaluation and treatment of physiologic derangements that promote bleeding are necessary in an injured child. Although definitive evaluation by laboratory assays may not be available immediately, early suspicion of coagulopathy based on clinical history, physical examination, and medical interventions may be lifesaving in a traumatically injured child. Even in the absence of a coagulopathy at presentation, it

is necessary to prevent iatrogenic coagulation disturbances. Dilutional coagulopathy can occur with the administration of as little as one unwarmed complete blood volume. After one to two blood volumes, platelets can be halved, and the activated partial thromboplastin time and prothrombin time can be doubled. In an injured child receiving blood products, coagulation studies should be sent early. As volume resuscitation continues, these studies should be checked frequently to refine blood product administration. Hypothermia may contribute to coagulopathy during resuscitation and must be aggressively prevented by various warming methods, including infusion-warming devices, increasing the resuscitation room temperature, and warm blankets.

If a patient has normal coagulation values but continues to bleed diffusely, an underlying bleeding diathesis should be considered. von Willebrand disease is the most common congenital bleeding disorder and has traditionally been assessed by a bedside bleeding time. However, uncertainty about the sensitivity, reliability, and predictive value of the bleeding time has led to a decline in its use. A platelet function assay, PFA-100, has been compared with bleeding time and is considered a superior screening test for primary hemostasis disorders. Thromboelastography is recommended to assess and treat the coagulation state of an actively bleeding trauma patient.⁶⁴

Recombinant factor VIIa can be used for controlling severe bleeding in blunt trauma patients. Several papers address its use in coagulopathic trauma patients requiring emergent craniotomy. It has been shown to reduce the size of intracranial hematomas and reduce need for transfusion with packed red blood cells (PRBC) and plasma.^{65,66} Thromboembolic complications following factor VIIa administration have been reported in adults and children, and, therefore, its use should be judicious.

Although the overall physiology of coagulation in children is nearly identical to that of adults, there are some special considerations in injured children. The neonate's relatively immature liver and initial nutritional needs increases the likelihood that vitamin K-dependent clotting factors will be decreased. Trauma resulting from abuse in infants and children frequently includes occult head injuries and the release of potent thromboplastins. Young children may also have an undiagnosed congenital bleeding disorder. Compared with adults, the relative health of the cardiopulmonary and renal systems allows children to tolerate significant hypovolemia and large-volume resuscitation that may result in a dilutional coagulopathy. The medical disorders and medications that can promote bleeding in adults also apply to children, although most are far less prevalent in the pediatric population.

In the ICU, patients are at an increased risk of pathologic thrombosis secondary to endothelial damage and indwelling central catheters. Traumatic and pharmacologic paralysis, in addition to bed rest, contributes to venous stasis. Although the risk of deep venous thrombosis and thromboembolic disease is lower in prepubertal children compared to adults, it is more prevalent than previously recognized.⁶⁷ Hypercoagulable states occur across the age spectrum, and children with nephrotic syndrome, inherited forms of thrombophilia, and some rheumatologic disorders are at increased risk of pathologic clot formation. Prophylaxis with low-dose heparin or automated venous compression stockings should be used in appropriate patients.

Nutrition

Nutritional support of critically injured children is extremely important and may improve outcomes in injuries such as TBI and burns. A major difference between adult and pediatric nutritional support is the fact that children have a requirement for maintenance of growth and development. Pediatric patients have lower energy stores and an approximately 50% higher resting basal metabolic rate compared to adults.

Similar to adult trauma patients, a state of hypermetabolism exists in critically ill pediatric patients and pediatric trauma patients. Critically ill pediatric patients often require increases in protein energy to compensate for the increased resting metabolic rate. The enteral route for nutritional support is preferable, and a growing body of research

has been performed demonstrating the benefits of enteral versus parenteral nutrition. In a recent meta-analysis, the benefits of enteral nutrition included lower risk of infection and reduction in hospital length of stay.⁶⁸ Other proposed benefits include preservation of intestinal mucosal integrity, with decreased bacterial translocation and a reduction in multiple organ failure. Enteral feeding is also more cost-effective than parenteral nutrition in pediatric patients.⁶⁹ When enteral feeding is not possible, it is best to support the patient with total parenteral nutrition.

Owing to impaired gastrointestinal (GI) motility in critically ill trauma patients, enteral feeding may be poorly tolerated. Gastric emptying is often delayed following severe head injury. Additionally, many of the medications used during treatment of traumatically injured patients may affect GI motility (including narcotics, benzodiazepines, barbiturates, and catecholamines) and can adversely affect feeding tolerance. Therefore, many patients with severe TBI may not tolerate full enteral nutrition. In these situations, “trickle” or low-volume feeds have been advocated to prevent intestinal mucosal atrophy.

Large gastric residual volume associated with lack of tolerance of gastric feeding may increase the incidence of aspiration pneumonia. Continuous gastric infusion of formula, addition of prokinetic agents, or transpyloric feeding may improve feeding tolerance. In some pediatric trauma patients, enteral feeding may not be realistic, and the most important action is to provide nutritional support as soon as possible, with the decision of enteral versus parenteral support individualized to the patient.

Sedation and Pain

Injured children commonly require analgesia and anxiolysis during therapy and management of various injuries. There are myriad drugs that can be safely used to provide appropriate levels of analgesia and anxiolysis in children.

In addition to providing pain relief and anxiolysis, sedatives and analgesics may reduce elevated ICP, facilitate mechanical ventilation, prevent shivering, provide anticonvulsant activity, and minimize long-term psychological trauma from untreated pain and stress.¹³ The importance of restoring and maintaining circulating intravascular volume before administering sedatives cannot be overstated, as children may be “surviving” on endogenous catecholamine release, thereby barely maintaining adequate blood pressure and tissue perfusion. Administration of even small doses of any sedative in this situation may precipitate cardiovascular collapse and cardiac arrest. Empiric treatment of presumed hypovolemia should precede administration of sedatives in an acutely injured child.

In the initial setting of evaluating an acutely injured child, small doses of narcotics such as fentanyl, given in incremental doses (0.5 µg/kg per dose, up to 1 to 2 µg/kg) titrated to effect, can be useful in both providing analgesia and allowing a more detailed examination. A child with painful injuries (e.g., fractures, multiple abrasions) is often more cooperative and allows a more thorough examination after receiving adequate analgesia. Concerns about masking the presence of intraabdominal injury are unfounded, as the cooperation achieved from the analgesia outweighs the difficulty in examining an agitated, screaming child who is experiencing acute pain. It is rarely necessary to administer benzodiazepines or other anxiolytic drugs in the acute setting of pediatric trauma, provided adequate analgesia is provided. In a mechanically ventilated patient, benzodiazepine (midazolam, diazepam, lorazepam) administration by intermittent dosing or by continuous infusion is commonly used to provide anxiolysis. Recently, infusion of dexmedetomidine has been used for sedation.

A variety of short-acting drugs can be used to provide sedation for endotracheal intubation. A detailed analysis of the advantages and disadvantages of these drugs is beyond the scope of this chapter. Sodium thiopental (4 to 6 mg/kg) is commonly used in a hemodynamically stable child in this setting because it is rapid acting (onset within 30 to 60 seconds) and can be used to treat elevated ICP. Further, sodium thiopental (1 to 2 mg/kg every 15 to 30 minutes) can be used

following successful intubation to maintain unconsciousness during transport to the ICU, operating room, or radiology department. The use of thiopental for sedation for radiographic procedures in a non-intubated, spontaneously breathing patient should be reserved for elective situations in fasting patients, and it should be administered by an anesthesiologist. Pentobarbital may be substituted for sodium thiopental.

Except for inducing general anesthesia, the use of propofol for critically injured children is controversial and is rarely necessary in the acute setting. A poorly defined syndrome of metabolic acidosis and myocardial failure has been reported after giving propofol by continuous infusion in the critical care setting. Nevertheless, many experienced pediatric intensivists use propofol for short intervals, especially during the weaning of narcotic-dependent children from mechanical ventilation.

Nonaccidental Trauma

Abuse is a common cause of traumatic injury in infants and young children.^{70,71} Nationally, it is estimated that approximately 1600 children died due to abuse or neglect in 2014, a rate of 2.13 per 100,000 children.⁷² Children younger than 12 months accounted for 43.7% of these fatalities, and 85% were younger than 4 years. Recognition of inflicted injury is important to ensure appropriate care, prevent recurrence of abuse, protect siblings, and comply with reporting mandates. A multidisciplinary team is optimal for treating children with inflicted injuries. The team should consist of a pediatric trauma surgeon, the treating staff, a medical social worker, and a child abuse pediatrician.

A delay in seeking care is common in children with abusive injuries. Injury history may be absent, incomplete, or inconsistent with physical findings or the developmental capability of the child. Domestic violence is common in families of abused children. Children with inflicted injuries that have more subtle findings and patients with intact families are more likely to be misdiagnosed as accidentally injured. This may have serious repercussions, including further injury and death.⁷³ Children with abusive injuries have worse outcomes than those with accidental injuries, with higher injury severity, mortality rates, and accumulated costs.⁷⁴ Having a high index of suspicion for inflicted trauma is critical in assessing an infant who presents with lethargy, apnea, cyanosis, mottling, poor perfusion, or seizures without an obvious history of trauma.

Evaluation of children with inflicted injury should reflect the occult nature of many abusive injuries. The constellation of subdural hematoma, traction-type metaphyseal (bucket-handle) fractures of long bones, posterior rib fractures, and retinal hemorrhages are characteristic of inflicted injuries in infants. Although TBI is the leading cause of morbidity and mortality in abused children, some head injuries may not be easily diagnosed clinically.⁷⁵ Therefore, a nonambulatory infant with any type of abusive injury should have CT or MRI studies of the brain. The sudden deceleration with forceful striking of the head against a surface is an important mechanism in inflicted brain injuries in children. Hypoxic-ischemic insults and other mechanisms also appear to play a role. Subdural hemorrhage, classically localized at the parieto-occipital convexity or posterior interhemispheric fissure, is the most consistent autopsy finding in abusive head trauma (AHT). Subdural hematoma results from rotational deceleration forces that cause shearing of bridging cortical veins. Retinal hemorrhages are present in the majority of children with inflicted injuries, but their absence does not rule out abuse. Infrequently, accidental head injuries may cause retinal hemorrhages.⁷⁶ Therefore, an evaluation by a pediatric ophthalmologist is recommended in all children with suspected AHT. A skeletal survey should be done in all children with serious injury due to abuse or suspected abuse. Screening for abdominal trauma is also important, either through imaging or laboratory studies. A psychosocial evaluation is critical in families of children with inflicted injuries to help support the family during a time of crisis and evaluate for other comorbid factors including domestic violence, substance abuse, and mental illness.

Rehabilitation

Once life-threatening conditions have been treated and the overall medical condition stabilized, the pediatric trauma patient should be assessed for the restoration of maximal functional independence. It is the role of the pediatric rehabilitation medicine team to identify, assess, and promote maximum restoration of physical, cognitive, and psychosocial functioning in each patient. Members of the rehabilitation team, including occupational therapists, physical therapists, speech therapists, social workers, and schoolteachers, provide their expertise in returning the patient to maximum independent function. As a first step, it is important to identify the patient's functional deficits and subsequent level of disability and handicap as they relate to the patient's home, community, and school settings.

The rehabilitation process should begin early in the patient's critical care stay, as physical and occupational modalities may limit the adverse physiologic effects of prolonged immobilization. For instance, muscles lose their flexibility and bulk with inactivity, resulting in diminished strength and endurance. Joints become stiff and contracted, and skin breaks down, resulting in pressure ulcers. Interventions include passive joint range of motion, isometric strengthening, and appropriate bed positioning. Orthotic devices, placed at joints (e.g., elbows and ankles) in a neutral position, limit contracture formation. Speech and occupational therapists can evaluate oral motor function to assess safe swallowing and feeding, decreasing the patient's risk of aspiration. The dietitian evaluates the patient's nutritional status, providing recommendations for appropriate diet and caloric intake. The social worker and child life specialist provide the patient and family members with emotional and educational support during the patient's acute critical care stabilization.

It is through the collaborative efforts of the pediatric trauma team and the pediatric rehabilitation team that the survivor of a pediatric trauma maximizes functional independence and can be successfully discharged home.

Brain Death and Organ Donation

Clinical guidelines for the determination of brain death were first published in 1987 by the American Academy of Pediatrics.⁷⁷ These guidelines were revised in 2011 by the American Academy of Pediatrics, the Child Neurology Society, and the Society of Critical Care Medicine and establish the minimum standards that must be met before brain death can be declared in children. These guidelines state that two examinations including apnea testing must be performed following achievement of physiologic stability and in the absence of confounding factors (e.g., hypothermia). These exams must be separated by an observation period depending on the child's age. For newborns up to 30 days of life, the period is 24 hours, while in infants and children 31 days to 18 years the period is 12 hours. Apnea testing should demonstrate no respiratory effort during the test and a final PaCO_2 20 mm Hg above baseline and more than 60 mm Hg. Ancillary studies (e.g., EEG or radionuclide cerebral blood flow) are not required or a substitute for neurologic exam. The guidelines allow for the use of ancillary studies under special, well-defined circumstances, and a second exam is still recommended.⁷⁸

Trauma patients represent a large percentage of those who are declared brain dead in a pediatric ICU and, therefore, represent a large pool of potential organ donors. There continues to be a wide gap between the number of organs available for transplantation and the number of patients requiring transplants, with more than 100,000 patients currently awaiting transplantation in the United States. Improvement in consent for organ donation is one way to decrease this gap. Despite widespread acceptance of and support for organ donation

among the general public, only 40% to 60% of families give consent for donation. Consent rates for donation are improved when the family understands the concept of brain death and when the understanding occurs before the request for donation (decoupling). In addition, the consent rate is maximized when the requester has specialized training or is a member of the organ procurement organization (OPO). In pediatric trauma patients, involvement of the attending physician in the request process may also have a beneficial effect on consent rates.⁷⁹

In an effort to increase organ donation, federal regulations were issued in 1998 governing how potential organ donors should be identified and approached.⁸⁰ All hospitals must have an agreement with an OPO and must notify the organization of patient deaths. The procurement organization then determines the patient's suitability for organ donation. In addition, the hospital must have an agreement with a tissue bank and eye bank to coordinate tissue and eye donation. The family of every potential donor must be informed of the option to donate organs or tissues.

KEY POINTS

1. Injury is the leading cause of death in childhood. Trauma systems and trauma centers improve outcomes in injured patients. Pediatric trauma centers improve outcomes in children, and this is especially evident in traumatic brain injury (TBI). Care by a multidisciplinary trauma team led by a pediatric trauma surgeon and pediatric intensive care specialist improves outcomes.
2. Children are initially evaluated and treated by the American College of Surgeons Advanced Trauma Life Support (ATLS®) algorithm. The priorities of evaluation and resuscitation are identical to adult trauma; however, children have unique physiologic and anatomic differences that must be taken into consideration during initial evaluation and treatment.
3. Nearly 3000 children aged 1 to 14 years die each year as a result of TBI. Primary injury occurs based on linear and rotational forces. Secondary injury occurs following impact and is considered to be preventable (e.g., hypoxia). Treatment strategies for TBI should be aggressive to prevent secondary injury. Survivors of TBI frequently have life-long morbidities.
4. Determining the mechanism of injury and understanding the unique physiologic and anatomic considerations in children allow the trauma team to predict the organ systems injured and direct evaluation to these areas. Understanding injury patterns allows for the trauma team to minimize radiation exposure in children, which should be kept at a minimum.
5. Nonaccidental trauma is a major cause of morbidity and mortality in children under 4 years of age. Trauma providers must be vigilant in detecting injuries that are inconsistent with the mechanism provided or the child's developmental age. Suspected abuse must be reported to state agencies and should be thoroughly investigated in a multidisciplinary manner with a pediatric trauma surgeon, medical social worker, and a child abuse pediatrician.

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Transplantation is an increasingly utilized treatment option for patients with organ failure. In 2014, 27,737 organs were transplanted in the United States, with over 122,000 patients on the waiting list.¹ Despite advances in immunosuppression and postoperative management, utility of transplantation is nonetheless dependent on the number of available organs. The majority of donor organs are cadaveric, of which 90% are from brain-dead (BD) donors. Increasing the rate of donor registry participation and consent has the greatest impact on the number of available organs. However, approximately 20% to 30% organs are lost before procurement despite aggressive medical management after intent for donation has been made.¹ This statistic highlights the profound physiologic variations occurring at the time of brain death and the suboptimal quality of resuscitation because of various reasons.² An intensivist can have a profound impact on the number and quality of organs salvaged by understanding the physiology of brain death and strategies used by organ procurement organizations (OPO) to optimize transplantation success. Establishment of clear guidelines, resuscitation endpoints, and an intensivist-led team can increase organ recovery from BD donors.³

■ DECLARATION OF BRAIN DEATH

The initial process of organ donation requires heightened awareness of potential donors on the part of intensive care unit (ICU) team. Often, potential donors are excluded by caregivers based on notions of donor criteria or ethical concerns regarding the conflict of care. Members of a local OPO are trained specifically to interact with families regarding organ donation issues in such a manner that a caregiver and an OPO are not seen in mutual opposition. With the permission of the family, blood may be sampled to determine the suitability of a donor before brain death. If devastating, unsurvivable head injury is recognized in a potential donor, basic resuscitation may begin before the declaration of brain death. Once brain death is confirmed based on standard criteria (see Chapter 178), the ICU team should act quickly to stabilize the physiology of the donor and decrease the time to transplantation.

■ PHYSIOLOGY OF BRAIN DEATH

Brain injury resulting in herniation occurs after rostrocaudal progression of ischemia. Events leading to brain death include hypertension with bradycardia (Cushing response) as the pons becomes ischemic. Further involvement of the medulla creates unopposed sympathetic stimuli that trigger a catecholamine “storm.” This surge of catecholamines damages end organs by inducing both severe vasoconstriction and proinflammatory response. Spinal cord ischemia and loss of sympathetic denervation result in severe hypotension. This is exacerbated by simultaneous ischemia of the pituitary and hypothalamus and the loss of homeostatic control. These events occur in varying magnitude or velocity, thus making management even more difficult. The resulting physiology is characterized by hemodynamic instability along with various secondary complications listed in Figure 173-1.

■ INITIAL DONOR RESUSCITATION

Care of BD donors requires multiple modalities and frequent reassessment to ensure that resuscitation endpoints are met. Donors often have

associated traumatic injury and chronic health problems. Moreover, treatment strategies administered before brain death are often directed toward maintaining cerebral perfusion, often to the detriment of other organs. Post-declaration management focuses on reversing this state and preventing further organ damage.

Various organizations provide algorithms for the standard management of BD donors. Protocols may be organ or donor specific.^{4,5-7} The United Network for Organ Sharing (UNOS) has provided a sample standard pathway involving an initial workup and therapy (Fig. 173-2). Regional OPOs can develop their own protocol based on this pathway (Fig. 173-3). These algorithms focus on ongoing resuscitation and provide evidence-based therapy, as well as a platform for future research in the field, both nationally and within regional donor networks. Immediate goals include establishing baseline organ function and stabilizing organ physiology. If not already in place, a central venous catheter and arterial catheter are inserted. Blood, urine, and bronchial cultures are obtained, and baseline biochemical values and infectious titers are determined. Lungs and heart are evaluated by performing basic chest radiography, echocardiography, and bronchoscopy. Blood typing and crossmatch are performed, after which initial graft allocation efforts are initiated by an OPO coordinator.

Most OPOs use critical endpoints as donor management goals. These are used to maximize the number of organs that can be transplanted per donor. These physiologic goals are specific but are also fairly broad and similar to basic resuscitation. Typical goals are listed in Box 173-1. A UNOS study in the Southwest region of the United States found that meeting 7 of 9 goals significantly increased organs transplanted per donor.⁸ This was true for criteria met at the time of donation and at the time of consent. However, only approximately 15% of donors met these goals. This illustrates the importance of goal-directed care and timeliness of its implementation. Standard ICU protocols should also be employed to prevent complications. Gastrointestinal and deep vein thrombosis (DVT) prophylaxis should be continued appropriately, blood products administered for anemia or coagulopathy, aspiration precautions instituted, hypothermia avoided, and electrolytes and acidosis corrected. Standard insulin protocols should also be continued because donors can be profoundly hyperglycemic. Serum glucose level of <180 mg/dL is associated with higher organ yield per donor and is consistent with the current general ICU guidelines.⁹

■ ORGAN-SPECIFIC CONSIDERATIONS AND CONTROVERSIES

Cardiovascular

Cardiovascular management after brain death is important to maintain perfusion and preserve the heart for donation. Catecholamine surge during herniation induces considerable myocardial damage.¹⁰ Right ventricle strain commonly occurs after increased pulmonary capillary perfusion and pulmonary overflow injury from increased vascular resistance.¹¹ Contractility must be frequently reassessed and quantified by performing echocardiography because regional wall abnormalities often resolve before donation.

Initial resuscitation includes crystalloid administration guided by central venous pressure (CVP), pulmonary capillary wedge pressure,

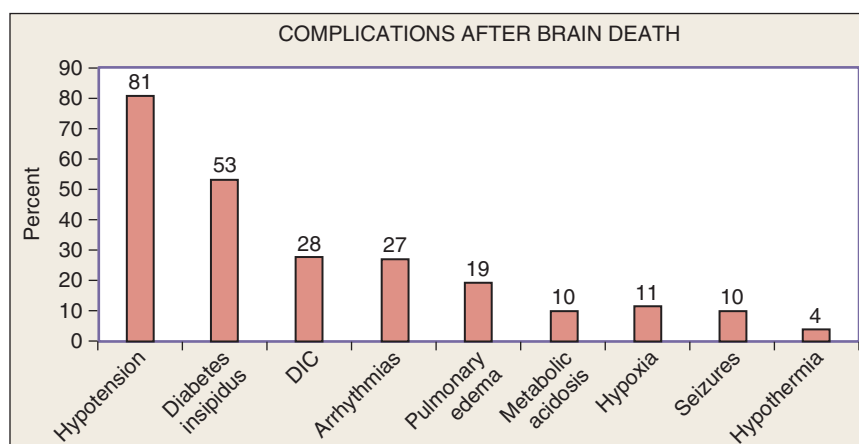


FIGURE 173-1 ■ Complications after brain death. (Adapted from Smith M. Physiologic changes during brain stem death—lessons for management of the organ donor. *J Heart Lung Transplant* 2004;23:S217-22.)

BOX 173-1

Physiologic Endpoint Goals in a Potential Organ Donor

Mean arterial pressure: 60-100 mm Hg
 Central venous pressure: 4-10 mm Hg
 Left ventricular ejection fraction: >50%
 Use of ≤ 1 vasopressor at a low dose*
 Arterial blood gas pH: 7.3-7.45
 Urine output: 0.5-3 mL/kg/h
 Serum glucose level: <150 mg/dL
 Serum sodium level: 135-155 mEq/L
 PaO₂:FiO₂ ratio: >300

*Dopamine ≤ 10 $\mu\text{g/kg/min}$, neosynephrine ≤ 60 $\mu\text{g/kg/min}$, or norepinephrine ≤ 10 $\mu\text{g/kg/min}$. (Adapted from Malinoski DJ, et al. The impact of meeting donor management goals on the number of organs transplanted per donor: results from the United Network for Organ Sharing Region 5 prospective donor management goals study. *Crit Care Med* 2012;40(10):2773-80.)

or other noninvasive measures (most recently echocardiography) to assess volume status. After adequate volume loading, vasopressors are often required to maintain perfusion pressure. End organ perfusion should be monitored by measuring oxygen delivery or central venous oxygen saturation. Protocols based on traditional volume and vasopressor management have increased the number of heart donations in the past (Fig. 173-4).^{5,12}

Previously used vasopressors include dopamine, neosynephrine, epinephrine, norepinephrine, and vasopressin. The immunomodulatory function of catecholamines makes them attractive for managing a donor's proinflammatory condition.¹³ Dopamine is less favored because it may suppress anterior pituitary hormones and may induce tachyarrhythmias.¹⁴ Treatment with high levels of norepinephrine and epinephrine is associated with cardiac and kidney graft nonfunction.^{15,16} Vasopressin administration is ideal since it is depleted in the face of pituitary ischemia and can reduce the dose of catecholamines administered.¹⁷ Therefore, vasopressin is used more in hormone replacement therapy (HRT) than as a true vasopressor. Low-dose supplementation increases the rate of high-yield procurement (>4 organs per donor) and should be used as a part of donor resuscitation.¹⁸

Pulmonary

Like the heart, lung function in the donor is affected by physiologic changes associated with brain death. Pulmonary edema after brain death results from elevated afterload due to catecholamine surge combined with increased venous return and decreased left ventricular function.¹⁹ Sympathetic discharge also increases inflammation of the

lung parenchyma and capillaries, leading to edema and failure.²⁰ These effects are significant because pulmonary edema and inflammation reduce lung donation rates to less than 20%.²¹ Standard criteria for lung donation include a clear chest x-ray and PaO₂/FiO₂ ratio of >300.²² Once a suitable donor is identified, aggressive lung-specific management is performed.⁴ Most protocols involve the use of frequent chest physiotherapy and bronchoscopy, diuretics, strict aspiration precautions, empiric antibiotics, and steroids.²³ Lung recruitment maneuvers and frequent bronchoscopy increase oxygenation and lung utilization.²⁴ Lung protective strategies involving low tidal volumes and moderate positive end-expiratory pressure prevent further barotrauma.²⁵ For the donor population specifically, acute lung injury is more common in those treated with increased tidal volumes; therefore, sustained recruitment maneuvers should be used with caution.²⁶ Similarly, excessive oxygen administration should be avoided because it can induce inflammatory cascades and apoptosis.²⁷ Diuretics are administered to decrease CVP for decreasing alveolar-arterial oxygen gradient. However, restriction of CVP does not increase lung utilization. Therefore, diuretics are less frequently used at present.²⁸

Renal

BD donors are typically volume depleted secondary to aggressive mannitol use and diabetes insipidus. Strategies for preventing renal injury include avoidance of nephrotoxic agents and maintenance of hydration. Large volume administration improves kidney and liver graft function by correcting hypernatremia.¹⁵ In contrast, hypervolemia exerts deleterious effects by inducing right heart strain and lung dysfunction.

Crystalloids are primarily used for initial resuscitation. Some societies advocate the use of colloids such as albumin to prevent water accumulation in the lungs. However, limited data are available to support this.²³ Hypertonic saline may modulate inflammation and is beneficial for donor resuscitation. However, sodium levels should be monitored closely because this can worsen graft function.^{29,30}

Endocrine

One of the more debated aspects of donor management is the use of hormonal therapy. A donor develops a variable panhypopituitary state after ischemia.³¹ Administration of desmopressin as DDAVP treats the subsequent diabetes insipidus that can further complicate fluid management. Similarly, vasopressin helps with catecholamine function, as stated previously. Dysfunction of the anterior pituitary gland is less consistent, with the variable effects of hormones given to counteract the loss of corticotropin and thyroid-stimulating hormone.³²

Initial enthusiasm for HRT was based on nonrandomized data that showed increased organ yield after the administration of a hormone cocktail containing triiodothyronine (T_3), corticosteroids, insulin, and vasopressin.^{6,12,33,34} Therefore, hormone cocktails became a part of the UNOS protocol for managing cardiac donors. Using this protocol,

animal models demonstrated beneficial reduction in vasopressors when given HRT.³⁵ However, more rigorous examination has indicated that combination hormone therapy has not been universally supported. Criticism of HRT focuses primarily on the thyroid and steroid components of therapy, which will be examined more closely.

| Critical Pathway for the Organ Donor | | | | | |
|--|--|---|---|---|---|
| Patient name: _____ ID number: _____ | | | | | |
| Collaborative Practice | Phase I Referral | Phase II Declaration of Brain Death and Consent | Phase III Donor Evaluation | Phase IV Donor Management | Phase V Recovery Phase |
| <p>The following professionals may be involved to enhance the donation process.</p> <p><i>Check all that apply</i></p> <ul style="list-style-type: none"> Physician Critical care RN Organ Procurement Organization (OPO) OPO co-ordinator (OPO) Medical Examiner (ME)/Coroner Respiratory Laboratory Pharmacy Radiology Anesthesiology OR/Surgery staff Clergy Social worker | <ul style="list-style-type: none"> Notify physician regarding OPO referral Contact OPO ref: Potential donor with severe brain insult OPC on site and begins evaluation Ht _____ Wt _____ as documented ABO as documented _____ Notify house supervisor/charge nurse of presence of OPC on unit | <ul style="list-style-type: none"> Brain death documented Time _____ Date _____ Pt accepted as potential donor MD notifies family of death Plan family approach with OPC Offer support services to family (clergy, etc) OPC/Hospital staff talks to family about donation Family accepts donation OPC obtains signed consent and medical/social history Time _____ Date _____ ME/Coroner notified ME/Coroner releases body for donation Family/ME/Coroner denies donation—stop pathway—initiate post-mortem protocol—support family. | <ul style="list-style-type: none"> Obtain pre/post transfusion blood for serology testing (HIV, hepatitis, VDRL, CMV) Obtain lymph nodes and/or blood for tissue typing Notify OR and anesthesiology of pending donation Notify house supervisor of pending donation Chest and abdominal circumference Lung measurements per CXR by OPC Cardiology consult as required by OPC (use reverse side) Donor organs unsuitable for transplant—stop pathway—initiate post-mortem—support family. | <ul style="list-style-type: none"> OPC writes new orders Organ placement OPC sets tentative OR time Insert arterial line/2 large bore IVs Possibly insert CVP/Pulmonary Artery Catheter See reverse side | <ul style="list-style-type: none"> Checklist for OR Supplies given to OR Prepare patient for transport to OR IVs Pumps O₂ Ambu Peep valve Transport to OR Date _____ Time _____ OR nurse reviews consent form reviews brain death documentation checks patient's ID band |
| Labs/Diagnostics | | <ul style="list-style-type: none"> Review previous lab results Review previous hemodynamics | <ul style="list-style-type: none"> Blood chemistry CBC + diff UA C & S PT, PTT ABO A Subtype Liver function tests Blood culture X 2 / 15 minutes to 1 hour apart Sputum Gram stain & C & S Type & Cross Match # units PRBCs CXR ABGs EKG Echo Consider cardiac cath Consider bronchoscopy | <ul style="list-style-type: none"> Determine need for additional lab testing CXR after line placement (if done) Serum electrolytes H & H after PRBC Rx PT, PTT BUN, serum creatinine after correcting fluid deficit Notify OPC for PT >14 PTT <28 Urine output <1 mL/Kg/hr >3 mL/Kg/hr Hct <30 / Hgb >10 Na >150 mEq/L | <ul style="list-style-type: none"> Labs drawn in OR as per surgeon or OPC request Communicate with pathology: Rx liver and/or kidneys as indicated |
| Respiratory | <ul style="list-style-type: none"> Pt on ventilator Suction q 2 hr Reposition q 2 hr | <ul style="list-style-type: none"> Prep for apnea testing: set FiO₂ @ 100% and anticipate need to decrease rate if PCO₂ <45 mm Hg | <ul style="list-style-type: none"> Maximize ventilator settings to achieve SaO₂ 98–99% PEEP = 5cm O₂ challenge for lung placement FiO₂ @ 100%, PEEP @ 5 X 10 min ABGs as ordered VS q 1st | <ul style="list-style-type: none"> Notify OPC for BP <90 systolic HR <70 or >120 CVP <4 or >11 PaO₂ <90 or SaO₂ <95% | <ul style="list-style-type: none"> Portable O₂ @ 100% FiO₂ for transport to OR Ambu bag and PEEP valve Move to OR |
| Treatments/Ongoing Care | | <ul style="list-style-type: none"> Use warming/cooling blanket to maintain temperature at 36.5° C–37.5° C NG to low intermittent suction | <ul style="list-style-type: none"> Check NG placement and output Obtain actual Ht _____ and Wt _____ if not previously obtained | | <ul style="list-style-type: none"> Set OR temp as directed by OPC Post-mortem care at conclusion of case |
| Medications | | | <ul style="list-style-type: none"> Medication as requested by OPC | <ul style="list-style-type: none"> Fluid resuscitation—consider crystalloids colloids, blood products DC meds except pressors and antibiotics Broad-spectrum antibiotic if not previously ordered Vasopressor support to maintain BP >90 mm Hg systolic Electrolyte imbalance: consider K, Ca, PO₂, Mg replacement Hyperglycemia: consider insulin drip Oliguria: consider diuretics Diabetes insipidus: consider antidiuretics Paralytic as indicated for spinal reflexes | <ul style="list-style-type: none"> DC antidiuretics Diuretics as needed 350 U heparin/kg or as directed by surgeon |
| Optimal Outcomes | The potential donor is identified and a referral is made to the OPO. | The family is offered the option of donation and their decision is supported. | The donor is evaluated and found to be a suitable candidate for donation. | Optimal organ function is maintained. | All potentially suitable, consented organs are recovered for transplant. |

Shaded areas indicate Organ Procurement Coordinator (OPC) Activities. Copyright © 2003, 2001, 1998 UNOS (United Network for Organ Sharing) All rights reserved.

The Critical Pathway was developed under contract with the U.S. Department of Health and Human Services, Health Resources and Services Administration, Division of Transplantation.












FIGURE 173-2 ■ Critical pathway for organ donor. (Adapted from Smith M. Physiologic changes during brain stem death—lessons for management of the organ donor. J Heart Lung Transplant 2004;23:S217-22)

Continued

ADULT STANDARDIZED ORDERS Page 1 of 2

DA Donor # _____



Initiate only after approval by Donor Alliance Coordinator. All orders are STAT unless otherwise noted and will be ordered throughout donor management according to donor's physiological status.

Donor Alliance accepts Donor as of ____/____/____ :____ MST.

Treatment Orders

- ☐ 1. **DISCONTINUE ALL PREVIOUS MEDICATION ORDERS EXCEPT PRESSORS & ANTIBIOTICS.**
- ☐ 2. Weigh patient and measure height in inches (if not already done).
- ☐ 3. Monitor BP (Keep MAP >60, SBP >90), cardiac rhythm, pulse oximetry, CVP continuously. Document VS every hour and PRN.
- ☐ 4. Hourly I & O. Notify coordinator if UOP is < 0.5 ml/kg/hr or > 5 ml/kg/hr (<____ or ____>).
- ☐ 5. Maintain patient's temperature between 35.5-37.5° C (95.9°-99.5°F). Order warming or cooling devices as needed.
- ☐ 6. Turn/suction Q 2 hours and PRN (May use rotation bed if available).
- ☐ 7. OG/NG Tube to low intermittent wall suction with Q4 hour abdominal assessment.
- ☐ 8. Vent Settings: A/C FiO₂____ V_T____ RR____ PEEP____
☐ ABG on FiO₂ 100% x 1 after bronch, then titrate FiO₂ to maintain SaO₂ greater than 95%
- ☐ 9. CXR Q4 hours
☐ Do first CXR **after** bronch and have read STAT
- ☐ 10. Surgical consult for: ☐ Arterial line ☐ Central Line ☐ Lymph Node Removal
- ☐ 11. Flush eyes with NS every 2 hours & keep covered with NS moist gauze

Laboratory Orders

- ☐ 1. Type and cross for 4 (four) units of PRBC, prefer CMV Negative or Leukopore reduced. Have blood bank stay 4 (four) units ahead at all times.
- ☐ 2. **STAT** labs to include:

| | | | |
|---|--|-------------------------------------|--|
| <input type="checkbox"/> ABO Confirmation | <input type="checkbox"/> Liver Enzymes | <input type="checkbox"/> PT/PTT/INR | <input type="checkbox"/> Lipase |
| <input type="checkbox"/> Basic Metabolic Panel | <input type="checkbox"/> LDH | <input type="checkbox"/> Calcium | <input type="checkbox"/> Lactate |
| <input type="checkbox"/> CBC with Differential | <input type="checkbox"/> GGT | <input type="checkbox"/> iCa | <input type="checkbox"/> Sputum Gram Stain ONLY. NO culture |
| <input type="checkbox"/> UA with Micro | <input type="checkbox"/> Alk. Phos | <input type="checkbox"/> Mg | <input type="checkbox"/> Qualitative Urine Pregnancy test x1 |
| <input type="checkbox"/> CPK, CK/MB, Troponin I | <input type="checkbox"/> Amylase | <input type="checkbox"/> Phosphorus | |

Other Labs: _____

NOTE When ordering these tests, feel free to order the panels used by your hospital.

IV Fluid Orders:

- ☐ 1. Maintenance IV fluid: _____ at _____ ml/hr
- ☐ 2. Replace urine output IV ml for ml with _____ every hour
- ☐ 3. Bolus IV _____ ml of _____ over _____

Special Studies and Consults:

- ☐ **Cardiac Studies:**
 - ☐ STAT 12 lead EKG
 - ☐ 2D Echo with on-call physician interpretation (**Check with coordinator prior to ordering Echo**)
- ☐ **Pulmonary Consult** to "determine organ function for transplant." Consult to include:
 - ☐ STAT Bronchoscopy. (Please obtain two samples of bronchial lavage for testing)
- ☐ **Intensivist Consult** Indication: _____

Organ Recovery Coordinator Signature

@_____
Date/Time

Donor Alliance, Inc.
Page 1 of 2

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Effective: 04/30/10
QA/Doc Approval: RLM

FIGURE 173-2, cont'd

Thyroid

Thyroid hormone replacement for donors was first examined in baboon studies in the late 1980s. Novitsky et al. observed the reversal of cardiac dysfunction after administering T₃.³¹ However, further animal studies could not demonstrate any benefit of T₃.³⁶ Similarly, numerous human studies were unable to show a beneficial effect of T₃ on cardiac function, inotropic support, or organ yield.^{37,38} Moreover, studies assessing thyroid hormone replacement with thyroxine (T₄) have yielded conflicting results.³⁹

Revised UNOS recommendations indicate that administration of vasopressin, diuretics, and steroids rather than thyroid hormones may increase organ yield.⁴⁰ A review and meta-analysis of thyroid administration in BD donors showed beneficial effect in all case series and retrospective reports but did not show any beneficial effect either alone or in combination with other hormone therapies in randomized controlled trials.⁴¹ Statistical issues complicate both retrospective and prospective reports. The strongest evidence thus far is provided by a retrospective review; however, this review examined a large data set of


| | |
|---|------------------|
| ADULT STANDARDIZED ORDERS Page 2 of 2 | DA DONOR # _____ |
|  <p>DONOR ALLIANCE Organ & Tissue Donation</p> | |
| Medication Orders | |
| <div style="display: flex; flex-direction: column;"> <div style="margin-bottom: 10px;"> <input type="checkbox"/> 1. SoluMedrol 2 gm IV Piggy Back x 1, then 1 gm IV Piggy Back Q 8 hours </div> <div style="margin-bottom: 10px;"> <input type="checkbox"/> 2. Antibiotic Coverage: <div style="margin-left: 20px;"> <input type="checkbox"/> Cefazolin 1gm IV Piggy Back Q 6 hours <input type="checkbox"/> Continue use of current antibiotic coverage (write out specific drug route frequency) </div> </div> <div style="margin-bottom: 10px;"> <input type="checkbox"/> 3. Duo Nebs UD Q4° OR Combivent MDI 4 puffs Q 4 hours </div> <div style="margin-bottom: 10px;"> <input type="checkbox"/> 4. Levothyroxine (T4) protocol Please give the following in rapid succession just prior to starting T4 drip: <div style="margin-left: 20px;"> <input type="checkbox"/> D50 50ml IV Push <input type="checkbox"/> Regular Insulin 20 units IV Push <input type="checkbox"/> SoluMedrol 2 gm IV Piggy Back if not already given as above. <input type="checkbox"/> Levothyroxine (T4) 20 mcg IV Push <input type="checkbox"/> DRIP: Start Levothyroxine (T4) gtt IV (Infusion strength of 200 mcg T4 in 500 ml 0.9% NaCL) <div style="margin-left: 20px;"> <input type="checkbox"/> Start at 10 mcg/hr (25 ml/hr) – may titrate up to 30 mcg/hr (75ml/hr) to keep SBP >90 <input type="checkbox"/> Attempt to wean vasopressors after starting T4. </div> </div> </div> <div style="margin-bottom: 10px;"> <input type="checkbox"/> 5. Vasopressin continuous infusion: Begin infusion at 0.04 units/min IV, to a maximum of 0.2 units/min IV, titrate to maintain SBP > 90 mmHg. </div> <div style="margin-bottom: 10px;"> <input type="checkbox"/> 6. DDAVP (Desmopressin): Administer _____ mcg IV Push now <div style="margin-left: 20px;"> <input type="checkbox"/> Repeat dose PRN for urine output exceeding _____ mls for > 2 hours. </div> </div> <div style="margin-bottom: 10px;"> <input type="checkbox"/> 8. DDAVP continuous infusion: Mix 12.5 mcg in 250 ml 0.9% NaCL and administer at a rate of 0.5 mcg/hr IV. Titrate to maintain urine output 2-3 ml/kg/hr. </div> <div style="margin-bottom: 10px;"> <input type="checkbox"/> 9. Dopamine continuous infusion. Start at 3 mcg/kg/min IV, titrate to maintain SBP of > _____. Notify Coordinator if dose reaches ≥ 15 mcg/kg/min. </div> <div style="margin-bottom: 10px;"> <input type="checkbox"/> 10. Naloxone (Narcan) 8mg IV Push x1 dose after CXR (Only if PaO₂ ≥ 300 on 100% FIO₂ on ABG). </div> <div style="margin-bottom: 10px;"> <input type="checkbox"/> 11. Calcium chloride 1gm IV Push </div> <div style="margin-bottom: 10px;"> <input type="checkbox"/> 12. Potassium chloride _____ meq IV Piggy Back NOW over _____ </div> </div> | |
| Additional Orders: <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> <div style="border-bottom: 1px solid black; height: 15px; margin-bottom: 5px;"></div> | |

FIGURE 173-3 ■ Adult standardized orders. (Reprinted with permission from Donor Alliance, Inc. of Colorado.)

over 66,000 donors.⁴² Multivariate analysis of this data set indicated a beneficial effect (increased organs procured per donor) of thyroid hormone administration independent of other factors. More importantly, thyroid hormone administration did not exert detrimental effects on graft survival. Therefore, use of thyroid hormones varies according to OPOs and to a donor's physiology.

Corticosteroids

The prominence of inflammatory mediators in BD donors plays a significant role in the management. The ischemic brain increases the levels of core inflammatory mediators that then cross the blood-brain barrier.⁴³ Increase in the levels of free radicals after

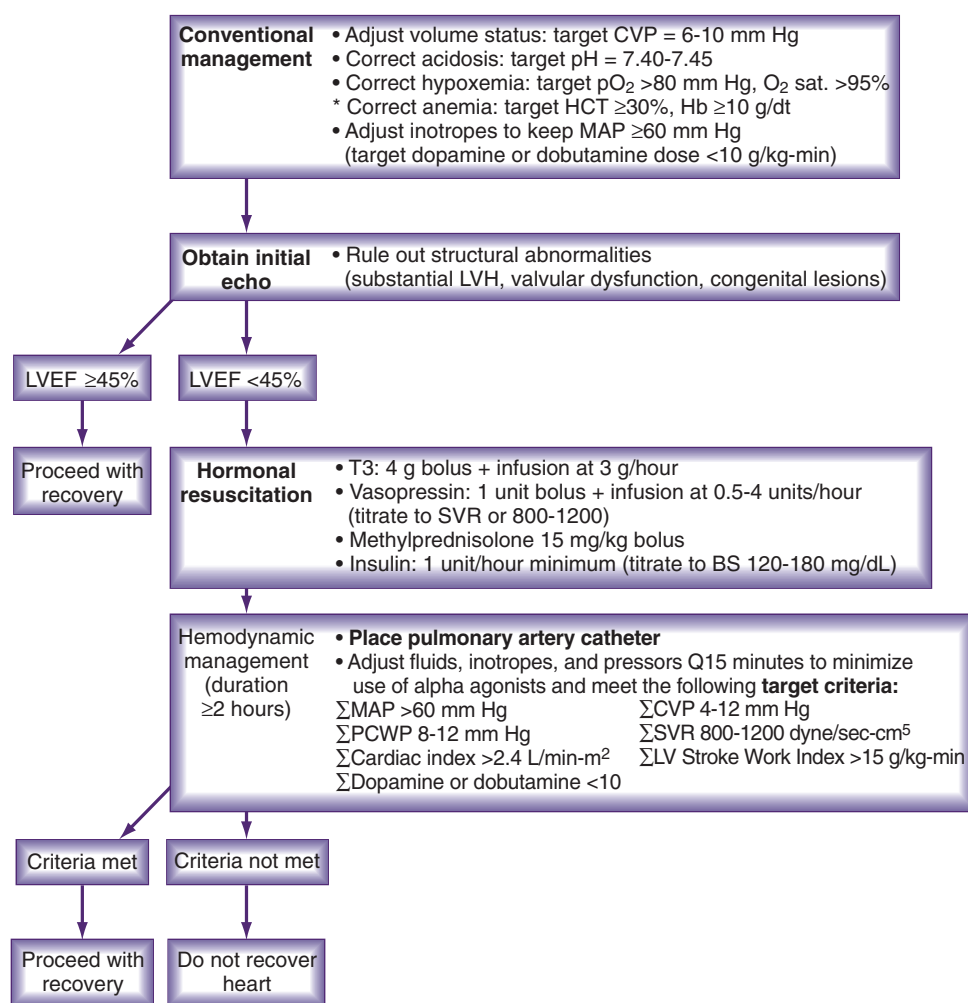


FIGURE 173-4 ■ Recommendations for cardiac donor management. (Adapted from Rosengard BR, Feng S, Alfrey EJ, et al. Report of the Crystal City meeting to maximize the use of organs recovered from the cadaver donor. Am J Transplant 2002;2:701-11.)

ischemia-reperfusion injury increases the local expression of adhesion molecules and influx of leukocytes (referred to as *passenger leukocytes*) in the transplanted organ.⁴⁴ These primed leukocytes can then affect graft rejection in the posttransplant period. Several studies have demonstrated increased rejection of the kidneys in BD donors compared with that in living-related, unrelated, or donation after cardiac death donors.^{45,46}

Corticosteroids are administered in donors to attenuate inflammatory response, to reduce rejection, and to increase organ yield. Methylprednisolone is typically given as a single bolus or a drip. Low doses of steroids in the form of hydrocortisone have also been used.⁴⁷ This decreased dose reduces hyperglycemia and need for insulin while maintaining comparable organ retrieval rates in donors receiving high-dose methylprednisolone. Few studies have evaluated steroid use in isolation from other hormonal therapies. The CORTICOME study showed no beneficial effect on graft recovery despite reducing the need for vasopressors in donors receiving hydrocortisone alone.⁴⁸ One can argue that reduction in vasopressor requirement can increase the number of organs that meet the criteria for donation. However, this needs to be studied in further studies. Similar to thyroid hormone administration, the overall quality of evidence for steroid use in BD donors is questionable. Most randomized trials on steroid administra-

tion have yielded neutral results, whereas observational studies have generally demonstrated improved hemodynamics and oxygenation status, increased organ yield, and improved graft function. Despite these mixed results, steroids are a widely utilized tool for organ donor resuscitation.

CONCLUSION

Donor management is unique in critical care in terms of perceived benefit versus risk: a life already lost has the potential to affect the lives of many others. Limited supply of cadaveric donor organs requires attentive pretransplant management to increase their availability and function. Maintenance of organs after brain death is extremely difficult because of hypothermia, acidosis, hypovolemia, pulmonary edema, cardiac arrhythmias, and profound hypotension. Important aspects of management include identification of potential donors, early hemodynamic stabilization with volume and vasopressor resuscitation, frequent reassessment of organ function and resuscitation endpoints, and provision of hormone replacement when indicated. Designated protocols can help focus on resuscitation and ensure the development of evidence-based guidelines. Although newer therapeutic modalities are promising, they require further research.

KEY POINTS

1. Brain death imparts profound changes to physiology including hemodynamic instability and loss of homeostatic control due to hypothalamic and pituitary ischemia.
2. Up to 30% of transplantable organs are lost during the management of the brain-dead donor.
3. Goal-directed care of the donor after declaration of brain death can increase organ yield.
4. The cornerstones of donor management include intravascular resuscitation, vasopressor administration, and hormone replacement therapy.

ANNOTATED REFERENCES

Malinoski DJ, Patel MS, Daly MC, et al. UNOS Region 5 DMG workgroup. The impact of meeting donor management goals on the number of organs transplanted per donor: results from the United Network for Organ Sharing Region 5 prospective donor management goals study. *Crit Care Med* 2012; 40(10):2773-80.

Published from a regional UNOS workgroup, this demonstrates how poorly even the basic tenets of resuscitation are met in donor management.

Rosendale JD, Kauffman HM, McBride MA, et al. Aggressive pharmacologic donor management results in more transplanted organs. *Transplantation* 2003;75:482-7.

This is a landmark review of the UNOS database, with specific attention to use of hormone therapy and effect on organ yield. Although controversial due to cohort size and retrospective nature of the study, this is a widely cited paper for proponents of hormone resuscitation.

Selck FW, Deb P, Grossman EB. Deceased organ donor characteristics and clinical interventions associated with organ yield. *Am J Transplant* 2008;8:965-74.

A review of UNOS donor data, this paper highlights donor characteristics that increase organ yield. Of note, it demonstrates that steroids, diuretics, and DDVP are positive predictors, but it does not support thyroid hormone use. It is of interest to compare this paper to that of Rosendale et al. above.

Smith M. Physiologic changes during brain stem death—lessons for management of the organ donor. *J Heart Lung Transplant* 2004;23:S217-22.

This review provides a thorough yet concise overview of the physiologic changes that occur during brain death. The paper provides a good introduction to the subject.

United Network for Organ Sharing website <<http://www.unos.org/>>.

The UNOS website contains continuously updated information for patients and practitioners regarding all aspects of organ transplantation. Donor data can be uploaded or requested from the site. Recommendations and pathways for donor management are also provided.

■ References for this chapter can be found at expertconsult.com.

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HISTORICAL PERSPECTIVE

The increasing gap between the number of organs available for transplantation and the number of patients listed for transplantation has become a rate-limiting step in reducing both wait times and wait list deaths in patients awaiting transplantation. Before the passage of the first United States brain death law in the state of Kansas in 1970,¹ donation after cardiac death (DCD, or donation after circulatory death) was the primary mode of organ donation in the United States. Donor death was determined according to traditional cardiopulmonary criteria—that is, absence of pulse and blood pressures without cardiac activity.

Early organ procurement strategies were relatively crude and variable, which in turn prolonged warm DCD ischemia time (time from donor circulatory arrest to cold perfusion) and resulted in poor outcomes.² Impact of the variability of circumstances surrounding donor death, and thus the duration of ischemic time, on DCD graft outcomes did not become apparent until experiences with organs donated after brain death (DBD) increased.

The need for diagnosing brain death was a culmination of critical care physicians' growing ability to maintain physiologic organ function in patients with little or no hope of neurologic recovery after central nervous system (CNS) insults. The concept was first introduced at a CIBA Foundation meeting in England in 1965 and was subsequently endorsed with formal diagnostic criteria by Harvard Medical School in 1968.^{1,3} A new debate was sparked over the precise definition and timing of death and the concept of futile care. Acceptance of this medically, philosophically, and legally novel concept of certifying death while maintaining perfusion in a potential donor to guarantee procurement with minimal warm ischemia time (WIT) and graft damage revolutionized transplantation. Because early experience with DBD organs showed superior outcomes, use of DCD organs declined and was subsequently abandoned.⁴

The success of DBD organs along with the refinements in medical and surgical techniques exponentially increased the number of transplants performed in the United States. The 1984 National Organ Transplant Act led to the formation of the United Network for Organ Sharing (UNOS), a nonprofit entity that provided a basis for standardizing organ procurement organizations (OPOs) throughout the United States, and the Organ Procurement and Transplantation Network (OPTN). Early national OPTN data showed that 10,794 deceased donor transplants were performed in 1988.⁵ Six years later, these numbers increased by nearly 50% to 15,210 transplants. Moreover, the number of lung grafts from deceased donors increased annually from 33 to 708.⁵ Intestinal transplantation also increased with the introduction of DBD donors. The first intestinal transplant was performed in 1990; by 1994, 96 patients with intestinal failure received intestinal transplants.⁵ Concomitant advances in critical care reduced mortality in patients with end-stage organ disease, thereby resulting in increasing wait lists and decreased attrition. This is referred to as the growing "gap" between organ supply and transplantation demand. For example, despite the increased number of transplant centers and utilization of living donors in 1995, only 33% of registrants waiting for kidney transplant underwent transplantation.⁵ However, the rate of transplantation decreased to 10% during 1998 to 2002.⁶

Moreover, the numbers of young and previously healthy DBD donors stagnated because of several statutory changes in areas of gun

control, automobile safety (airbags, seatbelts, and lowering of legal blood alcohol limits), and helmet use. This decreased traumatic fatalities and changed the face of DBD organ donors.⁷ The demographics of a typical DBD donor transitioned from a young healthy person who was rendered brain dead because of a devastating head trauma to an older person with medical problems who was rendered brain dead because of a neurovascular insult. This transformation eroded some benefit of using a DBD donor and prompted a search for other options.

Because the use of live donor organs has not kept pace with the growing deficit of organ donors, strategies such as regenerative medicine and gene/cellular therapy, mechanical devices and xenotransplantation (use of grafts derived from animal donors) for treating end organ diseases and organ replacement have been explored. However, these strategies are not ready to replace durable organ replacement. Further, the activity surrounding social and legislative approaches, including increased public awareness, donor registration activities, and interest in presumed consent (requiring individuals to opt out of organ donation to prevent consideration for donation at death), may have peaked because of cultural and philosophical objections. Therefore, transplantation is again being performed using organs procured from DCD donors.

In the early 1990s, the Maastricht German transplant group rekindled interest in DCD organs⁸ by showing equivalent long-term outcomes in recipients receiving both DCD and DBD renal transplants.⁹ DeVita highlighted that the University of Pittsburgh Medical Center (UPMC) introduced the nation's first institutional policy to permit and regulate DCD.¹⁰ The need for such a policy arose when several patients/families asked to participate in donation after previously electing withdrawal of life-sustaining treatment. This request fell outside the current parameters of donation policies and guidelines. The UPMC policy became the first concrete model to use cardiopulmonary criteria to determine death for organ procurement.¹¹ Moreover, this policy highlighted a milestone in the evolution of transplantation. Since then, DCD has been adopted by many OPOs and hospitals nationwide. By December 2006, OPTN bylaws required that all OPTN members have a DCD donor protocol in effect.¹¹ Moreover, The Joint Commission now requires that all accredited institutions develop and implement standardized DCD policies.¹²

After more than a decade of ongoing scrutiny surrounding ethical issues and outcome assessment, several key issues regarding DCD remain controversial in both the lay and medical communities. These include (1) criteria for identifying potential DCD donors, thus avoiding financial and emotional burden of "failed" DCD, (2) optimization of DCD donor management, and (3) standardization of DCD procurement protocols to ensure a successful multidisciplinary effort with reproducible results. These issues will be explored in this chapter after a brief discussion on the definition and current status of DCD.

IDENTIFICATION AND CATEGORIZATION OF POTENTIAL DONATION AFTER CARDIAC DEATH DONORS

Although seemingly straightforward, successful utilization of a DCD donor involves identification and classification of potential donors, appropriate diagnosis of death, compliance with local policy of

mandated wait time between death pronouncement and procurement, and familiarity with exclusion criteria for DCD.

The initial step in DCD organ transplantation is the recognition of potential donors with sufficient time to prepare and preserve optimal organ function before procurement. DCD is defined as organ procurement after the determination of death, which is characterized by an irreversible cessation of cardiopulmonary functions.¹³ Critical care physicians and OPO staff must be familiar with diagnoses and clinical circumstances that qualify a patient as a potential DCD donor. Candidates are patients in whom withdrawal of futile life-sustaining treatment is being planned. Because optimal preservation of organ function is facilitated by coordinated perimortem care, graft quality can be compromised in situations where a patient's wishes regarding organ donation are unknown or where DCD is not offered as an option until late. Organ suitability may decline while attempts are being made to educate staff and families. Moreover, a treating physician must ensure that for patients on life support, withdrawal of life support must be independent of the decision to donate organs. At present, an OPO is responsible for coordinating surgical recovery and for preserving and transporting organs and tissues.¹⁴ An OPO should be notified within 1 hour as soon as a patient's death is imminent from natural causes or withdrawal of life support.

The once popular practice of managing potential DCD donors by placing vascular and/or intraperitoneal catheters to infuse cold organ preservation solution before the availability of consent for procurement¹⁵ has now largely been abandoned. This practice stimulated contentious debate from both the medical and lay communities; moreover, unlike several European countries, no US state adopted this presumed consent into law.

Management of DCD donors is facilitated by a classification scheme developed by Maastricht group in 1994¹⁶ and revised in 2000.¹⁷ Maastricht categories define potential donors by circumstances under which cardiovascular death occurs. A distinction is made between donors whose cardiopulmonary failure is uncontrolled or emergent (categories 1, 2, 4, and 5) and those whose death according to cardiopulmonary criteria occurs in a controlled manner after withdrawing futile life-sustaining support (category 3). The revised Maastricht classification is outlined in Table 174-1. Recent initiatives in the northeast United States involve training prehospital personnel to rapidly converse with preconsented victims of unsuccessful resuscitation after cardiopulmonary arrest (category 2) to determine potential DCD donors.¹⁸ Category 3 donors constitute the majority of United States and European DCD donors.¹⁷ It is difficult to compare DCD outcomes according to Maastricht categories because few authors use this

classification when reporting DCD results. Therefore, for uniformity, the remainder of this chapter will focus on category 3 donors.

Category 3 standardization is outlined in Figure 174-1 (the UNOS Critical Pathway for DCD). Typical patients may have the following characteristics: absence of or hyperactive respiratory drive, lack of adequate respiratory muscle strength, and severe hypoxemia or inadequate circulation in the absence of treatment with inotropic or vasopressor drugs. These patients are usually supported using ventilators or mechanical circulatory assistance such as ventricular-assist devices (VAD) or intraaortic balloon pumps. These patients may have also experienced severe neurologic insults but may not have met brain death criteria. Conscious patients usually develop degenerative neuromuscular diseases or end-stage cardiopulmonary diseases and are often ventilator or VAD dependent. These patients or their families may decide to discontinue life-sustaining support and request their organs to be donated.

The other category of potential DCD donors includes patients with impending cardiopulmonary death, the timing of which is either predictable based on patient-/family-requested withdrawal of care or unpredictable because of premature cardiac arrest before withdrawal. Given the lack of perfusion in DCD donors, prompt identification of death is needed to minimize organ ischemia, especially if uncontrolled cardiac arrest occurs. Organ procurement from DCD donors under uncontrolled conditions is technically feasible but is not physiologically ideal because of the inherent ischemic insult.

Various modalities have been proposed to help physicians identify death based on the absence of cardiac sounds, pulse, respiration, and response to stimuli. Confirmatory tests such as intraarterial monitoring or Doppler studies recommended by the Institute of Medicine (IOM)¹⁹ can be used to expedite the confirmation of death; however, these tests are not widely accepted at present. A DCD work group assembled in 2006¹³ indicated that electrocardiographic silence was not required for determining death but was sufficient to show the absence of circulation.

However, there is no agreement on the observation time required to rule out spontaneous unassisted cardiopulmonary resuscitation or autoresuscitation. The DCD work group¹³ and the Society of Critical Care Medicine (SCCM)²⁰ recommend that potential donors should be observed for at least 2 minutes but not more than 5 minutes to ensure the absence of spontaneous circulation. These recommendations pertain to the period between the loss of circulation and declaration of death and not between the declaration of death and organ procurement. Fugate et al. identified variability among DCD protocols within the United States, particularly for defining the observation of potential donors to rule out autoresuscitation.²¹ Although most centers followed the 2-to-5-minute observation period, there was variability in the definition of the period starting either before or after declaration of death, thus implying a total of 10 minutes. A prospective study by Dhanani et al. on the timing of determination of death in DCD donors showed that the longest period of arterial blood pressure (BP) resumption after declaration of death was 89 seconds.²² Moreover, only 4 of 41 patients examined showed return of BP after cessation; however, this only lasted between 1 and 172 seconds. Given the variability and limited data on the duration of observation, specific guidelines for the precise minimal duration of irreversible circulation are warranted. At present, local protocols are used to stipulate the requirements of the determination of death and duration of observation time before organ procurement.

An important part of identifying potential DCD donors includes predicting the occurrence of rapid physiologic deterioration and death in less than 30 to 60 minutes (depending on the organ to be procured) after withdrawing life-sustaining treatment.¹³ Failure of a potential donor to progress to cardiac death within the prescribed time disqualifies the donor because of the extent of organ WIT. Factors such as age, comorbidities, and preterminal vasopressor requirement can be used as predictors; however, no strict criteria have been universally adopted.²³ Lewis et al. from the University of Wisconsin developed a tool that uses clinical parameters to predict the suitability of DCD candidates.²⁴ This

TABLE 174-1

Maastricht Donation After Cardiac Death Categories^{16,17}

| CATEGORY | DESCRIPTION | CONDITION |
|----------|---|--------------|
| 1 | Cardiac arrest outside hospital and no resuscitation attempted | Uncontrolled |
| 2 | Cardiac arrest followed by unsuccessful resuscitation either inside or outside hospital | Uncontrolled |
| 3 | Cardiac arrest after planned withdrawal of life support | Controlled |
| 4 | Cardiac arrest in a brain-dead patient awaiting organ procurement | Uncontrolled |
| 5* | Unexpected cardiac arrest in an intensive care unit | Uncontrolled |

From Koostra G, Daemen JHC, Oomen APA. Categories of non-heart-beating donors. *Transplant Proc* 1995;27:2893-4.

*From Sánchez-Fructuoso AI, Prats D, Torrente J, et al. Renal transplantation from non-heart-beating donors: a promising alternative to enlarge the donor pool. *J Am Soc Nephrol* 2000;11:350.

Critical Pathway for

Donation After Cardiac Death (DCD)

Patient Name _____

UNOS ID Number _____

| Collaborative Practice | Phase I Identification & Referral | Phase II Preliminary Evaluation | Phase III Family Discussion & Consent | Phase IV Comprehensive Evaluation & Donor Management | Phase V Withdrawal of Support /Pronouncement of Death/Organ Recovery |
|--|--|---|--|---|---|
| <p>The following health care professionals may be involved in the DCD donation process:</p> <p>Check all that apply:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Physician (MD) <input type="checkbox"/> Critical Care RN <input type="checkbox"/> Nurse Supervisor <input type="checkbox"/> Medical Examiner / Coroner <input type="checkbox"/> Respiratory Therapy (RT) <input type="checkbox"/> Laboratory <input type="checkbox"/> Pharmacy <input type="checkbox"/> Radiology <input type="checkbox"/> Anesthesiology <input type="checkbox"/> OR/Surgery Staff <input type="checkbox"/> Clergy <input type="checkbox"/> Social Worker <p><input type="checkbox"/> Organ Procurement Coordinator (OPC)</p> <p><input type="checkbox"/> Organ Procurement Organization (OPO)</p> | <p>Prior to withdrawing life support, contact local OPO for any patient who fulfills the following criteria:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Devastating neurologic injury and/or other organ failure requiring mechanical ventilatory or circulatory support <input type="checkbox"/> Family and/or care giving team initiate conversation about withdrawal of support <p>Following referral, additional evaluation is done collaboratively to determine if death is likely to occur within one hour (or within a specified timeframe as determined by caregiving team and OPO) following withdrawal of support</p> <p>Patient conditions might include the following:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Ventilator dependent for respiratory insufficiency: apneic or severe hypopneic; tachypnea ≥ 30 breaths/min after DC ventilator <input type="checkbox"/> Dependent on mechanical circulatory support (LVAD; RVAD; V-A ECMO; Pacemaker with unassisted rhythm < 30 beats per minute. <input type="checkbox"/> Severe disruption in oxygenation: PEEP ≥ 10 and $\text{SaO}_2 \leq 92\%$; $\text{FiO}_2 \geq .50$ and $\text{SaO}_2 \leq 92\%$; V-V ECMO requirement <input type="checkbox"/> Dependent upon pharmacologic circulatory assist: Norepinephrine, epinephrine, or phenylephrine ≥ 0.2 ug/kg/min; Dopamine ≥ 15 ug/kg/min <input type="checkbox"/> IABP and inotropic support: IABP 1:1 and dobutamine or dopamine ≥ 10 ug/kg/min and $\text{CI} \leq 2.2$ L/min/m²; IABP 1:1 & $\text{CI} \leq 1.5$ L/min/m² | <p>Physician</p> <ul style="list-style-type: none"> <input type="checkbox"/> Supportive of withdrawal of care and has communicated grave prognosis to family <input type="checkbox"/> Review DCD procedure with OPC <input type="checkbox"/> Will be involved in withdrawal/pronouncement <input type="checkbox"/> Will designate a person to be involved with withdrawal and/or pronouncement <p>Family</p> <ul style="list-style-type: none"> <input type="checkbox"/> Has received grave prognosis <input type="checkbox"/> Understands prognosis <input type="checkbox"/> In conjunction with care giving team, decide to withdraw support <p>Patient</p> <ul style="list-style-type: none"> <input type="checkbox"/> Age _____ <input type="checkbox"/> Weight _____ <input type="checkbox"/> Height _____ <input type="checkbox"/> ABO _____ <input type="checkbox"/> Medical Hx _____ <input type="checkbox"/> Surgical Hx _____ <input type="checkbox"/> Social Hx _____ <input type="checkbox"/> Death likely < 1 hour following withdrawal (determined collaboratively by evaluating: injury, level of support, respiratory drive assessment) | <ul style="list-style-type: none"> <input type="checkbox"/> Support services offered to family <input type="checkbox"/> OPC/Hospital Staff approach family about donation options <input type="checkbox"/> Legal next-of-kin (NOK) fully informed of donation options and recovery procedures <input type="checkbox"/> Legal NOK grants consent for DCD following withdrawal of support <input type="checkbox"/> Family offered opportunity to be present during withdrawal of support <input type="checkbox"/> OPC obtains _____ Witnessed consent from legal NOK for DCD _____ Signed consent Time _____ Date _____ Detailed med/soc history <p>Notification of donation</p> <ul style="list-style-type: none"> <input type="checkbox"/> Hospital supervisor <input type="checkbox"/> ME/Coroner notified _____ ME/Coroner & releases for donation _____ ME/Coroner has restrictions <p>Stop Pathway if –</p> <ul style="list-style-type: none"> <input type="checkbox"/> Family, ME/Coroner denies consent <input type="checkbox"/> Patient determined to be unsuitable candidate for DCD <input type="checkbox"/> Patient progresses to brain death during evaluation – refer to brain dead pathway | <ul style="list-style-type: none"> <input type="checkbox"/> MD, in collaboration with OPO, implements management guidelines. <input type="checkbox"/> Establish location and time of withdrawal of support <input type="checkbox"/> Review plan for withdrawal to include: <ul style="list-style-type: none"> - Pronouncing MD (should be in attendance for duration of withdrawal of support, determination of death, and may not be a member of the transplant team) - Comfort Care - Extubation and discontinuation of ventilator support - Establish plan for continued supportive care if pt survives > 1 hour or predetermined time interval after withdrawal of support <input type="checkbox"/> Notify OR/Anesthesia _____ Review patient's clinical course, withdrawal plan and potential organ recovery procedures _____ Schedule OR Time _____ <input type="checkbox"/> Notify recovery teams <input type="checkbox"/> Prepare patient for transport to prearranged area for withdrawal of support <input type="checkbox"/> Patient transported to prearranged area <input type="checkbox"/> Note: Should the clinical situation require pre-mortem femoral cannulation, the following should be reviewed: <ul style="list-style-type: none"> - family consent or understanding - MD inserting cannula | <ul style="list-style-type: none"> <input type="checkbox"/> Withdrawal occurs in _____ OR _____ ICU _____ Other _____ <input type="checkbox"/> Family present for withdrawal of support _____ yes _____ no <input type="checkbox"/> OR/Room prepared and equipment set up <input type="checkbox"/> Transplant team in the OR (not in attendance during withdrawal) <input type="checkbox"/> Care giving team present <input type="checkbox"/> Administration of pre-approved medication (e.g. Heparin/Regitine) <input type="checkbox"/> Withdrawal of support according to hospital/MD practice guidelines Time _____ Date _____ <input type="checkbox"/> Vital signs are monitored and recorded every minute (See attached sheet) <input type="checkbox"/> Pt pronounced dead and appropriate documentation completed Time _____ Date _____ MD _____ <input type="checkbox"/> Transplant Team initiates surgical recovery at prescribed time following pronouncement of death <input type="checkbox"/> Allocation of organs per OPTN/UNOS policy <input type="checkbox"/> If cardiac death not established within 1 hour or predetermined time interval after withdrawal of support – Stop Pathway. Patient moved to predetermined area for continuation of supportive care. <input type="checkbox"/> Post mortem care administered |

FIGURE 174-1 ■ UNOS Donation after Cardiac Death Critical Pathway⁵

| | | | | | |
|----------------------------------|---|---|--|--|---|
| | | | | <ul style="list-style-type: none"> - Time and location of cannula insertion - If death does not occur, determine if cannula should be removed | |
| Labs / Diagnostics | | <ul style="list-style-type: none"> ○ ABO ○ Electrolytes ○ LFTs ○ PT/PTT ○ CBC with Diff ○ Beta HCG (female pts) ○ ABG | | Repeat full panel of labs additionally: <ul style="list-style-type: none"> ○ Serology Testing infectious disease profile ○ Blood cultures X 2 ○ UA & Urine culture ○ Sputum Culture ○ Tissue typing | |
| Respiratory | <ul style="list-style-type: none"> ○ Maintain ventilator support ○ Pulmonary toilet PRN | <ul style="list-style-type: none"> ○ Respiratory drive assessment RR _____ VT _____ VE _____ NIF _____ Minutes off ventilator _____ ○ Hemodynamics while off ventilator HR _____ BP _____ SaO₂ _____ | <ul style="list-style-type: none"> ○ ABGs as requested ○ Notify RT of location and time of withdrawal of support | <ul style="list-style-type: none"> ○ Transport with mechanical ventilation using lowest FiO₂ possible while maintaining the SaO₂ >90% | |
| Treatments / Ongoing Care | Maintain standard nursing care to include: <ul style="list-style-type: none"> ○ Vital signs q 1 hour ○ I & O q 1 hour | | | | <ul style="list-style-type: none"> ○ Post mortem care at conclusion of case |
| Medications | | | | <ul style="list-style-type: none"> ○ Provide medications as directed by MD in consult with OPC | <ul style="list-style-type: none"> ○ Heparin and other medications prior to withdrawal of support |
| Optimal Outcomes | The potential DCD donor is identified & a referral is made to the OPO. | The donor is evaluated & found to be a suitable candidate for donation. | The family is offered the option of donation & their decision is supported. | Optimal organ function is maintained, withdrawal of support plan is established, and personnel prepared for potential organ recovery. | Death occurs within one hour of withdrawal of support and all suitable organs and tissues are recovered for transplant. |

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FIGURE 174-1, cont'd

resulted in the development of guidelines to predict the likelihood of circulatory death within 2 hours after withdrawing life support. Kaufman et al. proposed four readily obtainable clinical criteria: (1) requirement for vasopressors to support BP, (2) absence of primary brain injury, (3) history of mechanical ventilation for ≥ 6 days, and (4) respiratory rate of less than 20 breaths/minute (in the absence of mechanical ventilation).²⁵ They noted that presence of two or more of these indicators accurately predicted death within 60 minutes after withdrawing life-supporting treatments, with a sensitivity and specificity of 81% and 78%, respectively. Robust analysis of retrospective DCD data would enable intensivists and OPO staff to precisely identify potential DCD donors, help minimize financial impact on and resource drain from hospitals and donors that “fail to progress,” and prevent unnecessary stress and disappointment for families during a psychologically vulnerable time.

Familiarity with relative and absolute contraindications for DCD, some of which overlap those associated with DBD, is important. These include multiple-operated abdomen, active sepsis, active or recent

extracranial primary malignancy, and active hepatitis B infection. With regard to virologic status, OPOs are well versed in performing rapid serologic testing to rule out latent viral infections and should be involved as early as feasible to initiate testing.

CURRENT STATUS OF DONATION AFTER CARDIAC DEATH

Volume

UNOS disseminates US transplant-related data and has reported DCD statistics since 1994.⁵ Data are available on the UNOS website (www.unos.org) and in UNOS annual reports. The annual number of DCD donors increased steadily from the mid-1990s to the early 21st century (Table 174-2). In all, 42 DCD recoveries were performed in 1993, which represented <1% of the total recoveries in that year. In 2012, DCD recoveries showed a 12-fold increase of 12% of all organ procurements.⁵

TABLE 174-2

Number of Donation After Cardiac Death Organs as a Percentage of Total Deceased Donor Organs Procured by Year⁵

| YEAR | # DECEASED DONORS | # DCD DONORS | DCD AS A PERCENTAGE OF TOTAL DONORS |
|------|-------------------|--------------|-------------------------------------|
| 1993 | 4861 | 42 | 0.86 |
| 1995 | 5362 | 64 | 1.20 |
| 1997 | 5478 | 78 | 1.43 |
| 1999 | 5825 | 87 | 1.49 |
| 2000 | 5985 | 104 | 1.74 |
| 2001 | 6080 | 169 | 2.77 |
| 2002 | 6190 | 156 | 2.52 |
| 2003 | 6456 | 268 | 4.15 |
| 2004 | 7150 | 319 | 4.46 |
| 2005 | 7593 | 556 | 7.32 |
| 2006 | 8019 | 538 | 6.71 |
| 2007 | 8086 | 793 | 9.80 |
| 2008 | 7990 | 728 | 9.11 |
| 2009 | 8022 | 803 | 10.01 |
| 2010 | 7943 | 831 | 10.46 |
| 2011 | 8125 | 956 | 11.77 |
| 2012 | 8144 | 993 | 12.19 |

DCD, Donations after cardiac death.

Outcomes

Despite ethical controversies, the real barrier to the widespread acceptance of DCD graft utilization is the poor outcome observed in early DCD experiences. Suboptimal organ function characterized by primary nonfunction, delayed graft function (DGF), and/or abbreviated graft survival have traditionally threatened the success of DCD organs because of warm ischemic insult associated with cardiopulmonary arrest.¹⁰ Although these observations were valid at that time, they accumulated during early experiences with transplantation and were thus inherently confounded by era bias.

On a cellular level, DBD and DCD organs show different injury profiles. DBD is characterized by a surge in serum catecholamines because of brain death, which induces hypotension and subsequent organ hypoperfusion. Animal studies have shown that hemodynamic instability of DBD organs may be further exacerbated by inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and IL-8 that directly affect renal grafts.²⁶ In vivo studies evaluating DCD kidney grafts have shown less upregulation of inflammatory markers²⁷ relative to that in DBD grafts; however, these studies showed that prolonged WIT induced alternative pathways of injury, primarily those related to hypoxia. Rosenberger et al. found that hypoxia-inducible factors were correlated with renal allograft ischemia time.²⁸ These results suggested that increased incidence of DGF with DCD grafts was associated with a hypoxia-specific (and in some cases potentially reversible) injury. The primary lesson from the early DCD era was that the metabolically active renal cortex, biliary epithelium, pulmonary alveoli, and pancreatic islets were sensitive to ischemia, with warm ischemic injury manifesting as acute tubular necrosis, ischemic-type biliary strictures (ITBS), pulmonary fibrosis, and impaired β -cell function, respectively, and that these manifestations were postulated to translate into and account for both poor initial graft function and long-term complications.^{29,30,31} However, contemporary outcomes for each organ have improved.

Kidneys

Recent data have shown equivalent outcomes for DCD vs. DBD grafts. Droupy et al. reported improved outcomes and showed that

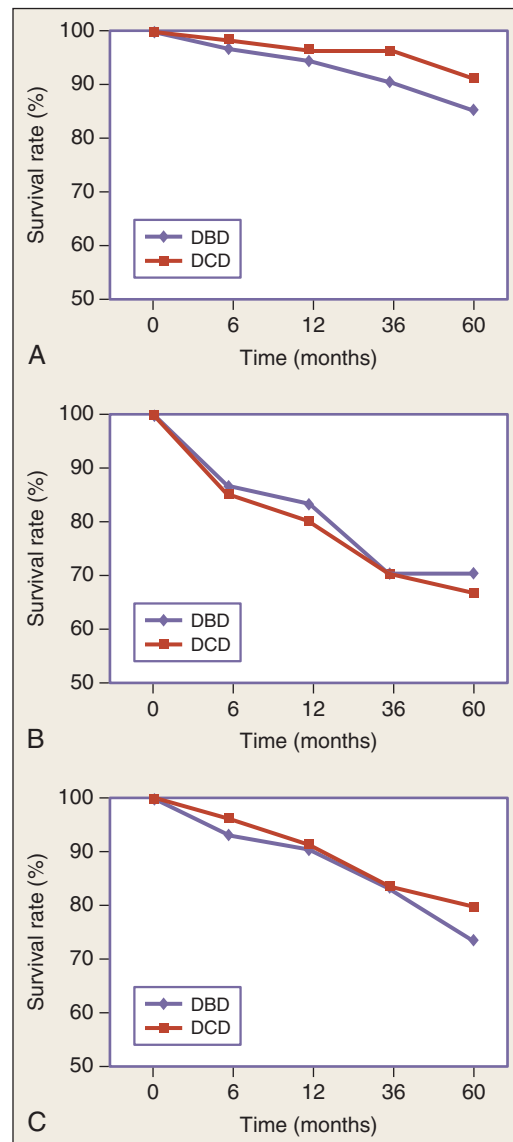


FIGURE 174-2 ■ (A) Ten-year graft survival after kidney transplant (donation after brain death vs. donation after cardiac death).³³ (B) Current outcomes after donation after cardiac death simultaneous pancreas-kidney transplant.³³ (C) Current outcomes after donation after cardiac death pancreas transplant.³³

intermediate- and long-term patient and graft survival in recipients of controlled DCD kidney grafts was equivalent or comparable to that of DBD.³² In addition, Droupy et al. reported that DCD and DBD renal grafts examined for 10 years showed equivalent survival despite higher initial incidence of DGF in the DCD cohort. Salvaggio et al. analyzed UNOS/OPTN data and showed similar results³³ (Fig. 174-2A). More recently, Summers et al. evaluated UK registry data and found no statistically significant difference in 5-year kidney graft survival in DCD vs. DBD recipients ($P = 0.97$).³⁴ Factors affecting graft function include donors' age of >60 years (compared to donors' age of <40 years) and prolonged cold ischemia time (CIT; >24 vs. <12 hours). These factors are associated with decreased survival of DCD and DBD grafts.³⁵ It is likely that the DGF rate among recipients of the two types of grafts is narrowed by the use of the pulsatile perfusion pump. Perfusion pumps, which are often used successfully with both standard and extended-criteria deceased donor kidney grafts, are increasingly being used with DCD kidney grafts. Lodhi et al. reported a decreased risk of

DGF associated with pulsatile perfusion compared to cold storage in recipients of DCD kidney grafts, which was similar to that observed in recipients of DBD kidney grafts.³⁶ A meta-analysis by Bathini et al. on the use of cold perfusion pumps suggested a trend of 1-year graft survival; however, the overall differences were not significant.³⁷ Other strategies to maximize graft function and minimize injury after transplanting DCD grafts include ex situ perfusion (ESP) and normothermic regional perfusion (NRP). NRP leverages the circulation of warm, oxygenated blood to reduce kidney injury. Valero et al. found that NRP considerably reduced PGNF and DGF³⁸; however, these findings should be confirmed by performing randomized clinical studies.

Pancreas

Much of the available outcome data on the transplantation of DCD pancreatic grafts are derived from cases of simultaneous pancreas-kidney (SPK) transplants. These data show that graft and patient survival rates in recipients of DCD pancreatic grafts are similar to those in recipients of DBD pancreatic grafts³³ (Fig. 174-2B). Transplantation of DCD pancreas alone grafts by using the same protocols as those used for DCD SPK grafts has provided favorable results³³ (Fig. 174-2C). Siskind et al. analyzed UNOS data from 1996 to 2012 and found no statistically significant differences in graft and patient survival rates at 1, 3, 10, and 15 years in recipients of DCD and DBD pancreatic grafts.³⁹

Liver

Early studies on recipients of DCD liver grafts have provided mixed results, with both graft and patient survival rates being significantly lower compared with those in recipients of DBD liver grafts.⁴⁰ In addition, these studies reported higher recipient morbidity and mortality rates.^{41,42} However, recent studies on the transplantation of DCD liver grafts have shown improved outcomes. Abt et al. reported intermediate- and long-term patient and graft survival in recipients of DCD liver grafts; however, this was less significant compared with that in recipients of other DCD grafts.⁴³ They also showed that 1- and 3-year patient survival rates of recipients of DCD liver grafts were similar to those of recipients of DBD liver grafts; however, graft survival rates of DCD liver grafts were lower.⁴³ (Table 174-3). Dubbeld et al. showed no statistically significant differences in 1- and 3-year patient and graft survival rates among recipients of DCD and DBD liver grafts when selected for donor age, serum transaminase levels, length of intensive care unit (ICU) stay, and vasopressor use. However, transplantation of DCD grafts was a risk factor for ITBS compared with that of DBD grafts ($P < 0.001$).⁴⁴ Moreover, survival of DCD liver grafts was more sensitive to WIT, thus justifying the procurement limit of 25-30 minutes after circulatory arrest (compared with up to 60 minutes for renal grafts). However, further studies should be performed to identify protocols for maximizing the quality of DCD liver grafts.

Lungs

Rapidly increasing utilization of DCD lung grafts, with improved outcomes, has encouraged clinicians to consider using these previously declined grafts.⁴⁵ Registry data from the Internal Society for Heart and

Lung Transplantation showed a 30-day mortality rate of <3% and 1-year survival rate of 89% that were not statistically different compared with those observed with DBD grafts.⁴⁶ Additional data from the United Kingdom Steering group for DCD lung transplants showed equivalent 1-year survival outcomes for DCD and DBD grafts ($P = 0.9$).⁴⁷ One evolving strategy for maximizing DCD graft function is ESP or extracorporeal perfusion that has been primarily studied in lung grafts, with some preliminary data on DCD grafts. ESP allows the assessment of graft through reassessment after the resolution of edema, via the evaluation of biochemical markers. Cypel et al. reported similar results for primary graft dysfunction, 30-day mortality, and 1-year survival with ESP compared to those with control lung grafts.⁴⁸ In all, 22 of 50 lung transplants were DCD grafts. This safe technique can help better identify the viability of DCD grafts and can improve transplantation outcomes.

Heart

Data describing DCD cardiac transplantation are scarce. To date, only five children have been documented to have received DCD grafts since 1996.⁵ Outcomes are inconclusive because of the limited number of recipients. DCD heart grafts are difficult to use because of unavoidable WIT. Nevertheless, DCD cardiac transplantation is technically feasible. The first human cardiac transplant, which was performed 40 years previously, was made possible by using a DCD heart that functioned well after a single electric shock.⁴⁹ A new era of DCD cardiac transplantation may begin with the advent of preconditioning therapy.

Because of the aforementioned OPTN and Joint Commission mandates, the number of OPOs facilitating DCD organ recoveries in a given year is increasing. In the last year reported, 56 of 58 OPOs facilitated at least one DCD organ procurement.⁵ The majority of DCD organs were kidneys (1593).⁵ The net effect of the current practice and improved outcomes has been to shift the paradigm of the binary cadaveric donor (DBD vs. DCD) to a spectrum of standard-to-extended criteria, with a DCD donor potentially falling along one of many points on that spectrum based on specific factors. The presence of distinct extended criteria factors in either a DBD or DCD graft may confer a higher risk of graft failure than an optimal DCD. The next logical question is whether increased volume of DCD procurements has affected transplant volumes and recipient outcomes or whether widespread adoption of DCD has shifted would-be DBD donors to DCD status without increasing transplant volume. This will be addressed in the final segment of this chapter.

PRINCIPLES OF DONATION AFTER CARDIAC DEATH DONOR MANAGEMENT

Because every organ from a DCD donor sustains some degree of unavoidable ischemic damage, several protective strategies to increase graft viability have been proposed. Interventions can be considered in premortem or intraoperative phases.

Premortem

1. Placement of large-bore arterial and venous catheters for perfusing cold preservation solution.¹⁴
2. Administration of systemic anticoagulants such as heparin (30,000 units) along with recombinant tissue plasminogen activator (50 mg)⁵⁰ or streptokinase⁵¹ to prevent vascular thrombosis during low flow state.
3. Administration of vasodilators such as phentolamine, chlorpromazine, or trifluoperazine to prevent agonal vasospasm induced by hypoxia and surging catecholamine levels.^{52,53}
4. Ischemic preconditioning: Brief preinsult ischemic challenges trigger protective mechanisms that allow compensatory tissue physiology at the time of cardiac arrest, which is suggested to be mediated by heat shock proteins.^{54,55} This effect has already been observed with phenylephrine in an animal model of non-heart-beating cardiac transplant.⁵⁶

TABLE 174-3

One- and Three-Year Outcomes of Donation After Cardiac Death and Donation After Brain Death Liver Transplantation⁴³

| TYPE OF GRAFT | YEAR AFTER TRANSPLANTATION | GRAFT SURVIVAL | PATIENT SURVIVAL |
|---------------|----------------------------|----------------|------------------|
| DCD | 1 | 70.2% | 79.7% |
| | 3 | 63.3% | 72.1% |
| DBD | 1 | 80.4% | 85% |
| | 3 | 72.1% | 77.4% |

DBD, Donation after brain death; DCD, donation after cardiac death.



SOP Form # PO47-F3
 Effective Date JUN 23 2009
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 Rev # 006

DONATION AFTER CARDIAC DEATH (DCD) DONOR DATA FORM

| | | | | | |
|--|-------------|--|---------------------|------------------------------------|--|
| Date: _____ | | UNOS ID: _____ | | LifeGift ID: _____ | |
| Enter OR | Time: _____ | Cross-Clamp | Time: _____ | | |
| Withdrawal of Support | Time: _____ | Cannulation, abdominal aorta | Time: _____ | Flush start/stop time: _____/_____ | |
| Mannitol/Heparin Admin | Time: _____ | Cannulation, thoracic aorta | Time: _____ | Flush start/stop time: _____/_____ | |
| Pronouncement | Time: _____ | Cannulation, portal vein | Time: _____ | Flush start/stop time: _____/_____ | |
| Incision | Time: _____ | Cannulation, pulmonary artery | Time: _____ | Flush start/stop time: _____/_____ | |
| Time from withdraw to Pronouncement _____ minutes | | Family present for withdrawal: <input type="checkbox"/> Yes <input type="checkbox"/> No | | | |
| Time from pronouncement to Cross-Clamp _____ minutes | | Location of withdrawal: <input type="checkbox"/> OR <input type="checkbox"/> ICU <input type="checkbox"/> Other: _____ | | | |
| Total Warm Ischemic Time (withdraw to cross-clamp) _____ minutes | | Care and Comfort Administered by Hospital Staff: <input type="checkbox"/> Yes <input type="checkbox"/> No | | | |
| Start Time: _____ | | | Urine output: _____ | | |

| | Min 1 | Min 2 | Min 3 | Min 4 | Min 5 | Min 6 | Min 7 | Min 8 | Min 9 | Min 10 | Min 11 | Min 12 | Min 13 | Min 14 | Min 15 | Min 16 | Min 17 | Min 18 | Min 19 | Min 20 |
|----------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| BP | | | | | | | | | | | | | | | | | | | | |
| MAP | | | | | | | | | | | | | | | | | | | | |
| HR | | | | | | | | | | | | | | | | | | | | |
| RR | | | | | | | | | | | | | | | | | | | | |
| O2SAT | | | | | | | | | | | | | | | | | | | | |
| Initials | | | | | | | | | | | | | | | | | | | | |
| | Min 21 | Min 22 | Min 23 | Min 24 | Min 25 | Min 26 | Min 27 | Min 28 | Min 29 | Min 30 | Min 31 | Min 32 | Min 33 | Min 34 | Min 35 | Min 36 | Min 37 | Min 38 | Min 39 | Min 40 |
| BP | | | | | | | | | | | | | | | | | | | | |
| MAP | | | | | | | | | | | | | | | | | | | | |
| HR | | | | | | | | | | | | | | | | | | | | |
| RR | | | | | | | | | | | | | | | | | | | | |
| O2SAT | | | | | | | | | | | | | | | | | | | | |
| Initials | | | | | | | | | | | | | | | | | | | | |
| | Min 41 | Min 42 | Min 43 | Min 44 | Min 45 | Min 46 | Min 47 | Min 48 | Min 49 | Min 50 | Min 51 | Min 52 | Min 53 | Min 54 | Min 55 | Min 56 | Min 57 | Min 58 | Min 59 | Min 60 |
| BP | | | | | | | | | | | | | | | | | | | | |
| MAP | | | | | | | | | | | | | | | | | | | | |
| HR | | | | | | | | | | | | | | | | | | | | |
| RR | | | | | | | | | | | | | | | | | | | | |
| O2SAT | | | | | | | | | | | | | | | | | | | | |
| Initials | | | | | | | | | | | | | | | | | | | | |

FIGURE 174-3 ■ Donation after cardiac death monitoring form.

However, use of these premortem measures is limited because they are not a part of standard end-of-life care and because some authors suggest that these measures potentially hasten death.⁵⁷ The SCCM and IOM indicate that these medications and devices can be used as long as they do not cause any significant harm to the patient^{58,59} and as long as family consent is obtained wherever practical. That they are of no direct benefit to the patient is countered by the fact that they improve the likelihood that the patient's wish of organ donation will ultimately be realized.

Operative

The conduct of operative procedure is dictated by the tenets mentioned above. The procurement team is not physically present at the time of death, and recovery of organs is accomplished expeditiously with careful coordination of numerous personnel, equipment, and resources. To do so, the operative team prepares and drapes the patient upon arrival to the operating room (OR). The team outlines the necessary

instruments and maneuvers requested by OPO staff to ensure a seamless procedure. The team is then escorted from the OR and is notified by the OPO staff if the patient is pronounced within the prescribed time frame. After withdrawal life support and before incision, the OPO staff will complete a monitoring form (Fig. 174-3) that details minute-by-minute hemodynamic and oxygenation data.

Once the patient has been pronounced, the operative team returns gowned and gloved and infuses cold perfusate through a cannula or a standard terminal aortic cannula placed during the premortem phase after rapidly accessing the abdomen. Next, rapid but careful in situ cold dissection is performed because the potential for vascular injury increases without the benefit of pulsatile flow to assist the identification of aberrant anatomy. Finally, organs are packaged and implanted in the recipient as soon as possible to mitigate the added negative impact of CIT.

The two most common contingencies that the team must be prepared for are unexpected cardiac arrest while awaiting withdrawal of life support and failure to progress after withdrawal. Appropriate

intravenous access, a ventilator, and a special supply cart must be available and stocked with an oxygen tank, cardiac monitor, and adequate supply of sedatives and narcotics. The patient's wishes regarding resuscitation leading to donation must be determined from the patient or his or her family as early as possible.

DETERMINATION OF DEATH: THE EXACT SCIENTIFIC CONCEPT?

The 1980 Uniform Determination of Death Act (UDDA) established that death is determined when there is irreversible cessation of circulatory and respiratory functions.⁶⁰ Most often, death is declared based on the cessation of cardiac and pulmonary functions; however, required asystolic time is perhaps the single most contentious issue in the debate surrounding DCD.^{61,62} In simple words, the longer you wait, the more uncertainty there is about organs, and the shorter you wait, the more uncertainty there is on whether the person is dead.⁶³

As the limits of life-sustaining practices are expanded, medical professionals are encouraged to maintain focus with reference to the UDDA. The term *irreversible* can be interpreted as a shifting paradigm or as per Wilner, a concept that is subject to serial displacement by advancing clinical science. Wilner further highlighted that the question of death is thus reformulated to explore whether the morally relevant time of death is reached when death is certain despite the administration of all possible medical interventions or whether death is assured once all ethically permissible remedies have been utilized.⁶ Although consensus is yet to be reached on the time at which death is irreversible, it is logical that once a principled decision is made not to correct a loss of function, the loss becomes irreversible.⁶⁴

No investigator has documented autoresuscitation after >89 seconds of combined circulatory and respiratory arrest.^{22,65} However, the standard applied by most US hospitals ranges from 2- to 5-minute asystolic interval (pulselessness, apnea, and unresponsiveness). This broad standard is addressed by SCCM's statement that "there is no ethically or physiologically important distinction between the two minute observation period utilized by the University of Pittsburgh, the 5 minutes recommended by the IOM, and the 10 minutes."⁶⁶ Ostensibly, the standard does satisfy proponents of the waning possibility of autoresuscitation after 89 seconds of asystole and addresses ethical concerns raised by these proponents. Because of the paucity of empiric evidence, IOM

continues to encourage investigators to perform additional studies on this matter.

A final logistic issue in the determination of death is the management of patients who progress very slowly to be considered for donation. This occurs in approximately 5% to 10% potential donors.²³ Most programs disqualify donors from solid organ donation if cardiac activity is noted 60 minutes after withdrawal of life support because these donors do not meet the criteria for death because their organs would have sustained excessive warm ischemic injury.⁶⁷ Therefore, contingency plans should be devised so that these patients receive appropriate end-of-life care.

FINAL CONSIDERATIONS

Despite the success of DCD kidney, liver, and pancreatic grafts, several unmet challenges and questions remain regarding the transplantation of these grafts. These fall within the realms of medical and ethical concerns.

One area of likely future research concerns the real numeric advantage of using DCD grafts. Although the number of DCD grafts used in the United States has significantly increased, the overall number of transplants has not increased accordingly⁵ (Fig. 174-4). It is unclear as to what increase (if any) in available donor organs can be expected by promoting the utilization of DCD organs. Moreover, it is unclear whether the identification of DCD donors will convert would-be DBD donors to DCD donors. In addition, it is unclear whether the decrease in the number of wait-list deaths and the gap will shift the cost and burden from wait-list complications to posttransplant complications, with longer lengths of stay, increased readmissions, increased complexity of diagnostic evaluations and immunosuppressive drug regimens, and increased rate of recipient morbidity and mortality. These questions can be better answered once homogeneous, prospective data are collated.

One controversial topic involves the evaluation of pediatric patients. Koogler et al. reported that 28% of pediatric patients could qualify as DCD donors after withdrawing life support.⁶⁸ The authors estimated a 42% increase in organ donation if these patients were evaluated for DCD instead of only DBD. However, because a potential pediatric donor is physiologically extremely resilient, no tools are available at present to predict the likelihood of DCD in this patient population compared with that in the adult population.

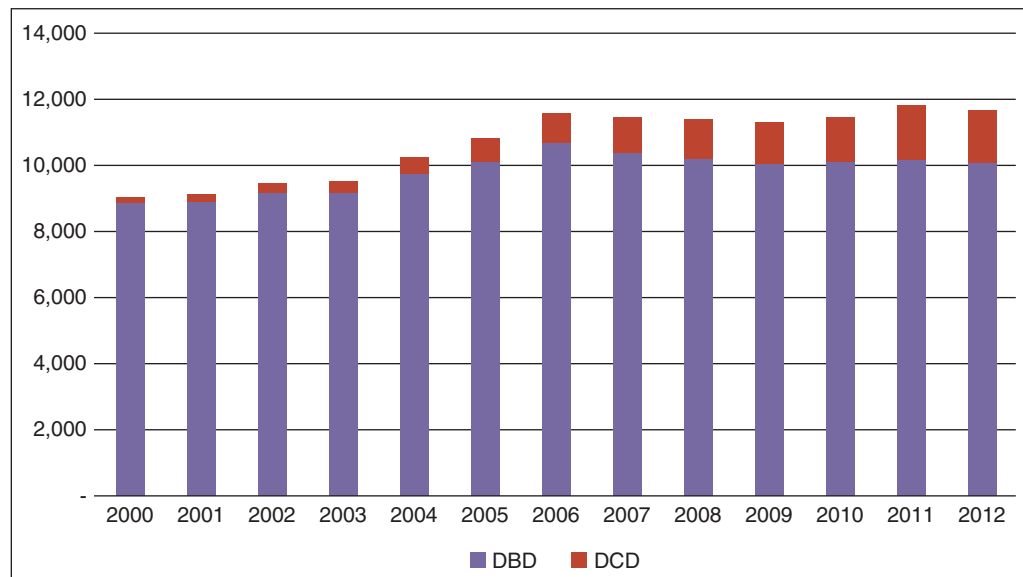


FIGURE 174-4 ■ Total number of transplants in the United States performed using donation after brain death and donation after cardiac death grafts.

Furthermore, it is unclear how DCD will ethically affect the public's trust in the health care system and organ procurement and transplantation. On the recipient end, it is unclear whether the differential results associated with DBD versus DCD transplantation will mandate that a recipient be allowed to decline an organ donation based on the knowledge of physicians' concerns regarding the DCD process. As noted by the UPMC group and IOM, an emphasis on patients' and families' wishes is paramount for the success of any DCD program. The public will be guided by medical information. However, the practice of transplantation, which is donor driven, will be guided in a way that information is buttressed by open communication with the lay public.

Last, the concern of the lay public is that physicians caring for patients who are potential donors have shifted the focus of care from the dying patient and that there exists a latitude to violate the "dead donor rule" (comprising two complementary ideas: (1) the patient must be dead before organ procurement and (2) organ procurement must not be the cause of donor's death).⁶⁴ This concern in the public's mind may translate into fear that their likelihood of receiving aggressive life support will be compromised by consenting for organ donation. These misperceptions are particularly damaging when the overriding goal of the transplant community is to maintain and build public support of maximizing organ donation.

CONCLUSION

An Opportunity for Standardization

Appropriate management of DCD donors requires the integration of several fundamental principles for protecting the rights and interests of donors and for preventing the care of DCD organs from superseding the care of the dying patient. Debate arises in the paradox that can emerge from attempts to protect those interests while preserving the suitability of potential grafts. Hence, the role of an intensivist and/or palliative care physician (terminal care of patients and pronouncement of death) and managing OPO must be rigidly defined; the two factions must travel distinct paths to achieve their shared ultimate goal. Ozark summarizes this by stating "as a general rule two discussions—whether to forego life-sustaining therapy and whether to donate organs—must be made separately and on their own individual merit."⁶⁹ Ideally, discussion regarding the withdrawal of life-sustaining treatment should come first to prevent bias by the issue of transplantation.

The push for optimal palliative care is the hallmark of recent critical care management initiatives.^{21,70} Dying patients who also wish to be DCD donors present a special challenge because they require care that is not only comparable to that given to all dying patients but also sensitive to the concerns described above. The SCCM has offered recommendations specific to DCD.^{66,71} These guidelines supplemented by individual transplant center reports and UNOS pathway (Fig. 174-1) provide direction for intensivists caring for patients who wish to become DCD donors. It is vital that all health care providers involved in this process be comfortable with, and knowledgeable about, their specific role so that the patient's wishes can be respected.

Because pain relief is the single most important goal in palliative care in the final hours of life, there is a firm ethical, legal, and medical justification for using analgesics and anxiolytics in this scenario. Because some patients require higher doses than others, doses are given with the knowledge that unintended effects such as hypotension or respiratory depression may compromise organ viability. Therefore, it is critical that the interest of the dying patient is represented by a completely different entity than that responsible for representing the interests of the donor. If any question arises regarding the practitioner's ability to maintain an objective position, consultation from hospitals' palliative care and ethics teams should be sought.

In 2006, in the first criminal case against a transplant surgeon for the death of a donor, the defendant allegedly administered high doses of an analgesic and anxiolytic to a potential donor to hasten his death before organ procurement.⁶¹ Although the surgeon was acquitted, the case highlighted the potential legal ramifications of recovery teams'

involvement in the care of a dying patient. There is a consensus that "medications given to provide comfort are reasonable, even if they might hasten death" but "no medication whose purpose is to hasten death should be given to the patient."¹² Failure to attend to potential DCD donors' comfort in contemporary practice is considered suboptimal end-of-life care and should be managed only by the physician(s) caring for the patient.

The need for data collection during DCD evaluation is to standardize definitions of death without variability among hospitals or OPOs. For instance, the definition of the start of WIT remains variable, with some advocating a threshold of systolic BP of <80 mm Hg, some advocating a mean arterial pressure of 50 mm Hg, some advocating a systolic BP of <50 mm Hg, and some advocating a decrease in arterial oxygen saturation to <80%.⁴³ The lack of a universal definition renders comparison of outcomes between centers and organs difficult. Although the asystolic interval to be observed remains a matter of institutional policy, it is prudent to recommend the development of standardized criteria. Highly sensitive maneuvers used to document the absence of circulation, such as intraarterial pressure monitoring or echocardiography, may be helpful if a short asystolic interval is used.

Active debate exists regarding the optimal location of life-support withdrawal. Arguments for ICU withdrawal stem from proponents who prefer to provide families a normal setting to grieve, albeit briefly, at the bedside of their loved one. Others argue that effective and expedient progression to donor mode allows most successful procurement and can only occur in the operating room. At present, there is no standard protocol, and each facility is responsible for dictating a protocol for their institution.

Wiley noted that "the initial University of Pittsburgh policy called for the withdrawal of care to occur in the OR," which offered the advantage of minimizing the need to transport a patient after death and permitting the prepping and draping of the patient before death. This protocol was denounced for subjecting the patient to "a desolate, profanely 'high-tech' death surrounded by 'masked, gowned, and gloved strangers.'" The initial experience in Pittsburgh showed some truth to the proposition that presence of family at the patient's bedside at the time of death may be more important to the patient and his/her family than organ donation or location of death. When three of the first four families who were approached for DCD provided consent only when they were allowed to be physically present at the time of death, the Pittsburgh policy was changed to allow families into the OR or to move the withdrawal of care to the OR holding area. The area selected for the withdrawal of life support should allow family members to be present, accommodate necessary monitors and equipment, and be close enough to the OR to allow rapid transport immediately after death.⁷² Other programs followed in kind. According to the 2000 IOM report on DCD, a family's need to be present and involved in the dying process is generally widely cited in the development of hospital policies on the setting of withdrawal of life-supporting care.⁵⁹

The widening gap between suitable donors and patients in need of transplant continues to be the only issue that keeps solid-organ transplantation from achieving its complete potential in offering improved survival to patients with end-stage organ disease. Because current practices and outcomes have shifted the paradigm of binary cadaveric donor (DBD versus DCD) to a spectrum of standard criteria to extended criteria, the ultimate impact of the estimated unrealized annual 22,000 DCD donors⁷ on the actual number of organs available for transplantation will remain unclear until sufficient data are obtained under similar protocols. Although ethical questions regarding DCD persist, the process, which is increasingly practiced in a standardized manner, accommodates the needs of dying patients as well as those of patients awaiting transplantation, with improving success. Several organizations, including the SCCM,⁶⁶ UNOS,⁵ and IOM,⁵⁹ have endorsed the concept and issued relevant guidelines. As experience grows, attitudes change, and outcomes improve, DCD may have a significant impact on the number of organs available for transplantation and thus the quality of life of patients awaiting and receiving cadaveric organs.

KEY POINTS

1. Before **donation after brain death (DBD)**, procurement of organs from donors was referred to as non-heart-beating donation or **donation after cardiac death (DCD)**.
2. DCD organs are subjected to a variable duration of **warm ischemic time**, which negatively affects early and late graft function.
3. DCD organ procurements were reintroduced to expand donor pool and reduce wait times and wait-list deaths.
4. DCD lung, liver, kidney, and pancreas grafts are increasingly used, and outcomes have now improved with experience.
5. In the contemporary era of intensive care unit care and donor shortages, DCD may be the only effective method of organ donation for terminally ill patients who do not meet DBD criteria but wish to donate organs.

■ References for this chapter can be found at expertconsult.com.

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Nearly a quarter of the deaths in the United States occur in the intensive care unit (ICU),¹ and the majority of patients who die in the ICU have had life-sustaining measures limited or withdrawn.^{2,3} A decision to withhold or withdraw life support is often preceded by a family conference addressing the goals of care and treatment plans. Family conferences addressing the care of critically ill patients can be watershed events, clarifying the prognosis, defining goals of care, and providing support to family members and surrogate decision makers. Since most critically ill patients lack decisional capacity,⁴ families and other surrogates are often centrally involved in medical decision making. The care of most critically ill patients should involve an explicit discussion with surrogate decision makers about goals for care and treatment plans. Coping with a critically ill family member is challenging for surrogate decision makers, and many feel ill equipped to make decisions on behalf of their loved ones. Skilled communication by an interdisciplinary ICU team is associated with improved outcomes for patients and family members.⁵

Leading an effective family conference requires specific teachable clinical skills, and our aim is to present an evidence-based approach to communication with families of critically ill patients. This chapter first provides an introduction to medical decision making, with a particular emphasis on shared decision making. We will discuss a rationale for the importance of family conferences for all critically ill patients and address practical issues including the considerations of physician reimbursement and billing. We then present an evidence-based approach for family conferences, highlighting competencies, and protocols that have been developed to improve physician-family communication. Finally, we address the issues of cultural competency and spirituality as they relate to the care of critically ill patients and their families.

MEDICAL DECISION MAKING

Models of Medical Decision Making

Physician-patient or physician-surrogate involvement in decision making regarding life-sustaining treatments can be conceptualized on a spectrum, with parentalism at one end, autonomous decision making at the other, and shared decision making in between. Shared decision making describes a relationship in which information is passed from physician to patient or surrogate, and both parties share opinions about treatment choices before a decision is jointly reached. There is a consensus among multiple critical care societies in Europe and North America that shared decision making should be the default model for physician-patient and physician-surrogate decisions regarding continuing, withholding, or withdrawing life support in the ICU setting.^{6,7} Although most patient surrogates prefer a shared decision making approach,⁸ there is considerable heterogeneity among patients and families with regard to their desired level of decision control. In the interest of patient- and family-centered care, it is imperative to individualize one's approach. One study showed that American physicians use the full spectrum of decision-making models but do not routinely assess the surrogates' desired level of involvement in medical decision making. Rather than individualizing their approach to match surrogate preferences, individual physicians often have one approach that they use with all surrogates.⁹

Surrogate Decision Makers

The experience of family caregivers and surrogate decision makers is undeniably challenging. Surrogates struggle with emotional conflict and competing values, attempting to both honor the wishes of their loved one and promote harmony within the broader family.¹⁰ Caregivers are often under tremendous stress and have higher rates of psychological symptoms than the general public.¹¹ Specifically, the prevalence of anxiety and depression symptoms in family members of critically ill patients is remarkably high,^{5,12} and the symptoms of posttraumatic stress have been shown to be present in a majority of family members of critically ill patients. One study showed that 82% of family members who were asked to participate in medical decision making demonstrated symptoms of posttraumatic stress 90 days after patient discharge or death.¹³

In addition to the effective difficulty inherent in coping with a sick loved one, surrogate decision makers are asked to participate in complex medical decision making with which they may have very little prior experience. Communicating clearly about the goals of care and the withdrawal of life-sustaining interventions, as well as exploring patients' and families' wishes can contribute to the family support and satisfaction.¹⁴ Though clinicians may be familiar and comfortable with the fast pace of ICUs, the tempo of medical decision making can pose a particular challenge to surrogate decision makers. One study showed decreased family satisfaction associated with a longer ICU stay but increased satisfaction when the process of withdrawing life-sustaining interventions was prolonged,¹⁵ especially for patients with a longer ICU stay. This suggests that families may benefit from time to come to terms with medical decisions and their personal feelings of loss.

Substituted Judgment Versus Best Interest

Substituted judgment is upheld as the highest standard for surrogate decision makers.^{16,17} In the absence of an existing healthcare directive, clinicians ask that surrogate decision makers imagine what the patient would want were he or she able to participate actively in decision making. Despite widespread endorsement of the substituted judgment standard by the medical community, ethical and practical concerns have been raised,¹⁸ including the fact that patients frequently change their minds regarding medical decisions and preferences, making an estimation of a patient's wishes more difficult. This is especially true among patients who have not completed an advance directive.¹⁹⁻²¹ That said, though many patients evolve and change with regard to treatment preferences, most studies evaluating preference stability have shown that a majority maintain consistency in their wishes regarding medical decisions,^{22,23} particularly patients who have engaged in advance care planning and those who are seriously ill.²⁴

Some authors have raised concerns about the accuracy with which surrogate decision makers can predict what choices patients would make.¹⁸ A meta-analysis by Shalowitz et al.²⁵ found that surrogate decision makers were 68% accurate in their predictions regarding patient treatment preferences. In cases in which surrogates are inaccurate in substituted judgments, their stated preferences on behalf of the patient more closely represent their personal beliefs about end-of-life care.^{26,27} A majority of seriously ill and older patients prefer to defer complex decision making to their physicians and family rather than

having their advance directive strictly followed,²⁸ perhaps reflecting the understanding that it can be difficult to imagine what one's preferences might be given the many variables and unanticipated subjective experience of being critically ill.

Although there is significant variability in the amount of decision control desired by patients over their designated surrogates, the majority of patients prefer the implementation of a substituted judgment standard over the best interest standard.²⁹ Furthermore, there is heterogeneity in the factors weighed by surrogates in medical decision making, including substituted judgment, but also factors such as shared experiences with the patient and the personal values and preferences of the surrogate decision maker.^{30,31} Although this is a complex issue; substituted judgment should be a higher standard for decision making than the best interest standard.

Role of Advance Directives

The absence of an advance directive has been identified as a barrier to effective end-of-life care in the ICU setting,³² although significant and valid concerns have been raised as to their usefulness and relevance.³³ Advance directives were not widespread in the past: one small retrospective study of 61 patients found that one-third of those who died in the hospital entered with advance directives³⁴; however, others have described a much lower usage of between 5% and 11%.³⁵⁻³⁷ Although advance directives have not consistently been shown to change the type of care provided to dying patients,^{33,38} some studies have shown that the presence of an advance directive is associated with higher family assessment of the quality of the dying process for patients in the ICU,³⁹ greater use of hospice, improved communication,⁴⁰ an increased frequency of DNAR orders and better quality of life in the final week of life.⁴¹ Advance directives can be helpful to surrogate decision makers, lessening the burden involved in attempting to employ substituted judgment. Importantly, advance directives should be completed as part of a process of advance care planning that allows patients, their family members, and clinicians to explore the patient's values, goals, and preferences before documenting those preferences in an advance directive. Therefore, although more progress needs to be made in the role advance directives play in guiding end-of-life care, there is value in advance care planning for those patients who ultimately require critical care.

FAMILY CONFERENCES IN THE ICU

Importance of Family Conferences for All Critically Ill Patients

Robust communication among clinicians, nurses, and families of all critically ill patients is important, not only for families of patients who are imminently dying. Family members who felt that communication in the ICU was inadequate were at higher risk for posttraumatic stress disorder,¹³ even those with loved ones who survived their ICU stay. Furthermore, families of patients who survived their ICU stay are more likely to be dissatisfied with their ICU care with respect to domains, such as inclusion in decision making, communication, emotional support, and respect and compassion shown to family, as well as the consideration of family needs.⁴²

Practical and Logistic Considerations

Practical and logistic issues can shape the experience of surrogate decision makers in a critical care setting. Even physical space can have an important effect: a French study⁴³ found that family members of patients in private ICU rooms had a lower incidence of anxiety and depression symptoms compared with families of patients in multi-bed rooms. The same group also found that the absence of a dedicated room for family conferences was associated with increased anxiety symptoms among family members of critically ill patients.¹² Accessibil-

ity of physicians and the access to information also correlates with family satisfaction; inaccessibility has been correlated with conflicts related to prognosis,⁴⁴ suggesting that surrogate decision makers are more satisfied when clinicians are accessible and comprehensive in their communication.

Billing and Reimbursement

According to the guidelines from the Center for Medicare and Medicaid Services (CMS), U.S. physicians are permitted to bill for time spent consulting with surrogate decision makers either in person or by telephone. Furthermore, critical care clinicians are permitted to bill for critical care time for these discussions, provided that the patient is unable to participate in giving a history and/or making treatment decisions and the discussion is necessary for determining a treatment decision. Documentation for these conversations must include:

- The medically necessary treatment decisions for which the discussion was needed
- That the patient is unable to participate in giving history and/or making treatment decisions
- The necessity of the discussion and a summary of the medical records to support this necessity⁴⁵

Palliative care clinicians in the United States are recognized as an independent medical subspecialty by Medicare and, as such, can bill for their consultative services. Previously, prolonged service codes, frequently used in palliative care billing, required that additional time is spent "face-to-face" with the patient, meaning that time spent in meetings outside of the patient's room between clinicians and surrogate decision makers were not compensated. This changed in 2009, such that clinicians can now bill for prolonged service time spent charting, reviewing records, coordinating care with other clinicians, and importantly, meeting with surrogate decision makers outside of the patient's room.⁴⁶ Claims have been denied for palliative care specialists who are credentialed in the same specialty as the primary team physician, although these denials have been successfully appealed.⁴⁶ Of course, specifics regarding the billing for both critical care and palliative care specialists change over time, so clinicians will be well served to familiarize themselves with the most updated billing guidelines.

Evidence-Based Approach to Communication During Family Conferences

Patients and families are consistent in defining high-quality care in the ICU: timely, clear, and compassionate communication by clinicians; clinical decision making focused on patients' preferences; patient care maintaining comfort and dignity; and family care with open access and proximity to patients, interdisciplinary support in the intensive care unit, and bereavement care for families of patients who die.⁴⁷

Family conferences in the ICU setting are challenging, both for families and clinicians, but it is important to remember that the optimal skills to facilitate these sessions are both teachable and rooted in evidence. Utilizing these skills has the potential to improve outcomes for both patients and family members. Studies suggest that planning conferences early in the ICU stay is beneficial⁴⁸; family conferences held within the first 72 hours of ICU stay are associated with both decreased use of critical care resources among patients who die⁴⁹ and higher family assessments of the quality of death and dying.³⁹ Consistent communication across the medical team is also important; having a "preconference" prior to family meetings can ensure that families are given a consistent message.⁵⁰ As discussed earlier, having a dedicated room for family conferences is also associated with decreased anxiety among family members.¹²

It should come as no surprise that empathic communication is one of the cornerstones of leading an effective family conference. Focusing on listening to concerns of family members is particularly important. Most physicians spend a majority of time talking rather than listening when meeting with patients and families.⁵¹ Families have been shown to have higher levels of satisfaction and lower levels of perceived

TABLE 175-1 **Empathic Communication in Family Conferences**

| CATEGORY | SAMPLE STATEMENTS |
|--|--|
| Empathy about surrogate decision making | <i>Withholding or Withdrawing Life Support:</i> "This is really hard. There's not a right answer to this situation." <i>Determining Patient's Wishes:</i> "It is very difficult to be in a position like this where you have to put your own personal feelings aside and try to advocate for what you think he would want." <i>Fear of Making a Mistake:</i> "Many families in your situation worry they will look back and think, was there something we missed or something that could've been done earlier? In her case, I do not think that would be true." |
| Empathy about critical illness in a loved one | <i>Making Sense of the Disease Process:</i> "I know it is very important to try and understand as best as possible what happened to see if we can make sense of this." <i>Difficulty in Understanding Medical Information:</i> "This is a lot of information to take in. Please feel free to ask any questions you might have." <i>Physical Changes:</i> "It must be really hard to see your loved one like this." <i>Receiving Bad News:</i> "It is hard to understand why something bad just can happen to anyone, and when it is someone you love and care for, that is even more difficult." <i>Uncertainty:</i> "We pretty much have to take it day by day, and I know that this uncertainty makes things even more challenging." |
| Empathy about confronting death in a loved one | <i>Helplessness:</i> "It must be so difficult facing this loss and feeling like there is nothing you can do to change things." <i>Dying:</i> "Letting go is so difficult, but I believe you are doing her a great service by honoring her wishes at this time." |

Adapted from Selph RB, Shiang J, Engelberg R, Curtis JR, White DB. Empathy and life support decisions in intensive care units. *J Gen Intern Med* 2008;23:1311-7.

conflict with clinicians who speak less and listen more.^{5,51} Family satisfaction is associated with the use of empathic statements, although this is a commonly missed opportunity: one study found that one-third of physicians in the ICU missed an opportunity to use empathic statements in family meetings.⁵² Table 175-1 summarizes categories and examples of empathic statements that can be used by clinicians in family conferences. The “Ask-Tell-Ask” approach advocated by Back et al.⁵³ (Table 175-2) is a helpful tool to assess baseline knowledge and evaluate the understanding of the information provided.

Assurances to families and surrogates that patients will not be abandoned before death and that efforts will be made to provide comfort and minimize suffering and statements of explicit support for medical decisions to either continue or withdraw life-sustaining interventions are associated with higher levels of family satisfaction.⁵⁴ The use of the VALUE mnemonic (value, acknowledge, listen, understand, and elicit, summarized in Table 175-3) to enhance clinician-family communication has been shown to improve mental health outcomes, including symptoms of depression, posttraumatic stress disorder, and anxiety in family members.⁵ Interestingly, family meetings using this tool were somewhat longer than the usual care meetings, and the percentage of family speech was also higher.

Discussing Prognosis

Despite the ethical responsibility to inform patients about prognosis, many clinicians are uncomfortable doing so and identify it as one of

TABLE 175-2 **“Ask, Tell, Ask” Approach to Discussing Difficult Communication Tasks**

| STEP | FUNCTION | SAMPLE PHRASES |
|--------|--|---|
| “Ask” | Ask the patient/patient surrogate to describe his/her understanding of his/her medical disease and prognosis. | “It would help me to know what your other doctors have told you about your father’s illness.” |
| “Tell” | Explain to the patient/patient surrogate, using simple, straightforward language, what you understand about his/her medical disease and prognosis. | “Unfortunately, it looks like your father’s illness is getting worse. With a disease as serious as his, 9 out of 10 patients will die within 1 month, and 1 out of 10 will be alive at 1 month. If your father survives this illness, it is very likely he will have significant disability and will likely be unable to live independently.” |
| “Ask” | Assess the patient’s/patient surrogate’s understanding. | “I want to make sure that I explained things clearly. Can you tell me, in your own words, what I just told you about your father’s illness?” |

Adapted from Back AL, Arnold AM, Baile WF, Tulsky JA, Fryer-Edwards K. Approaching difficult communication tasks in oncology. *CA Cancer J Clin* 2005;55:164-77.

TABLE 175-3 **VALUE Tool to Enhance Communication in the ICU**

| | |
|---|------------------------------------|
| V | Value family statements |
| A | Acknowledge family emotions |
| L | Listen to the family |
| U | Understand the patient as a person |
| E | Elicit family questions |

Adapted from Lautrette A, Darmon M, Megarbane B, Joly LM, Chevret S, Adrie C, et al. A communication strategy and brochure for relatives of patients dying in the ICU. *N Engl J Med* 2007;356:469-78.

the most difficult parts of their job.⁵⁵ Physicians in the ICU are more likely to discuss functional prognosis rather than the likelihood of survival. In one study,⁵⁶ clinicians did not discuss the survival prognosis in over one-third of family conferences in which the attending physician anticipated there would be a discussion of withholding or withdrawing life-sustaining interventions or discussing serious news. Since patients with a poor prognosis are more likely to decline life-sustaining treatments,^{57,58} discussion of the prognosis is critically important. Interestingly, surrogates rely upon far more than just the prognostic information provided to them by physicians,³¹ although most try to balance their assessment of the patient with the information provided by physicians in understanding prognosis. Surrogates also report that they understand and appreciate explanations of the uncertainty involved in prognostication,⁵⁹ although evidence suggests that the surrogates’ understanding of prognostic information is low, even when they rate the quality of prognostic communication highly.⁶⁰

Experts recommend framing prognosis numerically rather than using nonspecific terms (e.g., “1 in every 10 patients” rather than “uncommon” or “low risk”), framing prognosis both positively and negatively, and using consistent denominators when presenting rates of risk (e.g., “9 in every 10 patients with illnesses as severe as your father’s will die within 1 month,” and “1 in every 10 patients with illnesses as severe as your father’s will be alive in 1 month”).⁶¹ In addition, family members of critically ill patients report that they prefer numeric

estimates.⁶² Despite these recommendations and preferences of family members, a minority of critical care physicians use numeric estimates in discussing prognosis⁶³ and/or verify whether or not surrogate decision makers have understood the information provided using a method (e.g., “teach-back”).

Discussing Resuscitation

Most patients and their families have little personal experience with the critical care setting or with cardiopulmonary resuscitation (CPR). Knowledge of the probability of survival from CPR affects patients' choices about code status.⁵⁸ Unfortunately, many people base their assumptions on the likelihood of surviving CPR on information from the lay media, such as medical dramas on television, which dramatically overrepresent favorable resuscitation outcomes.^{64,65} Consensus guidelines have highlighted specific recommendations in discussing resuscitation with patients,⁶⁶ some of which may also help guide discussions with surrogate decision makers. The authors recommend that, among other events, admission to a critical care unit should serve as a trigger for a discussion of resuscitation preferences.

Another important recommendation is that the discussion be framed to review the overall goals of care rather than merely focusing on code status. It is also important to make a distinction between life-sustaining interventions and CPR, describe cardiac arrest and care plan options (including palliative care) in detail, offer quantitative information about the patient's likelihood of surviving to hospital discharge and longer term survival and functional status after resuscitation, offer a code status recommendation, and focus on trust and rapport building. In summary, CPR in the critical care setting is best addressed in the context of the greater goals of care, including a candid discussion of the likelihood of CPR survival and care alternatives, such as palliative and symptom-focused care.

Role of the Interdisciplinary Team

The complexity of critical care requires the involvement of a multidisciplinary team. However, conflicts between nurses and physicians are common,⁶⁷ particularly in the setting of end-of-life care, and are a source of significant work stress and burnout.⁶⁸⁻⁷⁰ Enhanced nurse-physician communication and collaboration have been associated with higher patient satisfaction^{71,72} and a lower incidence of anxiety and depression symptoms among families of critically ill patients,¹² as well as lower rates of burnout among nurses and physicians.^{68,69} Improving communication among the multiple clinicians within the ICU (i.e., physicians, nurses, respiratory therapists, social workers, and spiritual care providers) would undoubtedly improve not only workplace relationships and stress but also patient care and integrated communication with families and surrogate decision makers.⁷³

Palliative care specialists are an increasingly common hospital resource. Involvement of a multidisciplinary palliative care team is associated with increased patient satisfaction as well as decreased rates of ICU admission following hospital discharge and significant cost savings.⁷⁴

Role of Protocols and the Importance of Individualization

Many of the communication strategies that have shown efficacy were implemented using interventions designed with specific protocols. The tenets of patient-centered care affirm the importance of tailoring our

communication and interactions to specific patients and their families, rather than resorting to a scripted dialogue. However, given the many missed opportunities in the current level of communication with patients and surrogate decision makers in the critical care setting,⁷⁵ it is reasonable to look to communication approaches that have been rigorously developed and studied. Specific guidelines on communication techniques and strategies are intended as a starting point, and clinicians are encouraged to integrate these with their personal approach and authentic voice, as well as to adapt their approach to the individual patient or family.

Cultural Competence

Cultural considerations are fundamental in talking with families and surrogate decision makers from diverse backgrounds. Using language interpreters and cultural mediators is critical in facilitating communication with patients and families who speak different primary languages than clinicians. Ideally, the role of an interpreter transcends mere strict literal translation. Interpreters can assume the role of a cultural mediator, helping to interpret content bidirectionally. Even with the best cultural mediators, however, there are challenges inherent when language discordance exists. Interpretation of family conferences is a difficult process that can include critical errors, and it is difficult to provide emotional support for families in this circumstance.^{76,77} Implementing best practices (e.g., a preparatory meeting with interpreters before the clinical encounter, speaking slowly, confirming the patient's or family's understanding, and debriefing with the interpreter after the clinical encounter) can facilitate better communication and decrease the potential for misunderstandings.^{78,79}

Spiritual Issues

Spiritual needs figure prominently for many critically ill patients and their families, often explicitly or tacitly shaping decision making about medical care,⁸⁰ although these considerations are rarely discussed in family conferences.⁸¹ Increased family satisfaction has been associated with the assessment of spiritual needs.¹⁴ Exploring underlying spiritual beliefs and values can be extremely important in supporting families and toward finding common ground on medical decisions through shared decision making. In addressing spiritual concerns, clinicians should use caution in not stepping beyond one's role as a clinician or trying to resolve existential and spiritual questions⁸⁰; rather, the focus should be on assessing potential spiritual needs, then making referrals for spiritual care providers.⁸²

CONCLUSION

Conferences with families of critically ill patients are crucial and are one of the more formidable clinical challenges faced by critical care clinicians. Many approaches to medical decision making exist, and there is significant variability among patients and patient surrogates regarding their preferred role. There is a consensus that shared decision making should be the preferred approach of clinicians although care must be taken to assess the family's desired role in medical decision making and individualize one's approach accordingly. Having a critically ill family member and functioning as surrogate decision maker are incredibly challenging for families, but stress associated with this situation can be mitigated through integrated, thoughtful, and empathic communication by physicians and other members of the critical care team.

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■ References for this chapter can be found at expertconsult.com.

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Two truisms of economics are that the supply of goods and services are finite and that supply is insufficient to meet all demands. The tension between supply and demand for food, water, energy, education, and other goods and services creates economies. All societies must determine how goods and services will be allocated to individuals. Although the term *rationing* connotes a specific process of allocation during circumstances of severe resource limitation (rationing coupons to allocate gasoline during World War II or one's daily ration of water on a life raft are examples of common use), *rationing* is a synonym for resource allocation. In this chapter, the terms will be used interchangeably.

Market-based economies allocate many resources on the basis of the ability to pay, but other strategies exist (Table 176-1).¹ In developed nations, some goods and services (e.g., healthcare and education) are treated differently from luxury goods and are allocated by society using criteria other than an individual's purchasing ability. Regardless of the strategy ultimately used to allocate medical goods and services, decisions to allocate medical resources are fundamentally identical to the decisions regarding the allocation of other resources. Since medical resources are finite, it is impossible to provide every effective treatment in every case where it might offer benefit, and the patient desires the care. Sometimes the decisions are *explicit*, with immediate repercussions—for example, the selection of one patient to receive a heart transplant when several might benefit from the solely available organ—or the decision to admit one patient to the last ICU bed when several patients are critically ill who would benefit from ICU admission. More frequently, the decisions are subtler and occur even when the supply of the therapy is not limited (e.g., the decisions to use cheaper antibiotics, sedative medication, or imaging modalities) when more expensive options might be beneficial. Finally, allocation decisions can be completely *implicit* and almost hidden. For example, the decision to build an ambulatory care clinic instead of adding ICU beds is an allocation decision with profound implications for the delivery of critical care services that is nearly hidden to the individual clinician and patient.

Although common and necessary, allocation decisions are stigmatized in medicine. Allocation decisions bring two major ethical principles into conflict: beneficence and justice. Beneficence guides clinicians to act solely in their patient's best interests while justice directs clinicians to act fairly.² This conflict may explain why euphemisms are frequently used to describe allocation decisions. For example, *triage*, *optimization*, *prioritization*, *cost-effective care*, and *basic health-care* all indicate some form of allocation decision.^{3,4,5} The purpose of this chapter is to explore these decisions in their many guises as they occur in critical care and to offer some guidance to the clinician for constructing processes for allocating resources in their ICU.

ALLOCATION VERSUS EVIDENCE-BASED MEDICINE

Decisions based solely on the evidence of efficacy of medical care are not rationing decisions. There is no medical obligation to provide and no societal obligation to pay for care that is harmful or ineffective. In fact, clinicians use special terms to describe interventions that fall into these categories including *futile*, *not the standard of care*, *medically inappropriate*, *wasteful*, or *experimental*.^{5,6} For example, an intensivist

who decides not to transfuse a critically ill patient with blood for a hematocrit of 27 is not rationing blood even though blood is an expensive and limited resource because there is evidence that this transfusion in many critically ill patients is of no benefit and may be harmful.⁷ The decision not to use human growth hormone, an expensive medication, in chronically critically patients is not a rationing decision because the available evidence suggests it is ineffective.⁸

Unfortunately, the assessments of benefit and harm are not as straightforward as the terms would suggest, and the line between effective, ineffective, and experimental often lies in the eyes of the individual clinician. Decision science has taught us that medical decision making is a complex process that frequently obscures the true rationale of the choice.⁹ In fact, judgments allegedly based solely on objective evidence of safety and benefit often incorporate a variety of subjective values and biases.¹⁰ These may include the value the clinician assigns to being wrong, the value assigned to trying to “rescue” a patient in imminent danger of death; the clinician's tolerance for uncertainty; the impact of the decision on the clinician's finances; biases about the patient's race, gender, functional status or age; and the cost or availability of the resource.¹¹ The transition from statements that summarize the evidence of benefit to recommendations that incorporate cost and other values is often very subtle. For example, the authors of a recent systematic review of colloid resuscitation in critical care conclude that “there is no evidence from randomized controlled trials that resuscitation with colloids reduces the risk of death compared to crystalloids in patients with trauma, burns, and the following surgery.”¹² This is a summary of the evidence of efficacy. Like all statements of evidence, it is impossible to prove the absence of efficacy of treatment. However, the authors conclude, “As colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, it is hard to see how their continued use in these patient types can be justified outside the context of randomized controlled trials.” The *Choosing Wisely* campaign, an initiative of the United States American Board of Internal Medicine, has carefully avoided the use of terms like *cost*, *value*, *cost-effective*, or *rationing* in favor of a framework of *evidence*, *safety*, and *medically necessary*.¹³ Avoiding treatments that lack demonstrated efficacy is certainly justified; however, it is notable that these efforts steadfastly avoid an explicit discussion of costs. For example, the critical care list of avoidable therapies in *Choosing Wisely* includes avoiding unnecessary blood transfusions and total parenteral nutrition in the first 7 days of critical illness but does not mention a long list of other unproven or harmful treatments in critical care (e.g., dopamine for septic shock or recruitment maneuvers in ARDS).¹⁴ Cost is listed as one criterion among five; the others include evidence, prevalence, relevance, and innovation. Fundamentally, what the authors are offering here is a cost-savings analysis without an explicit cost evaluation that may have been politically or socially unacceptable.

These examples show how assessments of cost can creep into recommendations for therapy even without an explicit assessment. Since clinicians and payers may be reluctant to admitting that they are incorporating cost or availability into the rationale for a decision, they may find decisions of futility or appropriateness less ethically problematic than rationing. In fact, these judgments may implicitly contain assessments of cost by incorporating cost into the definition. When is there sufficient evidence to move a treatment or diagnostic device from

experimental care to standard care? When is there sufficient evidence, absent evidence of outright harm, that treatment is ineffective as opposed to not yet of proven efficacy? These decisions are frequently made by consensus bodies using subjective or poorly characterized criteria. The amount of evidence will tend to be higher for treatments that are risky, expensive, and that lack any alternative. Conversely, the threshold for accepting a treatment as “standard” will be lower if it is inexpensive, safe, and offers the potential for the rescue of a patient in imminent threat of death. For example, consider the decision to elevate the head of the bed of mechanically ventilated patients to prevent ventilator-associated pneumonia. This is an inexpensive and safe treatment to offer patients. It would take less evidence to convince clinicians to use this treatment than to use kinetic beds or prophylactic topical antibiotics, which are more expensive and may raise safety issues. Therefore, the cost of an intervention may be incorporated into assessments of whether it is the standard of care.

These judgments are further complicated by the motivation of the decision maker. It would be difficult for an insurance company that is assessing whether a specific therapy is experimental or standard of care to be unbiased when its decisions affect its profits. Since medical decisions are so complex, and decisions in the ICU are further clouded by their immediacy and the illness of the patients, it is essential that clinicians understand their motivations and the evidence supporting their decisions and have a process in place for allocation.

| TABLE 176-1 Strategies for Allocating Resources | |
|---|---|
| PRINCIPLE | DEFINITION |
| Autocracy | To each according to the will of one |
| Democracy | To each according to the will of the majority |
| Equality | To each according to an equal share |
| Lottery | To each according to an equal chance |
| Capitalism | To each according to his or her ability to buy |
| Personal worth | To each according to his or her contribution to the community |
| Utilitarianism | To each so that the utility of the community is maximized |

■ ALLOCATION STRATEGIES

Given that an intervention is effective, clinicians will face decisions to allocate resources at the bedside. These decisions are usually separated into macroallocation decisions (involving groups of people and usually made at a managerial or health policy level) and microallocation decisions (made at the bedside and involving identifiable specific cases). A hospital’s decision not to hire additional ICU nurses is a macroallocation decision. A nurse manager’s decision to allocate a specific patient to share a nurse in the ICU rather than to receive 1:1 nursing is a microallocation decision. This chapter is primarily concerned with bedside allocation or microallocation decisions that clinicians make on a routine basis. There is an important interaction between micro- and macroallocation decisions since macroallocation decisions ultimately affect individuals (Table 176-2).

There are a number of approaches to allocating resources (see Table 176-1). While these are all feasible, they are not all equally ethical. The principles of equality, fairness, justice, and due process make some strategies less acceptable. The principle of utilitarianism directs resource allocation to maximize the “utility” or benefit of the most people for any given amount of resources. To the extent that “utility” can be measured by measuring patient outcomes, such as health-related quality of life and to the extent that we can estimate the effects of medical treatments on utilities, theoretically, we can calculate exactly which sets of medical treatments to pay for to maximize the benefit to the population. This is the fundamental principle underlying cost-effectiveness analysis, which is the quantitative embodiment of utilitarianism. Allocating medical resources through cost-effectiveness analyses has important limitations: (1) medical cost-effectiveness analyses cannot tell how much money to allocate to medical as opposed to other goods and services, just how to maximize health outcomes for any selected outlay of resources; (2) cost-effectiveness analysis methods may not fully account for some factors that society values (e.g., cost-effectiveness analysis routinely treats all human lives as equally valuable). However, society often places a very high value on saving identifiable lives in imminent danger of death and may not value additional years of life in the elderly as much as years of life in the young.¹⁵ Standard economic analyses may not value equal distribution as much as optimal distribution and, to this end, may discriminate in settings that society finds unacceptable¹⁶; and (3) a cost-effectiveness analysis is a mathematical technique that generates comparative outcomes for populations of patients. It is meaningless to speak of

| TABLE 176-2 Allocation Decisions at Different Levels | | | |
|--|--------------------------------|--|--|
| | DECISION MAKER | DECISION | RATIONALE |
| Not an allocation decision | Physician | Not to use human growth hormone in chronically critically ill patients | Evidence of harm in critically ill patients |
| | President of insurance company | Not to offer routine chest computed tomography screening for lung cancer | Lack of sufficient evidence of benefit |
| | Healthcare minister | Not to offer basic medical coverage to all people in the country | Endorses other goals than equal access to healthcare, for example, the importance of choice or the value of free market |
| Macroallocation decision | Physician | Not to admit routine postcoronary artery bypass patients to ICU | Limited ICU beds used for patients with more severe illness |
| | President of insurance company | Not to increase reimbursement for septic shock when new, expensive drug is approved | Hopes to limit cost of care for patients to increase profitability of insurance company |
| | Healthcare minister | To capitate reimbursement for hospital care | By providing single fee for all care, hopes to limit costs so that increased outpatient services can be provided |
| Microallocation decision | Physician | Decision not to admit a debilitated, elderly man with urosepsis to the ICU despite a request by the patient’s primary care physician | The intensivist’s deciding the patient was moribund and that the ICU’s resources could be used to reflect better on other patients |
| | President of insurance company | Denial of claim to pay for prostacyclin infusion for pulmonary hypertension. | A treatment specifically not covered by contractual arrangement with the insured patient |
| | Healthcare minister | Not applicable | Not applicable |

treatment as being “cost-effective” in an individual case in which the treatment either will or will not work.

The primary value of cost-effectiveness analyses as an allocation tool is the ability to compare various strategies.¹⁷ For example, one can compare the cost-effectiveness of captopril versus no captopril in survivors of myocardial infarction against using fluoxetine versus imipramine for major depression to decide whether to use captopril after a myocardial infarction, fluoxetine for depression, both, or neither. Cost-effectiveness analyses provide a ruler, regarding dollars per life-year or dollars per quality-adjusted life year (QALY) that allows these different treatments for different diseases to be compared. The crucial data that must be available to make these comparisons are information on the effect of the treatments on survival or health-related quality of life. Unfortunately, in critical care the number of treatments shown to improve survival or health-related quality of life is small. While we have data on strategies to reduce gastrointestinal bleeding, duration of mechanical ventilation, and catheter-related infections, none of these interventions has been shown to affect QALY.^{18–20} Therefore, the cost-effectiveness analyses for these interventions are expressed as dollars per gastrointestinal bleed prevented or similar.²¹ These ratios cannot be used to compare a treatment to prevent gastrointestinal bleeding with a treatment for myocardial infarction because the latter is expressed in dollars per QALY. Cost-effectiveness analyses with non-QALY denominators can be helpful in bedside rationing decisions when the intervention is shown to be equally or more effective and reduces cost. For example, special beds in the ICU have been shown both to prevent decubitus ulcers and to reduce the overall costs of care even when the cost of the bed is factored into the analysis. Therefore, the cost-effectiveness ratio (expressed in dollars per decubitus ulcer prevented) is a negative number.²² Non-QALY denominators are useless for comparative cost-effectiveness decisions in different diseases.

■ ILLUSORY COST SAVINGS

Since the earliest days of intensive care, technologic, workforce, and organizational innovations have been proposed as opportunities to reduce the exorbitant cost of critical care. In 1972 an optimistic author wrote, “[The] more promising approaches to cost reduction are all in an early stage of development now. Both deprofessionalization of the ICU by wider use of allied health personnel and the automation of therapeutic functions are just beginning to be applied.”²³ Despite the implementation of both of these measures, there is little evidence that cost increases in hospital- or ICU-based care have been curbed by technologic innovation. In fact, the opposite has occurred. This is not surprising since technologic innovation in other areas of healthcare, while often associated with better outcomes, is rarely a source of cost savings.

Cost analyses are problematic in medical care, and critical readers must be able to identify cost savings that are real and that will appear in their budgets, from savings in indirect costs that will be accrued elsewhere.²⁴ There are several common, but problematic, arguments about cost reduction in critical care: (1) that reduced ICU length of stay will reduce the cost of care in the ICU; (2) that reduced test ordering will reduce the cost of care in the ICU; and (3) that fewer admissions of futile-care patients will save money. It is important to recognize that not all calculated cost savings will be realized at the ICU or hospital level.

ICU costs are often inferred from the length of stay. For example, in a cost-effectiveness analysis of antibiotic-coated catheters, the authors assigned a cost of \$9738 to a catheter-related bloodstream infection.²⁵ Epidemiologic studies show that patients with catheter-related infections spend more time in the hospital, even after controlling for severity of illness.²⁶ The cost of a catheter-related infection is, in part, derived by simply multiplying the estimated number of extra days patients with catheter-related infections spend in the hospital times the cost (based on hospital charges) of a day in the ICU or ward. In fact, it is unknown if using antibiotic catheters shortens the ICU

length of stay since the randomized trials showing that antibiotic-coated catheters prevent infection were not sufficiently powered or did not show a reduction in mortality or length of stay.²⁰ Even if the antibiotic-coated catheters reduce the length of stay, money “saved” by reducing the length of stay is a different type of funds than the money spent in buying the catheters. By reducing the length of stay, the ICU will be able to care for more patients, but they will be sicker and more expensive patients.

Identifying treatments for specific conditions in the ICU that reduce overall costs, even if they have no effect on QALYs, is extremely useful to the intensivist allocating resources. Implementing economically dominant strategies is an easy allocation decision as they do not worsen patient outcomes and reduce costs. However, predicting the actual effect of any decision on the actual costs in an ICU or hospital is complex because each hospital performs cost accounting and budgeting in idiosyncratic ways. The effect of different payer mixes, contracts for nursing and respiratory therapist labor, allocation of indirect costs, and whether the ICU budget is fixed or grows with the number of patients served all influence whether allocation decisions accrue savings that can be appreciated at the ICU level. For example, the drug acquisition costs of once-daily medications are frequently higher than the medications administered more frequently. However, there are labor costs associated with administering medication more frequently that may offset the costs of the once-daily medication. Unfortunately, unless there is a sufficient workload reduction from changing to once-daily medication to fire a nurse, there will be little-realized savings. This is because labor costs are not infinitely scalable (e.g., if there is 15% less work to do, you may not be able to hire 15% less nursing hours). Patients who need 1:1 nursing care will continue to need this level of care regardless of whether the nurses are administering once-daily medication or not. It may be that changing medication routines improves care by more efficient use of nursing time, but this may not be reflected in a cost reduction. A reasonable criterion to consider for a proposed cost-saving intervention is whether it will reduce the amount of staff that need to be hired or whether it can reduce the acquisition costs for equipment or medication. If it will not, then cost savings is not likely to be realized in the ICU.

The cost estimate used in many cost-effectiveness analyses assumes that every day in the ICU costs the same. This is certainly true for what the hospital charges, from which these ICU costs were derived. However, this is not true in reality. The first few days in the hospital and ICU are far more expensive than the last days.²⁷ Patients are more likely to require active interventions and closer nursing care in the early days in the ICU. Clearly, interventions that reduce ICU length of stay cannot reduce early days in the ICU and simply eliminate later lower cost days. This is rarely accounted for in the cost analyses. This was validated at the national level as the United States healthcare costs peaked during a period when hospital inpatient days declined by 40%.²⁸ Therefore, the standard cost analyses overestimate cost savings likely to be realized by reducing the length of stay.

Reducing test ordering in the ICU has been offered as a technique for cost reduction. This is also a perfectly reasonable option to be offered on clinical grounds. Overtesting yields increased false positives that may lead to clinical complications in search of diseases that never existed. However, the actual cost reduction that will be seen at the ICU level by reducing test ordering is likely to be overestimated in a simple charge-based analysis of test ordering. The actual marginal cost of performing the 101st arterial blood gas test once the analyzer has already been purchased and the technician has been paid for the time to perform 100 arterial blood gases is minimal. If reductions in test ordering are of sufficient magnitude to staff the laboratory with fewer people or to forego purchasing new equipment, then significant cost reductions can be realized. In fact, depending on how indirect costs in the hospital are allocated, it is possible that a reduction in test ordering will place the clinical laboratory under considerable budgetary constraints. Fewer tests may reduce the amount of money that the laboratory director receives to cover staff costs that may not decrease in the same proportion as test ordering.

Patients may be admitted to the ICU even when they have a negligible chance of survival. It seems reasonable to assume that if these patients receive care outside the ICU that the resources that would have been expended without benefit in the ICU would be saved. On the surface, this appears to be a painless cost saving method that intensivists should look for. Unfortunately, a careful analysis of the potential savings from limiting care at the end of life shows that it is a relatively small amount of overall health care spending, that implementing these strategies may worsen overall health outcomes by affecting care that nonterminal patients receive, and that care would have to be withheld from young patients; some of whom would have had prolonged survival to achieve any savings.²⁹

STRATEGIES FOR BEDSIDE ALLOCATION OF RESOURCES IN THE ICU

Ultimately, allocation decisions will occur at the bedside in the ICU. A number of studies demonstrate that under settings of restricted access to ICU beds, physicians allocate these beds by the severity of illness. In these situations, the average severity of illness in the ICU increases as it does on the hospital ward.³⁰ Unfortunately, these decisions are also driven by arbitrary factors including age, gender, reimbursement, and physician power in the institution that can all affect access to ICU beds.³¹ It is important that clinicians plan in advance of these difficult decisions so that their deliberations are explicit, open, and guided by principles rather than ad hoc case-by-case decisions.

CASE 1: ADMISSION AND DISCHARGE CRITERIA

The Last ICU Bed

An intensivist is responsible for an eight-bed mixed medical-surgical ICU in a large community hospital that is currently full. Within minutes, she receives two calls, one from the emergency room where a 17-year-old has been admitted with diabetic ketoacidosis with severe acidosis and altered mental status but who is not intubated and one from a hospitalist who is seeing an 83-year-old severely demented patient on the ward who has developed acute respiratory failure and will soon require mechanical ventilation. There is only one open ICU bed, and none of the existing patients can be moved.

Perhaps the most difficult decision an ICU physician faces is the allocation of the ICU itself.³² Although this is a wrenching decision and has generated a literature devoted to triaging the last ICU bed, there is little evidence to indicate how frequently this occurs in actual practice. Mobile technology, flexible nursing staffing, and the availability of postanesthesia, emergency room, and step-down beds may make the ritual of the last ICU bed more a theoretic concern than an actual issue. The allocation of the last ICU bed feels particularly difficult because identifiable patients are affected by a very explicit decision. The decision is further complicated by the almost complete lack of data on the actual benefit of ICU care in specific conditions versus care on the ward. Few question that ICU outcomes are superior, but the relative benefit of ICU care and monitoring in specific conditions is unknown. Finally, the decisions must be made rapidly. A transplant committee also allocates a fixed resource, organs for transplantation; however, it can deliberate for weeks to prioritize recipients. The intensivist must allocate an ICU bed within minutes or hours.

The two most important steps in allocating the last ICU bed are to take steps to prevent it from occurring and to develop guidelines for managing the problem when it occurs. Strategies to prevent the last ICU bed phenomenon include staffing sufficiently for the anticipated volume of elective surgery or stopping planned surgery if sufficient ICU beds are not available. This includes arranging flexible nursing and monitoring options for caring for critically ill patients in other environments that are not physically in the ICU. Individual clinician biases and training can have a strong effect on the perception of the value of various life-sustaining treatments in the ICU.³³ To minimize the effect of these influences and maintain fair and equitable access to intensive

care services, admission and discharge criteria should be public, explicit, evidence-based, and fair. Public and explicit criteria allow all clinicians in the hospital to be aware of the policy. To the greatest extent possible, decisions should be evidence-based or, in the absence of evidence, appeal to national policy statements or local consensus.³⁴

Resolution

The intensivist went to the emergency room, evaluated the patient with diabetic ketoacidosis, placed arterial and central venous catheters, and arranged to have a nurse from the ICU float to the emergency room for the night to care for the patient in the emergency room. The patient with acute respiratory failure from the floor was intubated and admitted to the ICU's last bed.

CASE 2: TECHNOLOGY PURCHASE

Bedside Laboratory Testing

An intensivist is considering purchasing a point-of-care testing system to allow him to do arterial blood gases as well as certain chemistries and coagulation tests at the ICU bedside. The salesman has shown him data that says that the cost of performing the tests at the bedside is 40% less than the hospital laboratory charges, saving money for the patient and potentially making money for the ICU. Furthermore, the salesman presents data that the rapid turnaround of bedside testing leads to faster clinical decisions and a reduction in ICU stay by 1 day. The reduction in length of stay, argues the salesman, pays for the cost of the testing system in 18 months.

Arguments that increasing technology will ultimately lead to cost reductions have advanced since the beginning of intensive care.²³ When the purchase is being made primarily on the basis that it will be cost saving, or at worse, cost neutral, there are two important considerations for the intensivist to consider. Does the cost saving involve shifting fixed costs? Moreover, to what extent does the cost analysis rely on savings due to reduced nursing time or ICU days? Calculation of cost savings that fail to take into account the proper cost perspective that relies on shifting fixed costs and reduced labor time or ICU days to demonstrate cost savings may overestimate the actual cost savings.

None of the preceding discussion relates to the potential benefits of new technology. If clinicians feel that the evidence supports better patient outcomes from the technology and that it merits implementation regardless of economic consequences, then this is not a resource allocation decision. However, technologic innovation is rarely cheap, and the medical industry will usually try to persuade clinicians that the novel technology is not only better but that it also saves money.

When a clinical laboratory charges \$100 to perform an arterial blood gas, this is not because the reagents, analyzer rental, and 7 minutes of technician time to perform the test cost \$100. Most of the costs included in this charge reflect the fixed costs of maintaining a 24-hour-a-day, 7-day-per-week laboratory including quality controls, managerial costs, government reporting, and the laboratory's portion of janitorial and other services in the hospital. If the ICU switches to a point-of-care system and reduces the number of laboratory tests by 30%, none of these fixed costs will disappear. Unless the reduction in testing is so significant that the laboratory director can fire a technician or sell some machinery, the overall costs of running the laboratory will not be affected by the ICU's switch to point-of-care testing. If these fixed cost savings cannot be realized, then the laboratory director must still meet the budget demands of the laboratory in the face of reduced testing. The point-of-care appears to be less expensive because the fixed costs of maintaining an entire laboratory are not bundled into the purchase of the testing device, not because the tests themselves are fundamentally less expensive.

Resolution

The intensivist met with the director of the clinical laboratory. At this hospital, the budget of the laboratory was directly tied to the volume of

tests performed. If the ICU started to perform their own tests, the clinical laboratory would not be able to continue to provide its services. The ICU and laboratory directors instituted a quality improvement intervention to improve stat lab turnaround time with existing technology and decided not to purchase the point-of-care technology but to use those funds to buy some needed bedside mobilization equipment.

CONCLUSION

Allocation of resources in medicine is an unavoidable process. Clinicians do have control over whether these decisions are implicit or explicit, are made after open discourse or with no discussion, and whether the decisions are informed by available literature or not. Clinicians

in the ICU may, in fact, face fewer implicit allocation decisions than their colleagues in other areas because of the imminent risk of death in the ICU and society's value for protecting those lives. In fact, there is relatively little empiric evidence of how often intensive care services are allocated. The effect of different interventions on actual costs will vary depending on local factors including reimbursement and indirect cost allocation. Allocating ICU beds is the most challenging allocation decision most intensivists will face. The best time to handle these decisions is before they occur. Public, explicit triage and discharge criteria that are developed in collaboration with ICU users (e.g., emergency department, surgery, oncology) well in advance of the actual decisions are essential for fair and efficient use of intensive care resources.

KEY POINTS

1. Allocation of resources is synonymous with rationing and is an inevitable part of medical practice.
2. Clinicians often use a variety of euphemisms including triage, optimization, prioritization, and cost-effective care to obscure what are essentially allocation decisions.
3. Clinical decisions that are based solely on the evidence of risk, benefit, or patient utilities are not rationing decisions because they do not incorporate cost or availability.
4. Clinicians may implicitly incorporate cost or availability into their judgments of the evidence of risk or benefit in an attempt to avoid an explicit decision incorporating cost.
5. Allocation can occur at the macro level where decisions affect populations of patients or at the micro level where decisions affect individually identifiable patients.
6. Cost-effectiveness analysis is a quantitative methodology that applies a utilitarian approach to allocating resources to maximize the benefit to a population for any specified cost.
7. Cost is difficult to measure in complex endeavors like medical care.
8. Claims to reduce cost by reducing the length of stay, test ordering, or admission of patients who will likely die should be examined critically.

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Challenges the notion that significant reductions in ICU costs can be achieved by limiting intensive care at the end of life. The authors argue that while there are many very good ethical and medical reasons not to continue care for patients in the ICU when their prognosis is grim, the cost savings from these decisions are not likely to be enormous.

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FOUNDATIONS OF ETHICS IN CRITICAL CARE

All medical decisions are ideally made by the healthcare provider in tandem with the patient or a *surrogate decision maker* or a *healthcare proxy* speaking for the patient. The provider brings expertise in the science and practice of medicine, both knowledge and what Aristotle referred to as *phronesis*, or practical wisdom and both professional values and his or her own personal values. The patient or the surrogate decision maker when needed brings the values of the patient. Given the very nature of critical care medicine, the “best” treatment for a particular patient by a particular provider or team of providers cannot be known without the attention to these values. That many decisions in the care of critically ill patients are literally *life or death* questions coupled with the fact that critical care patients are infrequently able to speak for themselves at the time decisions are required combine to make the practice of critical care medicine particularly ethically challenging.

GOALS OF CARE AND MEDICAL DECISION MAKING

Surrogate Decision Making

Modern medicine has embraced the concept of shared decision making between patients and their physicians based on the principles of autonomy (for the patient) and beneficence and nonmaleficence (for the physician).^{1,2} This approach, as noted, is often more complicated in the intensive care unit (ICU). Whether decisions are made in the ICU to continue with aggressive and likely quite burdensome care or to withdraw care,³ there will often be some tension within the care team or between the care team and members of the patient's family (who may be conflicted themselves).⁴ In the ICU, as in other medical situations, this model of shared decision making affirms that patients have an ethical (and in many places, a legal) right to determine the goals of their medical care. Choosing which health-related goals to pursue for a patient who has temporarily or permanently lost decision-making capacity is an imperfect science, but an individual patient's wishes regarding care may have been made known in advance of a serious medical illness to the physician or to a specific preferred surrogate decision maker or to family or friends. The process by which patients, with or without the assistance and participation of their physicians, family members, or other close personal relations, plan for future medical care is called *advance care planning*.⁵ In general, the results of these deliberations are known as *advance directives*; defined broadly, they may be verbal or written and may be quite specific or very general. In this process, the patient may designate a preferred decision maker or healthcare proxy, may lay out general goals and values related to illness and medical treatment, and may determine what kind of care he or she would want in the settings of some anticipated situations. Subsequently, the advance directive helps direct medical care in the case of the patient's incapacity and comes into play only if the patient is unable to make his or her current wishes known.⁶ For example, a patient who awakens after a surgical procedure and is deemed to have decision-making *capacity* (see later) is asked outright about his or her wishes, and the advance directive is no longer necessary.

Advance directives have ethical authority in whatever form (including verbal), as long as the directive was promulgated within the requirements of valid informed decision making (see later) as a tool

for formally bringing the patient's values into consideration at a time when the patient is not capable of supplying them himself or herself. As noted, this method of approximating the patient's goals and values in times of serious illness is not perfect, and the reliability of a specific advance directive as “authentic representations of autonomous patient choices” is often suspected.⁷ Advance directives specific enough to guide the day-to-day clinical decision making in the ICU are rare; more commonly, the ICU physician is left to work with a surrogate to understand the priorities of the patient and then to make shared decisions for the patient. Even in situations in which the physician “knows what the patient would want,” the wise clinician will seek counsel from individuals who know the patient well to mitigate the risk of paternalism. Who then may and should act as surrogate? How should that surrogate make decisions for the ill patient?

In some cultures, physicians often turn to the “next of kin” for surrogate decision making. However, the legal status of surrogates varies from country to country, and in many jurisdictions this individual has no de facto legal or even ethical grounds for assuming this role. (However, in some cultures, religion, and legal traditions, serious decisions about life-sustaining care are not made by individuals but rightfully by the religious authority or clan leadership.) In a culture that favors individual autonomy, the best surrogate decision maker is the one chosen in advance by the patient.⁸ Often this individual comes from the patient's valued community; usually, this individual is a member of the patient's family or close social circle. In those jurisdictions in which such a hierarchy has been determined by law, a typical sequence might be (1) spouse, (2) eldest child, (3) next child, (4) parent, (5) sibling, and (6) close friend. Once a surrogate decision maker has been named, it may be helpful for the patient to clarify the role of the surrogate, from simply “tell the doctors what I want” to “use your judgment to make the best decision about my care.” Interestingly, when asked whether they would prefer that their advance directives be followed no matter what or that their care be discussed with their chosen surrogate, a majority of patients would cede authority to the surrogate along the lines of “use your judgment.”⁹

Even in situations where the appropriate decision maker is not the patient, it is helpful to have documented that the patient agrees with this approach. Similarly, some statement of the values to be used when deciding about medical treatment can be helpful.

Documentation of advance directives allows patients to make their values regarding and wishes for future care known, either formally or informally. As noted, these directives may also designate a specific surrogate decision maker who then has ethical and often legal standing to make medical decisions for the patient. In the absence of advance directives, the legally appointed surrogate or, in the absence of such a surrogate, those who know the patient well make decisions for the patient using substituted judgment based on his or her knowledge of the patient's health-related values. When no information is available about a patient's wishes or values, the decision makers should apply a “reasonable-person” or “best-interest” standard. In such cases, consultation with an ethics committee may be helpful.

Advance Directives

As noted, advance directives are formal or informal instructions to healthcare providers, family members, or others involved in a patient's care regarding treatment that may be required while the patient is unable to participate in medical decision making. The earliest form of

advance directive was the “living will.” Classically, the living will is restricted in terms of both scope and applicability. Living wills are usually reserved for patients with terminal illnesses and are typically restricted to statements about forgoing medical treatments that would “only prolong my dying”; they typically make explicit statements about the acceptability of discontinuing intravenous fluids and artificial nutrition if death is imminent and there is no significant hope for recovery. They usually do not provide instructions in the case of nonterminal illness and typically do not name a surrogate. A more generally useful legal document is the one that gives statutory authority to an individual to make medical decisions for a patient in the case of incapacity. This document is sometimes referred to as a *durable power of attorney for health care*. Similar to a durable power of attorney that provides legal decision-making authority for financial and other matters in the case of incapacity, this document provides legal standing to a named surrogate with regard to healthcare decisions. These documents typically provide an opportunity for an individual to give general information about healthcare preferences in a variety of situations. Some also provide an opportunity for the person to make a statement about the quality of life and the kind of life that would and would not be worth living. Preferences for organ donation, wishes for spiritual care, and even funeral arrangements are sometimes included.

Additionally, a number of advisory documents have been developed, including “values histories” and the medical directive developed by Linda and Ezekiel Emanuel.¹⁰ These documents may present a series of increasingly dire scenarios and ask about overall preferences (“do everything possible to prolong life,” “continue aggressive care but reevaluate often,” “keep me comfortable, but do not provide care that prolongs my life”), or they may ask more general questions about what makes the person’s life “worth living.” It is hoped that this information will be helpful to a surrogate who must decide whether to continue supportive care in the case of irreversible injury or damage or even to continue disease-oriented care in the case of critical illness and impaired decision-making capacity.

For a variety of reasons, advance directives have not achieved wide popularity. When they exist, they are often not specific enough to provide meaningful guidance.¹¹ Even when a detailed directive exists, questions often remain about whether the individual was adequately informed and, in some cases, whether the individual had decisional capacity at the time. For example, a patient’s advance directive says that she would never want to be on life support, but when she is asked about mechanical ventilation in the case of reversible respiratory failure from pneumonia, she says of course she would want that. Thus, following a legally executed advance directive without verifying what was meant by the patient and whether the written wishes apply to the current illness can be quite problematic. It could in fact result in a preventable death in a patient who, with proper education, would wish to be treated.

A more limited form of advance directive, known as a *code status*, is frequently sought on admission to the hospital. A code status is an advance directive that is specifically limited to a patient’s (or surrogate’s) preferences regarding cardiopulmonary resuscitation (CPR) and other measures in the event of a cardiopulmonary arrest. In many hospitals and other healthcare institutions, as a matter of policy, any patient who suffers a cardiac arrest is treated with interventions designed to attempt to reverse the life-threatening derangement, including CPR, electrical defibrillation, and intubation and mechanical ventilatory support. Because a patient who suffers a cardiopulmonary arrest will die in a very short time without interventions, the discussion about code status is as much about how a patient wishes to die, as it is about whether he or she wishes to live. Tomlinson and Brody distinguished three distinct rationales for a do-not-resuscitate (DNR) status¹²: (1) CPR has such a low likelihood of producing the desired outcome that it is effectively “futile,” (2) there would be an unacceptable quality of life after CPR, and (3) there is already an unacceptable quality of life, and cardiopulmonary arrest would be a welcome deliverance. While often conflated with wishes for treatment of a variety of current or future medical conditions, a decision about CPR may not

give much useful information about a patient’s preferences regarding other aspects of his or her illness. A patient may choose aggressive disease-oriented measures well into a severe illness but still choose to forgo resuscitation in the event of an arrest. This approach may be voiced in a statement such as, “I want to fight this thing with all I have, but when it is my time, I want to go quickly without suffering.” Such a statement would be an opportunity to address resuscitation status, in addition to addressing overall goals of care (see later).

Many ICU patients who are actively receiving intensive disease-oriented care have a DNR code status. Such a directive may save surrogates and family members from the emotionally difficult task of removing life-supporting care. A patient’s acceptance of DNR status may signify acceptance of the limits of medical science; refusal of DNR status in the setting of progressive irreversible illness may be an indication that the patient has an incomplete and perhaps unrealistic understanding of the illness. Further discussion addressing knowledge deficits or unspoken fears may increase the likelihood that the patient’s true wishes will be followed.

There are a number of common errors that may occur when discussing the code status. The first is failure to convey accurate information about the likelihood of success after an attempt at resuscitation. Many patients have an unrealistic impression of the utility of this intervention.¹³ Another type of error is failure to address postresuscitation issues, when caregivers mistakenly assume that “do everything in the case of a cardiopulmonary arrest” also means the patient wishes the care team to continue to “do everything” afterward. Patients who undergo CPR will most likely be incapacitated for at least a period after the resuscitation, even in the best scenarios. A third type of error is to not take the opportunity to identify a preferred surrogate decision maker, given the significant risk of temporary or even permanent brain injury after the attempt at resuscitation.

Any discussion of advance directives should attempt to answer at least three questions: (1) In the event of a cardiac arrest, do you want the healthcare team to attempt resuscitation? (2) If you become incapacitated, who do you want to make decisions for you? (3) If you were left significantly impaired after an attempt at resuscitation, under what circumstances would you want us to discontinue life-sustaining care? Additionally, preferences for resuscitation are best understood in the context of an individual’s values, beliefs, relationships, and culture.⁷

Many problematic end-of-life issues can be traced to a focus on interventions (“Would you wish to be intubated?”) without an adequate exploration of values (“What do you value about your life? What are the things that make your life worth living?”). It is also a mistake to think about advance directives as an issue limited to end-of-life situations. Advance directives are really just part of informed consent for any treatment, and discussion of advance directives is an important aspect of good medical care.

Informed Decision Making (Informed Consent)

In the United States, individuals are free to develop their own conceptions of happiness or a good life. By extension, choices about medical tests or treatment are made by patients in ways that maximize the likelihood of that good being achieved. This is called *patient autonomy*, and some would call it one of the core principles that define the relationship between a doctor and a patient. Respecting autonomy requires respect for the values and wishes of the individual. Additionally, the exercise of autonomy requires adequate information, the power of reason, and freedom of choice. Shared decision making happens when an autonomous individual has a conversation with the physician that incorporates the patient’s values (autonomy) and the values of the physician.

Brock discussed the basic requirements for informed consent and identified three critical elements: the person giving consent must be competent, informed, and able to make a decision free from coercion.¹³ *Competence* has several critical elements.¹⁴ First, the decision maker must be capable of understanding relevant information, which involves both memory and mental processing. Second, it requires the ability

to attend to and retain information, the ability to manipulate information, and the ability to foresee consequences. The third element is the ability to formulate and communicate choice. Some standards of competency strengthen this requirement by demanding the ability to communicate a *stable* choice (in this case, ambivalence may be a sign of incompetence).

To adequately participate in medical decision making, patients must have enough information to weigh the risks and benefits of various medical interventions. In the past, the standard for being informed was the standard practice of other physicians in the community.¹⁵ Subsequently, *informed* came to mean what a “reasonable person would want to know.” Because the main point of informed consent is to respect the rights and values of individuals, it is most appropriate to address this issue in terms of what a particular patient needs to know.¹⁶ In general, patients need to know about the illness and its natural history to make informed decisions about medical care. They need information about the effectiveness of treatment, the risks of treatment, and the likelihood of success with treatment. This information must be presented in a way that is understandable to the patient, at an appropriate educational level, and is in the patient’s language. Whether enough information has been transmitted can be assessed at the most basic level by simply asking a patient whether he or she has any questions. Brock writes of “informed understanding” and notes that this “permits an informed exercise in self-determination and promotes a decision most in accord with the patient’s well-being.”¹³ In addition, this approach values autonomy.

The decision must also be voluntary—that is, free of coercion. The decision maker must have the freedom to accept or refuse the intervention or test being proposed. Consent given as a result of undue coercion is generally not valid.

Informed consent in the ICU raises some special issues. First, as mentioned earlier, the decision maker is often a surrogate rather than the patient. The surrogate decision maker should have access to all relevant information the patient would need to make informed decisions; however, the surrogate should not routinely be given confidential information *simply because the patient is no longer competent*. An example may be helpful in illustrating this point. An HIV-positive patient in the ICU has designated a family member as his surrogate; however, the family is unaware of his HIV status. The ICU physician believes a central line is indicated for continued care and seeks informed consent from the family member. In this case, it may be possible to obtain true informed consent for the procedure without divulging the patient’s HIV status. Alternatively, a decision about a test or treatment specifically related to the patient’s HIV status may require that this information be divulged to the surrogate for him or her to make an informed decision.

The adequacy of a properly designated surrogate is usually assumed but should be questioned in two situations. The first is when the surrogate acts in contrast to the patient’s known wishes. Anyone who knows that the surrogate’s directions conflict with the patient’s expressed wishes has an obligation to work with the surrogate to come to a treatment decision more in keeping with the patient’s wishes or to seek outside assistance from the hospital ethics committee or the hospital’s legal department. The second situation occurs when there is doubt about the surrogate’s competence, specifically his or her ability to retain and process information. Again, the ethics committee or the risk management department can be of help in this situation. An important study by Schneiderman et al.¹⁷ demonstrated the value of ethics consultation for ICU patients. In that randomized controlled trial, patients receiving an ethics consultation had shorter ICU and hospital stays as well as a decrease in the use of “nonbeneficial treatments.” This study has led to a call in the literature for more frequent utilization of ethics consultations in the ICU.¹⁸⁻²⁰

FUTILITY

It is often said that “it is futile to define futility,” and this has never been truer than in the current era of medical care. Many diseases that were

once thought to be untreatable are becoming treatable, and diseases with high mortality rates are seeing a decline. It is now common for ICUs to have patients who would have been considered too old or too sick to warrant critical care decades ago. As more of these patients go on to survive the ICU, the boundaries of medical futility get pushed back even farther.

There are many definitions put forth for the term *medically futile*, but most prove inadequate for practical use. The term has been generally used to describe either a patient who simply could not be kept alive (i.e., refractory shock) or a patient in whom death was inevitable in the near future (i.e., advanced cancer). The term *terminally ill* probably better describes the second situation. Nevertheless, these concepts have often been invoked as a justification for limiting lifesaving interventions or denying admission to the ICU. However, this has become problematic. With modern medical interventions such as extracorporeal membrane oxygenation and others that can support vital organ functions, there are fewer times when physicians cannot keep a patient alive. Additionally, as patients with advanced illnesses are increasingly treated in ICUs with the goal of only a few more weeks or days of life, it becomes clear that one person’s definition of *terminally ill* may not be the same for another.

In 2015, several key professional societies (American Thoracic Society, American Association of Critical Care Nurses, American College of Chest Physicians, European Society for Intensive Care Medicine, and Society of Critical Care Medicine) jointly produced and published a statement addressing conflicts of this nature. Notably, the authors chose to avoid using the word *futility* whenever possible, given its subjective nature, and instead use the wording *requests for inappropriate care* to describe situations in which patients or family request care that the physicians feel is of no benefit based on poor prognosis. The statement made several recommendations for physicians addressing such requests.

First, institutions should try to prevent intractable treatment conflicts through proactive communication and early involvement of expert consultants. The term *potentially inappropriate* should be used, rather than *futile*, to describe treatments that have some chance of accomplishing the effect sought by the patient, but clinicians believe that competing ethical considerations justify not providing them. If there is disagreement, clinicians should explain and advocate for the treatment plan they believe is appropriate. Conflicts regarding potentially inappropriate treatments that remain intractable despite intensive communication and negotiation should be managed by a fair process of conflict resolution; this process should include hospital review, attempts to find a willing provider at another institution, and opportunity for external review of decisions. Finally, when time pressures make it infeasible to complete all steps of the conflict resolution process and clinicians have a high degree of certainty that the requested treatment is outside accepted practice, they should seek procedural oversight to the extent allowed by the clinical situation and need not provide the requested treatment.

The group further recommended that the use of the term *futile* should be restricted to the rare situations in which surrogates request interventions that simply cannot accomplish their intended physiologic goal. Clinicians should not provide futile interventions. The medical profession should lead public engagement efforts and advocate for policies and legislation about when life-prolonging technologies should not be used.²¹

In summary, ethics in critical care are founded on the same four primary directives common to all disciplines of medicine. Critical care decision making presents special challenges because these decisions often involve the life or death of patients who are unable to participate in the decision-making process. Although the balance between physician and patient responsibility for decision making may vary across cultures, the primary directive for physicians to act in the best interest of their patients is universal.

KEY POINTS

1. Ethics in medical care is based on four fundamental principles: beneficence, nonmaleficence, autonomy, and justice.
2. In the United States, competent patients have the right to make their own decisions about health care.
3. The process of making known one's wishes regarding future care is called *advance care planning*.
4. In the absence of an advance directive, a surrogate decision maker attempts to make medical decisions for a patient using substituted judgment. When no specific information is available about a patient, decision makers apply a "reasonable-person" standard and sometimes resort to a "best-interest" standard.
5. Discussions about advance directives should be rooted in the patient's values and goals for medical care, as well as the appropriateness of specific interventions.
6. Shared decision making is a process that combines patient autonomy and physician judgment.

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Brain death is a legal term that is defined in most countries as the irreversible cessation of functioning of the entire brain, including the brainstem. The diagnosis of brain death by neurologic criteria based on the current medical guidelines is a combination of clinical, radiographic, and laboratory data. After certain prerequisites, three essential components are necessary for this determination: (1) irreversible coma due to a known proximate cause; (2) the absence of brainstem reflexes; and (3) apnea. In select patients, ancillary testing may be necessary to supplement these clinical findings.

LEGAL AND MEDICAL DEFINITION

Currently, no standardized definition exists internationally for the term *brain death*. Within the United States, the legal basis for this definition originated from the 1981 Uniform Determination of Death Act (UDDA), which states that “death” can be defined as an “irreversible cessation of all functions of the entire brain, including the brainstem.” However, even this definition has been modified by some states with various amendments.

The medical definition and guidelines for the determination of brain death are also inconsistent internationally. In 2010, the American Academy of Neurology published updated practice parameters for the determination of brain death.¹ In 2014, a summary was published outlining the development of international guidelines for the determination of death with the phrase *cessation of neurologic function* being used in lieu of *brain death* or *brainstem death*.² Until these legal and medical terms are more uniformly defined, healthcare providers should be knowledgeable of the local laws, guidelines, and institutional regulations prior to the determination of brain death in a patient.

PREREQUISITES

Determination of brain death begins with establishing an irreversible and proximate cause for coma in a patient with continued cardiac function on mechanical ventilation. The irreversibility and proximate causes are established through a combination of the history of present illness, clinical examination findings, radiologic imaging, and laboratory data. The patient’s history and/or CNS radiology should be suggestive of a mechanism of injury to the brain that may lead to complete cessation of brain function. The gamut may include circulatory arrest with the absence of cerebral perfusion to a penetrating injury to the skull or a severe CNS infection with global cerebral edema with herniation. The patient’s clinical examination with no sedative agents should be that of a comatose patient who is defined as having eyes closed and no appropriate interaction to external environmental stimuli. Hypothermia (defined as a core body temperature below 36°C), CNS depressant agents, and neuromuscular blocking agents may obfuscate the clinical examination and need to be systematically excluded. Furthermore, severe electrolyte or endocrine abnormalities may also impact a patient’s mental status and need to be corrected before the diagnosis of coma.

COMA

The examination shows that the patient’s eyes are not held open voluntarily and that no movements are made to verbal or noxious stimuli.

Standard points of noxious stimulation include nail bed, supraorbital, or temporomandibular pressure.

Absence of Peripheral Motor and Sensory Responses

Noxious stimuli in the form of nail bed pressure or muscle pinching should produce no grimacing or withdrawal of the arms and legs. Occasionally, spinally mediated reflexes may remain intact. Differentiating spinally mediated reflexes from retrained motor responses due to cortical activity can be difficult at times and require neurologic expertise.

ABSENCE OF BRAINSTEM REFLEXES

Pupillary Response (Cranial Nerve II)

Pupillary responsiveness should be assessed with a bright flashlight. An ophthalmoscope can be used for magnification to assess for a subtle pupillary response. The pupils are usually round or oval and in mid-position (4–6 mm in diameter). Dilated pupils may suggest intact spinal sympathetic pathways or the release of stored norepinephrine from presynaptic terminals in the orbit. Infrared pupillometry may detect subtle pupillary responsiveness that may not be visible by the examiner.

Assessment of Eye Movements (Cranial Nerves III, VI, VIII)

Cervico-ocular Reflexes (“Doll’s-Eyes Maneuver”)

This maneuver can be performed only after a cervical spinal injury has been excluded. With the patient’s eyelids held open, the head is rapidly turned 90 degrees from midline to the right and the left. If the patient is intubated, the endotracheal tube should be moved with the patient’s head to avoid laryngeal damage or unplanned extubation. The term *doll’s eyes* refers to the expected conjugate horizontal movement of the eyes in the direction opposite to the head movement. This reflexive movement will only occur if the frontal cortex is not providing any input, such as in a comatose patient with intact brainstem reflexes. The absence of eye movements in a comatose patient during head movement is consistent with either upper brainstem dysfunction or a diagnosis of brain death.

Vestibulo-ocular Reflexes (“Cold Calorics”)

Once the cervico-ocular reflexes are determined to be absent, or in circumstances in which these reflexes cannot be tested due to cervical spine instability, the vestibulo-ocular reflexes should be assessed using cold calorics. First, the external auditory canal should be examined to ensure the absence of an obstruction. Given the clinical implications of diagnosing brain death, the presence of a tympanic membrane perforation should not preclude cold caloric testing. The patient’s head of the bed should be raised to 30 degrees. Ice-cold water (the authors use 60 mL) should be placed in a syringe and instilled into the ear while the patient’s eyelids are held open. The amount of water is less important than its temperature; the goal is to depress the temperature of the internal auditory canal. In a comatose patient with intact brainstem reflexes, the eyes should deviate toward the side of the cold water

stimulus. The absence of eye movements is present in a patient who is brain dead. The eyes should be examined for 1 minute after the ice water irrigation. After 5 minutes, the procedure should be repeated in the opposite ear.

Facial Sensation (Cranial Nerve V) and Motor Response (Cranial Nerve VII)

Reflexes involving the cranial nerves V and VII need to be absent before the diagnosis of brain death can be made. The corneal reflex can be assessed by placing a gentle stimulus across the cornea of each eye individually to assess for a blink response. This can be accomplished with a wisp of cotton; however, we prefer a drop of saline to prevent the development of corneal abrasions, which may preclude tissue donation. A jaw jerk can also be assessed by the examiner striking his or her finger (CN VII) placed on the chin to assess for jaw closure (CN V). The absence of a grimace response to the noxious stimulus of the supraorbital ridge or temporomandibular joint should also be tested.

Gag and Cough Reflexes (Cranial Nerves IX, X)

The gag response can be difficult to determine in patients with an endotracheal tube in place. Furthermore, the absence of a normal gag reflex in a significant proportion of healthy subjects renders this test less than useful in a comatose patient. Rather, a cough in response to deep endotracheal suctioning should be evaluated. The absence of a cough response is required for a determination of death by neurologic criteria.

■ APNEA TESTING

After meeting the criteria above, the examiner should proceed with apnea testing to fulfill the diagnosis of brain death. Due to the potential need for frequent arterial blood gases and hypotension during the apnea challenge, the authors place an arterial catheter if one is not already in place. The patient's systolic blood pressure should be maintained >100 mm Hg with adequate intravascular volume repletion and vasoactive agents if needed. The patient should be oxygenated with FiO_2 of 1.0 for at least 10 minutes to obtain a $\text{PaO}_2 > 200$ mm Hg. Longer periods of preoxygenation may be required, but apneic oxygenation should be provided as described in the next paragraph.³

Although the actual trigger for breathing during the apnea test is a decrease in the arterial pH, the test has traditionally been based on the rise of the PaCO_2 . The patient should be disconnected from the ventilator to prevent the false interpretation of artifactual breathing on the ventilator. An oxygen insufflation catheter should be inserted into the endotracheal tube at the level of the carina with the delivery of 100% oxygen at 6 L/minute to provide apneic oxygenation. Patients with poor baseline oxygenation can be placed on 10 cm of continuous positive airway pressure or an appropriate level to optimize baseline oxygenation. The patient's chest wall is closely watched for chest expansion, clavicle elevation, and abdominal excursion. Assuming a normal baseline PaCO_2 (35 to 40 mm Hg), the maximal respiratory drive is believed to occur at a PaCO_2 of 60 mm Hg. If an arterial blood gas shows a PaCO_2 of 60 mm Hg or greater with continued apnea, the diagnosis of brain death is met. Alternatively, an increase in PaCO_2 by 20 mm Hg also meets the criterion.

With an expected PaCO_2 increase of 3 to 6 mm Hg per minute, a target PaCO_2 of 60 mm Hg should occur within 8 minutes after discontinuation from the ventilator. Occasionally, it may take longer to establish this cutoff. The rate of CO_2 production may be affected by the patient's core body temperature and hemodynamics. Since pH is the main determinant of respiratory drive, an equivalent change in the arterial pH may be more reliable than a change in PaCO_2 . The pH should primarily be used in patients with an abnormal baseline PaCO_2 , such as those with underlying lung disease.

In the event the apnea challenge cannot be completed due to cardiac arrhythmias, worsening hypotension, or arterial desaturation, an ancillary test must be performed.

■ ANCILLARY TESTING

An ancillary test must be conducted to declare brain death if the apnea challenge cannot be performed or if uncertainty exists regarding the reliability of parts of the neurologic examination. The validity of these tests, however, remains to be determined.⁴ In several countries, ancillary testing is required by law. In the United States, the need for this type of testing is left to the discretion of the physician.⁵

Cerebral Angiography

Cerebral angiography remains the gold standard to assess intracranial blood flow; however, specific radiographic criteria to define brain death are lacking. The absence of intracranial flow on angiography at the level of entry of the carotid and vertebral artery to the skull has been suggested as being consistent with brain death. The presence of contrast in the external carotid circulation should be present to ensure an appropriate contrast injection. However, in upward of 30% of brain dead patients, there was proximal opacification of the intracranial arteries, with none having deep venous drainage.⁶

Computed Tomography Angiography (CTA)

The utility of CTA as an ancillary test to support brain death remains an issue of debate. In two systematic reviews, the sensitivity and specificity of CTA varied depending upon whether the arterial or venous phase of imaging was used.^{7,8} The sensitivity for brain death seems to be the highest (99%) with the absence of opacification of the internal cerebral veins.

Transcranial Doppler Ultrasonography

Transcranial Doppler ultrasonography (TCD) can be used to assess cerebral blood flow at the bedside, particularly in patients who are too unstable for a conventional angiography or CTA. A distinct pattern of oscillating flow or systolic spikes is typically seen on TCD. Occasionally, an absence of flow is also noted. However, caution must be taken since upward of 10% of patients may have thicker temporal bone windows that do not allow adequate insonation. Two systematic reviews suggest that TCDs have $>85\%$ sensitivity and $>95\%$ specificity; however, these values have a wide range, likely due to the operative dependent nature of the procedure.^{7,9} Nevertheless, TCDs may be helpful in deciding the optimal time to send an unstable patient for ancillary brain death testing.¹⁰

Radionuclide Imaging

Both planar scintigraphy and/or single photon emission computed tomography (SPECT) are utilized in the ancillary testing for brain death. Either of the radioisotopes Tc 99m hexamethylpropyleneamine oxime (HMPAO) or Tc 99m ethylene cysteine diethyl ester (ECD) may be used. The absence of radioisotope uptake into the brain parenchyma is consistent with absent intracranial blood flow and brain death. In a recent systematic review, planar imaging was found to have a sensitivity of 77.8% and specificity of 100% while SPECT was found to have a sensitivity of 90.1% and specificity of 100%.¹¹ As with other ancillary tests, "false-negative" cases for brain death have been reported in the literature.

Electroencephalography

The presence of electrocerebral silence according to published guidelines on electroencephalography (EEG) may be consistent with death by neurologic criteria.¹² The EEG will be affected by the same

confounding factors as the physical examination, such as hypothermia and sedative drugs. Furthermore, electrical activity that is frequently found in an ICU may cause artifacts on an EEG. Several contemporary series of patients have shown a minimal discrepancy between a clinical diagnosis of brain death and EEG findings. Limiting factors may include availability and technical expertise.

Other Tests

Experience with magnetic resonance imaging remains limited and cannot be recommended at this time. Somatosensory evoked potentials (SSEP) may be absent due to severe drug intoxication or hypothermia and should not be used for this purpose.¹³

KEY POINTS

1. Healthcare providers should understand the local laws and regulations regarding the determination of death by neurologic criteria.
2. After certain prerequisites are met, three essential components are necessary to determine death by neurologic criteria: irreversible coma or unresponsiveness, the absence of brainstem reflexes, and apnea.
3. In patients in whom an apnea challenge cannot be completed due to the development of clinical instability, ancillary testing must be performed.
4. Sensitivity and specificity of the various ancillary testing are variable, and the use of specific tests is largely determined by local practice and expertise.

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The intensive care unit (ICU) has evolved into a complex environment with multiple professionals practicing together to provide patient care. Technology and care options for critically ill patients have progressed, resulting in improved patient outcomes. While these advances benefit patients, they add to the complexity of care and knowledge needed by critical care providers. The aging population has further strained the healthcare system, creating a greater demand for critical care services. Thus, because of these changes, teamwork is an essential practice when providing care in the current ICU environment.

This chapter will address teamwork in critical care, components of effective teamwork, the impact of teamwork on patient outcomes, strategies to build effective teamwork, and barriers to teamwork in critical care.

THE IMPORTANCE OF TEAMWORK IN CRITICAL CARE

Several factors challenge the achievement of good teamwork in the ICU. Patients admitted to the hospital today have a higher acuity, yet due to cost constraints, there is an increased need for critical care beds and throughput; they are being cared for with shorter lengths of stay (LOS). With an emphasis on using the best and current evidence to guide practice, growth in critical care research makes keeping up with best practices difficult. Critical care practice occurs in a fast-paced environment of constant change in patient census, patient condition, staffing, and available resources, which can breed chaos. Increased oversight by regulators and third-party payers also affects practice, as caregivers struggle to observe fiscal restraint with scarce resources, without compromising quality of care. Clinicians must be able to individualize care, represent the patient's best interest, support family needs, achieve high satisfaction scores, and resolve complex ethical issues. These factors can breed stress, distress, or conflict. Moral distress, posttraumatic stress symptoms, depression, and burnout are all commonly found in critical care clinicians.¹

Healthcare regulatory agencies, commissions, and professional organizations have increased emphasis on the importance of collaboration to achieve quality outcomes. The Society of Critical Care Medicine (SCCM) has focused on delivering the right care, right now. They advocate the delivery of care by an integrated team of dedicated experts who learn, implement, measure, and improve it. Recognition of the importance of teamwork and collaborative practice extends all the way to the education of health professionals. The Interprofessional Education Collaborative (IPEC) published an expert report in 2011 outlining the importance of interprofessionalism and defined core competencies, one of which was teams and teamwork.² Nursing and Pharmacy serve as exemplars with the largest number of actionable skills in their accreditation standards.³

Leaders are gaining appreciation for how organizational structures and processes affect patient outcomes and the importance of highly functional teams. They are creating systems that allow teams to function at the highest level to reduce costs and improve patient outcomes. Successful hospitals will be those that can attract, train, and retain expert team members. Entry-level team members will more likely stay in an environment where they experience meaningful work and thrive within effective teams. This is one strategy to maintain team competence and reduce costly turnover. Top hospitals will build environments

with top-notch teamwork and an intolerance of poor performance and that is supportive of team members who vocalize concerns.

COMPONENTS OF EFFECTIVE TEAMWORK

Broadly, *teamwork* is defined as working well together to accomplish a common goal. Important components include communication, competence, trust, cooperation, coordination, respect, accountability, conflict resolution, and shared decision making.

Historically, healthcare professionals have practiced as individuals, demonstrating autonomy in their respective field of practice supported by its own body of research. ICU patients require multifaceted interventions by an interdisciplinary team of experts. This process requires moving away from isolated practice toward collaborative practice with other healthcare providers. Regularly scheduled interaction among the interdisciplinary team focused on patient-centric goals can foster greater collaboration and communication and can optimize patient outcomes. Through the exchange of ideas and expertise, practitioners become familiar with the nature and scope of one another's practice and are able to assess individual competence. This can build trust and promote the understanding of the unique contributions of team members and their interdependence for providing care. Focusing on the common goal to provide the best possible care for patients is key to reducing team conflict.⁴⁻⁶

Over time, trust and open communication promote respect. Team members begin to appreciate each other's skills, knowledge, and judgment. In collaborative practice, responsibility is shared, so that goal setting and decision making occur jointly.

Being a good team player is a key ingredient to a team's success. Given the obligation to provide the best care for our patients, every team member has the responsibility to make an optimal contribution, speaking up whenever his or her input could be helpful, and listening actively to others' input, while maintaining an open mind. Mutual support among the team (encouraging expression of ideas and positive professional communication) is important to build confidence and perceived value to the team. These actions can lead to collective intellectual capital by the team and potentiate clinical effectiveness.

Team leadership is also critical to performance. Good leaders generate two-way trust, respect, and communication. They have vision, self-confidence, enthusiasm, tolerance, and a commitment to excellence. They are organized and prepared, fulfill commitments, inspire shared missions, grow new leaders, model behaviors, challenge processes, tolerate ambiguity, and remain calm. Leaders who think out loud help novices develop their teamwork skills and competence. Leaders also set the tone for the function of the group and must demonstrate respect for the collective contribution of its members. Team members must ask for help when needed and express concerns without retribution in an environment that is psychologically safe. To have high-quality ICU teamwork, each team member should possess leadership characteristics, as team leadership often changes, depending on the issue at hand.

IMPACT OF TEAMWORK ON OUTCOMES

Despite the support for teamwork and the development of an interdisciplinary team model for the care of critically ill patients, research on

the relationship to outcomes is limited.⁷ A literature review on the effectiveness of patient care teams in a variety of healthcare settings found a limited effect on patient outcomes, and the added value of coordination of care was unclear.⁸ However, reports from studies in critical care have demonstrated positive effects.

Teamwork and Patient Safety

ICU patients are highly susceptible to medical errors. Severity of illness, intervention complexity and number, invasive devices, and ICU LOS put critically ill patients at a higher risk for adverse events and errors.⁹⁻¹² One comprehensive review of critical incidents in intensive care showed an increased incidence of adverse events when there was a deficit in nontechnical skills, including elements of teamwork.¹³

Ineffective communication and poor teamwork have been identified as significant contributors to patient errors and critical incidents in the ICU.^{12,14,15} Improved communication may reduce adverse events and errors.^{15,16} In medicine, the focus has been on what should be done with insufficient attention to planning or execution.¹⁰ To effectively carry out any ICU care plan, coordination between disciplines and departments with clear, specific communication about the treatment plan is needed. One initiative to improve teamwork in the ICU involved establishing physician-led multidisciplinary rounds, assessing bed availability daily, and using “bundles” of evidence-based practice care. The results included a significant reduction in nosocomial infections (ventilator-associated pneumonia (VAP), bloodstream and urinary tract infections), adverse events, and the cost of care. A team decision-making culture places the responsibility on the team rather than on the physician, empowering team members to contribute.¹⁷ More recently, multidisciplinary teams have implemented checklists for assessing each patient to improve communication among providers, enhance team knowledge, and better coordinate care.

The Veterans Administration reported improvements in team communication and quality of care after implementing a training program to enhance team performance, satisfaction, and patient outcomes.¹⁴ They credited their debriefing training and process with the avoidance of adverse events of wrong site/wrong procedures, improvements in surgical efficiency, fatigue management, active collaboration among disciplines, nurse job satisfaction and morale, and reduced errors in surgical patients.

Teamwork and Patient Outcomes

Intensivist-led multidisciplinary teams have been espoused as an ideal model for critical care. However, insufficient numbers of trained intensivists exist to meet current or future demands, and a limited number of ICUs have implemented intensivist staffing.^{7,18} Furthermore, outcome studies on intensivist-led care demonstrate mixed findings.^{7,18,19} One large patient cohort study compared the mortality outcomes from hospitals with daily multidisciplinary team rounds with and without intensivist models.⁷ Hospitals with high intensivist staffing and multidisciplinary team care had the most significantly reduced odds ratio of death. Interestingly, hospitals with multidisciplinary care, but low physician staffing, also had significant odds reduction in mortality, reinforcing the idea that patients benefit from care by a multidisciplinary team. Mortality has been significantly reduced in patients with acute lung injury cared for by multidisciplinary teams led by full-time critical care physicians.²⁰ The use of the intensivist-led team model also led to significantly reduced mortality, duration of mechanical ventilation, and rates for VAP in a military setting.²¹ A literature review summarized that the team model for ICU care delivery was associated with reduced mortality, ICU and hospital LOS, and the cost of care.²²

One hospital in Illinois implemented evidence-based bundles of care and a multidisciplinary daily goals rounding tool, resulting in decreased ICU LOS, improved protocol compliance, reduced VAP, bloodstream infections, falls, and pressure ulcers in surgical ICU

patients.²³ Cheung et al. did not find improved outcomes when the team met on a weekly basis and concluded that the meetings were too infrequent to impact patient outcomes.²⁴ Research indicates that teamwork can also improve timely discharge from the ICU through the coordination of efforts.²⁵

The ability to achieve patient goals in the ICU is impacted by team leadership and the management skills of attending physicians.²⁶ Written daily goals in the ICU improve communication about care expectations and the follow-through on treatment plans. Failure to complete treatment plans has been recognized as a key contributor to errors and increased ICU LOS.^{10,26} Fostering teamwork to accomplish daily goals can improve care effectiveness and patient safety.

Multidisciplinary teams developed to respond to shock in non-trauma patients resulted in decreased time to treatment, intensivist arrival, and admission to the ICU.²⁷ This led to a significant reduction in mortality and improved patient outcomes.

Teamwork and Team Outcomes

Attitudes and perceptions of the teamwork quality vary widely among institutions, units, individuals, clinicians, and professions. Communication, a key component of teamwork, has been associated with job satisfaction. Studies have shown a difference in perception about communication among practice disciplines in critical care.^{4,15,28-31} Nurses report a lower quality of communication with physicians than physicians report. In one survey of critical care nurses, only 33% ranked the quality of collaboration and communication with physicians highly as compared to 73% of physicians.⁴ The degree of open communication among ICU team members was correlated with a better understanding of patient care goals. A study by Huang²⁹ found that physicians, leadership, and nursing directors tended to overestimate nurses' attitudes on teamwork climate and working conditions. Weinberg³⁰ found that the quality of medical resident communication with nurses was dependent on a nurse's degree of cooperation and congeniality. The level of trust in information communicated also was dependent on the perception of nurse competence and the ability to relay relevant information in a timely manner. Nearly all physicians reported instances of poor communication with nurses. They did not see it as a threat to patient care, because they thought the nurses' role was to simply follow orders, suggesting these medical residents did not view nurses as colleagues and collaborators. Differing perceptions between nurses and physicians also exist regarding dying patients in the ICU.³¹ Nurses reported more moral distress and less collaboration than physicians. Nurses perceived the ethical environment as more negative and were less satisfied with the quality of patient care than were the attending physicians. Their evaluation of quality of care was strongly related to the perception of collaboration among disciplines. In critical care, the multidisciplinary team members are dependent on each other to accomplish the complex needs of patients, and all are accountable for the outcomes achieved. The strides being made in interprofessional health care education may help to reshape these paradigms.

When teamwork increases the efficiency of care, an increased sense of accomplishment can occur.^{32,33} Research has shown that nurses preferred communicating with attending physicians over first-year residents and valued shared understanding and open, accurate communication.³⁴ The more experienced nurses required effective communication with experienced physicians. Another study showed that nurse-to-physician communication was a significant predictor of nurse job satisfaction and the quality of the practice environment.³⁵ The degree of workplace empowerment and perceived quality of the environment was significantly related to communication between nurses and physicians.³⁶⁻³⁷ When a higher level of nurse-physician communication was reported, medication errors were reduced,³⁶ and when the timeliness of communication improved, the prevalence of pressure ulcers decreased.³⁷ This further reinforces the notion that good communication may lead to a sense of team ownership of the unit and patients and may translate into better overall care.

Finally, daily multidisciplinary rounds led by a hospitalist medical director paired with a nurse practitioner resulted in improved physician-to-nurse collaboration, particularly with residents. The nurse practitioner facilitated coordination of patient care and nurse-physician communication.³⁸

STRATEGIES TO ESTABLISH BETTER TEAMWORK

Since teamwork is so important for practice in the ICU, it is vital that steps be taken to implement team structures and processes that can help build teamwork in critical care. Models to develop strong teamwork have developed from industries with high risk for errors, including aviation, the military, and nuclear power. In these industries, effective teamwork is an important mechanism used to maintain safety, reduce errors, and increase efficiencies.^{39,40} Team members use specific processes for communication, leadership, coordination, and decision making to achieve positive team performance outcomes.

Although healthcare is different from these industries, lessons can be learned to improve teamwork in critical care.³⁹ Applicable strategies include standardizing work processes and using checklists to ensure patients are consistently receiving care based upon the best current scientific evidence and to improve teamwork skills, collaborative engagement, and communication. All interdisciplinary team members should be able to speak up when they identify potential patient safety hazards, and mechanisms should be developed to openly identify areas of high risk for errors and harm. A blame-free culture encourages team members to recognize, report, and thus minimize errors and learn from mistakes. Much like in an assembly line, when one team member recognizes the potential for harm, it must be pointed out and managed expeditiously.

Reader et al.⁴⁰ consolidated the research literature of the relationship between teamwork and patient outcomes in critical care. They emphasized that effective teamwork is crucial to provide optimal patient care in the ICU, and good leadership is vital for team interaction and coordination. Four key performance competencies are needed to build effective teams in the ICU: (1) team communication; (2) team coordination; (3); team leadership; and (4) team decision making.

Another strategy to engage ICU interdisciplinary teams is the involvement in quality improvement initiatives.⁴¹ Including key stakeholders from various professions is important for comprehensive team engagement when developing plans for practice improvements. Ongoing behavior modifications may be needed to engage all team members in the change. Good team leaders collaborate with team members to sustain quality efforts and help them through difficulties in adapting to change.

Barriers to Team Performance

Implementing teamwork strategies within healthcare has its challenges. Barriers to implementing a critical care team model can include local customs, hospital patterns, and reluctance to change despite proven benefit.²² Implementation requires a cultural shift. Hierarchic and status differences can present a barrier to team function and the ability of team members to openly contribute to the plan of care if they are not convinced that their input is important.^{28,42}

Another barrier to the intensivist-led team in the ICU is inadequate numbers of qualified physicians trained in critical care.¹⁸ The ability to recruit medical residents into critical care fellowships is challenging, particularly with concerns about financial compensation and the hectic lifestyle. Costs are also associated with implementing the intensivist model.^{18,22} While the absence of intensivist-led leadership presents more difficulty in implementing team models of care, establishing a multidisciplinary team in the ICU is still possible and improves outcomes.⁷

Another obstacle is that working as a team requires team members to forfeit some of their autonomy in practice.²² This may be difficult when team leaders place high value on their ability to independently

orchestrate care. The physician leader must be willing to engage members of the team and establish respect and trust for their contribution to discussion and decision making, as well as to create an environment that welcomes such activity.

Many practitioners in the ICU have not been trained in teamwork activities and are unfamiliar with the nontechnical skills required to perform well on a team.¹³ Individual team members' knowledge, skill, and personality characteristics influence their effectiveness on teams.⁸ One qualitative study showed that the amount of emotional distress that individual members experienced during medical crises impacts the function of the entire team through contagion of anxiety.¹ Another study on team interactions during crises found that in the postcrisis period, nurses were left with significant questions and emotions about the event compared to other team members.⁴³ Potential solutions to these barriers are interdisciplinary team debriefings and feedback sessions immediately after crises, assessing for anxiety and defuse emotional breakdowns during critical interventions. Leaders can evaluate gaps in teamwork competencies, and determine opportunities for team training in safe settings to prepare members emotionally for real events.

Programs Used to Develop Teamwork in the ICU

Programs designed to improve team core competencies and communication skills may be accomplished through experiential team learning. A pediatric ICU provided an interdisciplinary experiential learning day-long program to improve communication skills and relationship abilities when having difficult conversations with family members. The training included videotaped case scenarios, debriefing, and sharing their experiences. This approach resulted in improved communication skills, confidence, perceived preparation, and reduced anxiety.³²

Teamwork skills can be developed to improve the communication between physicians and nurses to improve care at the end of life (EOL).⁴⁴ Studies show that nurses and physicians differ in perspectives and burdens felt with EOL decisions. Strategies to improve communication among caregivers include joint grand rounds, patient care seminars, and interprofessional dialogue regarding EOL care during daily rounds. Teamwork can also be enhanced when multidisciplinary expertise is focused on key patient outcomes. One example was a critical care team that identified factors that interfered with mobility in mechanically ventilated patients.³³ The ICU team developed a strategy for early mobility in ventilated patients and measures to evaluate the effectiveness on patients' functional abilities and long-term outcomes.

Programs to improve patient safety and collaboration in the ICU have been developed using a crew resource management (CRM) approach.⁴² One group identified five key components needed for hospital CRM training: communication, task management, situational awareness, decision making, and leadership.⁴⁵ Program content on interpersonal communication, conflict resolution, and the nonthreatening critique of team performance and methods to improve system processes for care (e.g., using checklists and standardizing handoffs to relate key information, debriefings for patient errors, cross-checking, and ongoing review of patient care plans) can reinforce concepts. Courses like these can prepare team members to actively participate in decision making, voice concerns, and make recommendations for patient care in a constructive manner.

Simulation-based learning is another mechanism for training the team to function under specific circumstances. Team learning in scenario-based simulation exercises allows professionals to learn their roles and practice safely under circumstances outside of stressful clinical settings.

Simulation can be used for education on specific care topics involving teams. Examples include managing septic shock using high-fidelity mannequins and scenario-based videos,⁴⁶ resuscitation and management of acute respiratory failure, airway management, myocardial ischemia, trauma, and shock.⁴⁷ Simulation-based learning can be used

to improve handoff communication and reduce errors in relaying critical information across teams,⁴⁸ build teamwork competencies, and CRM.¹⁴

Multiprofessional Support for Teamwork in Critical Care

Key professional organizations support teamwork enhancements to drive improvements in practice. SCCM promotes an intensivist-led model for care by a team of multidisciplinary experts. Their guidelines for critical care delivery outline characteristics of the multidisciplinary team that support teamwork⁴⁹: medical and nursing directors with authority and coresponsibility for ICU management; collaboration with a team approach across disciplines; using standards, protocols, and guidelines for a consistent approach to care; coordination and communication for all aspects of ICU management; and an emphasis on certification, research, education, ethical issues, and patient advocacy.⁴⁹

The American Association of Critical Care Nurses actively supports teamwork within their healthy work environment initiative. Their website has tools to evaluate and promote teamwork (aacn.org). The Institute for Healthcare Improvement promotes quality improvement with teamwork as a key component in their initiatives, and their website (ihi.org) also has many useful team-building tools. The Agency for Healthcare Research and Quality has a comprehensive, evidence-based program to improve communication and teamwork skills among healthcare professionals called TeamSTEPPS. Information on this comprehensive program is housed on their website (teamstepps.ahrq.gov). Pharmacists have embraced collaborative practice as seen in their combined SCCM/ACCP position paper on critical care pharmacy services. The vast majority of fundamental, desired, and optimal activities uses collaborative practice wording.⁵⁰

EXAMPLES OF TEAMWORK IN CRITICAL CARE

Collaborative Practice Teams

Collaborative practice teams (CPTs) are groups assembled for a particular population to address issues related to clinical practice and outcomes. These teams are interdisciplinary in scope and function. They design initiatives to drive evidence-based practice and improve quality of care. A critical care CPT composition depends on the purpose of the team, patient population, and disciplines directly involved in the care of patients relevant to the team function (e.g., physicians, nurses, respiratory therapists, physical therapists, pharmacists, nutritionists, social workers, clergy, administrators, risk managers, infection control, safety officers, and quality improvement personnel). The goal is to capture expertise from multiple disciplines to improve the delivery of care. Examples of CPT initiatives are the development of disease-specific protocols, care “bundles,” order sets, and performance improvement campaigns. Some teams are formed to manage care for particular situations or patient types, such as medical emergency response teams who respond to calls about acute changes in patient condition outside of the ICU and facilitate timely assessment and treatment of patients to reduce development of further deterioration. Other specialty teams can be developed to assess and manage urgent clinical conditions, including stroke, sepsis,⁴⁶ and shock.²⁷

Daily Interdisciplinary Team Rounds

Daily interdisciplinary rounds on ICU patients enhance patient care.²² Teamwork is involved via discussion of the patient care plan. Daily rounds also provide opportunities to augment CPT initiatives. Communication regarding the plan of care by the team can be facilitated by using a daily goals checklist during rounds.⁵⁰ Team accountability for assignments and goals established during rounds occurs during reviews for completion at day's end. This approach has demonstrated improved team and patient outcomes.^{23,26,51,52}

Krinsky et al. developed a model to increase the implementation of measures to prevent venous thrombosis, VAP, and stress ulcers in ICU patients.⁵³ They integrated evidence-based strategies, a team communication tool, daily prompts in ICU progress notes to assess these complications, and real-time feedback of performance measures to correct behaviors. This model allowed the incorporation of these evidence-based practices using a team-based culture of patient safety.

CONCLUSION

As we struggle to increase patient safety, prevent harm, decrease chaos, and improve outcomes, mechanisms to integrate complex behavior into functional teamwork have become increasingly important. Harmonious and efficient integration of personnel and their respective expertise in the complex critical care environment is key to the delivery of high-quality intensive care. Ideally, care will be coordinated and delivered by a team with a high degree of mutual respect, who values and listens to all contributions, resulting in care that is efficient and timely.

KEY POINTS

1. An emphasis on teamwork to promote collaboration to improve outcomes and reduce costs has increased as the care of the critically ill has become more complex and resources more limited.
2. Barriers to ICU teamwork include increasing patient acuity, rapidly developing evidence-based practice, lack of teamwork competencies and training, insufficient physician-led multidisciplinary teams, increased oversight of critical care delivery, and the stressful nature of intensive care practice.
3. Key skills required for teamwork include communication, competence, trust, cooperation, coordination, respect, accountability, conflict resolution, and shared decision making.
4. With the increased focus on teamwork, several models of teamwork in the critical care environment and resources have become available.
5. Research shows that improved processes in teamwork and communication can lead to improved patient outcomes and healthcare team satisfaction.
6. The interdisciplinary team has an opportunity to partner together to drive quality improvements in the care of the critically ill.

ANNOTATED REFERENCES

Brilli RJ, Spevets A, Branson RD, et al. Critical care delivery in the intensive care unit: defining clinical roles and the best practice model. *Crit Care Med* 2001;29:2007–2019.

This article is the consensus report of two task forces of the SCCM. It represents the work of 31 healthcare professionals and practitioners, including statisticians and representatives from industry, pharmacy, nursing, and respiratory care and physicians who are involved in the practice of critical care. This report suggests that the best practice in critical care is collaborative practice with a multidisciplinary team.

Reader TW, Flin R, Mearns K, et al. Developing a team performance framework for the intensive care unit. *Crit Care Med* 2009;37:1787–1793.

This article summarizes evidence on the relationship between teamwork behaviors and patient outcomes. Skills required for effective team performance are identified. Synthesis of the existing literature yielded a framework organized around three aspects: input, team processes, and output. This framework can be used as a guide to team building in the ICU.

Curtis JR, Cook DJ, Wall RJ, et al. Intensive care unit quality improvement: a “how-to” guide for the interdisciplinary team. *Crit Care Med* 2006;34:211–218.

This article summarizes how a team can work together to accomplish performance improvement initiatives in the ICU. In this article, the systematic steps an interdisciplinary team can take to develop

or enhance quality improvement are summarized. Key roles for team members and leadership are identified.

American Association of Critical Care Nurses. AACN's healthy work environments initiative. Available at <http://www.aacn.org/wd/hwe/content/hwehome.pcms?pid=1&&menu=>.

The AACN has established an initiative to promote healthier work environments that allow teamwork to flourish. The website includes descriptions of ingredients for success in creating healthy environments, tools for assessing teams, and links to many other helpful resources.

■ References for this chapter can be found at expertconsult.com.

Institute for Healthcare Improvement (IHI). <http://www.ihl.org/ihl>.

The IHI has been very successful in teaching teams to use a rapid cycle change process to improve care delivery and patient outcomes. The website includes information on process improvement, tools for implementing change and evaluating progress, and guidance for addressing specific patient and system problems.

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In the beginning it was all about the art—magicians or medicine men who were thought to have special powers and could cure the sick through communing with a higher power. As societies became more complex and evolved, a more scientific approach began to influence the healing of the sick. Ancient Egypt provides us with one of the first documented pieces of evidence of this transition through the Edwin Smith Papyrus (17th century BC), covering 48 cases examining a variety of traumas to the human body. From here, the art and science of care metastasized many times over (and still today)—sometimes in conflict, but always progressing toward greater treatments, greater therapies ... greater understanding. For the past 50 years, the art and science of medicine have been struggling to come to terms with a new challenge/opportunity, one born out of necessity as therapies became more expensive and complicated. Ideally, the solution should set parameters, demands, and requirements but also provide a dynamic for enabling better use of resources, individual and organizational knowledge, and accelerating the pursuit of excellence. This opportunity, the business of medicine, is an integral part of health care today and in the future, and together with the art and science, is part of a new paradigm. It is time for a new construct—a model for health care that focuses on and weaves together leadership, talented professionals, innovation, reliability, excellence, sustainability, efficiency, effectiveness, and safety.

It is a truism that most performance is average, though often with large variation. But in the context where excellence is the only acceptable performance, average is failure. In the intensive care unit (ICU), where life is extremely fragile, *average* means patients are dying needlessly. The obligation is only excellence every time, for every patient. Those who are willing to make the commitment to strive for world-class performance should read on. There is a dearth of literature that directly addresses how leaders of ICUs can create a system, a culture, that engages the workforce, supports great teamwork, creates an environment for continuous and rapid innovation, astutely develops and deploys strategy, distinctly focuses on holistic patient excellence, and delivers care at the highest possible clinical competency with the greatest effectiveness and efficiency.

Organizations consist of numerous parts, systems, and functions all operating and, ideally but too infrequently, collaborating to produce an end result. Unlike the organs of the human body, in health care delivery, different components often struggle to operate in a coordinated and symbiotic fashion. Systems such as pharmacy, lab billing, ICU, operating room, emergency department, internal medicine, surgery, and graduate medical education programs frequently operate independently without the coordination necessary to produce reliably integrated operations. The parts seem more independent than interdependent, more competitive than cooperative, and more focused on their own efforts rather than on the results of the whole. Whereas each part has to remain viable and effective in order to contribute to the overall goals and purpose of the organization, all parts must operate in harmony for superior performance to be achieved and maintained. Using the Baldrige Performance Excellence Program (BPEP or Baldrige) as a framework (Fig. 180-1), this chapter provides guidance on how to design and manage the ICU to improve patient outcomes and, even more compellingly, to become and remain a role model for ICU care everywhere. The Baldrige framework is elaborate, and a full presentation is beyond the scope of this chapter. A complete guide to the framework can be found at www.baldrige.org.

■ BACKGROUND AND OVERVIEW

The BPEP began in 1987. It was the culmination of the inspiration of business and federal leaders to create a business performance framework and awards program to stimulate excellence, competition, and innovation during a time when the U.S. manufacturing and service industries were losing market share to foreign companies. The end result produced an evolving robust framework based on best practices across seven different but highly interrelated spheres. Organizations that pursue the Baldrige and submit an application can be recognized by the president of the United States for exhibiting role model practices. While there is an award component, most organizations adopt the framework for its demonstrable value rather than the recognition. Organizations around the world have adopted the Baldrige framework for improving organizational performance practices, capabilities, and results. Based on an extensive study of Baldrige applicants in 2011, the benefit-to-cost ratio of 820-to-1 represents cost savings from using the Baldrige framework, plus gains from consumer satisfaction, plus gains to the economy from resources saved. Since health care was added as an industry permitted to apply for the Baldrige Award in 1999, only 19 health care organizations have been recognized.

The Baldrige framework has been validated to guide organizational success at both a macro system level (organization level) and the constituent micro system level (division, service line, department, or unit). ICUs are prime candidates to benefit from application of the Baldrige platform. The fragile patient population requires highly reliable delivery of very precise care around the clock. The environment is complex, with multiple layers of caregivers and diverse technologies and medications, which are lifesaving yet life-threatening if performed improperly and occur simultaneously (e.g., mechanical ventilation, dialysis, and invasive monitoring). The opportunity for error/harm is high, the patients' tolerance for error is marginal, and the cost is huge. Improvement demonstrations (Keystone Project, Institute for Healthcare Improvement [IHI] and Veterans Health Administration [VHA], and New Jersey Hospital Association [NJHA] ICU collaboratives) have demonstrated that ICU patients are suffering unnecessary morbidity and mortality, and improvement in outcomes and cost is possible but requires a systems approach. For example, most U.S. ICUs lack intensivist staff, an intervention associated with a 30% reduction in hospital mortality and costs that has demonstrated improvement in eliminating the preventable deaths of 31,000 people each year from central line-associated bloodstream infections (CLABSI). The need to improve is urgent. Indeed, the Baldrige platform approach can serve to orchestrate improvement in this complex environment. ICU leaders can use the Baldrige framework to improve clinical and economic performance. This framework is goal-directed and measurement driven. Briefly, the Baldrige Health Care Framework is built on four integrated components: organizational profile, 11 core values and concepts, 7 categories of criteria for high performance, and differentiation of high performance versus average performance or scoring guidelines.

Organizational Profile

The first integrated component, the organizational profile, is a brief description of how the organization (or ICU) operates, its customers and their expectations, its primary services, core competencies, the



FIGURE 180-1 ■ Baldrige health care criteria for performance excellence framework: a systems perspective. (Adapted from www.baldrige.org.)

workforce (which includes all paid staff, medical staff, and volunteers) requirements/needs, critical success factors, and key challenges, to name a few.

What differentiates your ICU from the thousands of others? The organizational profile also introduces a new key factor of Core Competence that is defined at an extremely high level of performance compared to its more common definition that is close to a minimal standard. In the Baldrige framework, there are around 20 questions that ask the ICU to identify, with extreme clarity, the important elements that guide the delivery of care.

Eleven Core Values and Concepts

BPEP provides penetrating insight into what is needed to create and sustain a culture that is consistently high performing through the second integrated component comprised of 11 interrelated core values and concepts. They have been validated to be embedded in the beliefs and behaviors (the culture) of high-performing organizations:

1. Systems perspective
2. Visionary leadership
3. Patient-focused excellence
4. Valuing people
5. Organizational agility
6. Focus on success
7. Managing for innovation
8. Management by fact
9. Social responsibility and community health
10. Ethics and transparency
11. Delivering value and results

Seven Categories of Criteria for High Performance

The seven categories of health care criteria for performance excellence, which constitute the third integrated component, serve as the locus of role-model performance. The criteria are presented as a series of questions that ask how an organization's (or unit's) approaches (or methods) to work are designed and managed so that they are systematic (or repeatable), deployed to all locations and internal/external people as appropriate, are continuously improved, aligned with the key areas of

importance to the ICU, and integrated with other processes and systems to effectively deliver care. The criteria present direct actionable guidance by identifying existing strengths and opportunities for improvement. The even greater power lies not in the individual areas but rather in the interplay of the seven categories, which are as follows:

1. Leadership
2. Strategy
3. Customers
4. Measurement, analysis, and knowledge management
5. Workforce
6. Operations
7. Results

Differentiation of High Performance Versus Average Performance or Scoring Guidelines

The scoring guidelines serve as the fourth component of the framework. These four elements are critical to understanding performance, identifying opportunities for improvement and innovation, and achieving sustained excellence. Together, these "ADLI" characteristics differentiate high-performing organizations from average ones in that all work must be:

1. **Approaches** that are systematic (i.e., process or methods that are well ordered and repeatedly done in the way it is designed to be done, demonstrating reliability);
2. **Deployment**: full and complete deployment of the approaches/process/methods is done systematically everywhere it is supposed to be done—all sites, departments, units, and staff;
3. **Learning** to improve what has been fully deployed through measurement and evaluation for effectiveness as part of ongoing cycles of learning, improvement, and/or innovation (i.e., improvement is built into how work is done);
4. **Integration**: all work is aligned to and integrated with key factors such as the mission, the vision, the needs of ICU patients and family members, best evidence-based ICU medicine, ICU department objectives, to name a few; and harmonized with other key ICU/organizational processes and systems to achieve maximum efficiency and effectiveness.

High-performing organizations differentiate the results of their critical success factors from those of lesser organizations based on (1) whether current results are good, (2) how results trend over time (i.e., show consistently beneficial trends, and (3) how trended results compare with best-in-industry (role-model) performance.

How does all this relate to ICUs? ICUs across the country are the beneficiaries of medicine's most advanced techniques and technology serving the most critically ill patients and anxious, if not frightened, families. Yet ICUs struggle with increased complexity, higher costs, the absolute demand for error-free care, cumbersome documentation systems, staffing shortages, decreasing morale and low staff, and inconsistent customer/patient satisfaction and engagement. The human service purpose of ICUs is far too precious for ICU quality to be sub-optimal—a sign of leadership failure. Industry experts must find a road map that is proven to guide the pursuit of sustained excellence. The Baldrige framework is that singular, all-encompassing framework to total organizational and cultural excellence. Anything less than excellence is failure; high reliability in ICU care is not optional.

It is important to remember that the Baldrige program is not an improvement tool like Six Sigma or the Plan-Do-Check-Act (PDCA). Rather, it is a larger framework that provides guidelines and a structure to establish and sustain culture and processes that go *beyond* mere conformance to standards, differing from requirements such as those of The Joint Commission. Baldrige asks fundamental questions that will help lead and guide organizations—and ICUs—toward the highest levels of performance excellence humanly possible. It is how the work should be organized, managed, improved, and innovated. And, whereas the Baldrige framework asks these important questions, the ICU leaders need to provide the answers.

THE BALDRIGE INTENSIVE CARE UNIT

Category 1: Leadership

The leadership category provides insight on how leaders can guide their organizations to high levels of performance. It analyzes how clinical and nonclinical leaders use values, directions, and performance expectations, as well as a focus on patients, other customers, workforce engagement, innovation, and continuous improvement, as vehicles to secure systematic action and sustained excellence. In the Baldrige framework, leadership is not just an organizational chart of positions. It is also a system—a set of leadership behaviors that move and align the organization toward a common purpose with specific goals and objectives. Leadership systems include the formal and informal method of exercising leadership elements such as decision making, communication, setting expectations, organization of work, reward and recognition for high performance, and planning. Using the unit's mission, vision, and values (MVV), the ICU leadership system orchestrates a systematic approach to communicating and deploying key organizational requirements and expectations throughout the entire workforce by providing a single, unifying purpose to all actions that ensure success now and in the future.

The criteria for leadership are instructive as they relate to ICUs and are likely very different from the current approach. Within the ICU, opportunities exist for the leadership team to become a more instructive leadership system (Fig. 180-2) and promote a unit that demonstrates repeatable and fully deployed process across all areas of delivering ICU care. The leadership team ensures consistency of care across boundaries, incorporates and supports continuous cycles of improvement and/or innovation, and strategically aligns with the overall goals and objectives of the hospital.

To illustrate this point, the following example is offered: one ICU used a multidisciplinary leadership group to set and deploy the values, short- and long-term directions, and performance expectations throughout the unit. This team consisted of the intensivist physician leader, functional administrator, and nursing supervisor. The multidis-

ciplinary leadership group used a variety of tools and methods to communicate the values and directions of the unit, such as cascading employee development plans that correlated the high-level ICU goals and objectives such as absolute error-free care down to each employee, and articulating how they contribute to the achievement of those goals. Prior to this process of cascading accountability, the leadership team held four revolving all-ICU-participant meetings to get input from the workforce on key changes, ideas, and needs such as new equipment and guidelines for improving patient safety as they developed the strategic plan. Involvement of the workforce in planning demonstrates a departure from typical strategy processes, which usually live at the senior leader level, and are fostered upon the workforce for their less than enthusiastic or knowledge-based buy-in and engagement.

Consistent with the Baldrige criterion that asks how leaders review performance and translate their reviews into opportunities for continuous breakthrough improvement and innovation, the multidisciplinary leadership group met every month to review performance—using industry-standard metrics such as a balanced scorecard that specifically correlates with strategic goals and objectives designed to stretch performance more acutely toward excellence. For example, the leadership group, through its strategic planning process, identified teamwork and communication as areas for improvement as they related to patient safety and employee engagement. Using a cultural assessment tool to obtain the facts (*management by fact* is a Baldrige core value), it was discovered that over the past year, the ICU had a decrease in nurse satisfaction and an increase in issues identified via a nurse assessment of patient safety. After drill-down sessions with the doctors, nurses, pharmacists, patients, and others, the leadership group learned that communication between the nurses and the physicians was lacking and that patients were suffering—all impacting job satisfaction. In addition, the ICU was experiencing an unprecedented level of staff turnover. As a result, the leadership group added to each employee's job description the requirement to participate in quarterly teamwork and communication training sessions and added key patient high reliability safety indicator(s) to the annual individual evaluations. The intention was to drive accountability farther down to all workforce

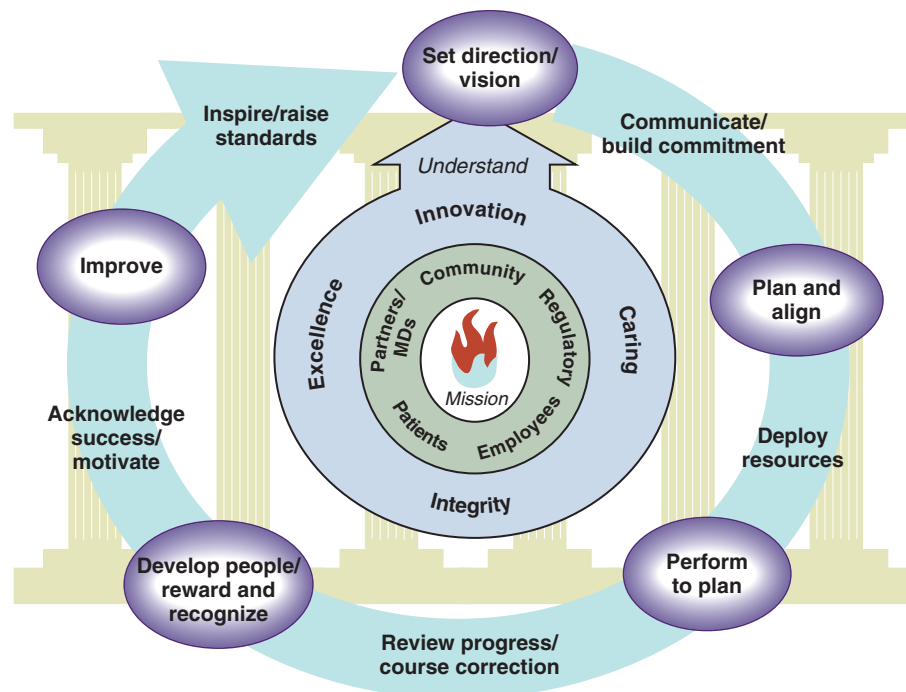


FIGURE 180-2 ■ Example of a leadership system (Sharp Healthcare, San Diego, CA). (Adapted from 2007 National Baldrige Application.)

members and link to new rewards and recognition initiatives. This process became systematic—repeatable—and the leadership team sought feedback from the workforce on the process's effectiveness and ideas of how to improve it even further.

In addition to the individual goal requirements, the leadership group set a unit goal to increase employee engagement, learning, and rates of improvement and innovation. Critical to this goal was the creation of improvement teams that were supported by the hospital and ICU leadership in terms of time, finances, and other resources. Through the strategic planning process, the multidisciplinary leadership group learned that the staff felt their efforts to change and improve patient care consumed large amounts of time and that these efforts were neither supported nor appreciated by senior leadership. The stress level and complexity of the ICU environment contributed to turnover and dissatisfaction. The leadership group realized that the creation of conduits for the staff to change, innovate, and improve processes that decreased complexity and raised satisfaction levels needed to occur rapidly. The leadership group put together a multidisciplinary action team, using a Lean/Six Sigma method of improvement, to design systems that would empower and motivate the staff to change and innovate. These were then presented to the multidisciplinary leadership group for implementation and tracking of performance.

Category 2: Strategy

This category deals with how the ICU develops its strategic objectives and more detailed action plans and how they are deployed throughout the unit. The ICU leadership system incorporates internal and external inputs to create short- and longer term strategy in the form of strategic objectives, action plans, and goals for the unit. These goals must align with the MVV of the unit and hospital to communicate a constancy of purpose. When the leadership team meets to discuss the strategic plan, it must consider how the strategic plan is developed, communicated, prioritized, benchmarked, and measured. In addition, it should consider how the ICU's strategic planning process incorporates the following:

- Customer (patient, family) and key stakeholder needs and expectations
- The competitive environment and collaborative opportunities within the community
- Technology and other innovations that might have transformational impact on ICU services
- Strengths and weaknesses of the unit
- Changes in the local, regional, or national environment
- Alignment with the unit's core competencies, the ICU's greatest area of expertise and capabilities that are of strategic importance and are frequently challenging for competitors or suppliers to imitate. They present a competitive advantage.
- Ability to execute the plans and long-term sustainability

To illustrate this concept, the following example is offered: ICU leaders organize a plan that answers the basic question, "How will we ensure the success of the ICU now and in the future? Together with the hospital's strategy, the ICU's MVV drive the entire decision-making and strategic planning process. While aligning with the MVV and other specifics such as an environmental assessment (data on the external and internal environment), a strengths, weaknesses, opportunities, and threats (SWOT) analysis, and past ICU performance, the leadership group uses the yearly strategic planning process to identify strategic advantages and challenges, the unit's key objectives and goals, key customer groups and segments, measurement strategies, workforce-related issues, opportunities to innovate, and action plans needed to achieve the strategic objectives. The strategic plan is not static; it is organic and constantly evolves and leaders remain agile as new opportunities and challenges emerge on the unit. The leadership group is always doing strategic planning, and the annual plan document serves as a foundation for beginning to accomplish excellence. The strategic plan creates clarity, purpose, and a vision of where the ICU is headed and how they plan to arrive at that destination.

Once the plan has been completed, it is cascaded down to all ICU staff for implementation with clear linkages to their role and contributions to the work. It gives meaning to their job. It answers the why question of why do we do this work? Each year, the overall planning process is updated according to key customer feedback, ICU performance analysis, organizational positioning, competitive data, and industry standards and trends. Integral to this process is the implementation of actionable measures of the strategic objectives. For example, part of this ICU's mission is "to simultaneously eliminate all preventable harm to the patient, while providing exceptional care." Bloodstream infections were identified by data analysis as one area of preventable risk for cardiac patients. After the multidisciplinary leadership group discovered that bloodstream infection was an area of concern (and benchmarked their results against local competitors, national averages, and best in class), its prevention became a key strategic objective for the following year, and action plans were designed to create systems that would lower and move to eliminate these infections. The plans included education and training on an infection bundle, staff empowerment tools to monitor conformance to standards, transparently monitoring and reporting infection rates, and further teamwork training, particularly around the use of an infection checklist.


Crucial to this process is how the ICU communicates the strategic plan to the entire unit. It is not only the leadership group that should know this plan; in high-performing organizations, every employee knows what's going on and how they fit in to the overall work. In our example, each employee was issued a cascade plan to guide work processes, goal setting, and professional development. These cascade plans list and strategically link and align the objectives of the hospital, the ICU, and the individual. The cascade plan is used quarterly as a performance assessment tool (Table 180-1).

All together, strategy development and implementation are important parts of an organization's approach to excellence and sustaining excellence. A plan is just that—a set of steps to achieve an end. The real challenge is in effectively executing the plan every month, week, day, and minute and remaining opportunistic and agile in the midst of changing circumstances.

Category 3: Customers

These criteria address how the ICU engages patients and stakeholders (1) to better serve their needs through specific voice of the customer methods, (2) to build relationships, and (3) to improve services based on the expectations of the identified customer groups. *Customer engagement* refers to patient/customer commitment to an organization's services. It is a much higher determination of relationship compared to mere satisfaction. At the ICU level, no patient or family member really wants to be loyal to an ICU, since it means their health is at serious risk, yet as leaders and managers, there is an obligation for the organization to deliver care at such amazing levels of distinction that if a patient or family member had to be admitted to the ICU, he or she would only want your organization and, in particular, your unit. Segmentation is a key element in this section of the framework. Most ICUs can predict with some relative confidence the types of patients who occupy their beds, and through segmentation of this population, it is possible to customize each aspect of care delivery to improve outcomes and service and eliminate inefficiencies and inconsistencies in experience.

The challenge for ICU leadership is to determine how to ensure consistency of practice in the midst of this urgency and complexity. Key to this effort is the need for the ICU to identify the types of patients (and their families) for whom they typically provide services, segment them according to needs and expectations, and then tailor health care services to meet their particular needs. The concept of "stages of relationship" in the framework is an important consideration for increasing customer engagement. It suggests that leaders think about the various phases of a patient's and family's interaction with the ICU—from admission, to their stay, to transferring to another unit, for example. During these stages, the needs of the patient and family

TABLE 180-1 Sample of Cascading Organizational Objectives**STRATEGIC OBJECTIVES TO INDIVIDUAL ACCOUNTABILITY**


| STRATEGIC AREA | ORGANIZATIONAL STRATEGIC OBJECTIVE | ICU ACTION PLAN LINK TO STRATEGIC OBJECTIVE | ATTENDING PLAN LINK TO ICU PLAN | MANAGER PLAN LINK TO ICU PLAN | BEDSIDE NURSE PLAN LINK TO ICU PLAN | OVERALL ORGANIZATIONAL METRIC |
|-------------------------|------------------------------------|---|--|---|--|--|
| Clinical patient safety | Lower mortality rates. | Adopt CUSP program. Reduce decubitus ulcers. | Participate in culture of safety survey and one improvement project. | Participate in culture of safety survey, and monitor ulcer bundle compliance. | Participate in culture of safety survey, and identify ulcers at earliest stages. | Mortality rate Decubitus ulcer rate |
| Clinical patient safety | Eliminate infections. | Implement evidence-based infection bundles. | Learn, implement, and innovate infection bundles. | Monitor compliance on infection bundles. | Learn and use safety checklist. | Number of infections |
| Workforce | Be the best place to work. | Be the best unit in the hospital. | Attend two teamwork training sessions. | Attend two teamwork training sessions. | Attend two teamwork training sessions. | Workforce engagement scores Top Box |
| Customer | Be the best place to receive care. | Achieve the highest customer engagement scores in the hospital. | Implement family rounds. | Implement morning staff huddles, covering one key service standard a week. | Implement "key words at key times" process. | Customer engagement scores Top Box |
| Operational | Reduce system waste by 5%. | Run Lean projects to reduce length of stay. | Lead or participate on a Lean waste reduction team. | Lead or participate in a Lean waste reduction team. | Identify three opportunities to reduce waste in daily work. | Length of stay |
| Financial | Increase financial sustainability. | Increase operating margin. | Complete medical record notes on time. | Maintain supplies, salaries, and other expenses within current year budget. | Achieve 100% accuracy on charge entry and documentation. | Operating margin |
| Innovation | Transform the delivery of care. | Implement ideas program. | Develop five "big ideas" for the ICU. | Teach, reinforce, and monitor the ideas program. | Submit 10 new ideas. | Number of nationally recognized best practices |

Action plans are the tactics to accomplish an objective. CUSP, comprehensive unit-based safety program; ICU, intensive care unit.

From www.safetyresearch.jhu.edu/QSR/.

members might change, signaling the need to alter certain systems and processes. In doing so, the ICU is better positioned to secure and/or increase their engagement at each stage of their relationship with the ICU and better manage its limited resources.

For example, cardiac ICUs see a variety of patient types, yet most can be broken into two large segments: short-term and long-term patients. Within these segments are subgroups of patients ranging from those recovering from coronary artery bypass grafts to those requiring ventricular assist devices. Care plans can be implemented that are customized to deliver the best outcomes for each of these groups and are consistent with the unit's goals and directions. Patients requiring ventricular assist devices tend to require prolonged ICU stays. Therefore, the ICU team develops a plan to coordinate resources efficiently to meet the needs and expectations of this long-term patient cohort, such as how a room is set up to accommodate family members. Similarly, the short-term patient cohort can be segmented according to needs and expectations to better use the unit's resources. For example, medications most frequently used by the short-term patient group can be trended over time for predictability, and the evidence shows that

just six medications actually account for over 85% of all medications given to these patients. These medications can then be located in a locked cart at the patient's bedside, reducing the need for the nurse to use the highly complex medication dispensing and delivery process, which at times is frustrating to patients awaiting their medications. Use of data to track and predict trends in medication usage can allow unit staff to work more effectively and better serve the needs of patients.

Medically, the talented professionals working in the ICU know what is best for the patient; however, the question remains: What do the patient and family need and expect in order to have a positive experience that *includes the family*, whose needs are too often unmet? To some, this might seem of limited significance, considering the condition of most ICU patients. Yet there should be a way to determine these additional customer/patient requirements, and ICUs should incorporate systems for gathering this information and apply it to the delivery of care in real time. For instance, one approach might be to follow up on the ICU experience by having a nurse from the ICU speak with the patient or family after transfer to the step-down unit. The information gained could be analyzed for trends and fed into a

prioritization system for planning and implementation. It could also become part of the transfer documentation so the incoming staff knows the patient's needs without having to query the family another time. For example, by talking to families, it was identified that they desired the type of seating and lighting that could allow them to take a brief nap between visits to their loved ones. The ICU can also proactively use quarterly focus groups and information gleaned from medical associations to elicit key knowledge to design care and even innovate care that is both medically optimal and patient driven.

In 2002, the Institute of Medicine recommended six tenets of the 21st century health care system. One of these is a focus on patient-centered care and involvement of the patient and family in the care plan. It is vital to the success of the ICU to make concerted efforts to identify the key requirements of their patients by segment and then build care plans around those requirements in each stage of relationship. Without this input, it is unlikely a given ICU will reach levels of world-class performance and excellence. And, it cannot know or take action on how the ICU performs in comparison to the ICUs of competitors. To ensure sustainability, the ICU must always identify, incorporate, and amend services with the changing needs of all their customers. Through leadership, role model behavior, and appropriate and effective communication, the workforce will feel empowered to incorporate the information gathered from the different patient segments and deliver care that is deemed appropriate based on the medical evidence and the wants and needs of the patient.

Category 4: Measurement, Analysis, and Knowledge Management

Now that the ICU has refined its leadership system, created its strategic goals and objectives, and gathered and used key patient data to set action plans and work processes, a robust and clear structure of measurement and analysis is needed to evaluate the effectiveness of the strategy and key health care systems and processes.

How does one measure performance, analyze performance, and use benchmarking information to support fact-based decision making, drive innovation, and ensure sustainability? How does one make certain everyone in the chain of delivery of ICU care has all the necessary information when they need it, and that it is in the correct form and accurate so the next clinical decision, diagnostic test, or treatment can be carried out in a timely manner? How does one make certain

that clinical information in the electronic health record is available rapidly on request, provides a complete holistic picture given the life-and-death reality of intensive care? And, in the interest of achieving high ICU performance, how does one make certain the sharing of knowledge (the great ideas, experiences, and talents of the workforce) is a cherished part of the culture and is actively (versus passively) managed?

In addition to measurement, this section addresses how the ICU manages knowledge, transfers information to staff and patients, and shares best practices within and outside the unit. The criteria ask us to think innovatively about how we measure performance, the importance of relationship among all outcomes (e.g., issues with the workforce could impact clinical outcomes), process and outcome measures, and what is the true measure of mission and vision achievement. Further, the criteria challenge us to create a structure for ensuring the measures are valid, ensuring the data are accurate and of high quality, reviewing performance, identifying opportunities for improvement/innovation, and translating them into priorities.

The ICU's key measures cascade down from the hospital's overall goals, which in this example fall into six areas of focus: clinical performance, customer engagement, workforce engagement, operational performance, population health, and financial performance (Table 180-2). During the strategic planning process, the leadership group, using input from the workforce, identified three or four leading indicators within each area that directly predicted the achievement of the key objectives and goals of the unit. These were then validated through a set of criteria asking certain questions:

1. Are the data collectible?
2. Do relevant, preferably high-performance comparisons exist?
3. Are the data understandable/translatable to action?
4. Does the measure provide actionable, credible, reliable, reproducible, and timely information?

Once validated, the measures become part of the unit's balanced scorecard, to indicate performance across a balanced set of areas of importance. Measures then are "drilled down" for each employee to create a line-of-sight from the big goals to their specific work. For instance, one of the unit's measures is zero infections, and subsequently the environmental staff who serviced the unit had a goal and a tracking measure of patient infections by room as one measure among others of a fully comprehensive approach and ICU cultural imperative to doing everything every time in ways that prevented the spread of

TABLE 180-2 Sample Key Measures of Intensive Care Unit Performance

| STRATEGIC OBJECTIVES | METRIC | 1-YEAR GOAL | 3- TO 5-YEAR GOAL |
|------------------------|--|---|--|
| Clinical excellence | Decubitus ulcers Infections Use of evidence for sepsis patients Use of ventilator bundle Rate of adverse drug events | Reduce 20% Zero bloodstream infections 100% of patients 100% of patients Zero | Reduce an additional 30% Maintain at zero Develop quality measures for transfusion 100% of patients Zero |
| Workforce excellence | Positive staff engagement (% of Top Box) | Improve 30% | Achieve above top 10% compared nationally |
| Customer excellence | Positive patient engagement (% of Top Box) | Improve 30% | Achieve above top 10% compared nationally |
| Operational excellence | Canceled surgery Length of stay Rate of diverted cases Use of agency nurses | Zero Reduce 30% Reduce 50% Zero | Maintain at zero Reduce an additional 20% Zero Zero |
| Financial excellence | Operating margin Drug costs | 5% Reduce 30% | 7% (reinvest in quality) Reduce an additional 15% |
| Innovation excellence | Number of clinical and/or process innovations implemented | Three new processes implemented | Twenty new processes implemented internally and three that impact nationally |

Top Box refers to counting only the highest box on a Likert Scale. For example, when measuring customer engagement on a 5-point scale, only those who rate the ICU as "excellent" are counted, not an average of those who rate "very good" and "excellent." Top Box is a more difficult assessment.

infections. Their job, and the communication of the leadership, is not just cleaning—rather it is helping reduce infections and improve patient safety.

As another example, the leadership group set a goal of zero catheter-related infections, a widely accepted target in health care. Data reviewed at the monthly leadership meeting revealed the incidence of bloodstream infections to be not only inconsistent but also generally increasing and the rate of infection to be not only well above that of best-in-class but also above previous performance levels. Achieving the agreed-upon and vital target of zero infections seemed impossible. The leadership group identified this as an opportunity for improvement and elected to convene a multidisciplinary team to reduce the number of bloodstream infections. This group replicated the high-reliability approach used in the Michigan Keystone ICU study that virtually eliminated these infections throughout the state.¹ The bloodstream infection reduction team used the weekly infection control data collected and implemented interventions such as a catheter checklist on line carts, empowering the nurses to stop catheter placement if physicians did not comply with the checklist items. In addition to investigating every infection as a defect, they also met to discuss and analyze their successes, asking how did we manage infection-free cases, to focus on successes and not just failures as input into infection-free training on teamwork and communication for the nurses and physicians. Continuous cycles of improvement were implemented, and the bloodstream infection trend data demonstrated a progressive reduction. Work processes related to catheter insertions became standardized in the unit and were ultimately communicated through the organization via a new policy and monitored for adherence.

It is also important for ICU leaders to consider how they manage the knowledge assets contained within the ICU. Baldrige defines knowledge assets as “the accumulated intellectual resources ... it’s the knowledge possessed by your organization and employees in the form of information, ideas, learning, understanding, memory, insights, cognitive and technical skills, and capabilities.” ICU leaders who are committed not only to high performance but also to distinctive performance should learn how to manage the unique knowledge of their units. A mechanism to maintain this knowledge, communicate it, and share it across the organization is vital to an ICU moving toward high performance.

In health care, all stakeholders—physicians, nurses, and administration—often have legitimate concerns about the validity of performance measures. Category 4 attempts to mitigate these concerns by developing a system of aligned measures, relevant comparisons to gauge results, a structure for reviewing these metrics, prioritizing them into opportunities for improvement and innovation, and establishing a robust framework for liberalizing data and information as transparent to all key stakeholders in the care process.

Category 5: Workforce

In health care, the term *workforce* traditionally means all paid individuals, yet Baldrige takes a different view—a more holistic approach—defining the workforce through the eyes of the patient. For decades physicians were considered customers by hospital leadership: treat physicians as customers and they will fill our beds. This is an outdated view that is no longer even minimally acceptable. In high-performing health care settings, doctors (paid or volunteer staff) are considered part of the workforce (sans certain benefits); engaged in planning, work system design, and budgetary authority. Specifically, Baldrige states *workforce* “refers to the people actively involved in accomplishing the work ... it includes your permanent, temporary, part-time personnel, independent practitioners, volunteers, and health profession students.” Through the eyes of the patient, the doctor is a member of the workforce in making my care, he/she is a leader of that workforce with regard to what is decided, ordered, and performed.

Similar to Category 3 (customer engagement), this section brings to the forefront the importance of an engaged workforce, meaning

the extent to which all members demonstrate a “commitment, both emotional and intellectual, to accomplishing the work, the Mission, and Vision of the organization” (or ICU). Here, leaders and staff are asked to determine the key factors that drive the engagement of a segmented ICU workforce, how to create a culture of high performance in the unit, learning and development opportunities, career progression, and hiring and organizing a workforce dedicated to achieving excellence.

All organizational and ICU results are lagging indicators of how well the workforce performs. ICUs that do not emphasize maintaining a workforce that is skilled, trained, engaged, motivated, and safe should expect undistinguished performance. The paragraphs that follow offer some insight into a few of the key components of this category.

In an ICU, different members of the workforce funnel in and out of the unit on a daily basis—from lab technicians, to various physicians, to dietitians, to nurses, to pharmacists, and so on. In a teaching hospital setting, the number is obviously greater with residents and students of numerous types. Managing the styles, personalities, and roles each of these groups play in the care delivery process in a highly complex area like the ICU is an extraordinary challenge that often gets overlooked and is left to traditional models of health care interactions. Each unit has its own culture, and leaders—together with the workforce—need to first identify the desired attributes of the culture and needs of the workforce, and then develop an approach to fostering and reinforcing the desired culture. For instance, in one ICU, one of the cultural expectations was that each employee should innovate at least one process each year, measured via their annual staff evaluations. In addition, the unit created two awards to celebrate the best innovations: “The Super Innovator” and “The Game Changer,” which were shared throughout the organization and published in the quarterly hospital newsletter. By adding this expectation, monitoring it, and creating reward systems, the ICU leadership demonstrated a commitment to aligning the goals of the unit with the actions of the workforce.

A work design that allows the workforce to achieve the highest levels of performance, while promoting collaboration, initiative, empowerment, and innovation, has to be the goal if patients are the true customers. So the question remains: How is this accomplished? Using the Baldrige criteria in their entirety is one way of achieving this end. The framework involves a set of characteristics of high-performing organizations inclusive of thematic linkages throughout all processes of an ICU. Specifically, how is work performed so that it is systematic (repeatable based on how it is designed to be done), fully deployed, continuously improved, aligned with other care provided to the patient, and also ensures the work is aligned with the MVV and strategic objectives of the ICU?

Taking this a step further and using the example of bloodstream infections, we can examine how teamwork and communication have helped reduce, if not totally eliminate, catheter-related infections through alignment of goals and objectives. After the leadership group identified bloodstream infections as a continuing strategic priority and funneled it through a working team, concerns arose regarding the nursing staff’s ability to intervene when physicians broke standard protocol for catheter insertion. A number of nurses reported situations in which they had tried to intervene despite the emphasis on patient safety and the widespread knowledge that these infections can be substantially eliminated, only to have the physician ignore their observations and proceed with central catheter placement that did not follow proper protocol, thus exposing the patient to increased risk for a bloodstream infection. Using this feedback, the leadership group insisted on full deployment of best practice and deployed multidisciplinary training on the tools and methodologies of teamwork and communication, such as situational awareness and safety briefings. In addition, the leadership group wrote a new policy that required physicians to stop and listen to the nursing staff if a potential for a bloodstream infection was observed or be subject to corrective actions. The result of this endeavor empowered the nursing staff to be supported

and feel comfortable intervening when patient safety might be at risk and reinforce the established safe practice.

Category 6: Operations

Up to this point, we have addressed ICU performance related to its leadership, strategic planning, patient relationships and engagement, performance review, access to information and knowledge, and workforce engagement—all in the context of high performance. Now we address the bottom line: How do we “make” excellent ICU care? It is time to think differently about how ICU care delivers value. The Baldrige criteria focus on delivering value in every step of health care design and delivery, improvement, and ongoing management. The criteria in category 6 provide ICU leaders with a structure and discipline to think through their delivery processes to ensure that all steps are value-adding, as measured by effective diagnosis and elimination of disease (to the extent possible), exceeding the expectations of all stakeholders, and capitalizing on the ICU core competencies. What care delivery management system can ensure that value is always delivered, outcomes do not suffer, performance levels do not decline, and safety prevails? Process management is the focal point for ICU high performance. It provides guidance on how the ICU identifies, designs, improves and innovates, transforms, and manages its health care services to achieve results when trended over time to approach, demonstrate, or sustain world-class performance. It obligates ICU leaders to clarify how these processes are continuously improved to achieve better performance, improve cycle times, reduce waste, reduce variability, and, of course, improve clinical outcomes. These criteria for performance excellence are key to avoiding being just average.

For example, it is important for the ICU leadership group to create work processes that deliver care based on the needs of all ICU constituents—patients, physicians, nurses, pharmacists, payers, and so forth—and align with the goals and objectives of the unit. The question needs to be asked: How do our processes ensure that we deliver value for those we serve, and how do we know we have been successful? Using this mantra as a guide, the leadership group in our ICU example aligned the work processes with the unit to continuously meet the expectations of each ICU customer segment in each stage of their relationship with us throughout the ICU experience. This involved a number of approaches; however, the ultimate deliverable was a system of work designed to achieve the key requirements identified in the ICU strategic plan. Data indicated that the lack of clarity around a given patient care plan and the role of each member of the care team were causing increased errors and longer stays. Using the goal of reducing harm and improving teamwork and communication among the unit's health care professionals (as stated in the strategic plan), the leadership group tested and implemented an evidence-based checklist developed by Peter Pronovost and colleagues that incorporates a multidisciplinary team approach to making rounds.² During these rounds, a daily goals sheet is used to communicate the care plan for the particular patient to the multidisciplinary team, consisting of physicians, nurses, pharmacists, and others. The use of this checklist over time led to a reduction in length of stay and adverse drug events, and both nurse and physician teamwork and satisfaction scores have improved. This mechanism is guided by several criteria in this Baldrige category dealing with the inclusion of patient expectations, testing to prevent errors, and achieving better performance by reducing variation in care. Unexplained and avoidable variation in care is one of the principal causes of failure in health care process and outcomes.

Health care is too full of waste, errors, and inefficient processes that do not add value. Over the past few years, an increasing number of improvement methodologies have made their way to health care, such as Lean Thinking, the Toyota Production System, High Reliability Methods, and in the 1990s, PDCA, to name a few. All of these tools offer opportunities to improve ICU effectiveness and value and are commonly in active use in high-performing organizations using the Baldrige framework, which asks how an ICU reduces variability,

improves outcomes, and shares learning to drive innovation. Yet, the Baldrige criteria go further and help an organization hold the gains from these types of improvement tools. One of the major challenges facing hospitals and ICUs is something called “diminishing returns.” This concept, somewhat akin to economics, dictates that after an organization exerts enormous amounts of time, energy, and other resources to improving a process, the gains often eventually erode back to previous levels of performance, primarily due to a culture that is not set up to sustain improvements. One notable exception was the Keystone ICU project in which reductions in bloodstream infections throughout the state of Michigan were sustained for over 3 years, largely thanks to efforts to improve culture, something akin to the cultural implications when successfully adopting the Baldrige framework. Through the seven integrated Baldrige criteria, it is possible to reduce the likelihood of diminishing returns and effectively address an issue and be able to focus on other initiatives while not worrying about losing ground.

The complexity of ICU care demands that its leaders employ methods of excellence at a greater intensity compared with other health care venues. Application of the Baldrige criteria, designed to enable any operating unit to achieve distinctive performance, is greatest in the ICU. Otherwise, we are left largely with less effective methods of management and improvement that have demonstrated, thus far, the inability to fully leverage the extraordinary talent that resides within. In such places, the care and the experience in delivering it remain woefully suboptimal.

Category 7: Health Care Results

In the end, the results of a given ICU are the ultimate measure of its performance. Now that the ICU has defined its mission, vision, and values, identified what its distinctive core competency is (or should be), set strategic objectives, become relentlessly patient-focused, established methods to ensure that all ICU staff have the required information and knowledge, and created work processes that inspire the staff and add value to the patient, it is paramount that the ICU use the data it collects (on its key objectives) as a feedback loop or mechanism to continuously review its performance and achieve the identified goals outlined in the strategic plan. Selecting measures and having a system or process for making the data actionable and understandable (such as a balanced scorecard) allow the ICU to constantly implement corrective strategies when an area for improvement is identified. This category does not deal with the deployment of key processes; rather, and quite simply, it involves the unit's ability to effectively align its mission, vision, and values and meet its stated goals and objectives as compared with both the competition and best-in-class benchmarks. Comparative performance is set at best-in-class: how else will the ICU leadership and workforce know that it is a role model for ICU care everywhere?

CONCLUSION

ICUs are places of emotion, extraordinary science, compassion, and sometimes high drama in the conflict between disease and injury, the will to live and the hopes of loved ones. Optimally, they are designed to enable the uniquely talented professionals who dedicate their careers to healing at the highest levels. Yet experience has proved with alarming frequency that the enormous and sometimes even heroic good that is accomplished is marred by what could or should have been done. Patients and their families enter our ICUs trusting that we will do what is needed, correctly and with compassion. There is only one standard of care acceptable—no excuses are permitted. The Baldrige program, the nation's formally adopted approach to excellence, is not just another improvement tool. Rather, it is a framework of systematic elements that are woven together to achieve the singular aim of excellence (Table 180-3). The Baldrige framework inspires leaders to create the culture through which every employee involved in the care of the very ill performs to his or her potential. It sets forth the

TABLE 180-3 Seven Categories of Health Care Criteria for Performance Excellence and Related Key Questions

| CATEGORIES | KEY QUESTIONS |
|--|---|
| 1. Leadership | How does the ICU senior leadership guide the unit through its governance system and organizational performance reviews? How does the ICU leadership ensure sustainability of all key processes at the highest levels of performance, considering innovation? |
| 2. Strategy | How does the ICU establish its strategic objectives and action plans that stretch the ICU, and how are they deployed and measured across the unit? |
| 3. Customers | How does the ICU determine customer/patient requirements, expectations, and preferences, and how does the ICU build relationships with its patients to increase customer/patient engagement in each stage of its relationship? |
| 4. Measurement, analysis, and knowledge management | How does the ICU select, gather, analyze, manage, and improve its measurement system, and how is this knowledge shared, transferred, and communicated throughout the unit? |
| 5. Workforce focus | How does the ICU's work system, staff learning, and staff motivation enable all workforce members to develop and utilize their full potential in alignment with the unit's strategic objectives, goals, and action plans? How do you determine the key factors of engagement for each workforce segment? What are they? |
| 6. Operations | How does the ICU's process management system, including both key processes and support processes, create value for the patient and staff? How do you know? |
| 7. Results | How do the ICU's results compare to competitors and industry benchmarks over time? Are they reflective of the ICU's strategic objectives? |

foundation through which leaders of ICUs can track and achieve results that are comprehensive, balanced, and presented in the context of true world-class performance. It probes the leadership structure to consider how key elements of organizational success are accomplished, how they are systematically deployed throughout the unit, how continuous improvement and the ability to transform is a system

property, and how all the work is aligned with the unit's mission, vision, and values.

ICUs are endowed with extensive human and technologic resources. The first question every ICU leader must ask is: Are we performing at the highest possible level? If the answer is no, then the obligation—not the option—is to achieve it and then sustain it.

KEY POINTS

1. The Baldrige program provides a construct and framework for systematic approaches to achieving excellence and transformation in clinical and organizational performance.
2. Four attributes differentiate high-performing organizations from average ones in terms of work processes: work is done systematically, systematic approaches are fully deployed throughout the organization, ongoing cycles of learning improve the deployed approaches, and all processes are aligned and integrated. These attributes produce results with sustained positive trends that are superior to the competition or industry comparisons.
3. Seven categories of criteria serve as the focus and road map for leaders to achieve role-model performance. These categories are tightly interrelated and provide actionable guidance by identifying existing work process strengths and opportunities for improvement.
4. The Baldrige criteria provide a thoughtful and systematic approach to ensuring attentiveness to patient and family drivers of satisfaction; segmented needs and expectations are integrated throughout the strategic planning process, action plan designs, and overall work processes.
5. The framework provides the ability to empower, motivate, and inspire the ICU and total organizational workforce to achieve its potential and deliver care that meets the needs of patients and families. Such care will be rooted in best-care practices and aligned with the strategic objectives, mission, vision, and values of the unit or organization.

References for this chapter can be found at expertconsult.com.

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Severity of Illness Indices and Outcome Prediction: Adults

Thomas L. Higgins

And he will manage the cure best who has foreseen what is to happen from the present state of matters.¹

Predicting outcome is a time-honored duty of physicians, dating back at least to the time of Hippocrates.¹ The need for a quantitative approach to outcome prediction, however, is more recent. Although a patient or family members will still want to hear a prognosis, there is increasing pressure to measure and publicly report medical care outcomes. In today's highly competitive healthcare environment, such information may be used to award contracts for care.² Information of variable quality is readily available on the Internet. The U.S. government maintains a Medicare hospital comparison website,³ and comparative information is also available from sites such as www.leapfroggroup.org.⁴ The Physician Quality Reporting System enacts penalties and provides incentives for Medicare providers based on quality.⁵ Local and regional initiatives to assess quality of care also exist. Public reporting of intensive care unit (ICU) performance, in the form of risk-adjusted mortality rates, is now mandated in six European countries⁶ and Veterans Administration (VA) hospitals in the United States.⁷ Estimates are that only 10% to 15% of U.S. ICUs are currently using scoring systems,⁸ but this will increase with the spread of integrated tele-ICU systems and pay-for-performance reimbursement. It has thus become essential for clinicians to understand the science behind these systems⁹ and how risk adjustment models may properly be applied. Risk adjustment systems allow a given outcome (e.g., mortality) to be given to both a patient's intrinsic (disease-related) risk and extrinsic (care-related) causes. Thus, performance (process of care) can be evaluated independent of the presenting condition (baseline risk). A focus on performance assessment, however, may detract from other potential uses for risk stratification, including assisting risk-benefit decisions, prognostication, resource allocation, efficient assessment of new therapy and technology, and modifications to individual patient monitoring and management based on the severity of illness.

Prognostication based on clinical observation is affected by memory of recent events, inaccurate estimation of the relative contribution of multiple factors, false beliefs, and human limitations such as fatigue.¹⁰ An outcome prediction model, on the other hand, will consistently replicate an estimate when considering relevant data. This presupposes that the model has been well developed and includes the most important predictive variables. Over time, we have learned that accepting patients in transfer,¹¹ sociodemographic factors,¹² and the time-point at which an outcome is assessed¹³ can lead to misinterpretation of supposedly objective measures. This chapter will discuss what can (and should) be measured, how benchmarking models are created and assessed, how the most popular models are applied in clinical practice, how this information may be utilized, and the pitfalls and confounders that may imply quality issues when none is actually present.

■ WHAT SHOULD WE MEASURE?

The ancient parable of the blind men and the elephant is relevant to ICU outcome assessment. What is perceived as "quality" depends not only on individual subjective experience but also in integrating multiple perceptions and understanding the limitations of any one observation. Table 181-1 lists over 80 potential metrics categorized into

process measures (what is done) or outcomes (what is achieved) in three bins: quality, efficiency, and patient/family experience. A particular unit may also choose to collect local data on resident and fellow performance, academic pursuits, or additional process measures such as organ donation or autopsy rates. Process measures are important insofar as they provide guidance to interpreting outcomes that are out of range. A high Foley catheter utilization rate will impact the rate of catheter-associated urinary tract infections. With so many metrics to consider, particularly in a multi-ICU hospital, dashboards have become essential. Figure 181-1 displays a "radar" display where every variable has been normalized, such that 1.0 indicates performance at benchmark and the red-shaded areas indicate concern. In this hypothetical example, the Neuro ICU appears to have issues with prolonged hospital length of stay (LOS), possibly related to hospital-acquired conditions. The medical ICU appears to excel at research, publication, and education, while having some issues with patient experience and wait times. Recognizing that some metrics, such as mortality rate and LOS, will be determined primarily by a patient's underlying physiology and health status, rates are normalized using the ratio of observed to expected, creating standardized rates.

A task force of the European Society of Intensive Care Medicine recently defined nine ICU safety and quality indicators based on a modified Delphi procedure. These include designation as an ICU, 24-hour availability of consultants, an adverse event reporting system, routine multidisciplinary rounds, a standardized handover process, rate of catheter-related bloodstream infections, unplanned extubation rates, ICU readmission rate, and reporting and analysis of the standardized mortality rate (SMR).¹⁴ SMR is one of the most frequently utilized outcomes worldwide.⁶ Unfortunately, the lack of standardization on quality metrics makes it difficult to compare quality across (and often within) countries.

Mortality is a commonly chosen ICU and hospital outcome because it is unambiguous and readily available from a variety of data sources. Mortality, while clearly important, does not necessarily reflect quality of care or other important issues such as patient/family satisfaction, return to work, quality of life, or even cost as early death results in a lower cost than prolonged hospitalization.¹⁵ There is poor correlation between hospital rankings based on death and those based on other complications.¹⁶ A retrospective cohort study from 138 U.S. ICUs contributing to Project IMPACT from 2001 to 2008 found that none of the 10 popular quality indicators (e.g., mortality, readmission, LOS, bundle compliance) consistently correlated with the other 9, which questions the wisdom of penalizing institutions for outcomes that are not under their control.¹⁷ There is also little standardization on how mortality should be defined—traditional ICU or hospital rates are subject to discharge bias,¹³ but time-based outcomes (30-day, 1-year mortality rates) require follow-up phone calls, querying nonhospital databases, or other intensive manual processes. Regionalized health information organizations or health information exchanges could make data collection less arduous but are not yet widespread or optimally functional.¹⁸

Other potential outcomes of interest include morbidity, organ failure, complications, ICU or hospital LOS, ICU or hospital

TABLE 181-1 Possible Metrics for Evaluating ICU Performance

| PROCESS MEASURES | QUALITY METRICS | EFFICIENCY | EXPERIENCE | OPTIONAL (LOCAL) |
|---|---------------------|---------------------------|-------------------------|-----------------------|
| Daily wakeup/screen for weaning readiness | ICU SMR | ICU LOS | Patient satisfaction | Trainee performance |
| Glucose control | Hospital SMR | Hospital LOS | Family satisfaction | Publications |
| Lung protective ventilation (Vt/IBW) | 1-year SMR | ICU occupancy (95% CI) | Delirium rate | Funded research |
| Semirecumbent position (HOB at 30) | Sentinel events | Bed turnover rate | Tracheostomy rate | Local research |
| Stress ulcer prophylaxis | CNS events (CVA) | ED to ICU transfer time | % transfer to SNF | Regional transfers in |
| Mobilization of patients | Cardiac events (MI) | ICU to SD/Floor time | Rehabilitation days | Workload (TISS) |
| Communication (Daily Goal transfer) | Respiratory events | Readmission to ICU | 1-year QOL/PICS | Organ donation rate |
| Antibiotic stewardship | Renal events (AKI) | Hospital readmission | Noise levels in ICU | Autopsy rate |
| Medicine reconciliation | GI events (GIB) | Cost/discharge | EOL care and DNR rate | |
| Handwashing | EMR (no cut/paste) | Cost/day | N:P staffing ratio | |
| DVT prophylaxis | DVT and HIT rates | Transfusion rates | MD:patient ratio | |
| Central line utilization and insertion | CLABSI rate | Ratio acute/LTAC days | Provider engagement | |
| Foley utilization and early removal | CAUTI rate | Palliative care referrals | Collaborative practice | |
| Ventilator and NIV utilization rates | VAP rate | Ventilator days | Procedure complications | |
| Assessing sedation RASS / CAMICU | | | | |

AKI, acute kidney injury; CAMICU, confusion assessment method–intensive care unit; CAUTI, catheter-associated urinary tract infection; CLABSI, central line–associated bloodstream infection; CVA, cerebrovascular event; DVT, deep venous thrombosis; ED, emergency department; EMR, electronic medical record; GIB, gastrointestinal bleeding; HIT, heparin-associated thrombocytopenia; LOS, length of stay; MI, myocardial infarction; N:P, nurse to patient; RASS, Richmond agitation-sedation scale; SMR, standardized mortality ratio; NSF, skilled nursing facility; TISS, therapeutic intervention severity score; VAP, ventilator-associated pneumonia.

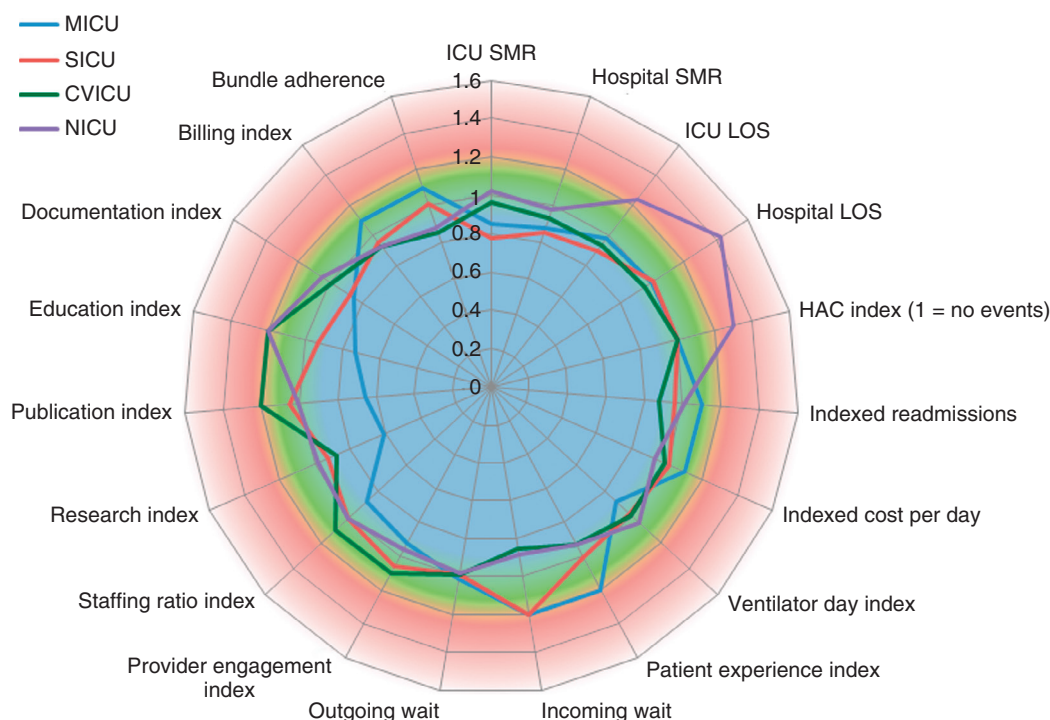


FIGURE 181-1 ■ Radar display of three hypothetical intensive care units, demonstrating a balanced scorecard approach to outcome assessment. Domains include metrics for quality of care (standardized mortality and hospital-acquired conditions), efficiency (standardized length of stay, readmissions, costs), subjective experience (family satisfaction, provider engagement, quality of life, wait times), and unit-specific measures such as publications, education, and quality of documentation. CVICU, cardiovascular intensive care unit; HAC, hospital-acquired conditions; ICU, intensive care unit; ICUSMR, intensive care unit standardized mortality ratio; LOS, length of stay; MICU, medical intensive care unit; NICU, neuro intensive care unit; SICU, surgical intensive care unit.

readmission, and health-related quality of life after hospital discharge.¹⁹ Events such as myocardial infarction, prolonged ventilation, stroke or other central nervous system complications, renal failure, and serious infection can be difficult to collect accurately. With electronic medical records and good coding, comorbidities may be identified by ICD-9 and international classification of disease (ICD)-10 codes,²⁰ but administrative records may not reflect all relevant events.²¹ ICU LOS is difficult to use as a proxy for quality of care because the frequency of distribution is usually skewed and the mean LOS is always higher than the median LOS owing to long-stay outliers.²² In addition, early death shortens the LOS, resulting in a nonlinear relationship between the two outcomes. It is difficult to develop accurate models for ICU LOS at admission²³; discrimination is usually inferior to that of mortality models based on the same database. A variety of regression methods have been applied to LOS prediction, with somewhat disappointing results.²⁴ More success has been achieved by combining variables from ICU day 1 and day 5; variables with the most impact include mechanical ventilation, the $\text{PaO}_2/\text{FiO}_2$ ratio, physiologic components, and day 5 sedation.²⁵

Patients readmitted to ICUs have increased hospital mortality and LOS. However, readmission rates are difficult to interpret without careful case-mix adjustment.²⁶ Readmission rates are affected by triage decisions when ICU beds are constrained, but one study suggests that readmissions are only slightly higher with bed constraints, and, in any case, do not appear to affect short-term patient outcomes.²⁷ In a retrospective study of 263,082 first-admission patients in 105 U.S. hospitals, the median unit readmission rate was 5.9% (interquartile range, IQR, 5.1% to 7.0%). Hospitals with high readmission rates, however, did not have higher standardized mortality rates or LOS after case-mix adjustment.²⁸

Patient satisfaction is an outcome highly valued by purchasers of health care, but it is subjective and requires substantial effort to quantify successfully.²⁹ Evaluation of ICU performance requires a combination of indicators, but risk adjustment has mostly been developed for short-term mortality outcomes, with only a few studies risk-adjusting for other indicators.

DATABASES AND DEFINITIONS

The quality of a risk stratification system largely depends on the database from which it was developed. Retrospective studies using existing data are quicker and less expensive but may be compromised by missing data, imprecise definitions, interobserver variability,³⁰ and changes in medical practice over time. Data derived from discharge summaries or insurance claims do not always capture the presence of comorbid disease³¹ if the number of reportable events is truncated, and this coding bias is most apparent in severely ill patients.²² Coding errors and algorithms that optimize diagnosis-related group reimbursement also reduce the validity of claims-derived data. A variety of methods can assess the quality of the database, such as reabstraction of a sample of charts by personnel blinded to the initial results. Kappa analysis is a method for quantifying the rate of discrepancies between measurements (values) of the same variable in different databases (i.e., original and reabstracted). A kappa value of 0 represents random agreement and of +1.0 represents perfect agreement, but this statistic must be interpreted in light of the prevalence of the factor being abstracted.³²

MODEL DEVELOPMENT

Once data integrity is ensured, there are several possible approaches that relate outcome to the presenting condition.⁹ The empiric approach is to use a large database and subject the data to a series of statistical manipulations (Box 181-1). Typically, death, one or more specific morbidities, and resource consumption (LOS) are chosen as outcomes (dependent variables). Factors (independent variables) thought to affect outcome are then evaluated against a specific outcome using univariate tests to establish the magnitude and significance of any relationship.⁹

BOX 181-1

Steps in Developing a Severity-of-Illness Model

Precisely define outcome(s) of interest.
Identify and define candidate predictor variables (data analysis, expert opinion).
Collect data, and ensure its accuracy (reabstraction, kappa analysis).
Examine continuous variables, and transform or dichotomize as necessary.
Perform univariate analysis (chi-square, Fisher's exact, Student's t-test) against outcome(s).
Perform multivariate analysis (logistic regression, neural nets, Bayesian, others).
Examine and adjust for interactions among variables.
Develop a score or equation that relates independent variables to outcome.
Test calibration of model (goodness of fit, typically Hosmer-Lemeshow method).
Test discrimination of model (ROC area C-statistic, sensitivity, and specificity).
Validate model with independent data, split sample, or jackknife techniques.
Obtain external validation in new settings, and customize as needed.
Publish in peer-reviewed journal.

WHAT INDEPENDENT VARIABLES AFFECT OUTCOME?

ICU-specific systems typically adjust for patient physiology, age, and chronic health condition; they may also assess admitting diagnosis, location before ICU admission or transfer status, cardiopulmonary resuscitation before admission, surgical status, and mechanical ventilation use. An ideal approach would use only variables that characterize a patient's initial condition, can be statistically and medically related to outcome, are easy to collect, and are independent of treatment decisions. There is also benefit to serial assessment of the condition as the influence of independent variables may vary throughout the hospitalization.³³ The Glasgow Coma Scale³⁴ (GCS) is frequently used as a component of ICU severity scores but can be difficult to calculate correctly in sedated patients. The Full Outline of UnResponsiveness score,³⁵ which includes information on brainstem reflexes and respiration, is emerging as an alternative with slightly better accuracy than GCS as a mortality predictor.

Measured variables such as "cardiac index" or "hematocrit" are preferred over "use of inotropes" or "transfusion given" because the criteria for intervention may vary by provider or hospital. Widely used models rely on common measured physiologic variables (heart rate, blood pressure, and neurologic status) and laboratory values (serum creatinine level and white blood cell count). Models may consider age and chronic health status and include interaction terms when variables are not independent. Items chosen for inclusion in a scoring system should be readily available and relevant to involved clinicians. Specialized scoring systems become necessary for specific patient populations (pediatric, burn, trauma, cardiac surgery) whose underlying physiology or treatment course differs from that of the general adult ICU population. For example, left ventricular ejection fraction and reoperative status are important predictors of outcome in the cardiac surgical population but are neither routinely measured nor directly relevant to other population groups.³⁶

If the independent variable is dichotomous (yes/no, male/female), a two-by-two table can be constructed to examine the odds ratio and a chi-square test performed to assess significance (Table 181-2). If multiple variables are being considered, the level of significance is generally set smaller than $P = 0.05$, using a multiple comparison correction.³⁷

If the independent variable under consideration is continuous (e.g., age), a Student's t-test is an appropriate choice for statistical comparison. With continuous variables, consideration must be given to whether the relationship of the variable to outcome is linear, exponential, or segmented across its range. Figure 181-2 shows the relationship of ICU admission serum bicarbonate to mortality outcome in cardiac surgical patients³⁸; data points have been averaged with adjacent values to produce a smoothed graph.³⁹ Serum bicarbonate values higher than

TABLE 181-2

Two-by-Two Contingency Table Examining Relationship of MOF After Open Heart Surgery (Outcome) to a History of CHF (Predictor) in 3830 Patients*

| PREDICTOR VARIABLE: HISTORY OF CHF | OUTCOME VARIABLE: MOF | |
|---------------------------------------|--------------------------|------|
| | YES | NO |
| Yes | 121 | 846 |
| No | 166 | 2697 |

*The odds ratio is defined by cross-multiplication $(121 \times 2697) \div (846 \times 166)$. The odds ratio of 2.3 indicates patients with CHF are 2.3 times as likely to develop postoperative organ system failure as those without prior CHF. This univariate relationship can then be tested by chi-square for statistical significance.

CHF, congestive heart failure; MOF, multiple organ failure.

Data from Higgins TL, Estafanous FG, Loop FD, et al. ICU admission score for predicting morbidity and mortality risk after coronary artery bypass grafting. *Ann Thorac Surg* 1997;64:1050–108.

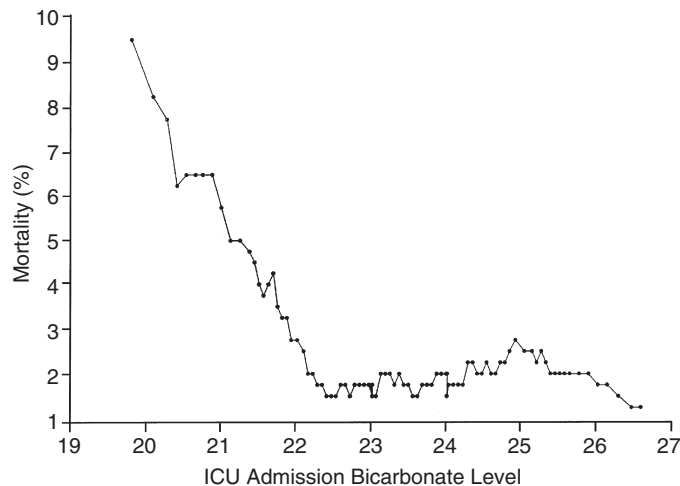


FIGURE 181-2 ■ A locally weighted smoothing scatterplot (LOWESS) analysis of the relationship between ICU admission bicarbonate level (x-axis) and mortality (y-axis). Individual patient data are grouped and averaged with surrounding data to produce a smooth plot. In this instance, the mortality rate appears to be stable with admission serum bicarbonate levels of 22 mmol/L and above but rises rapidly with lower values. Admission bicarbonate level of less than 21 mmol/L was given prognostic weight in the model that used these data. (Data from Higgins TL, Estafanous FG, Loop FD, et al. ICU admission score for predicting morbidity and mortality risk after coronary artery bypass grafting. *Ann Thorac Surg* 1997;64:1050–1058.)

22 mmol/L at ICU admission imply a relatively constant risk. Below this value, the risk of death rises sharply. Analysis of this locally weighted smoothing scatterplot graph suggests two ways for dealing with the impact of serum bicarbonate on mortality. One would be to make admission bicarbonate a dichotomous variable (i.e., >22 mmol/L or <22 mmol/L). The other would be to transform the data via a logarithmic equation to make the relationship more linear. Cubic splines analysis⁴⁰ can be helpful when the relationship between independent and dependent variables is not linear or cannot be described by a simple transformation.

Univariate analysis assesses the forecasting ability of variables without regard to possible correlations or interactions between them. Linear discriminant and logistic regression techniques can evaluate

TABLE 181-3

Variables in the MPM₀ III Logistic Regression Model

| VARIABLE | ODDS RATIOS (95% CONFIDENCE INTERVALS) | COEFFICIENTS (ROBUST STANDARD ERRORS) |
|--|---|--|
| CONSTANT | NA | −5.36283 (0.103) |
| PHYSIOLOGY | | |
| Coma/deep stupor (GCS 3 or 4) | 7.77* (5.921, 10.201) | 2.050514 (0.139) |
| Heart rate ≥150 bpm | 1.54 (1.357, 1.753) | 0.433188 (0.065) |
| Systolic BP ≤90 mm Hg | 4.27* (3.393, 5.367) | 1.451005 (0.117) |
| CHRONIC DIAGNOSES | | |
| Chronic renal insufficiency | 1.71 (1.580, 1.862) | 0.5395209 (0.042) |
| Cirrhosis | 7.93* (4.820, 13.048) | 2.070695 (0.254) |
| Metastatic neoplasm | 24.65* (15.970, 38.056) | 3.204902 (0.222) |
| ACUTE DIAGNOSES | | |
| Acute renal failure | 2.32 (2.137, 2.516) | 0.8412274 (0.042) |
| Cardiac dysrhythmia | 2.28* (1.537, 3.368) | 0.8219612 (0.200) |
| Cerebrovascular incident | 1.51 (1.366, 1.665) | 0.4107686 (0.051) |
| GI bleed | 0.85 (0.763, 0.942) | −0.165253 (0.054) |
| Intracranial mass effect | 6.39* (4.612, 8.864) | 1.855276 (0.166) |
| OTHER | | |
| Age (per year) | 1.04* (1.037, 1.041) | 0.0385582 (0.001) |
| CPR prior to admission | 4.47* (2.990, 6.681) | 1.497258 (0.205) |
| Mechanical ventilation within 1 hour of admission | 2.27* (2.154, 2.401) | 0.821648 (0.028) |
| Medical or unscheduled surgical admit | 2.48 (2.269, 2.719) | 0.9097936 (0.046) |
| Zero factors (no factors other than age from list above) | 0.65 (0.551, 0.777) | −0.4243604 (0.088) |
| Full code | 0.45 (0.416, 0.489) | −0.7969783 (0.041) |
| INTERACTION TERMS | | |
| Age × Coma/deep stupor | 0.99 (0.988, 0.997) | −0.0075284 (0.002) |
| Age × Systolic BP ≤90 | 0.99 (0.988, 0.995) | −0.0085197 (0.002) |
| Age × Cirrhosis | 0.98 (0.970, 0.986) | −0.0224333 (0.004) |
| Age × Metastatic neoplasm | 0.97 (0.961, 0.974) | −0.0330237 (0.003) |
| Age × Cardiac dysrhythmia | 0.99 (0.985, 0.995) | −0.0101286 (0.003) |
| Age × Intracranial mass effect | 0.98 (0.978, 0.988) | −0.0169215 (0.003) |
| Age × CPR prior to admission | 0.99 (0.983, 0.995) | −0.011214 (0.003) |

Odds ratios for variables with an asterisk (*) are also affected by the associated interaction terms.

CPR, cardiopulmonary resuscitation within 24 hours preceding admission; BP, blood pressure; bpm, beats per minute; GCS, Glasgow Coma Scale; ×, interaction between each pair of variables listed.

Reprinted with permission from Higgins TL, Teres D, Copes WS, et al. Assessing contemporary intensive care unit outcome: an updated mortality probability admission model (MPM₀-III). *Crit Care Med* 2007;35:827–835.

and correct for overlapping influences on outcome. For example, both a history of heart failure and depressed left ventricular ejection fraction predict poor outcome in patients presenting for cardiac surgery.⁴¹ As might be expected, there is considerable overlap between the population with systolic heart failure and those with low ejection fraction. The multivariate analysis in this specific instance eliminates history of heart failure as a variable and retains only measured ejection fraction in the final equation to avoid double-counting of this general risk.

Because linear discriminant techniques require certain assumptions about data, logistic techniques are more commonly utilized.⁹ Multiple logistic regression produces an equation with a constant, a β coefficient and standard error, and an odds ratio that represents each term's effect on outcome. Table 181-3 displays the results of the logistic regression used in the Mortality Probability Model III ICU admission model (MPM₀ III).⁴² There are 17 variable terms, and a constant term, each with a β value that, when multiplied by the presence or absence

of a factor, becomes part of the calculation of mortality probability using a logistic regression equation. The odds ratios reflect the relative risk of mortality if a factor is present. The challenge in building a model is to include sufficient terms to deliver reliable prediction while keeping the model from being cumbersome to use or too closely fitted to its unique development population. Generally accepted practice is to limit the number of terms in the logistic regression model to 10% of the number of patients having the outcome of interest to avoid “overfitting” the model to the developmental dataset. It is important to identify interaction among variables that may be additive, subtractive (canceling), or synergistic and thus require additional terms in the final model. In the earlier example, seven interaction items were added to reflect important observations in elderly patients,⁴³ where the very old without significant comorbidity frequently have better outcomes than unhealthy younger individuals.

The patient’s diagnosis is an important determinant of outcome,⁴⁴ but conflicting philosophies exist on how disease status should be addressed by a severity adjustment model. One approach is to define principal diagnostic categories and add a weighted term to the logistic regression equation for each illness.⁴⁵ This acknowledges the different impact of physiologic derangement by diagnosis. For example, patients with diabetic ketoacidosis have markedly altered physiology but a low expected mortality; a patient with an expanding abdominal aneurysm, conversely, may show little physiologic abnormality and yet be at high risk for death. Too many diagnostic categories, however, may result in too few patients in each category to allow statistical analysis for a typical ICU, and such systems are difficult to use without sophisticated (and often proprietary) software.

The other approach is to ignore disease status and assume that factors such as age, chronic illness, and altered physiology will suffice to explain outcome in large groups of patients. This method reduces manual data collection and avoids issues with inaccurate labeling of illness in patients with multiple problems and the need for lengthy lists of coefficients but could result in a model that is less accurate⁴⁶ and somewhat dependent on having an “average” case mix.⁴⁷ Regardless of the specific approach, age and comorbidities (metastatic or hematologic cancer, immunosuppression, and cirrhosis) are given weight in nearly all ICU models to help account for the patient’s physiologic reserve or ability to recover from acute illness. Yet, many influential variables (e.g., frailty⁴⁸ in elders, mental illness,⁴⁹ paraplegia) increase the risk of poor outcome but are seldom incorporated into models. For example, acutely intoxicated patients tend to have low in-hospital mortality, but striking rates of long-term mortality, particularly when street drugs are the intoxicating agent.⁵⁰ Do-not-resuscitate orders are a strong confounder in mortality evaluations⁵¹ but have only been included as a scoring variable in more recent models.⁴²

**VALIDATION AND TESTING
MODEL PERFORMANCE**

Models may be validated on an independent dataset or by using the development set with methods such as jackknife or bootstrap validation.⁵² Two criteria are essential in assessing model performance: calibration and discrimination. *Calibration* refers to how well the model tracks outcomes across its relevant range. A model may be very good at predicting good outcomes in healthy patients and poor outcomes in very sick patients yet unable to distinguish outcomes for patients in the middle range. The Hosmer-Lemeshow goodness-of-fit test⁵³ assesses calibration by stratifying the data into categories (usually deciles) of risk. The number of patients with an observed outcome is compared with the number of predicted outcomes at each risk level. If the observed and expected outcomes are very close at each level across the range of the model, the sum of chi-squares will be low, indicating good calibration. The *P* value for the Hosmer-Lemeshow goodness-of-fit *increases* with better calibration and should be nonsignificant (i.e., >0.05). Special precautions apply when using the Hosmer-Lemeshow tests with very large databases,⁵⁴ where massive numbers can produce significance without true importance.

TABLE 181-4 Classification Table

| PREDICTED OUTCOME | ACTUAL OUTCOME | |
|-------------------|----------------|----------|
| | DIED | SURVIVED |
| Died | a | c |
| Survived | b | d |

True-positive ratio = $a/(a + b)$ (sensitivity)
False-positive ratio = $c/(c + d)$
True-negative ratio = $d/(c + d)$ (specificity)
False-negative ratio = $b/(a + b)$
Accuracy (total correct prediction) = $(a + d)/a + b + c + d$
Adapted from Ruttiman UE. Severity of illness indices: development and evaluation. In: Shoemaker WC, ed. Textbook of critical care medicine. 2nd ed. Philadelphia: Saunders; 1989.

The second measurement of model performance is *discrimination*, or how well the model predicts the correct outcome. A classification table (Table 181-4) displays four possible outcomes that define sensitivity and specificity of a model with a binary (died/survived) prediction and outcome. Sensitivity (the true-positive rate) and specificity (the true-negative rate, or 1—the false-positive rate) are measures of discrimination but will vary according to the decision point chosen to distinguish among outcomes when a model produces a continuous range of possibilities. The sensitivity and specificity of a model when using 50% as the decision point will differ from that using 95% as the decision point. The classification table can be recalculated for a range of outcomes by choosing various decision points: for example, 10%, 25%, 50%, 75%, and 95% mortality risk. At each decision point, the true-positive rate (proportion of observed deaths predicted correctly), the false-negative rate (proportion of survivors incorrectly predicted to die), and overall correct classification rate can be presented. The C-statistic, or area under a receiver-operating characteristic (ROC) curve, is a convenient way to summarize sensitivity and specificity at all possible decision points. A graph of the true-positive proportion (sensitivity) against the false-positive proportion (1—specificity) across the range of the model produces the ROC curve (Fig. 181-3). A model with equal probability of producing the correct or incorrect result (e.g., flipping a coin) will produce a straight line at a 45-degree angle that encompasses half of the area (0.5) under the curve. Models with better discrimination will incorporate increasingly more area under the curve to a theoretical maximum of 1.0. An area under the ROC curve (auROC) higher than 0.70 is acceptable, with higher than 0.80 considered excellent, and higher than 0.90 outstanding.⁸ Most ICU models have ROC areas of 0.8 to 0.9 in their development set, although the ROC area usually decreases when models are applied prospectively to new datasets. The ROC analysis is valid only if the model has first been shown to be well calibrated.

A model may discriminate and calibrate well on its development dataset yet fail when applied to a new population.⁵⁵ Discrepancies in performance can also relate to differences in surveillance strategies and definitions⁵⁵ and can occur when a population is skewed by an unusual number of patients having certain risk factors, as could be seen in a specialized ICU.⁴⁷ Large numbers of low-risk ICU admissions will result in poor predictive accuracy for the entire ICU population.⁵⁶ The use of sampling techniques (i.e., choosing to collect data randomly on 50% of patients rather than all patients) also appears to bias results.⁵⁷ Models deteriorate over time,⁵⁸ owing to changes in populations and medical practice. These explanations should be considered before concluding that quality of care is different between the original and later applications of a model.

STANDARDIZED MORTALITY RATIO

Application of a severity of illness scoring system involves comparison of observed outcomes with those predicted by the model. The *standardized mortality ratio* (SMR) is defined as observed divided by

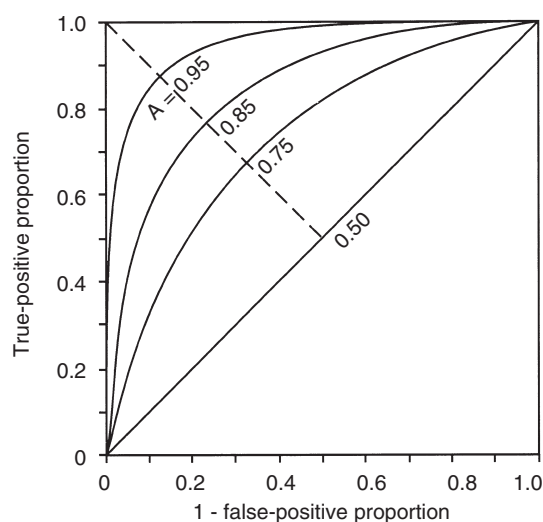


FIGURE 181-3 ■ Relative operating characteristic (ROC) curves. A coin toss gives an ROC of 0.5. In models that discriminate outcome, an increasing area under the curve, also called the *C-statistic*, is enclosed. (From Swets JA. Measuring the accuracy of diagnostic systems. *Science* 1988;240:1285–1294.)

expected mortality and is generally expressed as a mean value $\pm 95\%$ confidence intervals (CIs), which will depend on the number of patients in the sample. SMR values of 1.0 (\pm the CI) indicate that the mortality rate, adjusted for presenting illness, is at the expected level. Standardized mortality ratio values significantly lower than 1.0 indicate performance better than expected. Small differences in scores, as could be caused by consistent errors in scoring elements, timing of data collection, or sampling rate, cause important changes in the SMR.^{38,59} Different models applied to the same dataset may produce discordant results, with the same hospital being identified as performing better than expected by one model and worse than expected by another.⁴⁶

MODELS BASED ON PHYSIOLOGIC DERANGEMENT

Three widely utilized general-purpose ICU outcome systems are based on changes in patient physiology: the Acute Physiology and Chronic Health Evaluation (APACHE II,⁶⁰ APACHE III,⁶¹ APACHE IV⁴⁴), the Mortality Probability Models (MPM₀-II,⁶² MPM₂₄-II,³³ MPM₀-III),⁴² and the Simplified Acute Physiology Score (SAPS II,⁶³ SAPS III^{64,65}). MPM₀-II and SAPS II were developed from the same dataset and initially shared variables. All models have been regularly updated and are in at least their third generation. Although variables and weighting differ, all are based on the premise that as critical illness increases, patients will exhibit greater deviation from physiologic normal for a variety of common parameters such as heart rate, blood pressure, neurologic status, and laboratory values. Risk is also assigned for advanced age and chronic illness. Variables from these models have also been incorporated into the U.S. Veterans Administration hospital system model⁶⁶ (based on APACHE) and the California Outcomes Study⁶⁷ (similar to MPM₀-II and -III), as well as to models customized for international populations.

Acute Physiology and Chronic Health Evaluation

APACHE II was developed from data on 5815 adult medical and surgical ICU patients at 13 hospitals between 1979 and 1982; patients undergoing coronary artery bypass grafting, coronary care, or burn

treatment were not part of the initial analysis. Severity of illness was assessed with 12 routine physiologic measurements plus the patient's age and previous health status.⁶¹ Scoring was based on the most abnormal measurements during the first 24 hours in the ICU, with a maximum score of 71 points. The physiology score was then combined with coefficients to adjust the score for 29 nonoperative and 16 post-operative diagnostic categories, producing a mortality estimate.

APACHE II does not control for admission source or pre-ICU management, which could restore a patient's altered physiology and lead to a lower score and thus underestimate a patient's true risk.⁶⁸ Mortality estimates are most accurate for patients admitted directly from the emergency department and less so for inter- and intra-hospital transfers. Failure to consider the location prior to ICU admission could thus lead to erroneous conclusions about the quality of medical care.⁶⁹ Although the developers now consider APACHE II to have significant limitations based on its age, it is still in widespread use.

APACHE III, published in 1991, addressed limitations of APACHE II, including the impact of treatment time and location before ICU admission.⁶² The number of separate disease categories was increased from 45 to 78. APACHE III was developed on a representative database of 17,440 patients at 40 hospitals, including 14 tertiary facilities that volunteered for the study and 26 randomly chosen hospitals in the United States. APACHE III went through several partial updates between 1991 and 2003.⁴⁵ Compared with APACHE II, the ranges of physiologic "normal" are narrower; deviations from normal are asymmetrically weighted to be more clinically relevant. Interactions between variables were considered, and five new variables (blood urea nitrogen, urine output, serum albumin, bilirubin, and glucose) were added, while APACHE II variables serum potassium and bicarbonate were dropped. Information was also collected on 34 chronic health conditions, of which seven (AIDS, hepatic failure, lymphoma, solid tumor with metastasis, leukemia/multiple myeloma, immunocompromised state, and cirrhosis) were significant in predicting outcome. Customized models were developed for patient populations (e.g., cardiac surgery)⁷⁰ excluded from APACHE II. Overall correct classification for APACHE III was much improved over the prior model, and for the first time sequential scoring was introduced to update the daily risk estimate. APACHE III scores were also correlated with predictions for ICU LOS, need for interventions, and nursing workload.

APACHE IV was published in 2006⁴⁴ with refinements to address the impact of sedation on GCS, expand the number of diagnostic groups, and to add or rescale predictive variables (Table 181-5). APACHE IV, based on a sample of 110,558 patients in the United States, has excellent discrimination (ROC area = 0.88) and impressive calibration (Hosmer-Lemeshow C statistic 16.8, $P = 0.08$). Outcome assessment using the revised model differed substantially from prior versions. A hospital using APACHE III software in 2006, for example, (calibrated to 1988-89 results) might have congratulated themselves on a superb SMR of 0.799, whereas using APACHE IV would have revealed their SMR to be not different from average at 0.997. APACHE IV relies on physiologic abnormalities to account for 66% of the model's explanatory power. ICU admission diagnosis (using 116 categories) accounts for about 17%, with the remainder accounted for by age, chronic illness, location prior to admission, and interaction terms. There are limitations to the use of APACHE IV. First, the increased complexity of the model makes it impossible to use without dedicated software. The data entry burden, however, can be mitigated by porting data into APACHE from a hospital's clinical information system. Second, APACHE IV was developed and validated in ICUs in the United States, and international differences in ICU resources, triage policies, models of care, and bed availability impact benchmarking performance in a new environment.⁷¹ The authors also stress that "prediction for an individual contains variance" and that "a prediction is only an approximate indicator of an individual's probability of mortality."⁴⁴ As an example, they mention that the 95% CIs around a predicted mortality of 5% would typically be 3.9% to 6.5% and that the absolute ranges of CIs widen as the predicted rate increases. APACHE

TABLE 181-5

Variables Used in Acute Physiology and Chronic Health Evaluation IV

| VARIABLE | COEFFICIENT | ODDS RATIO |
|--|-------------|--------------|
| Emergency surgery | 0.2491 | 1.28 |
| Unable to access GCS | 0.7858 | 2.19 |
| Ventilated on ICU day 1 | 0.2718 | 1.31 |
| Thrombolytic therapy for acute myocardial infarction | -0.5799 | 0.56 |
| Rescaled GCS (15-GCS) | 0.0391 | 1.04 |
| 15-GCS = 0 | | 1.00 |
| 15-GCS = 1, 2, 3 | | 1.04 to 1.12 |
| 15-GCS = 4, 5, 6 | | 1.17 to 1.26 |
| 15-GCS = 7, 8, 9 | | 1.31 to 1.42 |
| 15-GCS = 10, 11, 12 | | 1.48 to 1.60 |
| PaO ₂ /Fio ₂ ratio | -0.00040 | 1.00 |
| ≤200 | | 1.00 to 0.92 |
| 201 to 300 | | 0.92 to 0.89 |
| 301 to 400 | | 0.89 to 0.85 |
| 401 to 500 | | 0.85 to 0.82 |
| 501 to 600 | | 0.82 to 0.79 |
| Chronic health items | | |
| AIDS | 0.9581 | 2.61 |
| Cirrhosis | 0.8147 | 2.26 |
| Hepatic failure | 1.0374 | 2.82 |
| Immunosuppressed | 0.4356 | 1.55 |
| Lymphoma | 0.7435 | 2.10 |
| Myeloma | 0.9693 | 2.64 |
| Metastatic cancer | 1.0864 | 2.96 |
| Admission source | | |
| Floor | 0.0171 | 1.02 |
| Other hospital | 0.0221 | 1.02 |
| Operating/recovery room | -0.5838 | 0.56 |

AIDS, acquired immunodeficiency syndrome; GCS, Glasgow Coma Scale; ICU intensive care unit. Adapted with permission from Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med* 2006;34:1297-1310.

IV has been recalibrated to APACHE IVa, and APACHE V is currently under development.

Mortality Probability Models

The original Mortality Probability Model (MPM) was developed on 755 patients at a single hospital using multiple logistic regression to assign weights to variables predicting hospital mortality.⁷² The MPM-II models were developed on an international sample of 12,610 patients and then validated on a subsequent sample of 6514.³³ A subscript (0, 24, 48, 72) designates time of the evaluation in approximate hours post admission. MPM-II, as with APACHE II, excluded pediatric, burn, coronary, and cardiac surgical patients and estimated hospital mortality risk based partly on physiologic derangement, using a smaller number of variables. However, MPM puts more weight on chronic illness, comorbidities, and age and less on acute physiologic derangement compared with APACHE. MPM models can use data obtained at ICU admission (MPM₀) and also at the end of the first 24-hour period (MPM₂₄), the latter covering a time interval more comparable to APACHE. While APACHE generates a score and then, with additional information, converts that score into a probability estimate of survival, MPM directly calculates a probability of survival from the available data. Because this involves a logistic regression equation, it is difficult to accomplish at bedside without a computer or programmable calculator. The MPM₂₄ variables account for differences in patients who remain in the ICU for 24 hours or longer versus those

who die early or recover rapidly. This line of reasoning has been further extended to create 48- and 72-hour models,⁷³ although these have not yet been updated from MPM-II to MPM-III. Additional variables in MPM₂₄, MPM₄₈, and MPM₇₂, but not MPM₀ are prothrombin time, urine output, creatinine, arterial oxygenation, continuing coma or deep stupor, confirmed infection, mechanical ventilation, or intravenous vasoactive drug therapy. Probability of death increases at 48 and 72 hours even if the MPM variables and coefficients are unchanged, implying that mortality risk is increasing in patients whose clinical profile remains unchanged over time.⁷⁴ The most important difference between MPM and APACHE is that the MPM₀ produces a probability estimate that is available at ICU presentation and is independent of ICU treatment. MPM also does not require specifying a diagnosis, which can be an advantage in complex ICU patients but may also make it more susceptible to error with changes in case mix⁴⁷ and generates, on average, a lower area under the ROC curve.

MPM₀-II became the mortality benchmarking component for the Society of Critical Care Medicine's (SCCM) Project IMPACT database launched in 1996. By 2002, it was apparent that mortality predictions based on mid-1980s results were outdated, and average SMRs in Project IMPACT hospitals had drifted to 0.85.⁷⁴ MPM₀-III was developed from a population of 124,855 patients in 135 ICUs at 98 Project IMPACT hospitals. Hospital mortality in this population was 13.8% versus 20.8% in the MPM₀-II cohort.⁴² All of the 15 variables from MPM₀ II remained associated with mortality, but the relative impact had changed. For example, gastrointestinal bleeding was no longer a serious risk factor, presumably because of advances in resuscitation, endoscopic procedures, treatment of *H. pylori*, and availability of proton pump inhibitors since the original study. Additionally, two new variables were added: "full code" resuscitation status at ICU admission and "zero factor" or absence of all MPM₀-II risk factors except age. Seven age interaction terms were added to reflect the declining marginal contribution of acute and chronic medical conditions to mortality risk in the elderly.⁴³ MPM₀-III calibrated well (Hosmer-Lemeshow goodness-of-fit 11.62; *P* = 0.31) with an area under the ROC curve of 0.823, similar to that of MPM₀-II. While the ROC area is lower than with APACHE, MPM users do not need to specify a diagnosis, which may be difficult in a complex patient with multiple problems. The simplicity of data collection and ability to generate a prognosis soon after arrival (rather than at 24 hours) are advantages. Limitations of the MPM₀-III include lower discrimination and use of a self-selected population of Project IMPACT participants in North America. While in theory, extreme case-mix differences might affect MPM performance, in practice, SMRs obtained using MPM₀-III versus specially constructed subgroup models were nearly identical in the 135 ICUs studied, suggesting specialized subgroup models are not usually necessary.⁷⁵ MPM₀-III has been prospectively validated on an additional 55,459 patients at 103 adult ICUs in North America and calibrates well with more contemporary Project IMPACT hospitals (78 units participating in both studies plus 25 new participants).⁷⁶ The Project IMPACT database was also used to update the resource utilization "Rapoport Teres" graph that plots severity-adjusted mortality versus severity-adjusted LOS⁷⁷ (Fig. 181-4).

The California Intensive Care Outcomes Projects (CALICO) was developed to produce public reports comparing outcomes for patients treated in California ICUs as part of the larger California Hospital Outcomes Project mandated by the State of California.⁶⁸ After evaluating risk models available in the early 2000s, the California Healthcare Foundation and the National Quality Forum endorsed a modified and recalibrated version of the MPM₀-II model termed "ICU Outcomes Model" or ICOM_{mort},⁷⁸ which has an auROC of 0.84 in prospective validation. The model includes 28 additional interaction terms and differs in patient exclusions from MPM-II and MPM-III. An additional model (ICOM_{LOS}) considers LOS. The CALICO project yielded several important findings, most notably that substantial (2-fold) variation exists in mortality rates among hospitals, even after risk adjustment.⁶⁸ Beginning in 2007, California required every ICU in the state to report severity-adjusted mortality rates. A recent study of 936,063 patients

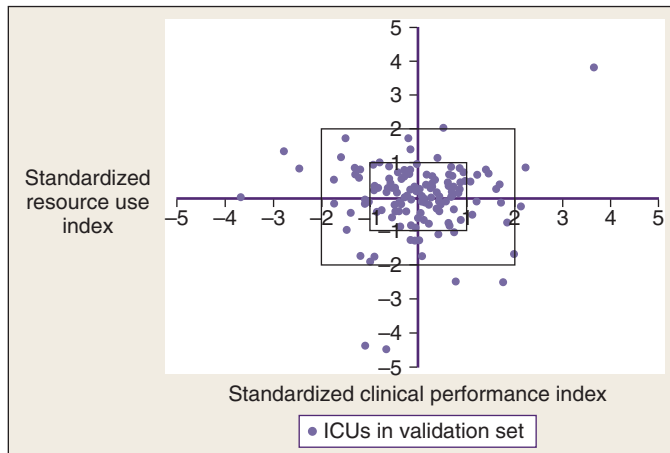


FIGURE 181-4 ■ Project IMPACT consolidates the display of MPM severity-adjusted mortality data (x-axis) with standardized resource use (weighted hospital days, y-axis). Hospitals within the 1 and 2 standard deviation boxes (most observations) are performing as expected. One hospital in the upper-right corner has superior performance in both dimensions. Four hospitals have longer than expected length of stay (negative numbers on standardized resource use), while being within range for mortality. Three hospitals have worse than expected adjusted mortality, while two have better than expected mortality; all are still within expected resource utilization. (From Nathanson BH, Higgins TL, Teres D, et al. A revised method to assess ICU clinical performance and resource utilization. *Crit Care Med* 2007;35:1853–1862.)

comparing the California experience to that of Arizona, Nevada, and Texas (which did not have public reporting requirements) concluded that while outcomes in California had improved, mortality rates also decreased in the control states.⁷⁹

Simplified Acute Physiology Score

SAPS II⁶⁴ was developed on 13,152 patients at 137 adult medical or surgical ICUs in Europe and North America, sharing the MPM-II dataset. Like MPM and APACHE-II, SAPS excluded burn patients, patients younger than 18 years, coronary care patients, and cardiac surgery patients. The outcome measure for SAPS II was vital status at hospital discharge. Seventeen variables were used in the SAPS II model: 12 physiologic variables, age, type of admission, and the presence of AIDS, metastatic cancer, or hematologic malignancy.

Not surprisingly, the SAPS II model also drifted out of calibration over time.⁶⁵ SAPS III, a multicenter, multinational study, collected data on 19,577 patients from 307 ICUs during the fall of 2002. SAPS II, when applied to this cohort, underestimated hospital mortality, and, while it discriminated well (ROC area, 0.83), calibration was poor, and model performance differed by geographic region. The final SAPS III model (Box 181-2), created based on 16,784 patients using logistic regression methods, contains 20 variables and has good discrimination (ROC area 0.848) and calibration (Hosmer-Lemeshow $C = 14.29$; $P = 0.16$).⁶⁶ Customized models were generated for seven worldwide regions to address geographic variation in population outcomes.

Intensive Care National Audit and Research Center Model

As noted earlier, risk adjustment models require validation and recalibration if they are to be applied in a new geographic setting.^{55,80} The Intensive Care National Audit and Research Center (ICNARC)

BOX 181-2

Variables Used in Simplified Acute Physiology Score Iii

Age (in years)
Comorbidities: cancer, cancer therapy (scored separately), chronic heart failure (NYHA IV), hematologic cancer, cirrhosis, AIDS
Length of stay before intensive care unit (ICU) admission, days
Intrahospital location before ICU admission
Use of major therapeutic options before ICU admission (e.g., vasopressors)
ICU admission: planned or unplanned
Reason for ICU admission
Surgical status at ICU admission: emergency, elective, or none
Anatomic site of surgery
Acute infection at ICU admission
Lowest estimated Glasgow Coma Scale score (points)
Total bilirubin (highest)
Body temperature (highest)
Creatinine (highest)
Heart rate (highest)
Leukocytes (highest)
Hydrogen ion concentration (lowest pH)
Platelet count (lowest)
Systolic blood pressure (lowest)
Oxygenation (P/F ratio)

BOX 181-3

Elements in ICNARC Score

Highest heart rate
Lowest systolic BP
Highest temperature
Lowest respiratory rate
Mechanical ventilation (Yes/No)
Lowest Pao₂/associated FiO₂ (P/F ratio)
Lowest pH
Highest serum urea
Highest serum creatinine
Highest serum sodium
Urine output (24 hours)
Lowest WBC
Paralyzed/sedated (Yes/No)
Lowest Glasgow Coma Scale score
Age, years
Source of admission
Diagnostic category
CPR (Yes/No)

Adapted with permission from Harrison DA, Gareth JP, Carpenter JR, et al. A new risk prediction model for critical care: the Intensive Care National Audit & Research Centre (ICNARC) model. *Crit Care Med* 2007;35:1091–1098.

collected data on 216,626 critical care admissions in 163 adult general critical care units in England, Wales, and Northern Ireland from December 1996 to August 2003.⁸¹ Logistic regression techniques were used to create the ICNARC model (Box 181-3), which includes 12 physiologic variables, age, source of admission, diagnostic category, and CPR status. This model has an ROC area of 0.863 and a Hosmer-Lemeshow C statistic of 64.2. This study also evaluated performance of APACHE II, APACHE III, SAPS II, and MPM-II on the same population. The ICNARC outperformed all other models in terms of discrimination (ROC area), but SAPS II had better calibration, while MPM-II had the best accuracy of average prediction, although these differences were all relatively minor. ICNARC, having no exclusions, may be applied to all critical care admissions regardless of diagnosis, and it calibrates well in the United Kingdom. ICNARC has recently been externally validated in 23,269 patients in 24 Scottish critical care units, with good discrimination (0.848) and calibration.⁸²

Veterans Affairs Intensive Care Unit Risk Adjustment Model

Arguably, the Veterans Affairs (VA) population in the United States could represent a specialized population, owing to being predominantly male (>97%). In 1996-97, the VA developed a customized, automated ICU risk adjustment tool⁶⁷ based on APACHE variables; this model has been validated, updated, and recalibrated.⁸³ Risk predictors include age, mutually exclusive ICD-9 diagnosis/procedure groups, comorbid disease groups, admission source, and 11 laboratory values measured during the 24 hours surrounding ICU admission. Revisions to the model refit the predictor coefficients and expanded the number of diagnostic categories from 38 to 84. The model has an impressive ROC area (0.874-0.877) in two data cohorts and calibrates well by Hosmer-Lemeshow statistics. SMRs derived from the VA ICU model correlate well ($r^2 = 0.74$) with those of the National Surgical Quality Improvement Performance (NSQIP) tool developed for surgical post-operative assessment. The VA model, however, has not yet been tested internationally or outside of the VA population.

Specialized Models

MPM, SAPS, and early versions of APACHE excluded patients younger than age 18, burn patients, and coronary care and cardiac surgical patients. Murphy-Filkins et al.⁴⁷ reported that performance of severity of illness models deteriorates when critical population values are reached for individual scoring variables, as might be seen in a highly specialized ICU. For example, 20% of the patients in the MPM-II database were aged 75 or older. When this percentage of elderly patients was experimentally increased to 42%, the model became unstable. Similar changes were seen if the proportion of patients with cardiac dysrhythmias, cerebrovascular disease, intracranial mass effects, coma, cardiopulmonary resuscitation before ICU admission, emergency admission, or gastrointestinal bleeding differed substantially from baseline values. Thus, severity of illness scoring systems should be used with caution when units become highly specialized to care for subsets of patients.

To address this issue, specific models have been developed for pediatric,⁸⁴ trauma,⁸⁵ and cardiac surgical populations.^{41,86-88} ICU admission physiologic values in the cardiopulmonary bypass population are determined by routine hypothermia, hemodilution, and deliberate control of hemodynamics by the operating room team. Important variables for predicting outcome after cardiac surgery are ventricular function, coronary anatomy, and heart valve pathology and reoperation status.³⁶ The Cooperative CABG Database Project, analyzing 172,000 patients, identified seven core variables (urgency of operation, age, prior heart surgery, gender, ejection fraction, percent stenosis of the left main coronary artery, and number of major coronary arteries with >70% stenosis) to be predictive of mortality.⁸⁹ The independent variables predicting morbidity do not perfectly overlap those predicting mortality or LOS, suggesting that different scores may be required to best predict various outcomes. Currently, the two most widely used preoperative cardiac surgical models are the Society for Thoracic Surgeons model⁹⁰ in the United States and the EuroSCORE-II⁹¹ in Europe; both have been updated from their original iterations.

The preoperative cardiac surgical models are useful for evaluating the results of an entire hospitalization but do not specifically address the ICU component of care. Operating room events can neutralize or amplify preoperative risk, depending on such events as reopening the chest, hemodynamic management in an emergency patient, and the degree of myocardial protection. In 5000 patients undergoing CABG, eight risk factors available at ICU admission appeared to predict hospital mortality, and an additional five factors also predict morbidity.³⁸ APACHE has also been successfully modified for use in cardiac surgical patients.⁷¹

Patients receiving prolonged mechanical ventilation (MV) are resource-intensive, and, although their mortality can be accurately

estimated, they have a disproportionate effect on ICU and hospital LOS which is magnified with high hospital MV volume.⁹² The ProVent model, measured on day 21 of MV, predicts overall 1-year mortality (48%) with acceptable discrimination and calibration⁹³ by assigning points for four categorical variables: age, platelet count, vasopressors, and hemodialysis.

SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE

The sequential organ failure assessment (SOFA) score was developed to quantify organ dysfunction of the respiratory, cardiovascular, hepatic, coagulation, renal, and neurologic systems. One to four points are assigned based on the degree of physiologic derangement; high scores imply poor outcome. A maximum SOFA higher than 15 is associated with more than 90% mortality.⁹⁴ SOFA is intended to be used sequentially, in part to address the issue that a first-day severity score has limited ability in predicting outcome when patients have a longer ICU experience with attendant events or complications. Although developed to assess organ failure rather than prognosis, SOFA (and similar scores, such as the Logistic Organ Dysfunction System [LODS]⁹⁵ and the Multiple Organ Dysfunction Score [MODS])⁹⁶ correlates with mortality. The change in score during the first 96 hours can help with prognosis: regardless of the initial score, an increasing score is associated with more than 50% mortality.⁹⁷

Most risk-adjustment models provide initial estimates for both ICU and hospital mortality, with the potential for updating predictions during the ICU stay. While subjective, the Sabadell score allows ICU clinicians to categorize patients at ICU discharge into good prognosis (0 points), poor long-term prognosis (>6 months) with unlimited ICU readmission (1 point), poor short-term prognosis (<6 months) with debatable ICU readmission (2 points), and death expected during hospitalization (3 points). Age and the Sabadell score correlate with ward mortality following ICU discharge with good calibration (AuROC, 0.88) and discrimination.⁹⁸ Patients with high predicted ward mortality would likely benefit from palliative care consultation. Conversely, less than 2% of patients with good prognosis die on the ward after ICU discharge.

ADMINISTRATIVE MODELS

Initial versions of the most popular models were developed by research teams using data largely collected manually using trained abstractors.⁴⁵ There has been interest in automating this process,⁹⁹ and with the widespread availability of electronic health records, real-time calculations have become routine. Although extracting relevant clinical variables can still be an informatics challenge, successful models based on administrative data have been developed for predicting in-hospital mortality for community-acquired pneumonia¹⁰⁰ and sepsis.¹⁰¹ With automated data collection, these models can extend beyond just ICU admissions to encompass all hospitalized patients. The next iteration of APACHE will reportedly address outcomes across venues and allow automated outcome predictions for all hospitalized patients. The Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC-II) database promises to promote research in epidemiology and clinical decision-rule creation by establishing a public-access, deidentified database.¹⁰² Caution is raised by a large Dutch study, however, where SMRs calculated using administrative data were unfavorable to those calculated using modified SAPS II clinical data, especially in institutions with a more severely ill population.¹⁰³

COMPARISONS AMONG MODELS

A number of papers have compared relative performance of the three most widely used ICU systems.¹⁰⁴⁻¹⁰⁶ Using data from 11,300 patients in 35 hospitals participating in the CALICO Project, APACHE IV, MPM₀-III, and SAPS II all showed adequate discrimination and calibration, with APACHE IV delivering the best predictive accuracy,

TABLE 181-6 Regional Application of Severity Scoring Models

| STUDY | COUNTRY | SYSTEMS | FINDINGS |
|------------------------------------|--|--|--|
| Arabi et al. ¹⁵⁶ | Saudi Arabia n = 969 | APACHE II MPM II ₀ and II ₂₄ SAPS II | Predicted mortality similar to that observed for all systems (SMR 1.0 to 1.09) Calibration best with MPM II ₂₄ Discrimination best with MPM II ₀ followed by MPM II ₂₄ , APACHE II, and SAPS; all ROC >0.79 |
| Capuzzo et al. ¹⁵⁷ | Italy Single center n = 1721 | APACHE II SAPS II | ROC area >0.8 both models Mortality in high-risk patients overpredicted by SAPS II and underpredicted by APACHE II |
| Katsaragakis et al. ¹⁵⁸ | Greece Single center n = 661 | APACHE II SAPS II | Good discrimination but poor calibration with both models Better performance with APACHE II |
| Livingston et al. ⁸¹ | Scotland 22 centers n = 10,393 | APACHE II APACHE III UK APACHE II MPM II ₀ MPM II ₂₄ | Discrimination adequate (ROC areas 0.74 to 0.795) Observed mortality significantly different from that predicted by all systems APACHE II had best calibration followed by MPM II ₂₄ and SAPS II |
| Markgraf et al. ⁷² | Germany Single center n = 2661 to 2795 | APACHE II APACHE III SAPS II | Observed mortality higher than predicted by any model Worst discrepancy with trauma, respiratory, neurologic, and renal disease Best calibration with APACHE II ROC area >0.8 all models |
| Moreno et al. ¹⁵⁹ | Europe 89 centers n = 16,060 | MPM II ₀ SAPS II | Discrimination adequate (ROC 0.822 for SAPS II, 0.785 for MPM ₀) Both models overestimated risk of death Large variations across subgroups of patients |
| Nouira et al. ¹⁶⁰ | Tunisia 3 centers n = 1325 | APACHE II MPM II ₀ and II ₂₄ SAPS II | Observed mortality higher than predicted except with MPM ₀ Good discrimination, poor calibration for all models |
| Tan et al. ¹⁶¹ | China (Hong Kong) Single center n = 1064 | APACHE II SAPS II | Discrimination good (ROC area 0.87 to 0.88) but calibration poor Both models overpredict mortality |
| Metnitz et al. ¹⁶² | Austria 22 ICUs n = 2060 | SAPS 3 | Original SAPS 3 overestimated mortality even with Central and Western Europe equation Calibration improved with customization |
| Poole et al. ¹⁶³ | Italy 147 ICUs n = 28,357 | SAPS 3 | Discrimination good Calibration poor—general and South Europe Mediterranean equations overestimated hospital mortality (SMR 0.73) |

albeit with longer data collection time.¹⁰⁷ Substantial variation occurred in ICU risk-adjusted mortality rates between ICUs, regardless of the model used.

Performance of three models based on 24-hour data (APACHE II, APACHE III-J, and SAPS II) was compared to that of three models based on admission data (MPM-II, SAPS III, and SAPS III-A using Australian coefficients) for 1741 patients in an urban university-affiliated teaching hospital in Australia.¹⁰⁸ SAPS II and SAPS III-A fulfilled predetermined calibration and discrimination criteria, APACHE II failed both criteria, and the remaining models discriminated well but overpredicted mortality risk. There did not appear to be an advantage in using 24-hour data versus data available at admission. The improved results with SAPS III-A versus SAPS III again underscores the benefit of customizing models with local coefficients. A Brazilian study found APACHE IV, MPM₀-III, and SAPS III to have good discrimination (AuROC 0.883, 0.840, and 0.855, respectively) but uniformly poor calibration leading to overestimates of in-hospital mortality.¹⁰⁹ Calibration was particularly problematic with SAPS 3, but APACHE IV and MPM₀-III also performed poorly at higher predicted mortality rates.

More recently, MPM₀-III, the ICOM_{mort} modification of MPM (also known as the National Quality Forum or NQF model), and APACHE IVa were compared based on a database of 174,001 ICU admissions from 2008 to 2012 at 38 U.S. hospitals.¹¹⁰ Only 109,926 patients (63%) met inclusion criteria for all three models. APACHE IVa offered the best discrimination and calibration and excluded fewer patients than

the other models. APACHE IVa overpredicted mortality by 1.5%, MPM₀-III overpredicted by 3.1%, and the ICOM-NQF model underpredicted by 1.2%. Calibration was best for APACHE IVa, which has implications for benchmarking using SMR when case mix varies among hospitals; this will be discussed below.

Table 181-6 summarizes the results of nine studies in which two or more of the risk-adjustment models were applied to a specific regional population. There is no consistent pattern to accuracy (discrimination), with examples of observed mortality higher than predicted, lower than predicted, as predicted, or predicted differently by different systems. There is also no consistent leader in calibration; it tends to be poor in many studies. Ratios of observed-to-expected mortality rates are influenced by case mix as well as by quality of care.¹¹¹

UTILITY OF SEVERITY OF ILLNESS INDICES

There are four major applications for severity of illness scoring systems:

1. Assessing ICU performance for quality improvement
2. Predicting and planning resource utilization and staffing
3. Comparing populations in clinical research
4. As one factor to consider in guiding individual patient care

Risk-adjusted outcomes data will be shared with a variety of “customers,” each of whom will have a different focus. In broad terms, clinicians and quality leaders will use data to drive improved care and

efficiency, while patients, governments, and payors will be more interested in comparing performance among institutions.¹⁵

QUALITY IMPROVEMENT AND BENCHMARKING

Meaningful evaluation of ICU performance must consider both severity of illness of the patient population and characteristics of the institution. *Benchmarking* refers to the process of comparing an individual unit's performance against established case mix-adjusted standards with similar ICUs or with the units' own data over time. Benchmarking need not be for morbidity and mortality outcomes alone; severity adjustment also helps explain variations in cost and ICU LOS.¹¹² Outlier LOS status is only partially predicted by severity of illness, and factors such as long ward stays before ICU admission and absence of an intensivist-directed multidisciplinary care team increase LOS.¹¹³

The mortality rate and LOS for patients transferred to a referral hospital is higher than that of nontransferred patients,¹¹⁴ and this referral bias¹¹⁵ has implications in profiling hospital quality. Medical patients transferred from another hospital have higher acute physiology scores but, even after adjustment for case mix and severity of illness, experience longer hospital and ICU stays and have more than twice the risk of hospital mortality compared with directly admitted patients.¹¹ These authors suggest that a referral hospital with a 25% transfer-in rate would suffer a penalty when undergoing profiling. Conversely, transferring patients to a tertiary care center has beneficial effects to the exporting hospital, since death is attributed to the receiving hospital.¹¹⁶ Transfer of mechanically ventilated patients from ICU long-term acute care (LTAC) facilities also significantly impacts reported mortality and LOS.¹¹⁷ Intrahospital transfers to a higher level of care after admission are also associated with excess mortality and LOS.¹¹⁸ As noted earlier, discharge practices affect risk-adjusted rates, with a greater impact on large hospitals and when in-hospital, rather than 30-day mortality rates, are considered.¹³

Factors unrelated to quality of medical care or patient severity of illness thus affect public reporting of SMR results. Does the benchmarking tool play a role? SMR was calculated for 47 ICUs at 36 U.S. hospitals using APACHE IVa and the ICOM-NQF models. Overall SMR was 0.89 using APACHE IVa and 1.07 using the NQF model. Disturbingly, the two models agreed on the significance and direction of the SMR only 45% of the time (Fig. 181-5). Units caring for more severely ill patients and with a higher percentage of patients receiving MV had the highest discordance.¹¹⁹ SMR and SMR rank position of ICUs also depend on whether the endpoint is in-hospital mortality or

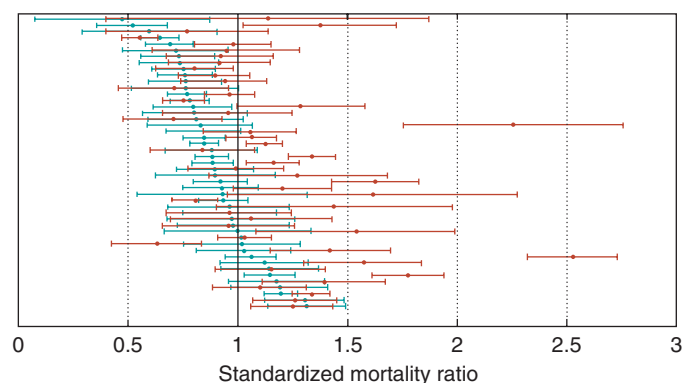


FIGURE 181-5 ■ Standardized mortality ratio (mean and 99% confidence interval) for 47 ICUs evaluated using APACHE IVa (blue) and the ICOM-NQF (red) models. Over half of the performance assessments are discordant. (From Kramer AA, Higgins TL, Zimmerman JE. Comparing observed and predicted mortality among ICUs using different prognostic systems: why do performance assessments differ? *Crit Care Med* 2015;43:261–269.)

mortality at 1, 3, or 6 months after ICU admission.¹²⁰ In an age of outcome-driven reimbursements, these discrepancies are financially important, as well as ethically troubling.¹²¹ Public disclosure and rank-ordering ICUs on the basis of SMR or other metrics is thus highly problematic. Identifying hospitals with higher than expected mortality has no effect on market share¹²² and, reportedly, does not improve process-of-care indicators.¹²³ Benchmarking relative performance among ICUs should likely be replaced by comparing improvement in performance over time. Furthermore, discrepancies between observed and expected outcomes should primarily be a marker to prompt more careful review.¹²⁴

Case volume is an important consideration for evaluation and reporting. SMR should not be presented as a single number but rather as a range that encompasses the 95% confidence intervals based on sample size. Units with a low mortality rate require larger numbers of patients; this is well illustrated in a study by Dimick examining the problems with small sample size when evaluating surgical mortality.¹²⁵

Risk-adjusted mortality rates can be displayed over time; usually quarterly in smaller units and monthly in larger facilities. Standard statistical quality control charts and cumulative sums (CUSUM, a sequential technique) can be used to detect changes requiring investigation.¹²⁶ Exponentially weighted moving average control charts are said to signal the fastest compared with other types of risk-adjusted control charts.¹²⁷ For comparisons among institutions, funnel plots (Fig. 181-6) are preferable to league tables, as they incorporate volume-based control limits that reduce the risk of spurious interpretation inherent in a ranked list.¹²⁸ Other investigators have argued that funnel plots have difficulty identifying outliers with small volumes, while identifying divergence of statistical, but not clinical, importance when the numbers are large.¹²⁹

PREDICTING AND PLANNING RESOURCE UTILIZATION

The Therapeutic Intervention Scoring System (TISS) was developed as a method for quantifying patient care and severity of illness.¹³⁰ TISS was supplanted as a prognostic tool by the newer scoring systems once it was realized that application of technology depended on local availability and local practice. TISS is now used primarily to quantify nursing workload and costs.¹³¹ The Rapoport-Teres graph (see Fig. 181-4) displays MPM risk-adjusted mortality on the x-axis and resource use (LOS) on the y-axis.⁷⁸ Similar displays are possible using other risk adjustment systems.

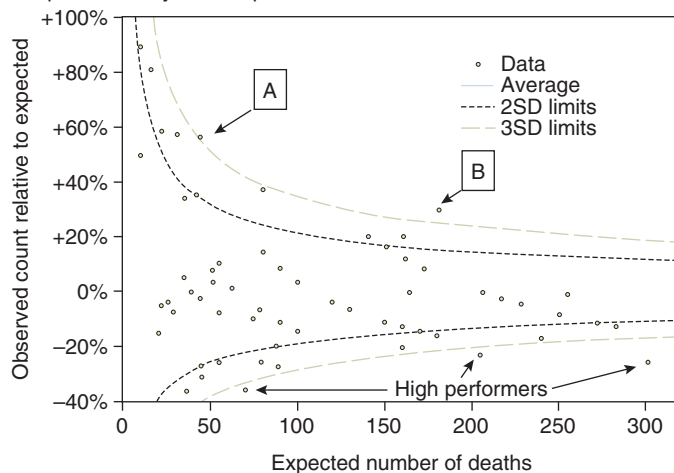
USE OF SEVERITY INDICES IN CLINICAL RESEARCH

Existing databases permitting severity adjustment make possible hypothesis-generating observations and conclusions about therapeutic choices in situations where randomized, prospective evaluations might not be permitted or funded. For prospective studies, severity scoring indices can be used to risk stratify the population before randomization, thereby reducing the number of patients recruited and thus the cost of clinical trials. Clinical studies have also used scoring systems as part of inclusion criteria and to show that control and study groups have similar disease burdens.¹³² Cytokine profiles correlate with APACHE and MPM scores in septic individuals¹³³; however, severity scores were not designed for this purpose, and calibration has not been assessed in the clinical trial population. There is the danger that inclusion of age and chronic health points may exclude younger, previously healthy patients from trial entry.¹³⁴

USES OF SEVERITY ADJUSTMENT FOR INDIVIDUAL PREDICTIONS

The short answer is that risk-adjustment models are designed for evaluating groups and not for determining care of individuals. The

Hospital mortality for ICU patients

**FIGURE 181-6 ■ Example of a funnel plot, using hypothetical data.**

The ratio of observed to expected deaths is plotted on the y axis, with number of deaths on the x axis. Two- and three-standard deviation limits are plotted, which helps identify two hospitals (A and B) as significant outliers ($P < 0.001$). Three hospitals (“high performers”) have significantly fewer deaths than expected. Note that the observed count relative to expected (similar to the SMR) is +50% (SMR 1.5) for the lowest volume hospital, which is still within the 95% confidence intervals. Hospital B has a lower SMR at 1.35 (+35%) but, due to volume, can be identified as a significant outlier. A template for generating funnel plots like this can be downloaded from <http://www.apho.org.uk/resource/item.aspx?RID=47242>. Accessed 2/9/15.

problems with using scoring systems for individual patient care decisions arises from attempts to apply a probability estimate, which may range from 0 to 1, to an individual for whom the result will be 0 or 1. No model is accurate enough to predict that a given patient will certainly survive or invariably die, so scoring systems alone cannot dictate decisions to direct or withhold therapy. Sequential risk estimates, an approach explored by APACHE,¹³⁵ MPM,³³ and SOFA,¹³⁶ improve prognosis by incorporating data reflecting patient response to therapy over time. Objective predictions of the need for next-day life support are used by APACHE III and IV to guide triage and discharge decisions.¹³⁷ Increases in organ dysfunction scores following admission generally carry a poor prognosis,¹³⁸ although others have reported limited ability of the SOFA or MODS tools to discriminate outcome.¹³⁹ A meta-analysis of 46 studies suggests that 3% to 7% of patients discharged from the ICU will die prior to hospital discharge¹⁴⁰; ICU readmissions in this same population were 4% to 6%.

Use of scoring systems to individualize therapy has not been well studied. Recombinant human activated protein C (rhAPC), now off the market, considered an APACHE II score higher than 25 as a criterion for drug administration based on post hoc subgroup analysis of the PROWESS trial.¹⁴¹ However, issues with this approach include wide variability in severity score between ICU admission and time of drug administration,¹⁴² the confounding effect of DNR orders,⁵¹ and bias against younger, previously healthy patients.¹³⁵ Further, an efficient emergency department may well stabilize the patients and lower the APACHE II score before arrival in the ICU.¹⁴³

Objectively calculated severity scores are not necessarily more accurate than physician or nurse intuition when dealing with individual patients.^{144,145} Accurate prognosis may be most difficult for patients with the highest risk of death. A multicenter study addressing the issue of medical futility found that divergent judgments on patient prognosis by doctors and nurses increased with higher SAPS II scores and longer ICU stays.¹⁴⁶ ICU physicians discriminate between

BOX 181-4**Potential Pitfalls in the Application and Reporting of Severity-Adjusted Outcome****DATA COLLECTION AND ENTRY**

- Inclusion of ineligible patients
- Missing variables and data management errors
- Substitution of available for properly timed data
- Transcription and data entry errors
- Improper communication between hospital clinical and risk adjustment applications
- Wrong diagnosis selected
- Administrative data reflective of clinical situation
- Deliberate “gaming” of the system—upcoding of comorbidities

MODELS

- Case-mix differences (critical threshold exceeded)
- Application to subsets of development population
- Changes in influence of variable with improving medical care
- Small clinical changes become large risk increments when continuous data are categorized.
- Lead-time bias

OUTCOMES

- Insufficient range of outcomes reported
- Use of proxy outcomes that inadequately reflect true status
- Patient lost to follow-up
- Chance variability masquerading as true difference
- Relationships of scores to resource utilization and costs reflect observed practice, not ideal

REPORTING

- Confidence intervals not reported
- Inadequate sample size
- Physician of record misidentified
- Computational errors
- Misapplication of group data to individuals
- Misinterpretation of statistical significance as clinical significance

survivors and nonsurvivors more accurately than SAPS II, MPM-I, or APACHE II.¹⁴⁵

APACHE, SAPS, and MPM scores are *specific*, having more than 90% ability to predict survival but are relatively *insensitive* in predicting death. Such information should not be taken as a rationale to rely on clinical judgment alone and forgo the use of formal scoring. The existing severity indices, despite their flaws, provide useful, objective information that can supplement clinical judgment for prognosis and triage, bearing in mind that patient autonomy and medical ethics also influence these decisions. Surrogates of critically ill patients generally appreciate reliable prognostic information but cope with unfavorable news in a variety of ways, including seeking information from other sources and avoiding or disbelieving prognostic information.¹⁴⁷

PITFALLS IN THE APPLICATION OF SEVERITY OF ILLNESS INDICES

The use (and abuse) of databases for profiling ICUs and/or individual physicians is growing, despite flaws in administrative databases and problems identified with the application of statistical models²¹ and physician profiling.¹⁴⁸ Assuming a properly developed model is applied, potential pitfalls in application fall into four major categories: data collection and entry errors,¹⁴⁹ misapplication of the model,^{11,47,58} use of mortality as the sole criterion of outcome, and failure to account for sample size and chance variability^{56,108,112} when reporting results (Box 181-4). Errors in the EMR tend to propagate and become immortalized in the absence of a data collector who might note and correct artifacts and out-of-range values.⁸ Upgrading hardware or software can lead to obscure errors. My personal experience in this regard involved bedside monitors where the arterial waveform could be labeled “ART” or “ABP” depending on nurse preference. Months after a software upgrade,

investigation of an increasing ICU SMR finally disclosed that only one field was automatically imported into the APACHE system; missing the other resulted in a default situation where abnormal blood pressures were not credited to the APACHE score, thus reducing expected mortality and increasing the SMR.

Determination of the diagnosis is prone to bias,¹⁵⁰ but using a system that is blind to diagnosis will be inaccurate if case mix is markedly skewed.⁴⁷ Less obvious is the fact that many models start the “clock” with ICU admission, the timing of which is not standardized¹⁵¹ and frequently influenced by local conditions such as ICU bed availability.¹⁵² ICUs also do not function in isolation in the process of care,¹⁴⁴ and the growing trend toward aggressive use of step-down facilities and off-site chronic ventilation and rehabilitation units raises the question of whether hospital mortality is valid when patients may be transferred to other facilities alive but are still technology dependent.^{13,153} The issue of lead-time bias (pre-ICU stabilization) requires consideration; assessment is further complicated for patients with multiple ICU admissions,¹⁵³ whose second ICU admission during a single hospitalization is frequently excluded from subsequent analysis.²⁶ Which ICU stay, for example, should be counted for a patient who has ICU observation after an uneventful vascular procedure and then develops complications requiring ICU readmission on the fifth post-operative day? It is increasingly necessary to evaluate the performance of an ICU system, which includes pre-ICU, ICU, and post-ICU care. Models now in development will address outcomes across the entire arc of care.

CONCLUSION

APACHE, MPM, and SAPS are highly developed, prospectively validated tools useful for comparison of ICU performance in the care of groups of patients. Specialized models are available for burn, trauma, sepsis, cardiac surgical, and pediatric patients. When used as intended, these models allow stratification of patients for performance assessment, utilization management, clinical research, and dissemination of outcome results. Important implementation considerations include careful data collections, appropriate matching of the model and the population under study, and use of proper sample sizes and CIs in reporting results.

None of the models can perfectly predict the outcome for an individual patient.¹⁵⁴ However, this limitation is true of almost any test utilized in medicine and need not preclude the use of prognostic estimates for clinical decision support. Physicians must be alert to the limitations of severity-adjustment models in performance-based assessment, because case-mix differences, inadequate sample sizes, or systemic errors in data collection can generate erroneous conclusions about the quality of care. In the end, what is measured is less important than what is done with the measurement. The encouraging news is that despite an increase in severity of illness between 1988 and 2012, risk-adjusted hospital mortality for patients admitted to U.S. ICUs has decreased significantly, an observation that would have been impossible without the benefit of severity of illness scoring systems.¹⁵⁵

KEY POINTS

1. Stratification of outcome based on risk factors is necessary when comparing outcomes obtained by different institutions, intensive care teams, and treatment strategies.
2. Although mortality is readily defined and easily captured, it is insufficient as the sole measure of clinical outcome and does not capture other important endpoints such as complications, quality of life, or costs.
3. Administrative data are plentiful but are typically less reliable than carefully collected clinical information. The quality of administrative databases can be improved by including laboratory information.
4. Most outcome stratification models are developed empirically by performing univariate analysis of independent variables against a chosen outcome and are then refined using multivariate techniques.
5. Model performance is assessed by measuring discrimination (typically by ROC-curve area) and calibration (typically by goodness-of-fit procedures).
6. The standardized mortality ratio (SMR) is created by dividing observed by expected mortality rates. Values less than 1.0, if statistically significant, suggest performance better than

expected. SMR rankings can be problematic due to chance variation.

7. The Acute Physiology and Chronic Health Evaluation (APACHE II through APACHE IV), the Mortality Probability Models (MPM), and the Simplified Acute Physiology Score (SAPS) are well-developed, prospectively validated models useful in adult general critical care units. The Intensive Care National Audit and Research Center (ICNARC) and Veterans Affairs Intensive Care Unit (VA ICU) models are also available. Customized models are useful in highly specialized ICUs or when evaluating population subsets such as pediatric, trauma, or cardiac surgery patients.
8. Outcome predictions are intended for groups, not individuals. Mortality probability estimates range from 0 to 1.0, but an individual patient will either live or die. Mortality predictions also vary depending on when the data were geographically and temporally collected; results at ICU or hospital discharge do not necessarily correlate with 30-, 60- or 365-day results. Use of scoring systems to direct therapeutic choices has not been adequately studied, and risk-adjustment systems should never be the sole criteria for directing or withholding therapy in an individual patient.

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- In total, 36,420 consecutive ICU admissions in 1999–2000 and a second cohort of 81,964 cases in 2002–04 were used to update the VA-ICU model. ROC areas were good. The VA-ICU population is overwhelmingly male (97.2%) and somewhat older. ROC area was 0.89, comparable to APACHE IV in this population, and better than MPM₂₄ II (ROC 0.84), SAPS III (ROC 0.86), or the SOFA score (ROC 0.81).
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■ References for this chapter can be found at expertconsult.com.

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Severity of Illness Indices and Outcome Prediction: Children

Anthony D. Slonim and Murray M. Pollack

Today's healthcare environment demands attention to evaluating care so that improvement efforts can be made. Evaluation efforts need to be systematic in their collection, analysis, and information use. Although it is important to draw attention to objective performance measures, information derived from an appreciation of the perspectives and expectations of stakeholders who experience the program under examination are also useful. However, for pediatric intensive care units (PICUs) that primarily include the patient and family, a broader group of stakeholders, including colleagues on the multidisciplinary team, nurses, physicians, therapists, pharmacists, and social workers, as well as regulators and payers who are all interested in the program's quality, should be included.

HISTORICAL PERSPECTIVE ON QUALITY

Quality in health care has received increased focus over the past several decades, beginning with Donabedian's influence showing that the fundamental concepts of structure, process, and outcome were as important to health care as they were to other industries (Fig. 182-1). Since then, focused efforts to advance the concept of quality in health care have been performed. In the early 1990s, a series of articles quantified adverse events and helped disentangle the elements of patient harm and its relationship to risk management. A few years later, President Clinton, through an executive order, chartered a commission to investigate the quality of health care more broadly. Despite these and a variety of other prominent efforts, discussions regarding the quality in health care remained relatively stagnant until the Institute of Medicine's (IOM's) series of reports. The first IOM report, "To Err Is Human," provided a wake-up call for the healthcare industry to consider how patients may be harmed. This was followed by "Crossing the Quality Chasm," which defined six "Aims for Improvement." These Aims included safety, effectiveness, equity, timeliness, patient centeredness, and efficiency and helped establish a framework through which clinical services, including those delivered to the critically ill child, could be evaluated.

The Institute for Healthcare Improvement (IHI), among other groups, became instrumental in providing clinicians with tools to help them focus on improvement work by defining and measuring what was to be improved and by when. Efforts aimed at improving the reporting and learning from adverse occurrences became noticed when President Bush signed the Patient Safety and Quality Improvement Act, which would become operationalized, in part, through Patient Safety Organizations several years later. In addition, Bush created the Office of the National Coordinator for Health Information Technology (HIT), which was intended to advance dramatically the use of electronic health records.

In 2009, when the nation was experiencing financial turmoil, President Obama signed the American Recovery and Reinvestment Act (ARRA) into law, which was initiated to stimulate the U.S. economy. Several important healthcare provisions were included in this legislation to advance Medicaid, HIT, funding for the National Institutes of Health Clinical Effectiveness Research, and health professions education and to provide an important clinical focus on wellness, prevention, obesity, and chronic disease. In 2010, the Affordable Care Act was

passed. This piece of legislation has created dramatic changes in the healthcare landscape. With healthcare reform taking hold, considerable advances including medical homes, accountable care organizations (ACOs), and pay for performance have gained additional significance and set the tone for healthcare quality for years to come. This has created and will continue to generate important opportunities and challenges for advancing care for critically ill children.

SYSTEMS OF CARE

Traditional engineering approaches focus on how systems work rather than on understanding the ways in which they fail or the effects of failure. There are several aspects of system design and maintenance that can affect the likelihood of failure. This is a fundamental distinction to how quality is viewed in health care. First, clinicians often approach quality improvement from the perspective of risk rather than the perspective of reliability. Mortality and morbidity conferences, peer review meetings, and root cause analysis all tend to focus on what went wrong in retrospect and the elements of failure, rather than on the system's reliability. Second, pediatric critical care clinicians function in complex systems of care yet have little training or experience in how to design and organize those complex systems to assure that the needs of the critically ill child are met. Routinely, providers will repetitively use work-arounds rather than redesigning processes to be safer and more efficient. Finally, in contrast to the engineering approach, clinicians are very interested in the effects of system failure, which in clinical parlance are the outcomes of care. While outcomes are important, several efforts in health care have also demonstrated the importance of managing the processes of care. The best examples of these efforts in pediatric critical care medicine are evidence-based clinical guidelines, checklists, and bundles of care, which represent tactical opportunities to specify how care should be delivered to arrive at the desired outcomes. Evaluating the systems of care depends on both methodologic and content-oriented analyses. The next sections will provide some important context in these arenas for evaluating pediatric critical care medicine.

DESIGNING FOR EVALUATION: METHODS

Program Elements

The ability to evaluate clinical services, including pediatric critical care services, depends on how well the evaluation program is built and implemented. When considering complex systems, it is often helpful to begin by identifying the focus areas for evaluation and improvement and prioritizing those based on the desired impact. Quality improvement and evaluation rely on four critical and interdependent functions: data and analytics, process improvement techniques, change management principles, and team facilitation (Fig. 182-2). Each one of these functions is important in its own right, but none of these is sufficient individually to accomplish successful improvement efforts. The use of *data* is fundamental for improving quality. Data should be objective, easy to measure and accurate and should establish a baseline of

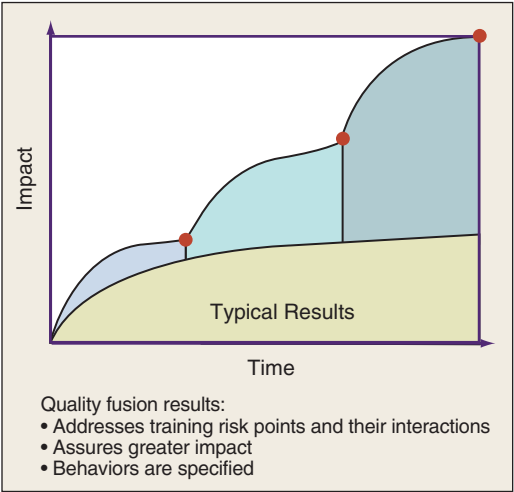


FIGURE 182-3 ■ Quality fusion. A concept for reaching higher gains in quality improvement and sustaining them for longer durations.

with relevance to their patients. The use of this “quality fusion” approach provides the PICU team with a greater impact on the initiative under study and also important sustinment when attention is diverted to the next improvement project.

**DESIGNING FOR EVALUATION:
CONTENT**

Organizing the different content elements of quality began in the latter portion of the 1970s when Donabedian described his “Attributes of Health Care” (Table 182-1). Pediatric critical care medicine was a new discipline at the time, and health care was itself still trying to define *quality*. By the time the IOM released its framework on quality using the six Aims in 2001, pediatric critical care medicine had matured considerably. The IOM framework provided a useful method to organize the approach to healthcare quality in the PICU. Each of the Aims had relevance to the provision of critical care services (see Table 182-1).

The IHI’s Triple Aim has taken hold as an important mechanism for evaluating the quality function from a content perspective (see Table 182-1). The reason the Triple Aim is so important is that it provides a construct that allows for evaluating clinical care at the provider, unit, and population levels and unifies strategies for safety and quality improvement within the context of a more integrated and collaborative care delivery model. In addition to focusing on clinical and service quality, the Triple Aim incorporates efficiency as a third element of evaluating care and is useful as an approach that can be applied to individual patients, groups, and populations of patients as is the case with emerging ACOs. These analyses are instructive for advancing improvements in care directly and for research and training.

**Improving Patient Care: Service and
Clinical Quality**

Service Quality

Service quality often encompasses a number of terms, including *empathy*, *compassion*, *needs*, and *respect*, that reflect the focus of attention on the patient and family. Additional components that help establish priority areas for the care of individual patients include health literacy under which the provision of information, communication, and education falls; attention to physical comfort; emotional support by relieving fear and anxiety; and the involvement of family and friends. Although “service with a smile” is important in caring for

TABLE 182-1 Key Elements for Evaluating
Quality Over Time

| DONABEDIAN'S ATTRIBUTES OF HEALTH CARE | IOM'S AIMS | IHI'S TRIPLE AIM |
|--|----------------------|--|
| Acceptability | Effectiveness | Patient quality (both clinical and service) |
| Effectiveness | Efficiency | Costs of care |
| Efficacy | Equity | |
| Efficiency | Patient centeredness | |
| Equity | Safety | |
| Legitimacy | Timeliness | |
| Optimality | | |

IHI, Institute for Healthcare Improvement; IOM, Institute of Medicine.

TABLE 182-2 Service Problems in
Specialty Care

| |
|--|
| SPEED OF SERVICE Delay in care or excessive waiting time Lack of explanation for delay |
| COORDINATION OF CARE Organization of the environment Availability of appropriate person to answer questions |
| RESPECT AND COURTESY Staff courtesy Treatment with respect and dignity |
| UNDERSTANDING OF TREATMENT Information regarding symptoms, medications, and treatments provided Patient or family included in decisions Adequate explanations provided Patient and family listened to |
| TRUST IN THE PROVIDER Availability of the provider Psychosocial support |

From Advisory Board Company. Service Innovations in Specialty Care: Enhancing Patient Satisfaction with Diagnosis and Treatment Selection. Washington, DC: Advisory Board Company, 1998.

patients and families, this broad compilation of terms demonstrates that service quality is a much more comprehensive approach that requires processes of care to be redesigned around the needs of patients and their families and not around the needs of the care team. Both elements of service are important to the successful care of the critically ill child and their family. The Healthcare Advisory Board identified several broad types of service problems in specialty care (Table 182-2) that remain relevant to the PICU even a decade after their publication.

Admission to the PICU, especially when emergent and unexpected, is an anxiety-provoking and fearful experience for patients and their families. For parents, the anxiety is generated from the lack of parental control; the appearance and discomfort of the child, both emotionally and physically; and the difficulty in communicating with staff. The age of the parents and their ability to focus on problems and participate in care are associated with an ability to cope with a critically ill child. Coping strategies for parents also include an ability to be supported by the PICU healthcare team. A variety of needs, including emotional, physical, and spiritual, have to be addressed by this support system. This can be accomplished by providing accurate information, allowing ready access to the child, and encouraging

parents' participation in their child's care. For hospitalized children, anxiety and stress may manifest themselves in behavior problems, especially in those with repeated or prolonged hospitalizations, those who are critically ill, and those with underlying mood or psychological disorders.

If family members perceive that emotional support is inadequate, their satisfaction with the experience and, more important, their long-term viability and cohesion as a family unit are at risk. Most families are satisfied with the care their children receive in the PICU and are particularly complimentary about the skill and competence of the nursing staff, as well as the compassion and respect shown toward their children, especially with regard to pain management. Attention to adequate pain and anxiety control is an essential component of the care of critically ill pediatric patients. Pain control addresses a fundamental need and is a compassionate practice that helps allay parents' anxiety and improve coping. The environment of the waiting area and the frequency of physician communication were both identified as detracting from parents' satisfaction with the PICU experience. The family's ability to function after the ICU admission of a child is dependent not only on their satisfaction but also on the severity of the child's illness, the duration of hospitalization, and the location of the hospital.

A customer service focus addresses such issues as wait for diagnostic testing or surgery. The healthcare providers' inattention to the flow of patients shows a lack of respect for patients and their families and can compromise the trust in the provider-patient relationship. Service quality can also extend beyond customer satisfaction to include patient outcomes. The ICU is a valuable resource for critically ill patients, and if ICU resources are not available when patients need them, adverse outcomes are possible. In this circumstance, the redesign of clinical processes has a direct effect in assuring that patients get services when and where they need them. For example, a child who experiences a cardiac arrest in the radiology suite is dependent on the ability of the institution to provide quick and definitive care in radiology rather than waiting to transport the patient to the ICU and delaying necessary therapies.

Clinical Quality

Clinical quality includes patient safety, clinical effectiveness, and efficiency in care. Although efficiency often points to lean processes, it also includes an approach that serves to minimize cost during the provision of care. Considerable focus relates to the "value proposition" in health care. Value is improved if quality for a given level of cost is improved. This is important, particularly when the evaluation frame shifts from individual patients to populations of patients.

Safety

Since the IOM's report on medical errors and patient safety highlighted the problem of iatrogenic injury in hospitalized inpatients, numerous stakeholders have begun to focus on reducing medical errors as a means of improving patient safety and reducing the harm associated with the delivery of health care. Adverse patient occurrences are inevitable in the high-risk environment of the PICU, but interventions aimed at reducing these adverse events can be designed once one understands how to evaluate clinical programs, the types of errors that may occur, and the circumstances that can contribute to them.

System Design as a Contributor to Safety Problems

The PICU environment may itself be an independent contributor to patient safety. Two characteristics contribute to the likelihood of errors in the PICU. The first is complexity, or the degree to which system components are specialized and interdependent. Complex systems are more prone to errors. The second characteristic is coupling. Tightly coupled systems have no buffer, and sequences are fixed, whereas loosely coupled systems can tolerate delays or variations in sequencing. Communication errors, equipment failures, system failures, and problems with teamwork are all associated with

complex and tightly coupled systems and can contribute to an unsafe environment in these settings. Equipment failures are an obvious and often unavoidable problem related to patient safety. However, communication failures, system failures, and teamwork problems can enhance the likelihood of errors and prevent an appropriate mitigating response when they occur. Appropriate attention to the physical layout and mechanisms for delivering care are important to ensuring a safe environment in the PICU.

Error Classification

Different classification schemes for medical errors have been developed, with some being easier to understand than others. Identifying critical incidents provides opportunities to make system improvements. However, system improvements may be limited unless there is a culture in which providers are held accountable for risky behaviors in the care process. This "Just Culture" approach provides a mechanism for accountability in the arena of patient safety. The IOM categorized medical errors based on their diagnosis, treatment, prevention, communication, and equipment failures. These categories have proven to be relevant for evaluating pediatric critical care services.

Several types of treatment errors also have relevance for the PICU. Medication administration errors occur frequently in the treatment of critically ill children and provide considerably more opportunities for medication errors and adverse drug events (ADEs). The PICU is an important setting for ADEs. Specific medication classes are prone to errors, including sedatives, vasoactive infusions, and parenteral nutrition. Acquired infections are important contributors to morbidity, mortality, and cost in the PICU. Our knowledge of the incidence, prevalence, risk factors, costs, and methods of improving bloodstream infections in the PICU has allowed us to demonstrate how care can be improved when providers use data to drive system change.

Interventional procedures are an important component of pediatric critical care practice. They provide the intensivists with the means to address a child's failing organ systems, but they are also associated with risks. Procedural risks are associated with both the insertion and maintenance of these devices. PICUs can address their rates of adverse occurrences related to both the performance and maintenance of commonly performed invasive procedures such as central venous access, mechanical ventilation, arterial cannulation, and intracranial pressure monitoring. Collaborative efforts that share best practice methods of inserting and maintaining these devices can demonstrably improve the complications associated with these procedures. In the ICU, considerable evidence has been accumulated regarding prophylaxis for gastrointestinal stress ulcers, deep venous thrombosis, pressure ulcers, and other adverse events.

Clinical Effectiveness

Evidence-based practice incorporates the best research evidence with clinical expertise and patient values to achieve the best patient outcomes. The practice of critical care medicine is highly variable among practitioners and institutions. Efforts to reduce the variability in care are provided by implementing practice guidelines, the use of clinical algorithms, and checklists.

Private, governmental, and subspecialty organizations have developed numerous guidelines to reduce unnecessary variability in care. The American Academy of Pediatrics and the Society of Critical Care Medicine have developed guidelines and policy statements to help improve the care of critically ill children. Guidelines can be heterogeneous with respect to their creation. At one extreme, results from randomized controlled trials are incorporated into the care guidelines; at the other extreme, the consensus of a group of practitioners is all that is required. This is important, because the success of any practice guideline is dependent on its ability to influence physician decision making.

Several important components of these guidelines are worth mentioning, because they will ultimately contribute to the acceptance of

the guidelines by the practitioners of critical care medicine. First, the guidelines should be grounded in the existing evidence base from randomized controlled trials. Second, when the evidence does not exist, the authors should assemble a multidisciplinary group of clinicians and researchers to reach consensus regarding treatment options. This is done to minimize bias by any one group of practitioners or any one discipline. Third, and perhaps the most important, the guidelines should be considered a “work in progress” that helps identify current deficiencies, from a data perspective, so that future research initiatives can be used to further support these guidelines.

Improving the Cost of Care

Economics demands that healthcare resources be delivered in a cost-effective and efficient manner while not jeopardizing the quality. The achievement of specific outcome goals is a measure of an ICU's quality. Costs vary with outcome measures. Mortality rates, efficiency rates, LOS, rates of nosocomial infection and readmission, and the presence of a teaching program all impact expenses and reimbursement. The quality at a given level of cost determines the value of a commodity. In this case, the commodity is ICU care.

The value of an individual ICU is increased by its ability to achieve selected measures of outcome while keeping costs to a minimum. This is concordant with the concept of efficiency as an aim in the IOM's model of healthcare quality. Intensive care services are a commodity, and those units providing quality care at a reasonable cost, as judged by efficiency and a similar patient mix, will be most appealing. Lessefficient ICUs will need to optimize efficiency or have cost-containment strategies imposed on them.

From a microeconomic perspective, patients who are sicker require more services in the ICU, stay longer, are more likely to die, and cost more to be treated. This is not new information. However, to balance the issues of cost and quality, ICUs should identify same-strata best-practices ICUs with similar cost drivers (e.g., severity of illness) and operate under a philosophy of targeted benchmarking to achieve comparability up to a specified level. To accomplish this, clinical scoring systems are frequently used to control for case-mix variables (physiology, diagnoses, and so forth) and thus allow for standardized comparisons. The LOS has become a standard in benchmarking ICU performance and quality, and reducing LOS is one method of reducing cost, although, as a variable itself, LOS is subject to differences in measurement. The standardized LOS ratio is that of observed to predicted LOS and is an indicator of resource use, adjusted for severity. The standardized LOS ratio can be used to compare a particular unit's performance over time, but it can also be used to determine whether a particular ICU's resource use is above or below that of similar ICUs.

Another method of assessing the efficiency of resource use in the ICU is to evaluate unique ICU therapies, that is, those that are best delivered in the ICU, such as mechanical ventilation and vasoactive infusions. Individual ICUs and physicians differ in their monitoring strategies; therefore, monitoring technologies should not be classified as unique therapies. The benefits of this approach are that it allows physicians to determine the proportion of low-risk monitor-only patients and compares the number of high-risk critical care patients requiring unique ICU therapies. Excess bed capacity leads to a higher ratio of monitored to high-risk patients and reduces the efficiency of the ICU. Opportunities to evaluate admission and discharge criteria as well as throughput issues, resulting from the inability to transfer ICU patients because of a high hospital occupancy rate, may serve to improve an individual ICU's efficiency.

EVALUATION DOMAINS AT THE PROVIDER LEVEL

The IOM framework is useful as an organizing principle to understand the healthcare quality from the perspective of the discipline of pediatric critical care or the ICU. Providers, when thinking about their practice,

tend to think differently about the healthcare quality. They often think about the care that they, rather than the healthcare team or the ICU, provide. Providers believe that they provide safe, timely, and effective care that corresponds to the latest evidence. They believe in engaging the child and family in the care and in treating all their patients fairly regardless of their personal characteristics or ability to pay. Donabedian's constructs of structure, process, and outcome are helpful in assisting different providers in identifying their role in the provision of quality care to patients because they know what is available to them to provide care, they believe that they understand their work, and they think that they understand what they are trying to achieve (Table 182-3).

Structure

“Structure” is usually interpreted from a “bricks and mortar” perspective. However, while the walls, monitors, equipment, and other technologies are certainly important structural elements, they are insufficient for the optimal delivery of health care. The people, including the patients, families, and providers of all disciplines; their knowledge of the child; their expertise; and their collaboration are needed to effect the best outcomes. Important evidence has linked the organization of the ICU and its management as key determinants of outcome. Taken together, these elements are the structural components of ICU care to which Donabedian might refer (see Table 182-3).

Process

Clinical processes are the interactions between providers and their patients and providers with one another. There is evidence that highlights the importance of team performance, in addition to clinical performance, for the establishment of outcomes. While nurses, by virtue of their training, tend to be process focused, physicians often lack this skill. Thus, when asked to address process steps, such as implementing the vascular access bundle, nurses are comfortable with the detailed specification of the process, which can make a difference in outcomes over time. Attention to the key processes of care are becoming recognized as important in determining outcomes, and a number of checklists, guidelines, bundles, and pathways have been developed to assure compliance with the many specification limits established in clinical care.

Outcomes

Finally, outcomes represent the culmination of the healthcare experience. Physicians often focus on outcome measures as a result of their work. In the ICU, mortality is a traditional outcome measure that is important, quantifiable, and often discussed (see Table 182-3). There are other outcomes of relevance including the use of ICU-specific therapies, LOS, cognitive and physical outcomes, and morbidities arising from the episode of care (see Table 182-3).

A major challenge of pediatrics has been the development of well-defined morbidity measures that are rapid, reliable, and objective; measure the child's status at the time of testing; and are applicable to a broad range of ages in a variety of environments. Although in-depth testing such as neuropsychological methods remain the clinical standard, other methods applicable to all pediatric ages and sufficiently rapid to be used in large samples were needed. The Glasgow Outcome Scale score was adapted to children in the Pediatric Overall Performance Category/Pediatric Cerebral Performance Category scores, but sufficient interrater reliability was only achievable when neighboring categories were combined; therefore, using these scores in outcome studies risked requiring very large sample sizes to detect significant differences. The history of outcome studies in adult medicine demonstrated the value of scales such as the activities of daily living scale. Such a functional status measure would enable researchers to track the trajectory of disease and recovery and might enable us to project future functional status, resource needs, economic impact, and other effects

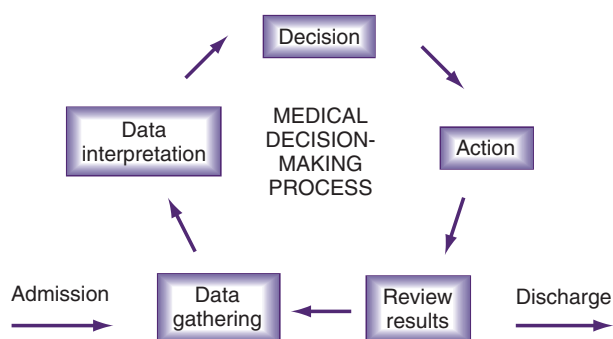


FIGURE 182-4 ■ Key elements of the medical decision-making process.

with patterns that are matched against a large mental library of similar conditions and patients. When the team is less experienced, the process is slow and prone to errors. The next step is decision making. Here, the physician may gather additional data by calling a consultant or ordering additional testing. If sufficient data have been gathered, the physician may formulate a medical treatment plan and reevaluate the plan's success as time progresses (see Table 182-3). The physician may recommend or perform a procedure, the outcome of which may assist with diagnosis or treatment. Nurses will incorporate their nursing diagnoses into the plan, and together the team will act with a comprehensive strategy for providing care. Finally, as the last step of medical decision making, the team must take action. A plan that is incoherent or not acted upon or a procedure or test that is thought about but not performed does not help the patient. These four steps allow the clinical team to think through and organize their work (see Fig. 182-4).

When evaluating the care at the provider level, there is often a deficiency in the available data by clinician. At this point, the best that many ICUs can do is to establish appropriate process steps in care and hold providers accountable for following these steps. Deviations from the process will occur because of differences in patient condition and case mix, but those deviations that are identified as random or reckless

can be dealt with through an environment that encourages a Just Culture. As evaluation tools at the provider level become more robust, so too will the evaluation of providers in the peer review process.

EVALUATION DOMAINS AT THE POPULATION LEVEL

Efforts in healthcare reform including the Patient Protection and Affordable Care Act (PPACA) have increased the focus on improving outcomes of care. These primarily include improving service and clinical quality and reducing cost. However, a major component of this legislation requires that populations be compared across these outcomes. The IHI's Triple Aim also differentiates itself by its applicability at both the individual and population levels.

A relatively new concept known as ACO assigns patients to specific providers to assure that appropriate care is delivered. Most ACOs exist for the adult Medicare beneficiaries and focus on primary care. It is likely that the total costs of care, including ICU care, will be included for these patients as these efforts mature. There are relatively few pediatric ACOs in the country today; however, it is likely that these will also expand as population-based care becomes more relevant.

Tools that allow the comparison of the severity of illness, both in the ICU and in the general population, are essential for assuring fair and equitable comparisons over time at the population level. It is possible that these new developments are likely to continue to advance innovative efforts of estimating disease burden and outcome, both mortality and morbidity, in populations of ICU patients.

CONCLUSION

Evaluating the current state of pediatric critical care requires a focus on both methods and content. From a content perspective, the Triple Aim has largely supplanted the IOM's Aim as the prevailing paradigm and can be applied at both the patient and population levels. Success in advancing quality in the PICU will depend on the ability to have providers appropriately focused on their discipline-specific processes of care in support of a much wider array of outcomes. What will follow is a better understanding of the influence that individual providers have on effecting these outcomes and enhancing provider-specific improvement activities for the benefit of patients.

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Dr. Donabedian in one of his seminal works provides an approach and definitions for the evolution of quality assessment in an industry that has been imported and used repeatedly over decades in health care. This work is foundational to many of the efforts by the Institute of Medicine.

Kohn LT, Corrigan JM, Donaldson MS (eds). Institute of Medicine Committee on Quality of Health Care in America: To err is human: building a safer health system. Washington, DC: National Academies Press, 2000.

The first, and most controversial, of five publications by the Institute of Medicine that highlighted the dramatic and often quoted cost of life and financial expense related to medical errors in health care. This volume became a call to action for the healthcare system not only in the United States but also around the world to address the silent epidemic of medical errors that occur in the provision of healthcare services.

Institute of Medicine Committee on Quality of Health Care in America. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academies Press, 2001.

The second publication in the Institute of Medicine series that provided a framework to organize the quality initiatives into the six Aims including safety, efficiency, patient centeredness, equity, timeliness, and equitable. This framework has been used by countless organizations to organize the quality agenda and provide a roadmap to making sustainable improvements.

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This manuscript highlights an important population of patients, children who are outliers for length of stay that suffer from both quality- and cost-related problems. It builds on an often conceived notion that a minority of patients and their demographics are responsible for the majority of health-related cost and quality concerns. This manuscript applies this approach to children with critical illness to help the industry better understand how few children can have care requirements that exceed the norms established for population inliers.

Steinbrook R. Health Care and the American Recovery and Reinvestment Act. *N Engl J Med* 2009;360:1057-1060.

This manuscript provides an overview of the American Recovery and Reinvestment Act (ARRA) and its relationship to healthcare. Although healthcare reform under the Obama administration is often considered to have started with the Patient Protection and Affordable Care Act (PPACA) in 2010, ARRA had a significant role in setting the stage from a financial incentive perspective so that PPACA could be implemented.

IHI Triple Aim Initiative. Available at: <http://www.ihi.org/Engage/Initiatives/TripleAim/pages/default.aspx>. Accessed on April 4, 2015.

The Institute of Medicine (IOM) had a major role in identifying the problems related to healthcare quality and organizing the work that needed to be accomplished. The Institute for Healthcare Improvement (IHI) has been an important participant and thought leader in assisting healthcare organizations with actually getting the work done. The IHI has conceptualized the "Triple Aim" that has largely supplanted the IOM's Aims as the prevailing paradigm for healthcare quality in the nation. This website provides an overview and many of the improvement efforts framed within this context.

Despite an increase in the incidence of critical illness syndromes such as severe sepsis and acute respiratory distress syndrome (ARDS), improvements in supportive care have resulted in improved survival.¹⁻³ Of approximately 6 million adults admitted to intensive care units (ICU) in the United States each year, more than 4.8 million survive.⁴ Traditionally, the focus has been on reducing short-term mortality. As more individuals survive their initial episode of critical illness, the goals of critical care extend beyond short-term mortality, and clinicians are challenged with the task of managing the consequences of those surviving critical illness.

Critical illness may result in long-term physical and neuropsychological dysfunction, ongoing healthcare utilization, and incurred costs.^{5,6} Although some survivors return to their precritical illness level of functioning and health, many others experience lasting impairments in cognition, mental health, and physical health or quality of life⁷ (Fig. 183-1). Any new impairment in one or more of these domains is termed *postintensive care unit syndrome* (PICS).⁸

In this chapter, we review the advances in our understanding of long-term outcomes after critical illness. Most literature focuses on long-term outcomes after acute lung injury and severe sepsis. We describe the epidemiology, risk factors, clinical manifestations, management, and outcomes for each domain of PICS.

COGNITIVE IMPAIRMENTS AFTER CRITICAL ILLNESS

Critical illness frequently results in new cognitive impairment, including deficits in memory, attention, and concentration.⁹⁻¹² The domains impaired in ICU survivors likely depend on the nature of the insult and its treatment as well as the presence of any preexisting neurologic abnormalities and individual characteristics such as age or comorbidities. A longitudinal cohort study in older adults who did not have premorbid neurocognitive impairments or dementia assessed neurocognitive function prior to and following acute care or ICU hospitalization.¹³ Individuals hospitalized for acute illness had a greater decline in neurocognitive function and new incident dementia than those not hospitalized. This finding suggests that acute or critical illness causes an abrupt decline in neurocognitive function that is not due to premorbid neurocognitive problems. A second study in patients with sepsis confirmed these findings. The Health and Retirement Study followed more than 27,000 older Americans, for whom neurocognitive function was assessed both before and after severe sepsis.¹⁴ Patients with severe sepsis developed new substantial and persistent neurocognitive impairment. Thus, factors associated with acute or critical illness may be causally related to neurocognitive decline in older critically ill patients.^{14,15} Similarly, Pandharipande et al. reported that a broad case mix of ICU survivors had important neurocognitive dysfunction comparable with mild dementia or moderate traumatic brain injury 1 year after their critical illness. This cognitive disability was present across different patient groups.¹⁶

The etiology of neurocognitive impairments is likely due to various factors that interact dynamically with preexisting and genetic variables to produce adverse outcomes. Current data suggest that unfavorable neurocognitive sequelae are not related to illness severity scores, age, smoking, or alcohol abuse. For example, neither length of ICU stay, Acute Physiology and Chronic Health Evaluation II scores, duration

of mechanical ventilation, and tidal volume nor days receiving sedative, narcotic, or paralytic medications are associated with neurocognitive impairments in critically ill ARDS survivors.¹² Thus, acute illness severity alone does not explain neurocognitive impairments experienced by ICU survivors. Possible pathophysiologic mechanisms include hypoxemia, cumulative use of sedatives or analgesics, hypotension, delirium, hyperglycemia, and sepsis and inflammation.^{10,17-19}

Early identification of cognitive impairment should, in theory, expedite appropriate evaluations and treatment. Evaluation for cognitive dysfunction in the critical care setting must be brief, easy to administer, and widely applicable.²⁰ However, currently available tests such as the modified mini-mental state examination and Montreal Cognitive Assessment are not validated to predict long-term cognitive dysfunction.^{20,21}

Management strategies to preserve cognitive function have been promoted, although strong evidence does not exist to support their use. These include screening for and minimizing delirium, reducing sedation, providing sedation interruptions, and preventing and mitigating risk factors such as hypoglycemia, hyperglycemia, hypoxemia, and hypotension.¹⁰

PSYCHIATRIC SEQUELAE OF CRITICAL ILLNESS

Psychiatric disorders, including depression, anxiety, and posttraumatic stress disorder (PTSD), are common among critical illness survivors. For instance, in a systematic review, Davydow and colleagues reported that 28% of ICU survivors had clinically significant depression.²² Similar to cognitive dysfunction, acute illness severity at ICU admission did not predict the development of post-ICU depression. Early post-ICU depressive symptoms were a strong risk factor for subsequent depressive symptoms, and post-ICU depressive symptoms were associated with substantially lower health-related quality of life (HRQoL). Compared with the population with general critical illness, post critical care depression seems more pronounced in ARDS patients.^{23,24} Risk factors associated with depression in this patient population include longer duration of mechanical ventilation, length of ICU stay, hypoglycemia, and cumulative sedation use.²³ Another study identified alcohol dependence, female sex, and younger age as risk factors for depression at 1 year in ARDS survivors.²⁵ The predictors of anxiety at 1 year included the ratio of arterial oxygen tension to inspired oxygen fraction and duration of mechanical ventilation.²⁵ The observed depression and anxiety post ICU treatment are likely multifactorial, and further study will be needed to better understand patient predisposition, illness, and treatment-specific determinants of affective morbidity and appropriate tools for diagnosis and monitoring.

Several studies have examined the relationship between critical illnesses and the development of PTSD. Schelling et al. were the first to introduce the concept of PTSD resulting from critical illness and traumatic experiences in the ICU.²⁶ Among their cohort of 80 long-term ARDS survivors, almost one-third reported impaired memory, nightmares, anxiety, and sleeping difficulties after ICU discharge, with a PTSD prevalence rate of 28%.²⁶ A meta-analysis of prevalence, risk factors, and prevention/treatment strategies for PTSD symptoms in critical illness survivors reported clinically important PTSD symptoms in approximately one-fifth of critical illness survivors at 1-year

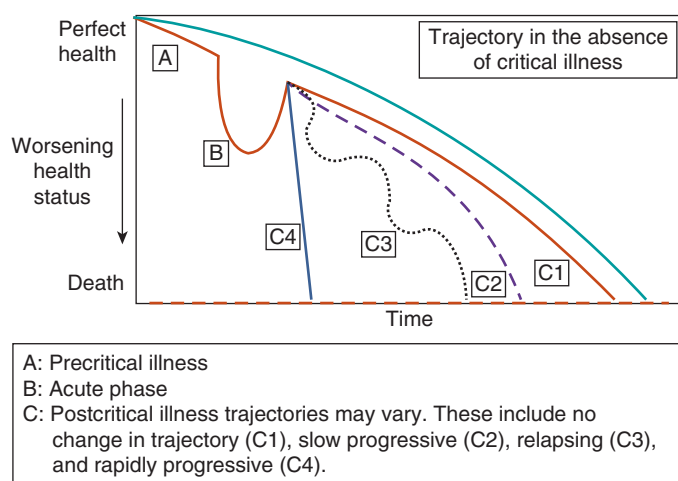


FIGURE 183-1 ■ Conceptual model describing chronic health status before and during critical illness and the trajectories of health during recovery. **A**, Health status trajectory prior to critical illness. **B**, Health status during the acute phase. Health status often worsens during this phase because of organ dysfunction. **C**, Trajectories during recovery. These include no change in trajectory compared with **A** (C1), slow progressive worsening (C2), relapsing (C3), and rapidly progressive (C4) health status. (Modified from Yende S, Iwashyna TJ, Angus DC. Interplay between sepsis and chronic health. *Trends Mol Med* 2014;20:234–238.)

follow-up.²⁷ Patients with underlying psychiatric comorbidities, benzodiazepine use, or early memories of frightening ICU experiences had the highest prevalence of PTSD.²⁷ In European studies, the use of an ICU diary was associated with a significant reduction in PTSD symptoms, whereas a self-help rehabilitation manual or nurse-led ICU follow-up did not reduce PTSD symptoms at 6 months.²⁷ Other interventions such as administration of stress dose steroids to antagonize the stress response and thereby alter traumatic memories are speculated to reduce psychiatric sequelae in critical illness survivors.²⁸

CRITICAL ILLNESS-ASSOCIATED NEUROMUSCULAR DYSFUNCTION

ICU-acquired weakness is common in patients with ARDS and other complex critical illness. Regardless of disease process, muscles and nerves are injured, resulting in prolonged mechanical ventilation and poor functional outcomes. Previous research has highlighted the concept of a continuum of weakness that begins with muscle injury documented within hours of mechanical ventilation²⁹ and may persist with incomplete recovery for years after ICU discharge. Muscle weakness and impaired function constitute an important morbidity of severe critical illness.³⁰

Critical Illness Polyneuropathy

Clinically, critical illness polyneuropathy (CIP) primarily manifests itself as a mixed sensorimotor neuropathy. CIP is very common in patients with systemic inflammatory response syndrome and sepsis, with an occurrence of 70% to 100% of longer ICU stay patients.³¹ It affects the limb and respiratory muscles, whereas facial muscles are usually spared.³¹ Limb involvement is symmetric and most prominent in the proximal muscle groups and in the lower extremities. Detection of the true incidence of CIP is complicated by lack of consensus on surveillance, timing, and nature of testing and limitations to testing because of patient sedation or poor cooperation, formal definition, and diagnostic criteria.³² Weakness may initially be absent or difficult to detect clinically in these patients, but subsequent electromyography

testing will demonstrate abnormalities showing an initial primary axonal degeneration of the motor neurons, followed by the sensory neural fibers, and this coincides with acute and chronic changes of denervation noted on muscle biopsies in affected patients.³³

In sepsis, the pathogenesis of CIP is linked to a perturbation in the microcirculation, with resultant axonal injury and degeneration. There is also evidence for a disruption of nerve action potential, which may be reversible over the course of the disease.³⁴ Other risk factors associated with the development of CIP include hyperglycemia, and tight glycemic control has been shown to reduce the incidence of CIP in critically ill patients.^{35–37} The exact pathophysiologic link between glucose control and neuroprotection remains unclear but may involve preservation of mitochondrial functioning, calcium homeostasis, or modulation of nitric oxide production.^{34,38–40} In contrast to earlier associations between neuromuscular dysfunction and use of neuromuscular blockers, subsequent research data have not been able to corroborate that previous association.⁴¹ Data on the association between glucocorticoid use and weakness remain controversial; however, a national multicenter prospective trial in acute lung injury survivors reported a significant association between mean daily corticosteroid dose with impairments in physical outcomes after 1 year.⁴²

Critical Illness Myopathy

The reported incidence of critical illness myopathy (CIM) varies between 48% and 96% in prospective studies that have included muscle biopsy as part of their diagnostic evaluation.³² Pathologically, CIM is characterized by a diffuse, nonnecrotizing myopathy associated with fatty degeneration of muscle fibers, fiber atrophy, and fibrosis.²⁹ This has been described in patients with sepsis and in those treated with corticosteroids and neuromuscular blockers. Patients clinically appear weak and paretic and are difficult to wean from the ventilator. They may be indistinguishable from patients with CIP. Muscle biopsy allows differentiation among these lesions.^{29,32}

The pathophysiology of CIM entails catabolism, inflammation, and derangement of membrane excitability. Protein catabolism and an increase in urinary nitrogen loss are observed in CIM.⁴³ Muscle biopsies in affected patients show low glutamine, protein, and DNA levels. There is evidence for the upregulation of the calpain, caspase-3, and ubiquitin proteolytic pathways in concert with an increase in apoptosis.^{43–45}

Oxidative injury is common in critically ill patients, and it may result in disruption of insulin receptor signaling in muscle, reduction in glucose availability, and impairment of myofibril growth and repair.⁴⁶ Preclinical data suggest that muscle inexcitability observed during the acute phase of CIM is due to inactivation of sodium channels.⁴⁷

Early Mobility and Rehabilitation

The results of studies examining the effects of physical rehabilitation on short-term outcomes in ICU patients have been mixed, and there is no evidence to suggest that it improves long-term outcomes. The heterogeneity of critically ill populations and our inability to risk stratify these patients because of the lack of detailed understanding of underlying pathophysiology may be a potential explanation for the conflicting results in studies examining short-term outcomes. Early mobility has been shown to be safe and feasible and to alter short-term outcome.⁴⁸ However, adoption into practice is lagging, as demonstrated by a less than 50% implementation rate among 500 surveyed U.S. hospitals.⁴⁹ Commonly cited barriers include equipment and staffing.⁴⁹

CRITICAL ILLNESS-ASSOCIATED MORBIDITY

Critical illness survivors face a substantially elevated mortality after discharge from the hospital, a problem best documented for severe sepsis. For example, we and others have shown similar rates of excess

postdischarge mortality among survivors of severe sepsis.^{50,51} In addition, the vast majority of severe sepsis survivors is either diagnosed with a new health condition or has worsening of existing health conditions.⁵¹ Persistent inflammation or a procoagulant state seen during recovery from sepsis^{52,53} may increase the risk of cardiovascular disease (myocardial infarction, stroke, and need for coronary revascularization),^{50,53} diabetes,^{54,55} and atrial fibrillation.⁵⁶ Indeed, severe sepsis is a complex disease process with a plethora of potential mechanisms to explain how different aspects of sepsis and the short-term care of patients with sepsis may drive late sequelae. Some of these pathways may be unique to sepsis while others may be shared with other acute illnesses. Further observational studies require sophisticated designs to isolate potentially causal pathways. In addition, the ultimate step will be to conduct experiments where patients are randomly assigned to alternative care strategies designed specifically to alter these pathways with the hope of improving long-term outcomes of sepsis.

■ CHRONIC CRITICAL ILLNESS

Patients who survive their initial acute illness but consequently experience persistent organ failures necessitating prolonged intensive care meet the definition of chronic critical illness (CCI).⁵⁷ This illness is characterized by high hospitalization costs, frequent postacute care use, and poor long-term survival.⁵ The clinical and financial burden of CCI is expected to increase in the coming years because of both an aging population and advances in the early management of critical illness resulting in more long-term survivors.^{58,59}

In a population-based sample of five U.S. states, we found that the prevalence of CCI based on a consensus definition has been increasing over time, with associated in-hospital costs exceeding \$25 billion per year.⁶⁰ These findings underscore the importance of CCI to the field of critical care, particularly for healthcare policy and planning. Spending on CCI is likely to rise further as the population ages, because the prevalence of CCI increases dramatically with age,⁶⁰ similar to other critical illness syndromes such as severe sepsis and ARDS.^{61,62} On the basis of age-related differences in patient preferences for intensive care near the end of life,⁶³ the prevalence of CCI may vary, necessitating a decision (either implicit or explicit) to undergo prolonged life support on the part of patients or their surrogate decision makers.⁶⁰

The most common initial diagnoses that lead to CCI were acute respiratory failure requiring mechanical ventilation and sepsis.⁶⁰ Both are characterized by an excessive proinflammatory state that can lead to prolonged organ failures, neuromuscular weakness, and neurocognitive dysfunction; all of these are the hallmarks of CCI.⁶⁴ This finding suggests that the early treatment of sepsis and acute respiratory failure is an important target for CCI prevention. By preventing organ failures early in the course of critical illness, novel treatments such as early mobility,⁶⁵ early resuscitation,² decreased tidal volumes,¹ conservative fluid management after shock resolution,⁶⁶ and avoidance of excessive sedation⁶⁷ may be powerful levers for stopping CCI before it occurs, minimizing the population burden of this syndrome. Hospital-acquired infections may contribute to mortality among hospitalized patients and to the burden of CCI.⁶⁸

■ QUALITY OF LIFE

Several studies have shown that severe sepsis impairs quality of life.⁶⁹ Each of the outcomes described earlier may affect the quality of life. Approximately a third of survivors of sepsis hospitalization at 6 months have significant impairments in various domains of quality of life. The impairments in cognition and physical function described earlier may persist, leading to problems in mobility and performing activities of daily living and disability. Furthermore, although many sepsis survi-

vors return home, approximately one-third require additional help at home or are in a skilled nursing facility, acute care hospital, or rehabilitation facility.

■ CAREGIVER AND FAMILY BURDEN IN CRITICAL ILLNESS

Caregiver outcomes and their interaction with ICU survivors have gained importance in understanding the effect of critical illness on the family unit.^{70,71} There is a considerable body of work evaluating these interactions in other medical conditions, such as stroke or cancer.^{72,73} These data show that caregivers who are challenged in their caregiving contribute to poor outcomes and threaten home care for survivors.^{74,75}

Studies indicate that the majority of ICU survivors who received long-term mechanical ventilation required the assistance of a family caregiver 1 year after their critical illness.⁷⁶ Providing such care may result in PTSD, emotional distress, depression, anxiety, and reduced HRQoL.⁷⁷⁻⁷⁹ In addition, caregivers experience significant burden because of a patient's physical and psychological dysfunction and lifestyle disruption associated with the challenges of managing complex care at home.⁸⁰

■ FUTURE DIRECTIONS

The findings that a large proportion of patients who survive critical illness have poor long-term outcomes, which may be attributed to critical illness rather than preexisting chronic health, have implications for endpoints of future clinical trials. Traditionally, primary endpoints included only mortality. Incorporating both morbidity and mortality in a primary endpoint, similar to endpoints used for stroke,⁸¹ is important.

Most interventions for critical illness were administered for brief duration, for days to weeks. Since the poor long-term outcomes may last for months, interventions that started in the ICU but continued for longer duration should be tested in future clinical trials.

Finally, future studies should understand the mechanisms underlying poor long-term outcomes. These translational studies can be conducted either in animals, by developing models that mimic human disease and studying long-term outcomes over several weeks, or in humans where cohorts are followed for several months after discharge and tissue samples are obtained longitudinally.

■ CONCLUSION

With the growth of intensive care and concurrent improvements in supportive care, patients are more likely to survive their initial episode of critical illness. Critical illness survivors subsequently face a wide array of problems, including developing functional deficits, neuromuscular and neuropsychological morbidity, and worsening of existing chronic diseases or development of new chronic diseases, which often result in permanent functional impairment. This results in ongoing high healthcare utilization and frequent hospitalizations.⁸²

In addition, there is growing recognition that the consequences of critical illness place substantial strain on families of ICU survivors, who often bear the brunt of ongoing complex informal home care.^{71,80,83} Only some of these adverse outcomes have been adequately studied, and specific interventions to prevent these outcomes have not been tested in clinical trials.

Future research needs to address the pathophysiology of consequences of critical illness (e.g., ICU-acquired weakness or neuropsychological dysfunction) to develop comprehensive rehabilitation interventions that incorporate the needs of patients and caregivers.

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Natural and man-made disasters have always been a part of life and are occurring with increasing frequency. They create varied degrees of chaos owing to mismatch of resources and needs, and they place a huge burden on healthcare systems. Restoring an affected society to its preevent status requires extraordinary efforts and incurs substantial costs. Thousands of people are injured physically and emotionally as the result of such events, and their effects continue long after worldwide attention has disappeared.

The devastating events of September 11, 2001, in the United States, subsequent acts of bioterrorism, and emerging infectious disease pandemics have brought new challenges to the field of disaster management and multidisciplinary hazard mitigation. Even though war- and terrorism-related disasters have gathered much attention, natural disasters have occurred with increasing frequency over the past decades. This has been attributed to the growth of human population in geographically disaster-prone areas, rapid industrialization, and increasing exposure to toxic and hazardous materials (HazMat).¹⁻³

Analyses of the response of different healthcare systems to major disasters in the past have demonstrated the need for a more clearly identified planning process to attend to the response to multihazard events.⁴ This provides a basic understanding of common disaster scenarios and highlights the role of intensivists in the medical response to disasters. It is important for practicing critical care clinicians to keep in mind that their role is first and foremost as a first receiver rather than a first responder; well-trained intensivists may be of much greater value remaining in the hospital setting rather than quickly mobilizing to the field, where their lack of situational preparedness may make them more of a hindrance than an asset.⁵

BACKGROUND

Major disasters occur regularly and cause widespread human death and suffering. Over the past two decades, more than 3 million lives have been lost worldwide to major disasters. A total of 39,073 people were reportedly killed by disasters alone in 2001, with the decade's annual average of around 62,000. Even though the numbers of geophysical disasters such as earthquakes and volcanic eruptions have remained fairly constant, recent years have seen the highest number of weather-related disasters.⁶ As populations grow and occupy spaces that are vulnerable to different hazards, disasters will increase in severity and impact. Events since the September 2001 terrorist attacks have brought attention to the effects of man-made disasters on the healthcare system and the need to anticipate and plan for such low-probability, yet catastrophic, events. Although there is basic similarity in the response to them, each type of disaster presents responders with unique demands. After any disaster, healthcare systems are tasked with preventing excessive deaths, mitigating suffering, and dealing with an often overwhelming inadequacy of resources. Over the past few years, disaster medicine has grown into a unique specialty to deal with planning and preparing for such cataclysmic events. It shares a common ideal with public health: "greatest good for the greatest number."³

A fundamental part of designing a medical response to disasters is to coordinate with healthcare personnel across the hospital system so that they overcome natural differences associated with each group and maximize efficient use of scarce resources. Because the sickest of all

viable patients will require intensive care, critical care physicians can play an invaluable part in coordination efforts. In addition to their usual role of being caregivers for patients in the intensive care unit (ICU), intensivists will be expected to help in triage decisions, transport critically ill patients, and treat the multitude of injured in a rational order. They can also help by providing essential medical care at the actual disaster site via mobile ICU teams. It is thus important for critical care physicians to be familiar with the basics of disaster management, acquire organizational and leadership skills, practice delivery of unconventional critical care, and be familiar with different disaster-related medical syndromes.

TERMINOLOGY

Physicians and healthcare personnel should be familiar with the basic nomenclature and terminology in disaster medicine. Clear, common, and concise definitions are important to effective communication and evoking appropriate responses in disaster situations. Uniform use of terminology across healthcare systems provides a basis for analyzing and constructing an effective disaster plan and response by all responders.⁷ Controversies surrounding the definitions of *disasters*, *hazards*, and *casualties* are included in the discussions that follow.

The word *disaster* connotes a subjective assessment that has various meanings to different people and has an inherent bias, depending on the person using it. For example, a local, state, or federal "disaster declaration" implies commitment of financial and other resources. Similarly, a disaster in one community is not necessarily the same in another. Currently, there is no uniformly accepted definition for the word *disaster*.⁷ De Boer recognizes the lack of a meaningful definition for the word and instead proposes the term *medical severity index*.⁸ This term, however, has not gained sufficient acceptance for routine use. Different modifiers can lead to different definitions of the term *disaster*. They include the type of disaster, geographic area involved, timing, onset of the event, size of the community affected, baseline resources available, and physical, psychosocial, and economic injuries caused by the event. However, from a healthcare standpoint, the most important variable that defines a disaster is its functional impact on the healthcare facility.⁷ Despite various attempts to clear this confusion, the issue remains unresolved.^{7,9,10} What follows are the commonly used definitions in disaster medicine from a healthcare perspective:

Hazard. An event with the potential to cause catastrophic damage. It may be a "naturally" occurring phenomena, such as volcano eruptions, or "man-made," such as nuclear power plant accidents.¹¹

Emergency. A natural or man-made event that significantly disrupts the environment of care (e.g., damage to an organization's buildings due to severe winds, storms, or earthquakes), resulting in disrupted care and treatment (e.g., loss of utilities, such as power, water, or telephones, due to floods, civil disturbances, accidents, or emergencies within the organization or in its community); or resulting in sudden, significantly changed, or increased demand for the organization's services (e.g., bioterrorist attack, building collapse, or plane crash in the organization's community).

Disaster. A hazardous event causing physical, psychological, social, economic, or even political effects on a scale such that the stricken community needs extraordinary efforts to cope with it and often

outside help or international aid.^{9,10} Medical disasters form a subset of this category, in which physical and/or psychosocial injuries exceed the medical response capabilities of the community affected.

Casualty. Any person suffering from physical and/or psychological damage by outside violence leading to death, injuries, or material losses. Again, the word has no standard definition and is sometimes used to imply injury, death, or both. It may also bear financial implications, because federal reimbursement may be approved only for people classified as casualties.^{7,9,10}

Potential injury-creating event (PICE) system. A new system developed to overcome the differences in disaster nomenclature. It uses the functional impact on the healthcare facility as the only determining factor to define an “emergency” or “disaster.” It uses four modifiers to communicate the impact caused by the situation on the healthcare facility.⁷

Multicasualty incident. A hazardous event that, regardless of its size, is containable by local emergency medical services (EMS). From an operational standpoint, an event becomes a multicasualty incident when its impact exceeds the day-to-day response routine to the EMS. Adjustments within the local response system are required to cope with this demand without the need to request outside help (level 1 response).¹²

Mass-casualty incident. A hazardous event that overwhelms local response capability. It is likely to impose a sustained demand for health services rather than a short, intense peak typical of many smaller scale disasters. This may require a level 2 response (neighboring and regional resources are activated) or a level 3 response (state, interstate, and federal resources are activated in the rescue and recovery process).¹³

Hazard vulnerability analysis (HVA). The identification of potential emergencies and the direct and indirect effects these emergencies may have on the organization’s operations and the demand for its services.¹⁴

CLASSIFICATION OF DISASTERS

Natural disasters arise from the forces of nature and include earthquakes, volcanic eruptions, hurricanes, floods, fire, and tornadoes. In addition, infectious disasters can be classified as epidemic or pandemic. Man-made disasters are due to identifiable human causes and may be further classified as complex emergencies (e.g., terrorist attacks) and technological disasters (e.g., industrial accidents).¹⁵ Other classifications include those based on onset (acute vs. insidious disasters), predictability, duration, and frequency. From a public health perspective, disasters must be defined by their effect on people and the healthcare system. The concept of functional impact to the healthcare system is paramount.^{15,16}

The PICE system attempts to create uniformity to address the wide spectrum of situations.⁷ The two major aims of this system are to communicate both the operational consequences to a hospital or community and the type and amount of outside assistance needed. Four modifiers for an event are chosen from a standardized group of prefixes, and a stage is assigned (Table 184-1). *Column A* (first prefix)

TABLE 184-1 PICE Nomenclature

| A | B | C |
|---------|---------------|----------|
| Static | Controlled | Local |
| Dynamic | Disruptive | Regional |
| | Paralytic | National |
| | International | |

PICE, potential injury-creating events.

Data from Koenig KL, Dinerman N, Kuehl AE. Disaster nomenclature—a functional impact approach: the PICE system. *Acad Emerg Med* 1996;3:723–727.

describes the potential for additional casualties. For example, a finite number of people injured in an airplane crash is a “static event,” whereas an ongoing fire is a “dynamic” event. *Column B* (second prefix) describes whether local resources are sufficient (“controlled”) or overwhelmed. If they are overwhelmed, the two modifiers “disruptive” and “paralytic” indicate whether they must be simply augmented or totally reconstituted. Paralytic PICEs are the most daunting of all situations, and they can be either destructive or nondestructive (Table 184-2). *Column C* describes the extent of geographic involvement. The *PICE stage* refers to the likelihood that outside medical help is required (Table 184-3). This PICE model provides important concepts for disaster planners, researchers, and responders. Using this system, disasters can be described both prospectively and retrospectively. PICE is a valuable tool for use in planning and disaster mitigation, but the system warrants validation on a wider scale. It may also require further refinement to delineate the type of aid needed by an affected community.⁷ Regardless of the type of classification used to categorize disasters, certain unique features are associated with each type of disaster. It is important to understand the common effects of different natural and man-made disasters to predict their impact and plan effectively. Some common disaster situations are reviewed next.

TABLE 184-2 Paralytic PICE

| DESTRUCTIVE | NONDESTRUCTIVE |
|-------------------|---------------------|
| Bomb explosion | Snowstorm |
| Earthquake | Employee strike |
| Tornado | Power failure |
| Civil unrest | Water supply cutoff |
| HazMat spill | |
| Fire | |
| Building collapse | |

HazMat, hazardous materials; PICE, potential injury-creating events.

Data from Koenig KL, Dinerman N, Kuehl AE. Disaster nomenclature—a functional impact approach: the PICE system. *Acad Emerg Med* 1996;3:723–727.

TABLE 184-3 PICE System Staging with Examples

| STAGE | PROJECTED NEED FOR OUTSIDE HELP | STATUS OF OUTSIDE HELP |
|-------|---------------------------------|------------------------|
| 0 | Little to none | Inactive |
| I | Small | Alert |
| II | Moderate | Standby |
| III | Great | Dispatch |

EXAMPLES OF PICE STAGING

| | |
|---|---|
| 1. Multiple-vehicle crash in a big city | Static, controlled, local PICE, stage 0 |
| 2. Multiple-vehicle crash in a small town | Static, disruptive, local PICE, stage I |
| 3. Los Angeles civil disturbance | Dynamic, disruptive, regional PICE, stage II |
| 4. SARS outbreak in China | Dynamic, disruptive, national PICE, stage III |

PICE, potential injury-creating events; SARS, severe acute respiratory syndrome.

From Koenig KL, Dinerman N, Kuehl AE. Disaster nomenclature—a functional impact approach: the PICE system. *Acad Emerg Med* 1996;3:723–727.

NATURAL DISASTERS

Earthquakes

Earthquakes are a model of a disaster that results in significant mortality,¹⁷ as can be seen in Figure 184-1. A homogeneous population well trained in both basic trauma and life support and the architectural design of the housing and public facilities of the stricken area are the two major determinants of outcomes for earthquake victims. The massive earthquakes in recent years in Turkey, Taiwan, Sumatra, Kashmir, Sichuan, and Haiti have shown us that a sound engineering design for earthquake resistance in civil structures such as schools and hospitals have a major impact on outcomes. In addition, urban earthquakes generate massive fiscal impact on the world in terms of reconstruction grants provided by wealthier countries for devastated urban areas. Moderately destructive earthquakes in the developing world usually cost up to \$10 billion in reconstruction; the needs of developing countries with urban earthquakes may cost an order of magnitude more.

Despite extensive experience and published literature dealing with medical response to earthquakes, the earthquake in Haiti shows that we are frequently doomed to relearn the lessons forgotten.

The Haiti earthquake occurred on January 12, 2010, and was of magnitude 7.0 on the Richter scale, resulting in some 230,000 mortalities and 1.5 million homeless. Let us consider first the military medicine response delivered, especially in the face of continuous exposure of the military medicine establishment to mass-casualty management in the wars in the Middle East.

Responders from the very experienced Israel Defense Forces (IDF) were air-deployed within 48 hours of the Haiti earthquake. This team had extensive experience over the years with international response and consists of 230 people. The team unpacked and built their portable hospital within 8 hours, and during 10 days of operation treated more than 1100 patients in a facility designed to provide 60 inpatient beds, including 4 intensive care beds and 1 operating room.¹⁸ Most of the

first wave of casualties presented with crushed limbs with open infected wounds, and the later arrivals presented with sepsis and poor chance of outcome. Despite the repeated experience from prior earthquakes showing that victims of crush syndrome and acute renal failure require emergency dialysis to prevent death, this facility relied on other international teams for dialysis. Their major dilemmas were practical implementation of the triage algorithm by military personnel to a civilian population. The simple priorities were urgency, resources available, and probability of saving life. Patients with brain injury, paraplegia due to spine injuries, or a low Glasgow Coma Scale score were immediately transferred to other facilities, since no neurosurgical capabilities were available. A triage panel of three senior physicians relieved individual physicians of personal accountability. Half of the intensive care capability was always dedicated to postoperative care, with the remaining two beds used for prolonged intensive care; only patients who were expected to stabilize within 24 hours were placed in these beds. The very early discharge policy permitted this facility to treat more than 100 patients per day.

Second, let us consider the response of the U.S. military, which had a considerable portfolio on providing disaster relief in catastrophic events such as the Indonesian tsunami that devastated Sumatra. The U.S. Naval Ship (USNS) *Comfort*, one of the hospital ships of the Military Sealift Command, was deployed as part of the mission termed *Operation Unified Response*. It started accepting casualties within 7 days of the earthquake. The ship is a 1000-bed facility that includes 75 ICU beds, blood bank, hemodialysis, pathology, physical therapy, morgue, and radiology with computed tomography and ultrasonography capability. It is staffed with 1000 active-duty U.S. medical personnel, including three physician intensivists, and it was allocated to stay up to 6 months.^{19,20} The first wave of casualties were critically ill trauma patients airlifted from field hospitals by U.S. helicopters. Within 72 hours, the *Comfort* admitted 254 patients, and the census rapidly increased to 430, more than a third of them pediatric cases. A team of six internists provided 24/7 coverage. Dozens of patients underwent mechanical ventilation simultaneously; the open-bay design did not allow for isolation, and the nurse-to-patient ratio was about 7:1. A large volume of hemodialysis was provided to patients with crush syndrome, leading to rapid depletion of dialyzers and dual-lumen dialysis catheters. The discharges exceeded admissions in about 2 weeks, and after a total of 629 admissions, the ship completed its mission. While the standard of care exceeded community expectations, the U.S. Navy personnel followed naval protocol and standards.

Third, let us consider the relearning of the lessons of civil-military collaboration in disaster response.²¹ A volunteer medical team with civilian personnel under the auspices of the international medical corps flew to the Dominican Republic and reached the Hôpital de l'Université d'Etat d'Haïti in Port-au-Prince after a long bus ride on January 17, 2010. There were more than 800 injured in the partially destroyed facility, with the primary diagnoses being crush injuries, compartment syndrome, infected fractures, and hemorrhagic shock. One physician and one nurse were covering up to 80 critically ill patients in the wards. An aftershock of 5.9 magnitude resulted in an exodus of casualties and higher rates of heat stroke in dehydrated hypovolemic patients exposed to tropical temperatures. Destruction of the prison system released 4000 criminals into the community, and no security was available until the arrival of a U.S. airborne infantry regiment. With the arrival of the USNS *Comfort* on January 20, evacuation of the most critically ill patients started, but a triage list developed rapidly, with ship facilities accepting preferentially complicated injuries, obstetric patients, and maxillofacial injuries. Patients with pelvic fractures, closed head injuries, complete spinal cord lesions, and mechanical ventilation cases were of too high acuity for the USNS *Comfort*. Family structures became fragmented, as separation of children from parents occurred. Yet the collaboration of civilian and military medical personnel was considered a success.

Next, let us consider the experiences of academic centers delivering care to victims of the Haitian earthquake on-site.²² The Miller School of Medicine of the University of Miami and Project Medishare had the

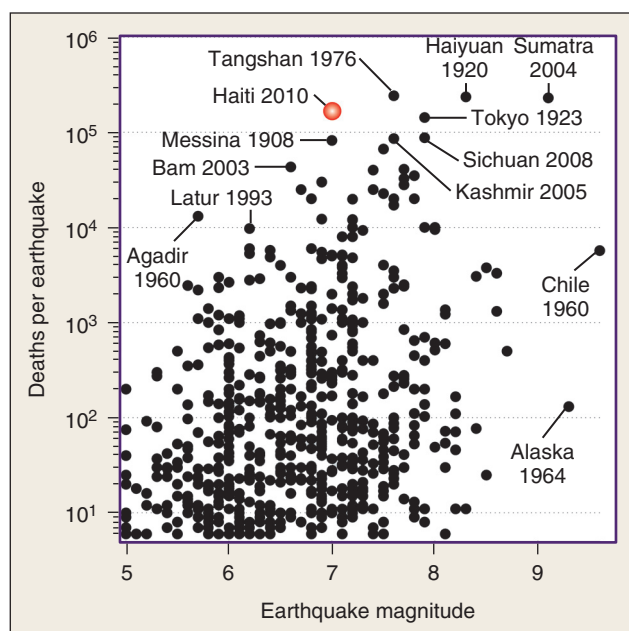


FIGURE 184-1 ■ Deaths from earthquakes since 1900. The toll of the Haiti quake is more than twice that of any previous magnitude 7.0 event and fourth worst since 1900. (From Hough SE, Bilham R. After the earthquakes: elastic rebound on an urban planet. New York: Oxford University Press; 2006; and Bilham R. The seismic future of cities. *Bull Earthq Eng* 2009;7:839-887.)

advantage of long experience of collaboration with Haiti and close geographic proximity, and they were able to provide emergency relief within 20 hours. Within 8 days, they were able to establish a field hospital at the city airport, and by January 21, 140 patients were transferred into the upgrade facility. The well-organized command center with satellite links for telephone and Internet access was available. A joint adult-pediatric triage team accompanied by Creole-speaking medical staff of Haitian origin was used. Multiple surgeries were performed under local peripheral nerve blocks, with guillotine amputations being frequent. The highest acuity patients were transferred to the IDF field hospital or the USNS *Comfort*. The command center eventually provided psychiatrists to manage the posttraumatic stress syndrome and a buddy system for the follow-up support.

Finally, one must consider the critical care response from New York City. Although many small teams and a large volume of supplies were dispatched, an organized response was delivered under the leadership of Dr. Ernest Benjamin, division chief of critical care in surgery at Mt. Sinai Hospital. Dr. Benjamin arrived in Port-au-Prince 3 days after the initial event, and after rapid assessment of needs and resources, organized the deployment of the 27-member critical care team to his home country, which arrived on January 20. The team remained on-site for 2 weeks and was responsible for postanesthesia and postoperative care delivery, with Dr. Benjamin being deputized as the director of critical care and recovery at the national hospital. The home institution effectively secured anonymous donations of private jets able to transport the team personnel and some 3000 pounds of medical supplies per flight. The team delivered intensive care with minimal technology but with kindness and dignity toward the suffering population. This was a truly integrated response with both language and cultural sensitivities and capabilities, which are very important in catastrophic situations that will take decades for the local population to recover from.²³

Experience in managing catastrophic international disasters continues to accumulate with unfortunate regularity. The preceding discussion suggests that combinations of dialysis, orthopedic surgery, pediatric trauma, security, transportation, posttraumatic stress treatment, and cultural and language sensitivities are crucial in earthquakes. Disasters produce well-defined syndromes with well-defined mortalities. It is the recovery phase that continues to require persistence and improvement. One of the most experienced managers and thought leaders in disaster management, Dr. Eric Noji, enumerated the most important factors in public health after disasters: environmental health, epidemic management, immunization, controlling the spread of human immunodeficiency virus/acquired immunodeficiency syndrome, management of dead bodies, nutrition, maternal and child health, medical services, and thorough public health surveillance. It is a common error to deliver a few weeks of heroic quality care and then abandon the population to the ravages of destroyed infrastructure, including public health organization.²⁴

Volcanic Eruptions

A volcano is a hill or a mountain built around a vent that connects with reservoirs of molten rock below the earth's surface.²⁵ Different types of eruptive events occur, including pyroclastic explosions, hot ash releases, lava flows, gas emissions, and glowing avalanches (gas and ash releases). Lava flows tend not to result in high casualties, because they are easily avoidable. The "composite" type of volcano is associated with a more violent eruption from within the chimney. These eruptions are associated with air shock waves, rock projectiles (some with high thermal energy), release of noxious gases, pyroclastic flows, and mud flows (lahars). Pyroclastic flows and lahars are often fast moving and are the main cause of damage and deaths from volcanoes, as evidenced by the small eruption of the Nevado del Ruiz in Colombia that killed more than 23,000 people.²⁶ The release of ash and its subsequent rapid buildup on building structures can be substantial, causing them to collapse within hours. Ash is also responsible for the clogging of filters and machinery, causing electrical storms and fires, and interfering with

communications. Ash is a main cause for respiratory-related syndromes and conjunctival and corneal injury. A variety of toxic gases (e.g., carbon dioxide, hydrogen sulfide, sulfur dioxide, hydrogen chloride, hydrogen fluoride, and carbon monoxide [CO]) are released during eruptions, causing bronchospasm, pulmonary edema, hypoxemia, cellular asphyxiation, topical irritation of skin and other mucosal surfaces, and death.²⁷ Damage to health infrastructures and water systems can be severe. Problems related to communication (ashes cause serious interference) and transportation (poor visibility and slippery roads) are likely. On the basis of the initial assessment, various needs can be anticipated. Reducing the risk for vulnerable groups of being exposed to ash, raising awareness of the risk associated with ash (health and mechanical risk), and maintaining food security conditions over the long term (lava, ash, and acid rain cause damage to crops and livestock) can help limit suffering.²⁸

Hurricanes, Cyclones, and Typhoons

The large rotating weather systems that form seasonally over tropical oceans are variously named, depending on their geographic region of origin.²⁹⁻³¹ They consist of a calm inner portion called the eye, surrounded by a wall of rain and high-velocity winds. On the basis of central pressure, wind speed, storm surge, and potential destruction, their severity is graded on a scale of 1 to 5 (Saffir Simpson scale).³⁰ They are among the most destructive natural phenomena. Cyclones during 1970 and 1991 in Bangladesh claimed 300,000 and 100,000 lives, respectively, because of flooding.³² The most devastating hurricane ever to hit the United States occurred in 1900 at Galveston, Texas. It claimed an estimated 8000 to 12,000 lives.³³ The greatest damage to life and property is not from the wind but from secondary events such as storm surges, flooding, landslides, and tornadoes. Ninety percent of all hurricane-related deaths occur from storm surge-related drowning.¹ The most common injury patterns include lacerations (during the cleanup phase), followed by blunt trauma and puncture wounds. Late morbidity can be due to postdisaster cleanup accidents (e.g., electrocution), dehydration, wound infection, and outbreaks of communicable diseases.^{31,34} Data from Hurricane Katrina confirmed data from previous meteorological events. The leading mechanisms of injuries are fall, lacerations, and piercing injuries, with cleanup being the primary activity at the time of injury.³⁵ Resources may have to be provided for an extended period after the initial inciting event, and significant resources may have to be provided for patients with chronic medical illnesses.^{34,36}

Floods

There are three major types of floods: flash floods (caused by heavy rain and dam failures), coastal floods, and river floods. Together, they are the most common types of disasters and account for at least half of all disaster-related deaths.^{37,38} The primary cause of death is drowning, followed by hypothermia and injury due to floating debris.^{39,40} The impact on the health infrastructures and lifeline systems can be massive and may result in food shortages. Interruption of basic public services (e.g., sanitation, drinking water, and electricity) may result in outbreaks of communicable diseases.^{38,40} Another concern is the increase in both vector-borne diseases (e.g., malaria and St. Louis encephalitis) and displacement of wildlife (e.g., poisonous snakes and rodents).^{39,40}

Landslides

Landslides are more widespread than any other geologic event. They are defined as downslope transport of soil and rock resulting from natural phenomena or man-made actions. Landslides can also occur secondary to heavy storms, volcanic eruptions, and earthquakes. Landslides cause high mortality and few injuries. Trauma and suffocation by entrapment are common. Pending an assessment, needs can be anticipated, such as search and rescue, mass-casualty management, and emergency shelter for the homeless.^{41,42}

Pandemic 2009 H1N1 Influenza A Virus

Pandemic H1N1 2009 is a new strain of influenza A virus that was first identified in Mexico and the United States on March 18 and April 15, 2009, respectively. It originated from the quadruple reassortment swine influenza (H1N1) virus closely related to the North American and Eurasian swine lineage. However, this new virus circulated only in humans, with no evidence of transmission between humans and animals.

Within weeks, the virus quickly spread worldwide through human-to-human transmission. On April 26, 2009, the Strategic National Stockpile of the Centers for Disease Control and Prevention (CDC) began releasing 25% of the supplies in the stockpile for the treatment and protection from influenza.⁴³ On June 11, 2009, the World Health Organization (WHO) declared the 2009 H1N1 influenza a global pandemic, generating the first influenza pandemic of the 21st century, with more than 70 countries reporting cases of H1N1 infection. By June 19, 2009, all 50 states in the United States, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands had reported cases of 2009 H1N1 infection. More strikingly, the CDC Emerging Infections Program estimated the number of hospitalizations and deaths in people aged 64 years and younger. The virus was most likely to strike children, young adults, and those with underlying pulmonary and cardiac disease. Pregnant women in their second and third trimester were also at high risk. Patients requiring intensive care had a remarkable prevalence of obesity.⁴³

Influenza vaccines are most effective not only to prevent but also to mitigate the severity of illness. The pandemic H1N1 influenza vaccine was promptly developed by the WHO and national authorities. A national influenza vaccination campaign was launched in the United States in October 2009, and the first H1N1 vaccine was made available at that time. Despite the rapid response of the authorities, developing countries in the Southern Hemisphere experienced delays and shortages of the vaccines. Thus, research and developmental work have been encouraging for developing a “universal” influenza vaccine that could provide efficacious cross-reactive immunity and induce broad protection against different variants and subtypes of the influenza virus.⁴⁴

Data show that about 8% of H1N1 patients were hospitalized (23 per 100,000 population); 6.5% to 25% of these required being in the ICU (28.7 per million inhabitants) for a median of 7 to 12 days, with a peak bed occupancy of 6.3 to 10.6 per million inhabitants; 65% to 97% of ICU patients required mechanical ventilation, with a median ventilator duration in survivors of 7 to 15 days; 5% to 22% required renal replacement therapy; and the 28-day ICU mortality was 14% to 40%.⁴⁵⁻⁵¹ Critical care capacity is a key element of hospital surge capacity planning.¹⁰ The proportion of ICU beds occupied by patients with H1N1 varied. In Australia and New Zealand, it peaked at 19%,⁷ while in Mexico, many patients required mechanical ventilation outside the ICUs.⁶ To match the surge capacity with increasing ICU demands during a pandemic is a difficult task, since uncertainty exists for many of these parameters. The disease brought a surge of not only critically ill patients but also patients who required prolonged mechanical ventilation and ICU management. Hospitals should maximize the number of ICU beds by expanding ICUs and other areas with appropriate beds and monitors. Elective procedures should be minimized when resources are limited, and critical care capacity should be augmented.

Safe practices and safe respiratory equipment are needed to minimize aerosol generation when caring for patients with influenza. These measures include handwashing and wearing gloves and gowns; using N95 respirators, which reduce the transmission of epidemic respiratory viruses; staff training in personal protective equipment (PPE); minimizing the use of bag-mask ventilation and disconnection of the ventilator circuit; and avoiding the use of heated humidifiers on ventilators, Venturi masks, and nebulized medications.⁵²

When the number of critically ill patients far exceeds a hospital's traditional critical care capacity, modified standards of critical care to

provide limited but high-yield critical care interventions should be the goal to accommodate far more patients. Triage criteria should be objective, transparent, and ethical and applied justifiably and publicly disclosed. The ICU triage protocols for pandemics should only be triggered when ICU resources across a broad geographic area are or will be overwhelmed despite all reasonable efforts to extend resources or obtain additional resources.⁵³ The Sequential Organ Failure Assessment score, though not validated, has been proposed to determine qualification for ICU admission during mass critical care.

The major characteristics of 2009 H1N1 influenza A infection were the rapidly progressive lower respiratory tract disease leading to acute respiratory distress syndrome (ARDS) with refractory hypoxemia. A substantial number of H1N1 ICU patients required advanced ventilatory support (ranging from 1.7% to 11.9%) and rescue therapies including high levels of inspired oxygen and positive end-expiratory pressure (PEEP), inverse ratio ventilation, airway pressure release ventilation, neuromuscular blockade, inhaled nitric oxide, high-frequency oscillatory ventilation, extracorporeal membrane oxygenation (ECMO), volumetric diffusive respiration, and prone-positioning ventilation.^{46,49,51,54} ECMO was successful in managing refractory hypoxemia in these patients in two studies. The median durations of therapy and survival rates to ICU discharge were 10 days and 15 days—71% and 67%, respectively.^{55,56}

As of March 13, 2010, the CDC estimates of 2009 H1N1 influenza cases, hospitalizations, and deaths in the United States since April 2009 were 60 million cases, 270,000 hospitalizations, and 12,270 H1N1-related deaths, respectively.⁵⁷ The virus did not mutate during the pandemic to a more lethal form. Widespread resistance to oseltamivir did not develop. The WHO declared an end to the H1N1 pandemic on August 10, 2010. The H1N1 virus is expected to take on the behavior of a seasonal influenza virus and to circulate for some years.

Ebola Update

In late 2013, Ebola virus disease (EVD) became an international disaster of crisis proportion in West Africa, primarily in the countries of Liberia, Sierra Leone, and Guinea. This became the largest outbreak of EVD in history, greater than all previous epidemics combined, with a total number of 24,000 suspected cases and 9714 deaths, all in the aforementioned countries; importantly, there have only been 34 suspected cases and 15 deaths outside of those countries.⁵⁸⁻⁶⁰ This point cannot be overemphasized. Although the mortality of confirmed cases has been documented to be as high as 68% in the affected nations of West Africa, if patients are quickly recognized and given appropriate aggressive supportive care, the case fatality ratio drops dramatically. There are, to date, no specific pharmacotherapeutic interventions available to cure EVD; the dramatically decreased case fatality ratio noted in developed nations is related to strict enforcement of isolation, hygiene, and use of supportive care.

With regard to the scope of the issue, the CDC predicted that the number of confirmed EVD cases would double approximately every 20 days, with estimated cases ranging as high as 1.4 million. From a mass-casualty perspective, it rapidly became clear that the aforementioned nations of West Africa did not have adequate governmental infrastructure to create Ebola treatment units nor were they able to strictly implement the necessary public health infrastructure of hygiene and isolation. At that point, important nongovernment organizations (NGOs) such as Médecins Sans Frontières, Red Cross, WHO, and worldwide military support intervened to create the lacking infrastructure.^{61,62}

When patients with EVD first started appearing in the United States, it required some fundamental reevaluation of the role of the CDC in such events. Normally the agency is tasked with providing information and guidance to both healthcare facilities as well as state and local health departments, but given the rapid, complex, and international nature of this particular epidemic, the routine approach of having state health departments manage these situations with oversight by the CDC was not particularly effective. The president

created the role of “Ebola Response Coordinator” to help provide a coordinated federal oversight for the U.S. approach to this disease. In addition, the CDC created Ebola “SWAT teams” that were sent in real time to appropriate locations to ensure appropriate resource allocation to hospitals, and, if necessary, transfer patients with suspected EVD to properly equipped regional centers. For example, in New York State, the governor mandated that eight medical centers (five in New York City alone) were to be designated centers for patients with suspected EVD and that all hospitals needed to develop strategic plans for initial management of patients with suspected EVD.⁶³

Interestingly, despite the extremely low number of actual patients who were diagnosed with EVD in the United States, a challenging problem was media management; an initial lack of clear federal leadership rapidly led to confusion, fear, and misinformation being spread throughout the country. As an example, the PPE recommendations from the CDC were not aligned with the recommendations from the WHO. This left hospital officials confused about the best manner in which to protect their employees. Eventually, the recommended approach became more aggressive, and there was agreement between the CDC and WHO regarding PPE.^{60,64-69}

In conclusion, major important lessons were learned during the outbreak of EVD, many of which have clear-cut implications for future epidemics. First, it became clear that for many developing nations, the existing governmental infrastructure is inadequate to provide appropriate containment, public health infrastructure, and treatment facilities; early aggressive intervention by a combination of NGOs and militaries is required to quell the spread. Second, the standard existing paradigm of local and state health agencies providing adequate resources, information, and guidance to health facilities may not be adequate; a rapid top-down federalized approach may be required. Clearly, more resources must be allocated to our federal health agencies to prepare for such possible events in the future.

■ OTHER NATURAL DISASTERS

Tornadoes occur most commonly in the North American Midwest. Over 4115 deaths and 70,000 injuries have been ascribed to them during the years 1950 to 1994. They cause widespread destruction of community infrastructure. Injuries most commonly seen are complex contaminated soft-tissue injury (50%), fractures (30%), head injury (10%), and blunt trauma to the chest and abdomen (10%).^{70,71} Firestorms, wildfires, tsunamis, winter storms, and heat waves are other natural phenomena capable of creating mass injuries from thermal burns, airway injury, smoke inhalation, heat-related disorders, and hypothermia.⁷²⁻⁷⁵

■ MAN-MADE DISASTERS

Transportation Disasters

Transportation accidents can produce injuries and death similar to those seen in major natural disasters. Some of the largest civilian disasters in North America have been related to the transportation of HazMat.⁷⁶ Motor vehicle accidents, railway accidents, airplane crashes, and shipwrecks are some of the common transportation accidents. They cause a wide range of injuries including multiple trauma, fractures, burns, chemical injuries, hypothermia, dehydration, asphyxiation, and CO inhalation. The hazard risk to a healthcare facility increases with its proximity to a chemical plant or highway, and such factors should be considered in the emergency preparedness plan of a hospital.⁷⁷

Weapons of Mass Destruction

Weapons of mass destruction (WMD) are those nuclear, biological, chemical, incendiary, or conventional explosive agents that pose a potential threat to health, safety, food supply, property, or the environment. Since the terrorist attacks in September 2001 and intentional

release of anthrax spores in the United States, there is growing concern around the world about the possible threat of chemical, biological, or nuclear weapons being used against a civilian population. The incidence of use of WMD to cause death and injury is rare. However, biological and chemical weapons are relatively accessible, and WMD are thought to be available to most foreign states and terrorist groups. In response to a WMD incident, healthcare personnel will be called on to manage unprecedented numbers of casualties in an environment of panic, fear, and paranoia that accompanies terrorism. Because most attacks occur without warning, the local healthcare system will be the first and most critical interface for detection, notification, rapid diagnosis, and treatment. The best defense in reducing casualties will therefore rest on the ability of medical and public health personnel to recognize symptoms and provide rapid clinical and epidemiologic diagnosis of an event. This requires that healthcare providers be well informed of potential biological, chemical, and nuclear agents. They must have a heightened index of suspicion and be able to identify unusual disease patterns to determine whether WMD are the etiologic agents of illness. Physicians will need to practice appropriate surveillance and reporting and develop knowledge of mass decontamination, use of proper PPE, and safety protocols related to a biological, chemical, or radiologic event.⁷⁸⁻⁸⁰ Salient characteristics and brief management strategies of different WMD are discussed here.

Biological Weapons

Biological weapons can be either pathogens (disease-causing organisms such as viruses or bacteria) or toxins (poisons of biological origin). Compared with other WMD, biological weapons are characterized by ease of accessibility and dissemination, difficulty in detection because of their slow onset of action, and their ability to cause widespread panic through the fear of contagion. They can be spread through various means, including aerial bombs, aerosol sprays, explosives, and food or water contamination. Multiple factors including particle size of the agent, stability of the agent, wind speed, wind direction, and atmospheric conditions can alter the effectiveness of a delivery system. The CDC has classified biological weapons into three categories (Table 184-4) based on the ease of dissemination; ability to cause high mortality, public panic, and social disruption; and requirement for special action for public health preparedness.⁸¹ Category A agents are of

TABLE 184-4 Triage Classification

| GROUPS | COLOR | SYMBOL | TYPE OF INJURY |
|-------------------------------|--------|--------|--|
| Priority I (emergent) | Red | R | CRITICAL: likely to survive if simple* care given within minutes |
| Priority II (catastrophic) | Blue | B | CATASTROPHIC: unlikely to survive and/or extensive or complicated care needed within minutes |
| Priority III (urgent) | Yellow | Y | URGENT: likely to survive if simple† care given within hours |
| Priority IV (nonurgent) | Green | G | MINOR: likely to survive even if care delayed hours to days |
| Priority V (none) | Black | X | Dead |

*Simple: care that does not require unusual equipment or excessive use of time or personnel.

†Assigned THIRD priority (after YELLOWS) when there are so many casualties that if resources are used in vain to try to save BLUE cases, the YELLOWS will needlessly die.

From Auf Der Heide E. Disaster response: principles of preparation and coordination. St. Louis: Mosby; 1989.

Full-text online edition available at: http://sheltercentre.org/sites/default/files/CVMosby_DisasterResponsePrinciples.pdf.

particular concern because they can cause widespread disease through their ease of transmission, result in high mortality rates, cause panic and social disruption, and require special attention during public health preparedness. General features that should alert healthcare providers to the possibility of a bioterrorism-related outbreak include⁸² the following:

1. A rapidly increasing disease incidence (e.g., within hours or days) in a normally healthy population
2. An epidemic curve that rises and falls during a short period
3. An unusual increase in the number of people seeking care, especially with fever or respiratory and gastrointestinal complaints
4. An endemic disease rapidly emerging at an uncharacteristic time or in an unusual pattern
5. Lower attack rates among people who had been indoors, especially in areas with filtered air or closed ventilation systems, versus people who had been outdoors
6. Clusters of patients arriving from a single locale and large numbers of rapidly fatal cases
7. Any patient presenting with a disease that is relatively uncommon and has bioterrorism potential (e.g., pulmonary anthrax, tularemia, or plague)

The main steps involved in managing a bioterrorist attack are containment, notification, confirmation, and directed antibiotic treatment and prophylaxis. In the event of a suspected bioterrorist attack, the CDC has issued protocols for early notification of local and state public health department agencies.⁸³ The Association for Professionals in Infection Control and Epidemiology in cooperation with the CDC devised the "Bioterrorism Readiness Plan," with a template for healthcare facilities to serve as a reference document to facilitate preparation of bioterrorism readiness plans for healthcare facilities. This tool guides infection-control professionals and healthcare epidemiologists in the development of practical and realistic response plans for their institutions in the event of a bioterrorism attack.⁸⁴ The reader is referred to other documents for a review of bioterrorism and critical care,^{85,86} as well as other resources and websites (Box 184-1).

Chemical Weapons

Chemical incidents are accidental or intentional events that threaten or do expose responders and members of the public to a chemical hazard. Agents that have been commonly used as chemical weapons are also used in industrial processes. Most industrial incidents occur at an interface between transport, storage, processing, use, or disposal of hazardous chemicals, where these systems are more vulnerable to failure, error, or manipulation. The catastrophic effect of these agents has been utilized several times in the past for military purposes, and with the proliferation of these weapons, civilian populations are now faced with a significant threat.⁸⁷ Typically, chemical warfare agents are classified into the following categories⁸⁸:

Nerve agents (e.g., tabun, sarin, VX, and soman) are organophosphates that inhibit an enzyme, anticholinesterase, resulting in the overstimulation of both muscarinic and nicotinic receptors. Muscarinic symptoms include lacrimation, bronchorrhea, bronchospasm, miosis, salivation, rhinorrhea, vomiting, and diarrhea. Nicotinic receptor stimulation produces muscle fasciculations, flaccid paralysis, tachycardia, and hypertension. They can also produce central nervous system effects (i.e., seizures and coma). Death is usually from respiratory failure. They are extremely toxic and have a rapid effect. Sarin presents as a vapor threat, and the onset of symptoms is within seconds, with a peak effect in 5 minutes. Exposed victims who are asymptomatic after 1 hour are unlikely to be contaminated. VX represents a liquid exposure, with as little as a drop being lethal. The onset to action and death is less than 30 minutes. The cardinal rule in decontaminating patients is to remove and dispose of all articles of clothing. Therapy is directed toward the predominating symptoms. Atropine is used for the relief of muscarinic symptoms, pralidoxime chloride (2-PAM) is used for nicotinic effects, and benzodiazepines are used for the central nervous system manifestations. Most of the care is supportive and includes mechanical ventilation for respiratory failure and treatment of arrhythmias.⁸⁹

Vesicants (e.g., mustard gas and lewisite) cause wounds on the skin and mucosal surfaces. They are capable of causing second-degree burns of the skin within 4 to 8 hours. Airway injury and edema can be severe and are dose dependent. Of concern to the ICU physician is the need for correcting fluid losses and maintaining the airway.

Pulmonary agents (e.g., chlorine gas and phosgene gas) mainly affect the respiratory system, inducing inflammation of the airway and the lung and leading to ARDS and death. Treatment is mainly supportive.

Cyanides bind to cytochromes in the mitochondria and inhibit cellular oxygen use. In smaller doses they cause tachypnea, headache, dizziness, anxiety, and vomiting. With higher doses, seizures, respiratory arrest, and cardiac arrest occur. They are highly toxic, and sufficient levels can cause death within 5 minutes of inhalation. They are most commonly inhaled but can also be absorbed through the skin. Care is primarily supportive with supplemental oxygen. Specific therapy is with amyl nitrates, sodium nitrite, and sodium thiosulfate.

Unlike biological weapons, disease secondary to release of chemical agents is likely to be more obvious, rapid in onset, and homogeneous. However, they pose serious problems for emergency care providers because of their potential to cause a large number of casualties rapidly and their potential for secondary contamination. Any emergency medical or public health response to a major incident involving a chemical warfare agent will require coordination among local, state, and federal organizations. First responders should be aware of access to specialized local and federal response teams, basic triage, and demarcation of the contaminated area, use of handheld devices for agent detection and identification, use of PPE, and knowledge of appropriate medical treatment and antidotes.

Nuclear Weapons and Radiation Accidents

A variety of terrorist applications of radiation exist that could produce varying degrees of damage to public infrastructure and operations, human casualties and illnesses, and most important, fear.

Radiation devices include radionuclides from the healthcare industries (e.g., brachytherapy and radiation oncology sources). The consequences of the exposure are dose and source dependent.

Radionuclide dispersal devices are also known as *dirty bombs*. These have limited nuclear yield but can contaminate a wide area.

Improvised nuclear devices are made of uranium or plutonium constructed by a nongovernmental source and limited by the critical mass of nuclear material. They yield less destructive power than a conventional nuclear warhead but are still capable of contamination effects.

BOX 184-1

Additional Disaster Information Resources

GENERAL DISASTER RESOURCES AND WEBSITES

1. Centers for Disease Control and Prevention. Emergency preparedness and response. Available at: <https://emergency.cdc.gov/>
2. World Health Organization. Natural disaster profiles. Available at: <http://www.who.int/hac/techguidance/ems/natprofiles/en/index.html>
3. Federal Emergency Management Agency. Disaster management. Available at <http://www.fema.gov/> or <http://www.ready.gov>

RESOURCES FOR RADIATION ACCIDENTS

1. Centers for Disease Control and Prevention. Radiation emergencies. <https://emergency.cdc.gov/radiation/>

RESOURCES FOR BIOTERRORISM

1. Centers for Disease Control and Prevention website for bioterrorism. Available at <http://www.bt.cdc.gov/>

Tactical and strategic nuclear weapons are those that are created by governments and vary in yields from 0.5 kiloton to greater than 1 megaton. Their destructive capacities are enormous, and they contaminate a vast perimeter of space depending on the yield.

Approximately 50% of the energy released from a nuclear bomb is due to the blast and shock waves, giving a majority of the survivors blast-related injuries and creating extensive infrastructure damage. About 35% of the energy released is thermal radiation (in orders of tens of millions of degrees), giving rise to high-degree skin burns. Depending on the size of the device and the altitude of detonation, an electromagnetic pulse is generated with the explosion. This is capable of disrupting all electrical equipment within 20 km to several hundreds of kilometers.⁹⁰ The radiation-related energy released gives rise to external contamination, systemic irradiation, and internal contamination-related illness. Immediate ionizing radiation consists of gamma, beta, neutron, and a small amount of alpha radiation. Residual radiation occurs in the forms of induced radiation and fallout. Induced radiation occurs because of neutron-induced gamma activity of the immediate soil, silicon, manganese, aluminum, zinc, copper, and sodium. The half-lives of the various substances are a few minutes to 15 hours. *Fallout* is the fusion of various radionuclides generated in the fission reaction with condensation, producing a snowflake-like debris that falls to earth. Fallout is a potential form of delayed radiation exposure and can cause internal contamination.⁹⁰

Surviving hospitals and staff near an impact area should serve as a triage center and transport victims to unaffected centers elsewhere through the notification of the National Disaster Medical System Hospital Activation System.⁹¹ Other agencies that have to be notified include the Federal Bureau of Investigation, Nuclear Regulatory Commission, Department of Energy, and Department of Defense. Large-scale decontamination should be managed outside the hospital area as far as is possible, but plans for indoor decontamination should also be in place. A radiation emergency area (both in and out of the hospital) should be designated, with checkpoints nearing the cold zone. Management plans for the safe disposal of human waste and bodies should be in place so as not to increase the exposure risk. Triage of patients should be done on the basis of doing the greatest good for the greatest number. On the basis of predictive models, isolated irradiation, burns, and blast-related injuries would constitute 40% of injuries. Combined injuries would account for the rest. Attending to trauma victims should take precedence over all other medical issues, because a given patient is not likely to succumb immediately from radiation injury.

Patient care should begin with the use of universal precautions and PPE.⁹⁰ Dosimetry readings of the area may help during triage, defining those with systemic irradiation injury (possibly received >450 rad exposure). In determining patient viability, three parameters are of the most use: time of onset of vomiting, decrease in the absolute lymphocyte count over a 24-hour period, and presence of conventional trauma burns.⁹² Victims who are not viable or who have lethal doses of radiation exposure are likely to benefit from supportive/palliative care.

Hazardous Materials Disasters

HazMat are substances potentially toxic to the environment or living organisms. Full-scale disasters from HazMat are relatively rare, but isolated incidents are among the most common in the community and are not limited to chemicals but can include various biological and radiologic materials. Knowledge of the types of industries present in the community would be helpful in developing a potential plan to deal with likely HazMat situations. Management of a HazMat situation requires attention to several key points: identification of the offending agent, appropriate PPE of responders, prompt containment of the agent, demarcating areas for decontamination (including removal and disposal of clothes and waste from the decontamination), and resuscitation of victims. Injuries secondary to release of HazMat can present as chemical burns, inhalational injury, and a variety of systemic injuries.^{93,94}

Armed Conflict

Armed conflict continues to be the most preventable and most destructive of man-made disasters in terms of human physical and emotional suffering, economic loss, and environmental destruction. Specific healthcare issues during these conflicts that are relevant to the intensivist include trauma from blast injuries, projectiles, and crush-related injuries; communicable diseases due to the breakdown of public infrastructure and mass displacement of populations; and burns and radiation-related injury.

MEDICAL DISASTER SYNDROMES

Disaster situations present with many unique medical syndromes that require specific therapy. Treatment of these entities is often difficult because of a large volume of patients, lack of qualified medical personnel on-site, and inadequate supplies and equipment. It is important to emphasize that initial recognition of the medical syndromes and appropriate intervention are critical to minimizing morbidity and mortality. Appropriate triage, knowledge of field management of each syndrome, flexibility to adapt to each situation, ability to ignore natural differences among different specialties, and recognition of limits of medical care that can be provided in overwhelming situations are key to a good disaster medical response. In the following paragraphs, we discuss commonly encountered medical syndromes in a disaster situation.

Blast Injuries

Bombs contain an array of compounds such as nitroglycerin, trinitrotoluene, and others that are encased in a metal or plastic case. Decomposition of the solid or liquid compound into gas leads to massive dissipation of energy and pressure that creates a blast wave (shock wave). This destructive effect can be increased by the presence of nuts, nails, and bolts in the casing. Water transmits blast waves more efficiently than air, with the greatest impact being on structures that are the deepest.⁹⁵ There are four types of blast injuries:

1. *Primary blast injury* is caused solely by the blast wave and almost always affects air-filled structures such as the lung, ear, and gastrointestinal tract. The presence of tympanic membrane rupture may indicate exposure to a high-pressure wave and is thought to correlate with more severe organ injury.
2. *Secondary blast injury* is caused by the rapid acceleration of small fragments caused by the blast injury.
3. *Tertiary blast injury* is a feature of high-energy explosions. They result from the collision of the flying victim against a hard surface.
4. *Miscellaneous blast-related injuries* encompass all other injuries caused by explosions. They include flash burns, inhalation injuries, and blunt trauma.

The most common injuries associated with fatality in blast incidents include subarachnoid hemorrhage (66%), fracture of the skull (51%), lung contusion (47%), tympanic membrane rupture (45%), and liver laceration (34%). Unfortunately, the extent of the blast injury cannot be assessed during the course of rapid triage examinations. In the absence of overt trauma, a focused physical examination should include examination for ruptured tympanic membrane, hypopharyngeal contusions, hemoptysis, and auscultation for wheezing. The presence of a ruptured tympanic membrane is almost always an indicator that the patient has been exposed to a blast wave powerful enough to cause serious damage. The thorax is frequently involved in a blast injury, manifesting with wheezing, hemoptysis, pneumothorax, hemothorax, and air embolism. Patients may have myocardial contusion as well. The presentation of serious pulmonary injury may be delayed. Pulmonary barotrauma is the most common fatal primary blast injury. Patients with nonpenetrating lung injury will likely have hypoxia requiring support ranging from oxygen therapy to mechanical ventilation. This may result from pulmonary contusion, systemic air embolism, and disseminated intravascular coagulation. Acute gas

embolism, a form of pulmonary barotrauma, is also associated with blast injuries. Air emboli most commonly occlude blood vessels in the brain or spinal cord, resulting in neurologic symptoms that must be differentiated from the direct effects of trauma. Patients thought to have gas embolism require decompression treatment. Administering 100% oxygen by tight-fitting face mask and left lateral recumbent position may help. Definitive treatment is with the use of hyperbaric oxygen. Patients with blast injury of the lung are likely to present with abdominal injuries that are usually more delayed. These include delayed bowel perforation and liver lacerations. The former may warrant exploratory laparotomy.⁹⁶⁻⁹⁹

Blast victims receiving general anesthesia have an increased mortality rate; other forms of local and spinal anesthesia are preferred, and general anesthesia should be deferred if possible for 24 to 48 hours. Intensivists should be aware of the increased need for resuscitation equipment, ventilators, and movement in and out of the operating room during such situations.

All patients with significant burns, suspected air embolism, radiation or white phosphorus contamination, abdominal signs of contusion/hematoma, or clinical evidence of pulmonary contusion or pneumothorax should be admitted to the hospital. Patients with tympanic membrane rupture and suspected pneumothorax should get some form of chest imaging, and a significant observation period may be warranted. Other investigations must be judiciously ordered, keeping in mind the limited availability of resources in a mass-casualty incident. Screening urinalysis for presence of hematuria, tests for CO poisoning (explosion in a closed space or associated with fire) and cyanide toxicity (due to combustion of plastics), and assessment of acid-base status may be indicated. Using abdominal computed tomography to rule out intestinal hematomas should be dictated by clinical signs and symptoms. Pregnant patients with blast injuries warrant special consideration, and appropriate consultation is necessary to rule out blast injury to the fetus.⁹⁷ Supplemental oxygen, maintaining spontaneous respiration, and low PEEP (if mechanical ventilation is required) are guiding principles. Routine corticosteroids and antibiotics are not warranted.

Exposure to white phosphorus explosives (e.g., in hand grenades) deserves special mention. Using a Wood's light in a darkened resuscitation suite or operating room may help identify white phosphorus light particles in the wound. White phosphorus injury can cause lung injury through irritation, as well as severe hypokalemia and hyperphosphatemia with cardiac arrhythmias and death. External burns should be lavaged with 1% copper sulfate solution. This forms a blue-black cupric phosphide coating and prevents combustion so that the particles can safely be removed.¹⁰⁰

Crush Injury Syndrome

Crush injury syndrome refers to systemic manifestations of extensive muscle damage caused by entrapment of victims under collapsed buildings or debris. Reported incidence depends on the type of disaster, ranging from 2% to 40%. Metabolic alterations from the release of muscle constituents into the circulation include myoglobinemia leading to acute renal failure, hyperkalemia, hyperphosphatemia, and disseminated intravascular coagulation. Muscle damage that occurs is due to not only direct crush injury but also vascular injury and insufficiency leading to altered compartment pressures and reperfusion injury. Inelastic fascial sheaths encase skeletal muscles in the forearm and lower leg and are particularly vulnerable to dramatic increases in compartment pressures, resulting in compartment syndrome. An intracompartmental pressure greater than 40 mm Hg lasting longer than 8 hours defines this syndrome. Pressures as high as 240 mm Hg can be seen with crush injuries. Compartment syndromes are seen with limb fractures, use of military antishock trousers, pneumatic splints, vascular injuries, and crush injuries. The affected limb may present with severe pain associated with passive stretch or extension, flaccid paralysis, and sensory loss. Capillary refill and peripheral pulses are usually present unless the compartmental pressure equals the diastolic pressure. Diagnosis requires a high degree of clinical suspicion

and entails prompt bedside measurement of compartmental pressures. A simple and easy method that can be performed in the hospital or field hospital is using an 18-gauge needle attached to a mercury manometer. In an ICU, pressure transducers used to measure central venous pressures can be attached to the 18-gauge needle to obtain the same information.¹⁰¹

Resuscitation of patients with crush injury (any victim crushed or immobilized for more than 4 hours) should begin in the field. After adequate intravenous access is achieved, isotonic fluid replacement with normal saline (rate of 1-1.5 L/h) should begin even before extrication of the crushed limb. If fluid therapy is delayed, the incidence of renal failure increases to 50%; delays of 12 hours are associated with a 100% incidence. Occurrence of renal failure is associated with a mortality rate of 20% to 40%. Urinary alkalization with sodium bicarbonate and mannitol or acetazolamide administration is used to maintain urine pH above 7.5. Although this is widely used, there are no prospective randomized controlled trials to support it. Dialysis may be indicated if aggressive fluid resuscitation fails, and this may create a huge demand for dialysis machines in disaster situations. Peritoneal dialysis if the abdomen is intact and continuous arteriovenous hemofiltration may be other useful options. However, the latter option is complicated by hemorrhage problems related to the use of heparin and immobilization. Life-threatening infections are common and may be increased in the presence of a fasciotomy. In unsalvageable limbs, it may be advisable to perform on-field amputations to avoid the systemic effects of a crush injury syndrome. For this purpose, ketamine is the anesthetic and analgesic of choice because of its safety profile in the field.¹⁰¹

Particulate Health Problems

Many disasters result in the release of copious particulate matter, causing a wide spectrum of respiratory illnesses including cough, wheezing, smoke inhalation injury, reactive airways disease, and ARDS. Volcanic eruptions with associated pyroclastic flows and ash fall are some of the most devastating producers of particulate matter. Mortality arises from suffocation by ash in the upper airways, ARDS, and inhalation burns. The massive building collapse and fires associated with the 2001 World Trade Center terrorist attack caused significant pulmonary complaints among rescue personnel.¹⁰²

Smoke inhalation injury resulting from exposure to noxious products of combustion in fires may account for as many as 75% of fire-related deaths in the United States. The three primary mechanisms that lead to injury in smoke inhalation are thermal damage, asphyxiation, and pulmonary irritation. Combustion uses oxygen in the airways and causes a decrease in fraction of inspired oxygen, leading to hypoxemia. Increased CO levels decrease the oxygen-carrying capacity of the blood and cause myocardial depression. Combustion of plastics, polyurethane, wool, silk, nylon, rubber, and paper products can lead to the production of cyanide gas, resulting in anaerobic metabolism and decreased oxygen consumption. Rarely, we may also find methemoglobinemia, which reduces oxygen-carrying capacity.¹⁰³ Mortality rate with smoke inhalation alone is about 10% but increases to about 77% in the presence of major burns or respiratory failure. Early deaths are mostly caused by airway compromise or metabolic poisoning. Laboratory workup should include co-oximetry; CO, methemoglobin, and cyanide levels (if there is discordance in measured saturation and pulse oximetry readings); blood lactate levels (a level >10 mmol/L that is refractory to restoration of adequate ventilation, oxygenation, and perfusion is considered a surrogate marker of cyanide toxicity) on blood gases; and a calculated alveolar-arterial pressure gradient. Initial blood gas measurements and chest radiograph may be normal. Carboxyhemoglobin level obtained in the emergency department does not correlate with tissue hypoxia or long-term neurologic sequelae; ideally, a carboxyhemoglobin level at the scene would be most valuable.

Serial bronchoscopy is indicated in the first 18 to 24 hours to assess airway edema and sloughing. Early bronchoscopy can be of diagnostic and therapeutic value, particularly when lobar atelectasis is

present. High-flow humidified oxygen is critical to reverse or prevent hypoxemia. About 50% of patients with an inhalation injury require tracheal intubation, and this increases in patients who have burn injuries. The need for intubation is determined by the need to maintain airway patency and pulmonary toilet and to provide positive-pressure ventilation. Positive-pressure ventilation with PEEP increases short-term survival and is associated with decreased tracheobronchial cast formation. Cyanide toxicity (levels >0.1 mg/L) should be promptly treated using a cyanide antidote kit. Recommendations for the use of hyperbaric oxygen in the setting of CO poisoning include CO levels greater than 25% to 30%, neurologic compromise, metabolic acidosis, or electrocardiographic evidence of myocardial ischemia, infarction, or dysrhythmias. Hyperbaric oxygen has been used in cyanide toxicity but has not been proven effective. The role of corticosteroids is controversial, and they can be detrimental if given in the presence of cutaneous burns. Empirically administered antibiotics are also in dispute. Common pitfalls in the initial management of smoke inhalation are using initial PaO_2 to predict adequacy of oxygenation, placing small-diameter nasotracheal tubes, intubating without applying PEEP, and restricting fluids for concomitant inhalation and burn injury.^{103,104} General measures that could be employed in a field setting include simple airway protection by clearing any particulate matter in the airway, supplemental oxygen, and nebulizer treatment if available. Patients with preexisting asthma and emphysema should be observed for exacerbations.

Acute Radiation Syndrome

Ionizing radiation can be either charged or uncharged particles (photons). Beta particles are capable of penetrating a few centimeters of tissue. Gamma rays and x-rays are capable of penetrating through tissue and concrete. Gamma, x-ray, and beta radiations are considered low linear energy transfer radiation. Alpha particles have no penetrating power past the keratinized layer of skin, but they take on clinical significance if they are internalized by ingestion or inhalation. Neutron emission (e.g., from nuclear reactors, nuclear devices, and industrial moisture detectors) is a highly potent radiation that penetrates deep and creates denser ionization trails. Alpha and neutron emissions are considered high linear energy transfer radiation and have more biological effects than low linear energy transfer radiation by a factor of up to 20. When the process of ionization occurs in living tissue, it denatures cellular DNA. This leads to impaired mitosis and subsequent organ failure. Large doses of radiation are considered to cause more biological destruction than fractionated doses. Systemic radiation illness and lethality from it can result from as little as 450 rad. Precise measurements of the amount of radiation after a nuclear accident will be delayed. Hospital gamma cameras are an invaluable resource for helping determine the exposure in an individual. Higher systemic doses are suggested by shorter onset of prodromal symptoms such as nausea, vomiting, and diarrhea. Serial absolute lymphocyte counts will screen those patients who have psychogenic vomiting. Acute radiation syndrome has four distinct phases.^{79,90,92}

1. *Prodromal phase*, characterized by nausea, vomiting, and diarrhea. Other symptoms of eye burning, abdominal pain, and fever can also occur with higher doses. This phase may last from 0 to 2 days, depending on the dose received.
2. *Latent phase*, in which the patient will have a period of relative well-being because of subsidence of the inflammation. However, ultimately the damaged cells will not be able to repair or regenerate. This may last for 2 to 3 weeks.
3. *Manifest phase*, in which the cellular deficits of various organs affected will become apparent. Mature cells of the skin slough off, revealing an atrophic dermis. Endothelial cells are not replaced, leading to vascular permeability. Mucosal linings slough, causing mucositis and diarrhea. Hematopoietic progenitor cells fail to produce cell lines, leading to anemia, thrombocytopenia, and neutropenia. Fibrosis of organ beds develops. This may last for up to 3 weeks.

4. *Recovery phase/death*, in which some stem cells may proliferate and lead to slow recovery, or there will be symptoms of progressive organ failure leading to death.

For radiation syndrome to occur, radiation must be of the penetrating type in a sufficiently large dose (>0.7 Gy), must be external, and must occur within a short time. The disease complex has three syndromes: bone marrow, gastrointestinal, and cardiovascular/central nervous system. Serial absolute lymphocyte counts should be measured immediately on suspicion of exposure (every 3 hours), because lymphocytes are among the most radiosensitive cells and reach nadir within 2 days, platelets reach nadir in 15 to 30 days, and neutrophils at about 30 days. Patients are immunocompromised and susceptible to infections, including septic shock. Gastrointestinal syndrome leads to mucosal sloughing, decreased nutrient absorption, and translocation of bacteria and endotoxin. Veno-occlusive disease may also develop if the dose is large enough. Cardiovascular and central nervous system disease develops with doses greater than 5000 rad, and death can occur in as little as 3 days from myocarditis, capillary leak, pulmonary edema, and brain edema. Pneumonitis and subsequent fibrosis can lead to respiratory failure and the need for ventilator support. Treatment of Acute Radiation Syndrome (ARS) is supportive. If internal contamination is thought to have occurred, enhancement of excretion and specific antidote therapy are warranted. For inhalational contamination, bronchoalveolar lavage may be necessary, and for ingestion, gastric lavage and purgative management are warranted. Plutonium and transuranic elements can be treated with chelating agents such as calcium or zinc diethylenetriamine pentaacetic acid. Radiocesium can be treated with Prussian blue, which helps enhance excretion in feces. Radioiodine exposure can be treated with potassium iodide. Uranium excretion can be enhanced by the alkalization of urine and with potassium supplementation.

Psychological Trauma

The psychological component in a traumatic event is often overlooked, with the major focus usually being on physical health issues. Studies evaluating the emotional impact from disasters indicate that a majority of victims, first responders, and mortuary volunteers will suffer some form of psychological trauma. Intensivists should be aware that behavioral changes may be due not only to the catastrophic insult but also organic causes such as head injury, inability to take predisaster psychiatric medications, and toxin or chemical exposure. Groups at risk, such as children, adolescents, and victims who have been exposed to traumatic stressors of bereavement, witnessing death, and situations evoking guilt, fear, or anger, should receive prompt psychiatric and posttraumatic counseling. Interventions, such as debriefing, eye movement desensitization and reprocessing, and critical incident stress management, may help minimize emotional suffering and morbidity.¹⁰⁵

Other Syndromes

Burns, blunt trauma, intraabdominal injury, head injuries, penetrating trauma, and hypothermia are some of the other disaster syndromes encountered in the field. Specific discussion of these entities is beyond the scope of this chapter; please see other reviews.⁵

DISASTER PREPAREDNESS

For intensivists to be able to deal with a disaster, it is paramount that they be a part of the disaster-planning effort. Disaster planning includes development of action programs to minimize loss of life and damage during a disaster, provide the greatest good for the greatest number of people, train healthcare personnel and civilians, coordinate response efforts, maintain adequate supplies of equipment and personnel, and rehabilitate the community after the disaster. Knowledge of potential disasters to which the community is prone should be an integral part of the planning process. Having an understanding of what the resources and capabilities are of the community, hospital, and its ICU on a

continual basis and provision for modular expandability are vital for any successful emergency response. The mere existence of a disaster plan does not ensure that the hospital system is actually prepared.¹⁰⁶ The following paragraphs elucidate some of the common issues and misconceptions related to disasters and common principles useful in designing a disaster plan. Subsequently, a pragmatic view is presented of the role of the ICU physician in a disaster situation.

Common Issues and Misconceptions in Disaster Planning

Typically, the hospital nearest to the disaster site will receive the bulk of the casualties. It is thus important to conduct a careful survey of a disaster plan's jurisdiction to identify potential sites (i.e., industries, nuclear reactors, and highways) and likely types of hazardous events that could occur in the area. Hospitals in the nearby area receive few disaster victims, and an average have at least 20% of their beds vacant. Disaster plans would thus need to include transfer agreements between hospitals and nearby ICUs to meet bed shortages by activating the National Disaster Medical System Hospital Activation System.^{91,106,107}

Very few casualties actually require hospital admission. A study of 29 mass-casualty incidents found that less than 10% of casualties required overnight admission under usual criteria (even though more were admitted because they were involved in the disaster rather than because of severity of their condition). Large numbers of casualties with minor conditions will appear at the nearest hospitals, often on foot or in private vehicles, police cars, buses, taxis, and other nonambulance forms of transport. Field triage stations are often bypassed, and this in turn causes enormous strain on the emergency department services.¹⁰⁸

Most of the logistical problems faced in disaster situations are not caused by shortages of medical resources but rather from failure to coordinate their distribution.¹⁰⁶ Inexperienced volunteers may not be familiar with the triage system or principles of personal safety, and massive numbers of volunteers can present serious administrative challenges. This results in disorganization and inefficiency.⁹³ Technical hazard sheets designed by the WHO for most disasters also suggest that medical personnel, blood donors, and blood products should not be sent empirically to a disaster site.¹⁰⁹

Principles in Disaster Planning

Existing Preparedness Requirements

In developing disaster plans, hospitals must take into account the broad national and local requirements imposed by various governmental agencies. Common agencies involved in this process include the Centers for Medicare and Medicaid Services (CMS) as well as The Joint Commission (TJC). The CMS's conditions for emergency preparedness and services establish minimum requirements for hospitals that participate in Medicare or Medicaid programs. Similarly, TJC standards apply to a full range of hospitals and are focused on four areas: (1) emergency preparedness management plan (Standard EC 4.1), (2) security management plan (Standard EC 2.1), (3) HazMat and waste management plan (Standard EC 3.1), and (4) emergency preparedness drills (Standard EC 4.2). Readers are referred to TJC website for the most up-to-date standards.¹¹⁰

Hazard Vulnerability Analysis

This is the first step of any disaster plan, with the main aim of identifying potential hazardous events and situations that can occur in or around the healthcare facility. This process of evaluating and predicting hazard risk is not restricted to geographic events but extends to institution-specific variables such as utility failures, local threats of gang-related activity, and presence of a local high-risk industry such as a chemical or nuclear power plant. TJC requires a formal documented HVA that is integrated with the emergency management plan, setting priorities among potential emergencies and also defining the hospital's role in the local community-wide emergency plan.¹¹⁰

Incident Command System

The Incident Command System (ICS) is designed to provide the basic architecture of an emergency management response. Major barriers to medical response arise from the lack of coordination among various public and healthcare agencies and from the lack of operational integration of various medical specialties. The ICS incorporates all these agencies and ensures a cooperative and effective response to a crisis. The concept of ICS resulted from the analysis of the devastating wildfires in Southern California in 1970 and has since been modified and successfully adapted to different disaster situations related to healthcare facilities.⁹⁶⁻⁹⁸ The ICS specifies a common terminology and a command structure with five functional sections:

1. **Command:** Unified command staff responsible for overall management of the incident
2. **Operations:** Performs the actual response work under the directives of the command center
3. **Planning:** Gathers relevant information and develops response strategies as the situation progresses
4. **Logistics:** Responsible for facility-wide supplies, equipment, personnel, and services. It also provides for basic services to personnel of the command center
5. **Finance:** Authorizes expenditures, maintains records, and provides documentation of the incident

There is a designated person who will have the authority to declare an emergency. All personnel involved in the command system should be aware of the exact predetermined location of the command center. The plan should also provide protocols that will guide notification and the sequence of mobilization of these personnel in a disaster situation. The command system must also have independent telephone lines to ensure uninterrupted communication with the external world in a disaster situation. Once initiated, the ICS has a built-in chain of command that would be responsible for triage of patients and allocation of personnel and resources.¹¹¹

Triage

Appropriate triage is a vital function during an emergency management response. This is a dynamic process that is not necessarily confined to the disaster site or the emergency department but is rather carried through several levels of the medical response pathway of a disaster response. Modern triage is based on the likelihood of survival in relation to the resources available at the time of the decision.¹¹² Problems often encountered in the triage process include the following¹¹³:

1. Lack of medical direction at the scene. Making triage decisions in a chaotic situation requires skill and experience and can often initially seem confusing and unmanageable. Lessons from the first Persian Gulf War showed that on-field triage was correct only 70% of the time. It is necessary to entrust experienced physicians with this job and to have simple and clear guidelines for the decision-making process. In addition to emergency physicians and trauma surgeons, critical care physicians bring with them the expertise to deal with complex and time-bound situations and are thus well suited to head a triage team.
2. Lack of interorganizational planning. Dynamic management of the triage process requires interorganizational coordination and flow of information. Up-to-date assessment of medical resources and personnel should be communicated from the command center to the triage site, and similar communication should occur from the scene to the command center. This will allow for rational and appropriate triage based on the availability of resources.
3. Transport of victims from the site by nonambulance vehicles to nearby hospitals.
4. There is no universally accepted form of triage. A recommended system uses a color-coded system to sort out disaster victims.¹¹²

Major Utilities, Supplies, and Equipment

Disaster plans and drills should factor in the possibility of internal and external power outages and related disruptions (ventilator and

monitoring device failures, communication failures including breakdown of cellular phones, and elevator failures) and water and gas supply shortages. The plan should have an up-to-date inventory of all supplies and capabilities of the facility. The numbers of ventilators in use and their absolute capacity, inventory of various ICU supplies, and vendor lists should be readily available if there is sudden demand for supplies. The disaster plan should allow for at least 2 days' worth of supplies. Regular drills will help identify various bottlenecks and provide knowledge of the absolute capacity of devices, equipment, and services in a disaster situation. Plans to evacuate critically ill patients to nearby hospitals in the event of failure of backup systems should be addressed. Since the anthrax attacks and the resulting strain on antibiotic supplies in 2001, more attention has been paid to the national repository of lifesaving pharmaceuticals and medical supplies called the *National Pharmaceutical Stockpile Program*. This response is a component of the CDC's larger Bioterrorism Preparedness and Response Initiative and is composed of a stockpile of pharmaceuticals, vaccines, medical supplies, and equipment to augment local and state resources in a disaster situation. After a federal decision to deploy, a "push package" will arrive by ground or air in 12 hours or less at any location in the United States. A CDC team accompanying the push package will then define shipments in the second phase.¹¹⁴

Security and Casualty Reception

Security is a major concern during natural or man-made disasters. Desire to seek immediate medical evaluation, panic, and curiosity are factors that place the healthcare facility and its personnel under enormous strain. Internal and external traffic control, protection of personnel involved in the response effort, and strict enforcement of staging and triage areas are key security-related issues. Law enforcement plays a more critical role during terrorist attacks or bioterrorism, and failure to maintain order will lead to rapid overwhelming of the facility's resources and a disorganized medical response. Because most victims will arrive at the hospital by foot or by personal vehicles, provision must be made for a predetermined staging area with adequate mass decontamination facilities and respiratory protective equipment.^{110,115}

ISSUES UNIQUE TO THE INTENSIVE CARE UNIT

The responsibility of caring for the most serious salvageable casualties in natural and man-made disasters will ultimately involve the critical care physician. As opposed to the overwhelming shortage of resources, lack of coordination among various agencies and specialties has been often cited as the main contributing factor to an ineffective emergency medical response. This response therefore requires the cooperation of not just physicians but also among prehospital medical personnel, nurses, and ancillary services such as radiology and laboratory services.⁵³

Possible roles for the intensivist as part of a disaster management planning team include the following:

1. Clear role definition and understanding of the overall organization of the emergency response plan
2. Knowledge of the usual limit, surge capacity, and absolute limit of ICU resources
3. Construction of appropriate staffing models

CRITICAL CARE IN UNCONVENTIONAL SITUATIONS

Mobile ICU Teams

There have been numerous examples in the medical literature describing extended critical care through mobile ICU teams. Using mobile

ICU teams has not been restricted to disaster settings but has also been used throughout the world during peacetime. Various factors that have to be considered in forming ICU teams are discussed next.

Personnel

On the basis of the anticipated needs of the disaster, appropriate specialists and ancillary personnel are chosen. Given the complexity and inherent unpredictability of staffing for disaster management, a flexible and adaptable approach must be taken to staffing such events.¹¹⁶

Training

Adequate predeparture training is essential for a coordinated and effective response. In addition, interaction and on-site training ensure effective functioning of a foreign medical unit and allow for the smooth transition of care to local physicians when the foreign team departs.⁹⁶

Casualty Assessment

Studies from the past and also the experience of the Israeli defense forces in providing care to earthquake victims in Turkey showed that the effectiveness of mobile ICU teams was limited by time. It may take 3 days to mobilize such an effort, and crucial time is lost before delivery of care. Efforts must thus be made to epidemiologically assess the efficacy of such teams. They should include review of the overall effort and adequacy of the ICU teams, outcome of victims, operational costs, and analysis of the structure and process of the ICU in the field.¹¹⁶

CRITICAL CARE TRANSPORT

Common principles involved in the safe transport of patients include the following¹¹⁶:

1. Rapid assessment of the severity of injuries, recognition of the need for transport, and anticipation of problems during transport
2. Safe movement of patients in and out of vehicles, continuous monitoring of vital signs, and recognition and treatment of problems encountered during transport
3. Documentation of the events during transport and provision of a detailed report to the admitting personnel

Types of Transport

Ground Transport

Ground ambulances have the advantage of rapid deployment, high mobility, and lower cost. However, patients and equipment are subject to significant deceleration and vibration forces. Equipment may vary depending on the size of the ambulance and usually includes blood pressure and electrocardiograph monitors, pulse oximeters, ventilators, and in some cases, modern support devices such as intraaortic balloon pumps.

Air Transport

It is beyond the scope of this chapter to provide a full detailed discussion of fixed-wing or rotary aeromedical transport, but it may be necessary during certain disasters to extricate victims via air.¹¹⁶

CONCLUSION

Understanding the characteristics of different disasters, developing an interdisciplinary approach to hazard mitigation, and knowledge of related clinical syndromes are key to an effective medical disaster response. To ensure an integrated and effective response to future disasters, it is necessary for critical care physicians to understand the fundamental principles in disaster medicine and participate in the disaster-planning process.

KEY POINTS

1. Disaster medicine is a unique specialty that has evolved over the past few years. It shares a common ideal with public health: "greatest good for the greatest number." Critical care medicine forms an indispensable part of this science because intensive care physicians not only care for the sickest of the salvageable patients in any hospital but also bring with them their clinical expertise in triage, resuscitation, and help in providing care outside the domains of the unit through mobile ICU teams.
2. Clear, common, and concise definitions are important in effective communication and evoking appropriate responses to disaster situations. The concept of functional impact of a disaster on the healthcare system is paramount while classifying disasters.
3. It is important to understand the common effects of different natural and man-made disasters to predict their impact on the healthcare system. Even though man-made disasters such as terrorist attacks have gained attention, the numbers of geophysical disasters such as earthquakes, floods, and hurricanes have remained fairly constant and place the greatest burden on the healthcare system.
4. Disaster situations produce many unique medical syndromes that require specific therapy. Knowledge and immediate recognition of different medical syndromes with appropriate interventions is critical to minimizing morbidity and mortality.
5. Disaster planning includes developing action programs to minimize loss of life and damage during a disaster, training healthcare personnel and civilians, coordinating response efforts, maintaining adequate supplies of equipment and personnel, and rehabilitating the community after the disaster. Knowledge of potential man-made and natural disasters to which the community is prone should be an integral part of the planning process. Common principles involved in the creation of an emergency response plan should be followed and applied from an ICU perspective.
6. With their natural role of caring for critically ill patients, intensivists bring with them unique abilities that can be applied to a disaster situation: a multidisciplinary approach to patient care, management skills, procedural expertise, and flexible attitudes.
7. Intensivists can also provide care outside the domains of the ICU through mobile ICU teams and transport of critically ill patients. Various factors have to be considered in forming such teams and in the safe transport of patients.

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Worldwide, there is a need for novel strategies to alleviate the lack of specialized medical care, including critical care medicine. Societal changes in demographics, epidemiology, and culture, as well as significant technological advances, have positioned telemedicine as a useful tool to narrow the gap between available and needed medical care. Thus far, it has been proved to be a disruptive technology, potentially altering traditional paradigms in the critical care environment, particularly in medical education, team organization, medical licensing, quality improvement, disaster response, and research. A recent report estimated that 10% of adult intensive care unit (ICU) beds are covered by some form of telemedicine service.¹ Its relative novelty has resulted in a constant state of flux for available technology, legislation, potential interventions that can be leveraged, and consequently, an ideal model of tele-ICU care. Here we present our perspective for the current state-of-the-art and practical considerations on these matters (Fig. 185-1).

DEFINITION

Telemedicine can be described as the technology-assisted delivery of medical health services from a distance. Potentially related benefits may include improved access and enhanced efficacy, quality, and efficiency in the delivery of healthcare services as well as an equality in distributing scarce resources and the reduction of costs.² Considerable controversy has resulted from the fixation of the health community in the ever-evolving technological aspects of telemedicine, rather than its potential as a tool to leverage otherwise traditional quality improvement interventions.

Although we can track the use of telecommunications with this purpose to the first half of the 20th century in Australia³ and decades later with NASA⁴ and the space race,⁴ it was not until the past 2 decades when critical technological developments allowed for an explosive increase in its use as an alternative for overcrowded traditional models of care.

Traditionally, telemedicine modalities can be classified into store-and-forward, real-time, or remote monitoring. In store-and-forward, medical information is sent electronically to a remote physician for assessment offline, without direct simultaneous interaction between a remote medical team and a telemedicine physician. In the real-time mode, a direct interaction exists between a telemedicine physician (or a physician extender) and a remote patient, physician, or medical team. Finally, remote monitoring implies the monitoring of a patient from a distance using different technologies depending on the physiologic system to be followed.⁵

TELEMEDICINE IN INTENSIVE CARE

The implementation of a new tele-ICU program should focus on each one of the following aspects:

1. Telemedicine-related laws and regulations at state and national levels
2. Technological platform
3. Staffing
4. Model of care

1. Telemedicine-Related Laws and Regulations

There are basic elements that any telemedicine program should consider to comply with national and state laws and technical regulations pertaining to the particularities of the telemedicine interaction (Box 185-1). The American Telemedicine Association has published core guidelines for baseline technical requirements and telemedicine operations, as well as guidelines for tele-ICU operations in particular.⁵ Policies that foster telemedicine use are being promoted in most states (state parity laws) and should be consulted to adjust the tele-ICU program model accordingly, given they will affect reimbursement and credentialing.⁶

In broad terms, signed patient consent must be obtained and patient confidentiality should be preserved at all times regardless of the model of care used in any tele-ICU program. A practitioner licensed in the state where the medical care is being delivered is mandatory during the teleconsultation, and by-proxy credentialing issues should be addressed between connecting hospitals. Moreover, documentation of the telemedicine consult should be in the patient's medical record.

Finally, the unique setting of virtual telepresence results in distinct communication needs that are different from the regular on-site, traditional team interactions, and "telemedicine etiquette" (Box 185-2). They should be kept in mind during telemedicine consultations to be efficient in the art of "the systematic finding and delivery of bad news to the remote team."

2. Technological Platform

A robust information technology department support is needed to ensure seamless communication between the tele-ICU team and remote ICUs.

The cost-efficiency of a tele-ICU technological platform reached a critical point a few years ago, when data transmission migrated from costly dedicated optical cable networks to wireless encrypted communication via Internet.⁷

Depending on the scope of the particular tele-ICU program, minimal hardware could include a simple telemedicine cart on both ends, escalating to fully autonomous robotic telepresence with access to remote electronic medical records (EMRs), medical imaging, and monitoring systems supplemented with automated rapid response algorithms^{8,9} (Fig. 185-2).

3. Staffing

Given the significant disparity between available and needed qualified specialists to meet current safety standards, the Leapfrog group has endorsed telemedicine as an appropriate alternative to reach these goals.¹⁰ It would be wise then to redesign the workflow of the existent and future ICU staffing considering the telemedicine time. In those tele-ICU programs with staff dedicated mainly to telemedicine, a minimum amount of time of direct clinical practice must be ensured to maintain proficiency.

Reimbursement for telemedicine care remains a significant challenge. In a national survey, 55% of respondents reported not billing for



FIGURE 185-1 ■ Telemedicine suite. From left to right panels: Panoramic room cameras, real-time monitoring, real-time connection with telemedicine cart, additional stations for access to remote EMR.

BOX 185-1

Telemedicine-Related Laws and Regulations

National telemedicine laws
State parity laws (U.S.)
Patient confidentiality/consent (Health Insurance Portability and Accountability Act)
By-proxy credentialing

BOX 185-2

Telemedicine Etiquette

- Identify yourself and the remote team
- Ensure patient confidentiality
- Respect the remote team's work
 - Listen to the remote team first
 - Connect in time
 - Keep teleconsultations as brief as possible
- Comply with telemedicine laws and regulations
- Objectively evaluate patient
- Advice based on the best available evidence

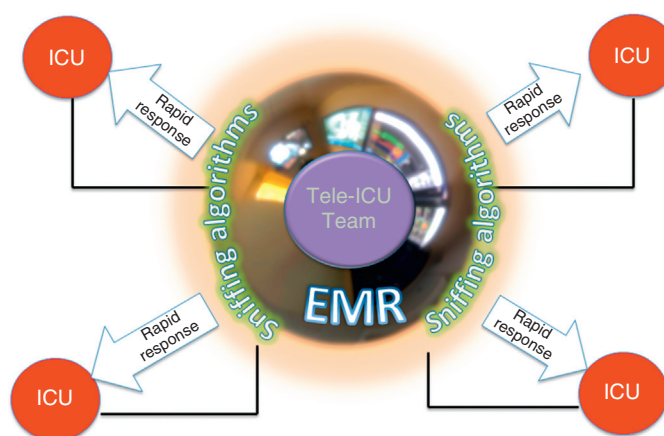


FIGURE 185-2 ■ Diagram of a state-of-the-art tele-ICU. An electronic database with physiologic data and other medical information is updated in real time in the EMR. A tele-ICU team works on surveillance of patient information assisted by remote monitoring, EMR, and sniffer algorithms. Once a dangerous trend is detected, the patient is reviewed with the remote team and a response is elicited.

telemedicine services.¹¹ A number of tele-ICU ventures have jump-started their programs with the assistance of grants. A common arrangement is also a contractual arrangement between connecting hospitals.

4. Model of Care

Tele-ICU in Adult Patients

Different models of care have been adapted for telemedicine in the critical care environment.¹² These models can range from physician-to-physician consultation with limited tele-ICU team involvement to fully autonomous telemedicine team intervention without the need of the presence of a physician in the remote place. Consequently, reports in the intensive care settings have shown conflicting findings related to any effect from a telemedicine system in patient outcomes.¹³

The reason for these discrepancies is not completely understood, and the quality of reported data has been suboptimal. In a systematic literature review and meta-analysis, Young et al. investigated more than 721 critical care and telemedicine articles as well as 2683 critical care or telemedicine abstracts, including 13 studies with more than 41,000 patients in their final analysis. The tele-ICU coverage was associated with a significant reduction in ICU mortality and length of ICU stay but not with in-hospital mortality or length of hospital stay.

There was a significant degree of heterogeneity in the studies included in their analysis and a striking degree of variation in how tele-ICU coverage was defined, the hospitals where it was evaluated, and the impact that tele-ICU coverage had on patient outcomes.¹⁴

Kahn has proposed a conceptual model to describe potential factors influencing the program success (Fig. 185-3). In this model, the effectiveness of a tele-ICU program was influenced by characteristics of both target hospitals and ICUs, as well as the telemedicine unit itself. When optimal, these characteristics may facilitate timely interventions and guideline adherence, leading to improved quality and efficiency of care. When suboptimal, telemedicine fails to change practice patterns and thus fails to improve quality. Identifying optimal characteristics or troublesome ones has proved more elusive.¹⁵

A growing body of evidence has accumulated over the years, suggesting a decrease in mortality and better quality of life associated with implementing tele-ICU programs in the critical care process. Lilly and colleagues, in a multicenter report including 432 patients from 56 different ICUs, observed that those tele-ICU interventions with early intensivists case involvement, adherence to best ICU practices, reduced response times to alarms, as well as encouraged use of performance data were associated with lower mortality and length of stay (Fig. 185-4).^{16,17} Likewise, in a program led by nurses screening best practices in ICU patients, Kahn et al. found improvements in the quality

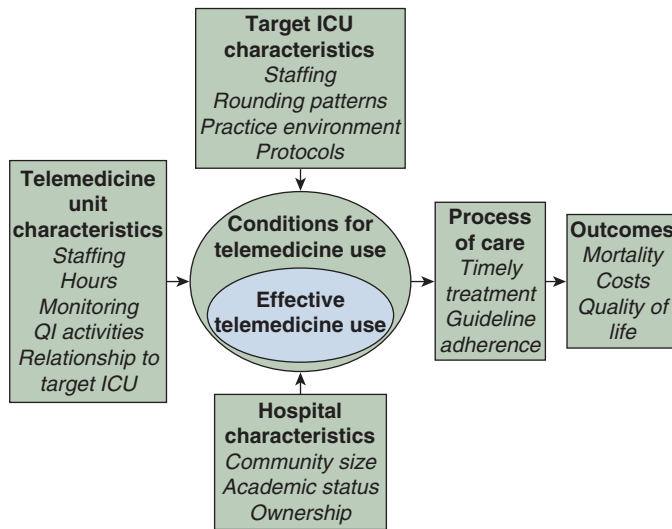


FIGURE 185-3 ■ Conceptual model for ICU telemedicine effectiveness. Under this model, the effectiveness of ICU telemedicine is determined by identifiable characteristics of the target hospital, the target ICU, and the telemedicine unit. QI, quality improvement. (From Kahn JM. ICU telemedicine: from theory to practice. *Crit Care Med* 2015; 42:2457–2458)

of care and a decrease in mechanical ventilation days and length of stay but no impact on mortality.¹⁸

Tele-ICU in Pediatric Patients

The disparity between available and needed expertise in critical care may be even more acute in children. The Institute of Medicine has reported that most children receive emergency care in general hospitals. While children make up for 27% of all emergency department (ED) visits in the United States, only 6% of them are properly equipped for pediatric emergencies. This likely affects the quality of care delivered to children presenting to EDs and, more acutely, in those located in underserved and rural communities.¹⁹

Telemedicine consultation for pediatric critical care shares similarities with the adult setting, as well as differences arising from the unique challenges offered by different and fragmented demographics, a wide range in patient size and physiology, and the coexistence of congenital malformations, among others. Consequently, a verbatim translation of an adult tele-ICU model for these patients may be unworkable, and proper adjustments should be made in maintaining a systematic approach in the teleconsultation format.

Reports related to the use of telemedicine in pediatric ICUs are relatively scarce, with some of them related with critical care consultation to rural and isolated populations. Heath et al. conducted 63 teleconsultations in 10 rural EDs. Most of the communications occurred without significant technical issues, and in 40% of them telemedicine was used to supervise the critical care transport team. A survey reported high satisfaction among consulting and referring physicians, with most of the providers perceiving telemedicine as improving patient care, being superior to telephone conversations, and allowing good provider-to-provider communication.²⁰ Yager et al. reviewed 56 consecutive telemedicine consultations for pediatric patients in the critical care setting. Communications occurred with the pediatric critical care fellow in 100%, nursing staff in 68%, and parents in 66% of their teleconsultations. Patient assessment, communication with multidisciplinary care team, and communication with a patient's family were the outcomes most often cited that would not have been possible via telephone. A change in medical management was noted following 32% of encounters.²¹

The use of an appropriate pediatric tele-ICU can facilitate decision making in remote sites, allowing for a more selective referral of patients to tertiary centers. This is of particular interest in the neonate with cyanosis. In a study from a prospectively collected multicenter database in infants matched for gestational age, weight, and diagnosis, Webb et al. reported that telemedicine shortened the time to diagnosis and significantly decreased the need for transport of infants with mild or no heart disease. They also found that the length of hospitalization and intensive care stay as well as the use of indomethacin and inotropic support were less in telemedicine patients compared with patients in centers without the availability of telemedicine.²²

We have reported our own experience with telemedicine in pediatric cardiac critical care in the international setting, eventually expanding to four hospitals in two Latin American countries. We conducted 1040 teleconsultations for 476 patients, 62% of them being in the most complex surgical patients. There was a difference in overall satisfaction, perception about telemedicine usefulness in education, and impact on medical practice among centers. We concluded that a “one-size-fits-all” approach may not be feasible in most international telemedicine settings, and prospective interventions should consider differences in staff composition, perception of needs, and patient population among centers.²³ In one of the international hospitals participating in our telemedicine program, we conducted a retrospective review of clinical records and a telemedicine database of patients admitted there during the initial 10 months of our program and compared with patients admitted during a preintervention period. We observed a shorter cardiac ICU and length of hospital stay in cardiovascular patients, as well as shorter preoperative and cardiac ICU length of stay in surgical patients.²⁴

Tele-ICU in Disaster Response

Probably one of the most compelling arguments for implementing a tele-ICU program is the continuous training and readiness for disaster response. In such dire situations and despite apparent preparedness, mid-course corrections or the need for improvisation is a common occurrence, including failure in logistics and communications. Although it is true that the very nature of natural or man-made disasters present unique and new challenges in every new presentation, it is also true that many of these problems arise from the fact that, once disaster response plans are made, they often end stored and forgotten, and the teams eventually become untrained. Roberts et al. published their experience with the use of a previously established tele-ICU program for disaster relief during the winter 2009 blizzards in the Baltimore metropolitan area. Given they had been using a telemedicine system for 5 years on a routine basis, they transitioned seamlessly to disaster response mode, conducting daily ICU rounds and coordinated care with the on-site team, assisted by robotic telepresence²⁵ together with remote access to EMR and imaging studies.

TELE-ICU IN THE FUTURE

Tele-ICU is an ever-growing field. The current supply-demand estimates in adult critical care projects a need for tripling the capacity of ICU case days compared with 2006. This is not and will not be sustainable in the foreseeable future.²⁶ Hence, a different paradigm for ICU care needs to be developed. Telemedicine will undoubtedly be an integral part of this new approach, perhaps enabling critical patients to be treated closer to their homes, family, friends, and support network while empowering local teams, providing best-evidence guidelines and quality assurance as well as accelerating the decision-making process to expedite definite treatment or else more compassionate, palliative, or end-of-life care. Integration through a continuum from home and the community to the critical care environment will incorporate early preventive strategies aimed at well-being preservation and risk avoidance, rather than the current reactive approach toward already established critical care disease, connecting presently disjointed practices in ambulatory medicine and critical care.

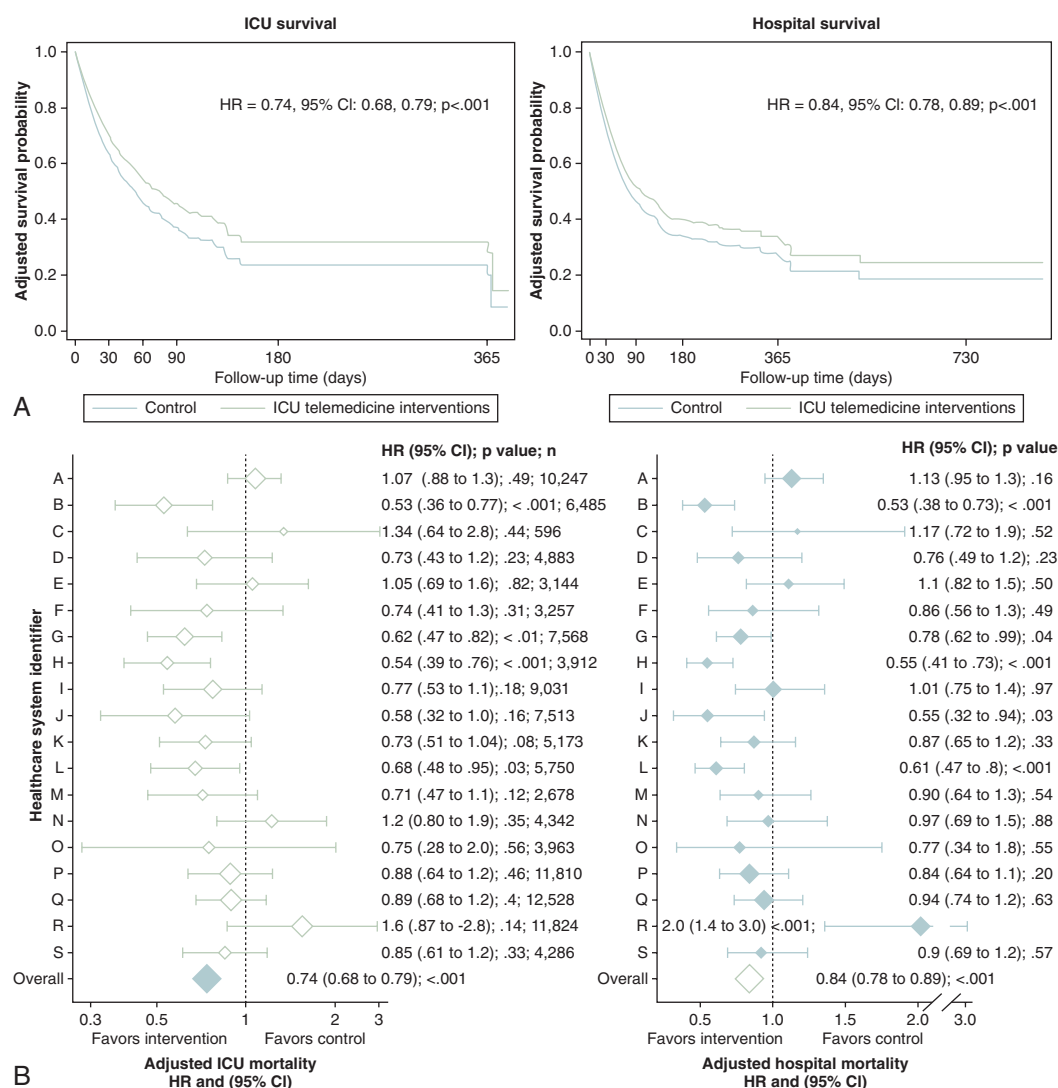


FIGURE 185-4 ■ **A**, Adjusted ICU-specific (*left*) and hospital-specific (*right*) survival estimated by Cox proportional hazards regression. Models adjusted for APACHE IV score, age, hospital, or ICU identifier (as a random effect), admission source, primary admission diagnosis, operative status, time from start of study enrollment, heart rate, admission and highest creatinine values, respiratory rate, admission hematocrit value, blood urea nitrogen, white blood cell count, Glasgow Coma Scale score, prothrombin time, anion gap, urine output (in the first 24 hours), base excess, and total bilirubin and albumin values. **B**, Adjusted ICU-specific (*left*) and hospital-specific (*right*) survival estimated by healthcare system. The center of the diamond represents the effect estimate, the bars represent 95% confidence intervals, the symbol size is proportional to the number of observations for the corresponding healthcare system, and the overall effects are presented as diamonds in the bottom row. HR, hazard ratio. (From Lilly CM, McLaughlin JM, Zhao H, Baker SP, Cody S, Irwin R; UMass Memorial Critical Care Operations Group. A multicenter study of ICU telemedicine reengineering of adult critical care. *Chest* 2014;145:500–507, Fig. 2.)

KEY POINTS

1. Tele-ICU has become a reliable strategy to enhance care in critically ill patients.
2. Fields potentially affected by telemedicine include medical team organization, medical education and licensing, quality improvement, disaster response, and research.
3. Tele-ICU operations should be in compliance with international, national, state, and local laws and regulations.
4. A systematic approach including quality improvement interventions may yield the best results in patient survival and length of stay.
5. Units with low-intensity day staffing may benefit the most from tele-ICU.
6. Pediatric critical patients present unique challenges, but experience is growing rapidly.

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Teaching success should be measured in terms of student performance, not the activities of the teacher. Delivering a carefully organized PowerPoint presentation, supervising problem-based workshops, or providing bedside clinical tutorials does not mean one has taught. Unless the learner has acquired new cognitive or psychomotor skills, teaching has not occurred.¹ An effective teacher takes responsibility for ensuring that students learn. If the teacher's perception is that providing a lecture or any instructional methodology fulfills this obligation, then the teacher is serving as "the" educational resource. The focus of this model is on what the teacher did and not on what the learner learned. Said another way, a teacher is someone whose students learn, not one who presents well.

Sritter described a different model, one focused on the student.¹ In this model, the teacher assumes responsibility for the learner's success and creates an environment conducive to learning by managing the educational resources. The teacher as a "manager" creates specific educational objectives, motivates students, utilizes various educational strategies, evaluates learning, and provides effective feedback to ensure the learner achieves all the educational objectives.¹

In the realm of medical education, there have not been significant changes to the principles of effective teaching, teaching theory, or providing feedback. Therefore, many of the topics discussed in this chapter are still relevant, even those described by Bloom, Mager, and many other cited authors with works dating back to the 1960s. What has changed, however, are the learning environments medical trainees face, requirements by medical education governing bodies, and the ways students can learn through advancements in technology. The goal of this chapter is to provide a detailed description of each of these steps, from creating educational objectives to providing feedback, so the teacher can apply the concepts, whether organizing and presenting a 1-hour lecture, a 1-day workshop, a 1-month elective, or a 1-year curriculum.

■ CREATING EDUCATIONAL OBJECTIVES

Educational objectives outline the skills and behaviors the student, resident, or fellow will be able to demonstrate after the teacher has completed a lecture, daily bedside instruction, 1-month elective, or fellowship training. Objectives should be developed for every instructional activity because they are a road map. They guide the teacher in developing an appropriate curriculum, they set unambiguous expectations for the learner, and they serve as a reference for evaluation and feedback.^{2,3}

Developing educational objectives involves three steps.^{2,3} First, using action verbs (e.g., defines, explains, demonstrates, identifies, summarizes, evaluates), the instructor describes a specific behavior the learner must perform to show achievement of the objective. An objective such as "teaches concepts of airway management" is not adequate because it defines what the teacher is doing and does not clearly describe what the learner should be demonstrating. Therefore, it neither serves as a road map for the teacher or the student nor does it identify a clear behavior the teacher can evaluate.

Second, the teacher should describe the conditions under which the behaviors are to occur. For example "given a scenario using human simulation, the student will evaluate the airway and demonstrate effective bag-mask ventilation." Finally, the criteria for acceptable

performance should accompany the objective—that is, "bag-mask ventilation will be followed by successful laryngotracheal intubation within 30 seconds." When written for a lesson plan or formal curriculum, the format of a learning objective should be "who" (learner) will "do what" (knowledge or skill being taught) by "when" (end of lecture, curriculum, or course) as measured by "how" (the method of evaluation).⁴

When teaching students a specific clinical skill—for example, how to manage a patient with hypotension—the teacher must establish that the learner has first mastered the lower cognitive domains, knowledge, and comprehension. This is called *scaffolding* and is based on a classical hierarchy of levels of comprehension described by Bloom.⁵ Learners will not be able to initiate an appropriate treatment for hypotension or evaluate effectiveness of treatment unless they can first list the causes of hypotension and describe the effect of preload on stroke volume. The teacher can ask some simple questions to better understand what level of cognitive domain the student is at, as well as how or why the student is at that point in order to progress to the next level. Using an example from the treatment of heart failure, a teacher could start with a comprehension-level question such as "What is the mechanism of action of furosemide?" This can advance to a higher level, such as analysis, with the instruction "Identify and break down the differences in development, presentation, echocardiography, and treatment for patients with systolic versus diastolic heart failure." At the highest level evaluation, an instruction might then be "Evaluate the evidence to support the role of angiotensin converting enzyme inhibitors in the symptomatology, rates of hospitalization, functional status, and mortality for patients with systolic heart failure."

Educational objectives specifically related to critical care medicine training programs should be developed in accordance with the expectations outlined in the Accreditation Council for Graduate Medical Education (ACGME) program.⁶ In addition to listing the specific cognitive and motor skills that must be taught, the ACGME has developed general core competencies that focus on patient care and not just knowledge acquisition.⁶ The six competencies include medical knowledge, patient care, interpersonal and communication skills, professionalism, practice-based learning, and systems-based practice.⁷ In recent years, the ACGME has evolved from simply assessing trainees subjectively on these competencies, to an evaluation system of milestones with better defined anchors for expected progression based on each clinical specialty.⁷ Examples of educational objectives for each competency and details of each specialty's milestones are available at www.acgme.org.

■ MOTIVATING STUDENTS TO LEARN

The next step in teaching as a manager is to motivate the students to want to learn. To accomplish this they must first value what is being taught. For them to value a specific goal, they need to understand why it is necessary to incorporate the material into their clinical practice.^{8,9} The affective domain addresses educational objectives that relate to valuing and applying the material. For example, the instructor should explain why certain educational goals have been chosen, why they are important, and the consequences of failing to incorporate them. Most important, the teacher needs to be aware of any inadvertent behaviors that may inhibit learning—providing negative feedback in front of

TABLE 186-1 Principles of Adult Learning

Adult learners benefit from:

1. Goal-oriented learning
2. Autonomy and self-directed learning
3. Relevant material to needs
4. Able to practice or trial what is being taught
5. Based on accumulated experiences and knowledge
6. Safe and respectful learning environment

others or demonstrating negative body language, for example. These concepts are consistent with the pillars and principles of adult learning listed in [Table 186-1](#).^{10,11}

The affective domain ties into the student's motivation, with the dichotomy of extrinsic and intrinsic motivators.¹² Extrinsic motivation is when the learner has to be told that an activity needs to occur. In medicine, this can be seen as the difference between studying to pass an examination compared to studying to improve delivery of patient care. Once a learner is able to reach this stage of valuing the learning experience, it not only makes teaching objectives easier for the educator to reach but also sets the stage for life-long learning. This is intrinsic motivation.

A particularly effective tool to get students to both learn and apply their cognitive skills to patient care is to put them in "simulated crisis situations," allowing them to make clinical mistakes and attempt to manage the consequences. Making mistakes in a simulated environment and experiencing the potential complications in real time has proven successful in getting medical trainees to acquire and incorporate cognitive and motor skills into their patient care.

LEARNING EXPERIENCES

There are numerous instructional methodologies a teacher can use to achieve educational objectives. Because adult learners prefer active learning, a curriculum that requires them to process information, participate in problem solving, and defend clinical judgment increases their enthusiasm for learning.⁹

Although frequently used, traditional lectures are not an efficient learning method.¹⁴ There are growing challenges to attending lectures with limited time and competing activities for medical trainees. Moreover, because didactic sessions are not interactive, the teacher does not have an opportunity to assess whether the learner understands the content and its applicability.

Small group sessions that incorporate problem-based learning and interactive workshops are more effective because they engage the students, force them to defend their decisions, and explain how they evaluate outcomes.¹⁴ A more recent development in management of an efficient learning environment is that of the "flipped classroom."^{15,16} A flipped classroom design is one where the students review the core content, such as renal replacement therapy, prior to attending the session and then use the time with the instructor to work through cases or problems and provide direct formative feedback. The growth of recording technology and podcasts provides the opportunity for an instructor to prerecord core content lectures and allow their time in the classroom to be used more efficiently to answer students' questions and work through the material without needing to repeat static elements of the content. Additionally these prerecorded lectures or podcasts can serve as an online reference library for students to return to for review or when they might subsequently encounter a particular topic in clinical practice.¹⁷

However, none of these methods teaches students or residents how to apply these skills to real-life situations. This is of particular importance in the current era where contact hours of exposure to patients are balanced by work hour regulations of medical trainees. Each year 210,000 to 400,000 patients die because of medical errors, an amount increasing from the estimated 98,000 in the landmark study by the Institute of Medicine in 1984.¹⁸ It is possible that giving students an

TABLE 186-2

Learning Objectives for Fourth-Year Critical Care Medicine Course

RESPIRATORY DISTRESS

- Evaluate a simulated patient in respiratory distress (tachypneic and hypoxicemic).
- Initiate appropriate oxygen therapy.
- Evaluate effectiveness of therapeutic intervention.
- Demonstrate effective bag-mask ventilation.
- Insert intravenous catheter for resuscitation.
- Evaluate patient for potentially difficult airway.

CARDIOVASCULAR

- Evaluate a patient with hypotension.
- Initiate therapy for a patient with hypotension (initiate intravenous fluids).
- Order appropriate diagnostic tests for evaluation of a patient with hypotension.
- Evaluate effectiveness of therapeutic intervention.
- Evaluate a patient with sinus tachycardia, develop a differential diagnosis, and order appropriate diagnostic tests.

ARRHYTHMIAS

- Evaluate a patient with sinus tachycardia, develop a differential diagnosis, and order appropriate diagnostic tests.
- Demonstrate defibrillation of ventricular fibrillation and pulseless ventricular tachycardia.
- Demonstrate airway management and cardiovascular resuscitation for simulated patients with ventricular fibrillation, ventricular tachycardia, pulseless electrical activity, and asystole.

opportunity to manage complex problems and anticipate consequences of their interventions in an environment where their mistakes do not result in untoward outcomes, where feedback is immediate, and where students can repeat their performance until they acquire these skills might improve patient safety.

Such instructional opportunities exist and have been available for years in the form of simulation. *Simulation* is defined as any training device that duplicates artificially the conditions that are likely to be encountered in an operation and may include low tech, partial task trainers, simulated patients, computer-based simulation, and whole-body realistic patient simulation. Work in cognitive psychology and education theory suggests that more effective learning occurs when the educational experience provides interactive clues similar to situations in which the learning is applied.¹⁹

What initially began as computerized software with a separate torso apparatus has evolved into complex whole-body computerized manikins. Current models, such as the Laerdal SimMan® 3G simulator provide trainees a high-fidelity manikin that can have spontaneous respirations, palpable pulses, pupils that react to light and can constrict (unequally if desired), sweat, seize, demonstrate cyanosis, and simulate various difficulties for airway management. Moreover, the trainees can practice skills such as bag-valve-mask ventilation, nasal or orotracheal intubations, cricothyroidotomy, chest tube placement, needle decompression, closed chest compressions, cardiac pacing and electrical defibrillation, among other procedures, with real-time feedback provided.²⁰

These computerized human simulators require trainees to integrate cognitive and psychomotor learning, along with multisensory contextual cues to aid in recall and application in clinical settings.^{21,22} Examples of learning objectives for fourth-year medical students and critical care medicine fellows using the simulator are listed in [Tables 186-2](#) and [186-3](#). Note, all objectives are written in terms of behaviors the student must perform, thus giving the teacher clear guidelines for evaluation.

No study has unequivocally demonstrated improvement in actual patient outcomes. Despite not showing these results in published data to present, simulation addresses the fundamentals of adult learning discussed previously. Simulation provides hands-on experiences without any direct risk to patient safety and can simultaneously address

the cognitive, psychomotor, and affective domains of learning that are essential to a successful curriculum. Moreover, organizations such as the Institute of Medicine endorse simulation as a tool to teach novice practitioners problem-solving and crisis management skills.

EVALUATION

Evaluation is an essential component of any education curriculum and should address whether the goals and objectives of the course were met. This refers to evaluating the learners, as well as the educator or curriculum developer. Evaluation tools and standards should be directly derived from the predefined teaching objectives from the curriculum. An educator and his or her curriculum can be deemed

successful if the goals and objectives outlined in the curriculum were completed by the students.²³ Acquisition of knowledge can be evaluated using written examinations. However, they tend to reinforce surface or superficial learning by rewarding students for memorizing facts for recall.

Performance-based examinations can be utilized to assess clinical competency, psychomotor skills, and judgment.²⁴ An example of a performance-based examination is the Objective Structured Clinical Examinations (OSCEs), which were developed by Harden and colleagues in 1975.²⁵ The examinations consist of several "clinical stations," each with its own specific educational objectives. The OSCE requires the learner to recall knowledge, outline a treatment plan, interpret a study such as an electrocardiogram, or perform a specific motor skill. Along these same lines, oral examinations are another example of OSCEs or simulated cases that allow students the chance to defend their decisions or the examiner the opportunity to challenge more advanced decision making from the examinee.^{26,27}

Probably the most common method of assessing clinical competency is to evaluate the learner's performance in real-life clinical situations. Several evaluation tools can be utilized in this environment. Global rating scales are used to evaluate patient care, knowledge application, interpersonal, and communication skills. These evaluations are typically conducted in retrospect and are used to summarize a performance at the end of a clinical rotation. This type of rating has the potential to be highly subjective, and if those performing the evaluation have not been trained, the results may reflect evaluation bias and lose validity.²⁸

Psychomotor skills and procedures are perhaps best evaluated with standardized checklists. Checklists should include the specific behaviors that have to be demonstrated to achieve a satisfactory evaluation.²⁸ Checklists should be developed, and all observers participating in the evaluation should prospectively agree on what constitutes a successful performance (interrater reliability).²⁹ An example of an evaluative checklist for intubation is demonstrated in Table 186-4.

360-degree evaluations and patient surveys are used to obtain feedback on communication, interpersonal skills, and professionalism. However, they are most reliable if there are 20 to 40 patient responses

TABLE 186-3 Learning Objectives for Critical Care Medicine Fellows

1. Assess the patient's airway.
2. Immediately call for help, and follow the difficult airway algorithm if difficulty is anticipated.
3. Have primary and secondary airway strategies available (at least one supraglottic and one subglottic strategy).
4. Demonstrate good head position (sniffing position).
5. Check oxygen source and ensure connection of tubing to oxygen source.
6. Ensure two good peripheral intravenous lines are available and functional.
7. Demonstrate one- and two-person bag-mask ventilation.
8. Use oropharyngeal or nasopharyngeal airway.
9. Establish working suction (check it yourself).
10. Check laryngoscope blades (have size 3 and 4 Mac and Miller blades available).
11. Have at least two sizes of endotracheal tubes available (recommended sizes: 7.0 and 8.0).
12. Check the balloon of the endotracheal tube.
13. Have stylet and CO₂ detector ready.
14. Have medications (etomidate [0.3 mg/kg] and succinylcholine [1 to 1.5 mg/kg] ready in the room).
15. Have two ampules of Neo-Syneprine and 250 mL of D₅W in the room in the event of hypotension.

TABLE 186-4 Respiratory Support

| | YES | NO | N/A | COMMENTS |
|--|-----|----|-----|----------|
| EQUIPMENT PREPARATION | | | | |
| 1. Assembles equipment correctly | | | | |
| 2. Ensures suction is available | | | | |
| DRUGS | | | | |
| 1. Provides adequate/appropriate use of muscle relaxants | | | | |
| 2. Provides adequate/appropriate use of sedative drugs | | | | |
| 3. Provides adequate/appropriate use of topical anesthetics | | | | |
| VENTILATION | | | | |
| 1. Ensures oxygen flow to bag | | | | |
| 2. Preoxygenates patient to 100% | | | | |
| 3. Provides adequate coordination of bag-mask support with spontaneous effort by patient | | | | |
| 4. Provides effective mask seal | | | | |
| 5. Provides effective ventilation by bag-mask | | | | |
| 6. Demonstrates appropriate use of nasopharyngeal or oropharyngeal airway | | | | |
| INTUBATION | | | | |
| 1. Demonstrates appropriate head positioning | | | | |
| 2. Provides cricoid pressure used | | | | |
| 3. Verifies endotracheal tube placement | | | | |
| COMPLICATIONS | | | | |
| 1. Prolonged laryngoscopy complications | | | | |
| 2. Number of intubation attempts _____ | | | | |
| 3. Esophageal intubation (duration in minutes _____) | | | | |
| 4. Bleeding from lip, mouth, nose | | | | |
| 5. Dental injury | | | | |
| 6. Failed intubation | | | | |

per student, which limits the use of this tool.²⁸ In present health care systems, this is a common method for evaluating physicians, such as the Press-Ganey system.³⁰ This could provide trainees early exposure to this form of evaluation, which they will face throughout their future careers.

■ PROVIDING EFFECTIVE FEEDBACK

The final step in being a manager of learning is to effectively utilize feedback to enhance learning. Too often feedback is used to fulfill an administrative function; it is provided as a summative report once the rotation is complete. This is referred to as “evaluative feedback.” Conversely, “formative feedback” is provided in real time with the goal of positively changing a learner’s behavior or skills. Effective feedback enhances affective learning, but when used inappropriately or done poorly, can also inhibit learning.³¹

Students want feedback; they want to know how they are performing and how their performance can be improved. Most students receive inadequate feedback during their training. Explanations for lack of feedback include a teacher’s concerns that the feedback will result in unintended consequences, will damage the student-teacher relationship, or will result in students evaluating the teacher as having performed poorly. None of these consequences will occur if the feedback is delivered correctly. Formative feedback is the only way to ensure the success of students, telling them what they have done well and, if necessary, what they need to do to achieve an educational objective. Without effective formative feedback, the behaviors go uncorrected, and the student develops a system of self-validation: “I did well because no one told me otherwise.”

For feedback to effectively change behavior without causing unintended consequences, several rules should be followed. First, all feedback should be based on how the student performed regarding a specific goal and/or objective of the program.³¹ This is another reason teachers must develop clear educational objectives. They serve not only as the framework for the curriculum but also as a reference for feedback. If feedback is provided in the context of specific performance, there should be no untoward consequence.³¹ For example, if the goal is for the learner to demonstrate effective bag-mask ventilation with appropriate chest excursion and adequate oxygen saturation, then the goal was either achieved or it was not. This is a statement based on an objective and is not a personal affront unless the feedback contains judgmental language. Second, feedback must include a description of how to succeed. In the example presented, if the patient was not effectively ventilated, the teacher should suggest repositioning the head, inserting an oral airway, and performing two-person bag-mask ventilation so there is a better seal with the mask. Third, the specific behavior the learner demonstrated should be addressed and not just interpreted.³¹ If students are late to rounds, do not assume they do not care or are lazy. Stating the expectation that rounds begin at 7 AM and that the expectation is for the trainee to be prepared by then assigns no judgment. Fourth, for feedback to be effective it should be an expected component of the learning tools.³¹ Therefore, the key to providing

TABLE 186-5 Examples of Poor and Better Feedback Comments

| STUDENT'S ACTION | POOR FEEDBACK | BETTER FEEDBACK |
|---------------------------------------|---|---|
| Late for rounds | "When you come late to rounds, you are being lazy." | "Every member of the team is expected to be on time for the start of rounds each morning." |
| Lack of empathy during family meeting | "You were very rude to the patient's wife." | "I noticed that you continued to speak when the patient's wife began to cry. Do you think that would have been a good time to pause and provide empathy through naming her emotions?" |
| Poorly written progress notes | "Your daily progress notes are sloppy and not well written. Do better." | "I noticed in your daily progress notes that you do not describe how or why you chose to treat the patient the way you did, or how he is responding to the therapy. These are some ways to elevate the quality of daily notes. Please try this approach tomorrow and I will follow up with you to see how they improved." |

feedback is for it to be timely and based on an objective behavior, not a subjective trait of the student. Students should be informed during orientation that they will receive daily feedback on their performance of the stated goals and objectives. In summary, feedback should be timely, specific and behavioral-based with suggestions for improvement.³¹ Table 186-5 provides examples of poor and better feedback statements based on these characteristics. Without successfully implementing feedback, the model of teaching described by Irby is incomplete.⁹

■ CONCLUSION

A teacher who begins every educational session with clear objectives, creates an environment where students want to learn, applies different educational strategies, evaluates learning, and provides formative feedback will help his or her students to successfully achieve the educational objectives. These guidelines are applicable for developing a bedside teaching session, a 1-month rotation, or a year-long curriculum for critical care medicine fellows.

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KEY POINTS

1. A teacher, serving as a manager, develops educational objectives, motivates students, organizes the curriculum, evaluates performance, and provides feedback.
 2. Educational objectives are an essential component of any instructional activity, setting clear expectations for the learner and serving as a reference for evaluation by the teacher.
 3. Adults prefer active learning; therefore, a curriculum that requires them to analyze, solve, defend, and evaluate increases their
- interest in learning. Medical simulation is an innovative addition to a critical care curriculum.
 4. Developing a valid assessment tool is essential in ensuring that the learner has achieved the educational objectives.
 5. Formative feedback should be provided during instructional activity to ensure the student’s success.

■ References for this chapter can be found at expertconsult.com.

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SUPRAGLOTTIC AIRWAY PLACEMENT: BEFORE PROCEDURE

Indications

- Supraglottic airway placement (SGA) use for managing the airway
 - When bag-mask ventilation is ineffective or impossible
 - Noninvasive maneuvers such as nasal and oral airway placement, jaw thrust, chin lift, two- or three-person efforts are ineffective or fail to maintain $\text{SpO}_2 > 90\%$.
 - Decision to utilize a supraglottic airway (e.g., laryngeal mask airway [LMA]) should be made rapidly to avoid desaturation or endangering the patient's safety.
- Primary use when mask ventilation difficulty is anticipated
 - Decision to use an SGA may be based on a known history of difficult mask ventilation. This could be done as a first step in managing the patient. Following preoxygenation with bag-mask assembly, placement of the SGA occurs immediately following pharmacologic induction. Alternatively, topical anesthesia preparation will allow placement of the SGA device; establish effective ventilation, then induce.
 - Suspected difficulty based on Langeron's criteria (two or more factors) + other factors
 - Obesity
 - Edentulous
 - Beard
 - Age >55 years
 - History of snoring, obstructive sleep apnea (OSA)
 - Macroglossia
 - Anatomic alteration of head/neck, dressing, cervical collar
 - Poor positioning
- Secondary use as a rescue airway device when ineffective or impossible mask ventilation exists or following difficult or failed direct or indirect laryngoscopy
 - Following induction of unconsciousness/apnea, bag-mask ventilation not effective
 - Upper airway collapse/obstruction (above supraglottic airway level)
 - Upper airway bleeding (e.g., tongue malignancy), to separate bleeding from lower airway
 - When intubation proves difficult or fails, an SGA can be placed to support oxygenation and then removed for further attempts or used as a conduit for intubation
 - Bridge to support ventilation/oxygenation while other methods are pursued, equipment is gathered, personnel are summoned
 - Ventilation/oxygenation prior to direct laryngoscopy/intubation
 - Fiberoptic bronchoscopy via SGA
 - Retrograde wire intubation: passing wire up through SGA, retrieve wire, remove SGA, advance endotracheal tube (ETT) over wire into trachea
 - Surgical airway (cricothyrotomy, tracheotomy) with SGA in place
- Semiselective use for ventilation/oxygenation support for procedures where bag-mask ventilation known or suspected to be difficult/cumbersome/patient intolerant to procedure without airway

support (e.g., OSA patient for upper endoscopy with moderate sedation)

- Bronchoscopy in patients intolerant to sedation (OSA, obese, debilitated, cardiopulmonary cripple)
- Percutaneous tracheostomy
- Upper endoscopy
- Transesophageal echocardiography (TEE)
- Brief procedure requiring unconsciousness and airway control

Contraindications

- Absolute
 - Airway obstruction (supraglottic and below)
 - Patient unprepared (awake, no topical anesthesia)
 - Elective use with aspiration risk or full stomach
 - Emergency short-term use for rescue of difficult airway is acceptable.
- Relative
 - Anatomic alteration of supraglottic area, glottis, hypopharynx
 - Tumor, abscess, foreign body, swelling
 - Emergency short-term use for airway rescue is acceptable.
 - Pregnancy, obesity, massive/multiple-injured patient
 - Emergency short-term use for airway rescue is acceptable.

Equipment

- Equipment for mask ventilation
- Induction medications, topical anesthesia medications, and equipment for intubation
- Disposable or reusable SGA device
- Lubricating jelly
- Syringe for cuff inflation/deflation
- Tape to secure SGA
- Bite block optional
- SGA includes many available models of the original LMA from LMA North America and the many available other brands with similar offerings.
- Choice of device is often based on cost, comfort with product.
- Evidence-based use exists for some but not all product offerings.
- Sizes range from neonatal to large adult and will vary by manufacturer.
- SGA sizes available should meet needs of patient population in your facility.
- Access to manometer to measure cuff pressure ($<60 \text{ cm H}_2\text{O}$)
- SGA access in facility may be best on code cart, airway cart or bag, rapid-response care cart, resuscitation areas in any and all areas where airway management may take place, either elective, urgent, or emergent.
- In the remote hospital location, SGA devices in a transportable airway bag or tackle box carried by the airway team is an excellent alternative.

ANATOMY

Though there are a variety of SGAs that occupy the periglottic area and surround the glottic opening with a cuff; most models differ very little

except in the manufactured materials, their flexibility or rigidity, ease of use, weight, and effectiveness. Most, but not all (e.g., Igel laryngeal mask) have an inflatable cuff that lies in the hypopharynx and essentially seals the supraglottic region (from the epiglottis down the cricopharyngeal sphincter). A sealed airway allows positive pressure ventilation to be delivered but is limited by the effectiveness of the cuff seal/periglottic mucosal surface interface. Many will allow effective airway pressurization to 10 to 25 cm H₂O pressure before leaking, while other models are specifically designed to allow much higher sealing thresholds (25–35 cm). These latter models are particularly effective in generating ventilatory support for the obese and morbidly obese patient and when confronted by low pulmonary compliance situations (congestive heart failure, acute respiratory distress syndrome, abdominal distention, pregnancy, ascites, and pulmonary fibrosis). Many manufacturers now offer SGA models with a portal that allows passage of a suction catheter or nasogastric tube to assist with evacuation of air or gastric contents from the esophagus and stomach. While handy, access to the aerodigestive tract is not guaranteed nor is the emptying process. Thus, the assumption that these SGA models are acceptable in nonfasting patients or those at risk for aspiration is not supported by published literature. Despite this, any patient who has a failed airway may benefit from SGA placement even if the risk of aspiration is elevated.

In general, placement of the SGA can be performed in the exaggerated “sniff” position to the other extreme, a neutral cervical spine. The SGA generally can be placed effectively when faced with little to no neck flexibility. The SGA is lubricated and then passed toward the roof of the mouth across the hard to soft palate, encouraging smooth advancement along the posterior throat so as to minimize getting hung up on the epiglottis. It typically comes to lie with its distal tip in the cricopharyngeal region. Unfortunately, the cuff end may buckle over on itself, come to lie over the glottic opening, or be displaced in a contorted position that impedes effective ventilation and oxygenation. The SGA may indeed be placed incorrectly but still function in near perfect form with effective ventilation; it is a peculiar airway device. It can be forgiving, yet it still requires skill and finesse to place it properly in most situations. Guidance by a skilled and frequent user is the best method to learn the details of its proper use. Ideally, it lies just over the glottic opening and allows access to the trachea. However, the SGA is frequently malpositioned or the epiglottis is folded over to a lesser or greater degree, partially or completely blocking the pathway to the glottic opening, yet ventilation and oxygenation remain unabated. This may be adequate for airflow to and fro but not for the passage of an ETT into the glottic opening. Hence, most generic SGA models do require fiberoptic-guided placement of an ETT because of the uncertain position of the SGA.

AFTER PROCEDURE

Postprocedure Care

- The SGA used in the semielective, urgent, or emergent setting is often of short duration (2–20 minutes), since the goal is typically to intubate the trachea. Hence the SGA acts as a rescue ventilation device and/or an intubation conduit.

Complications

Complications are not necessarily due to the SGA itself.

- Common
 - Sore throat
 - Complications inversely related to experience skill of operator
- Infrequent
 - Inability to properly insert
 - Inability to ventilate despite proper positioning (laryngospasm, patient biting, kinking of SGA tube), contributing to negative-pressure pulmonary edema
 - Mucosal injury, pressure-induced damage, nerve/vascular injury of airway structures

- Arytenoid dislocation, nerve damage, venous engorgement (all rare)
- Serious, rare complications
 - Obstruction of the glottic opening
 - Regurgitation/aspiration

OUTCOMES AND EVIDENCE

The LMA design offers a relatively short learning curve for the airway novice and affords fewer episodes of desaturation, less difficulty in maintenance of a patent airway, larger tidal volume than mask ventilation, and decreased arm and hand fatigue when compared with a conventional face mask. Its value in the ICU setting for assistance during emergency airway management is undeniable, especially during difficult intubation or when ventilation is not possible with a standard bag-mask assembly. Blind or fiberoptic-assisted tracheal intubation is an extremely attractive asset that the SGA device offers the clinician and provides an entirely novel rescue approach when conventional laryngoscopy and tracheal intubation prove troublesome or impossible. It is also useful in maintaining airway support in the intensive care unit (ICU) setting for patients who require repetitive general anesthetic or heavy sedation-analgesia for brief procedures, fiberoptic bronchoscopy, or diagnostic visualization of the airway. Recent work suggests that the SGA is better tolerated and produces fewer cardiovascular side effects than tracheal intubation. Insertion in the patient with an unstable cervical spine may be far easier than direct laryngoscopy, because its insertion does not absolutely require neck manipulation.

The device may be difficult to place into the hypopharynx in the presence of a small mouth, a large tongue or tonsils, hypertrophied lingual tissue, or a posteriorly displaced pharynx. However, the SGA often proves easier to use than conventional methods of airway control such as direct laryngoscopy. The threat of gastric dilatation and regurgitation/aspiration may lead some to avoid its use in the critically ill, but its excellent track record and very low incidence of regurgitation/aspiration (1/755 emergency insertions, Hartford Hospital, TCM) support its role as a primary airway rescue device when conventional methods fail. The role of the SGA as a rescue device in the elective and emergency setting is unparalleled, but further studies into its use in the emergency setting are needed to solidify its standing as the premier rescue airway device, regardless of which model is used.

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BOUGIE-ASSISTED INTUBATION: BEFORE PROCEDURE

Indications

- Exchange of tracheostomy tube
- Exchange of endotracheal tube (ETT) (Warning: most bougie models are approximately 55–65 cm in length and are shorter than the recommended airway exchange catheters. This may present a problem with maintaining control of the bougie during the

exchange, owing to its length [component within the airway and the length outside the mouth available to thread new ETT].)

- Assist with passing ETT into trachea when limited by the “line of sight”
 - Full view of laryngeal inlet (unable to pass ETT because of hang-up on cricoid ring)
 - Full grade I view but a restricted pathway to the glottis—e.g., boggy or edematous tissues, redundant pharyngeal mucosa. Thus, when passing the ETT, the grade I view becomes partially or completely obstructed.
 - Grade II or III view of the larynx with laryngoscopy (conventional)
 - Grade II: posterior third of glottis visible (Lehane-Cormack classification). More detailed classification (Cook-Yentis)
 - Grade III: no cords visible, only epiglottis visible; Cook-Yentis classification
 - Grade IIIa: only epiglottic edge visible
 - Grade IIIb: down-folded or floppy epiglottis is visible
 - Grade IV: no view of any airway structure; bougie use not recommended (Figs. E1-1 through E1-6)
- Combined use with a videolaryngoscope (VAL) to assist with ETT placement
 - Channeled VAL devices (Pentax AWS, AirTraq)
 - Unchanneled VAL devices (GlideScope, McGrath, Storz C-Mac)
 - Very difficult to manipulate the bougie “around the corner” of the models with blades of excessive angulation (GlideScope, McGrath). However, these models promote the likelihood of ETT delivery at an angle such that the tip impinges on the anterior tracheal wall or on the cricoid ring, thus limiting its advancement. Typically,

ETT rotation may allow advancement, but bougie placement via the ETT may allow the bougie tip to slip off the impingement and allow ETT passage.

- Excellent adjunct with conventionally shaped “Video C-Mac”
- Useful if ETT is located just proximal to glottic opening and the bougie is passed through the existing ETT and then manipulated into the trachea
- Use of the bougie to determine the location of the ETT (esophagus vs. trachea)
 - Hang-up test (Cheney’s sign)
 - Bougie tip will hang up on carina or main stem bronchus, compared to simply passing unimpeded into the esophagus.
- Useful in cardiac arrest or clinical situation in which it is difficult to discern proper ETT placement—i.e., cardiac arrest with no detectable EtCO₂ or access to such devices.

Contraindications

- Unfamiliar with its use
- Recent tracheobronchial reconstruction

Equipment

- A tracheal tube introducer “bougie” is an inexpensive, disposable, easily transportable airway device that requires minimal setup time, no battery or electrical power, and is noted on all the major airway-management algorithm lists of desired airway devices that should be immediately available.
- A variety of manufacturers offer bougie models in 55- to 65-cm length.
- Solid and hollow bougie models are offered by some manufacturers.
- Distinct black markings along the length of the bougie assist the clinician with the depth of insertion.

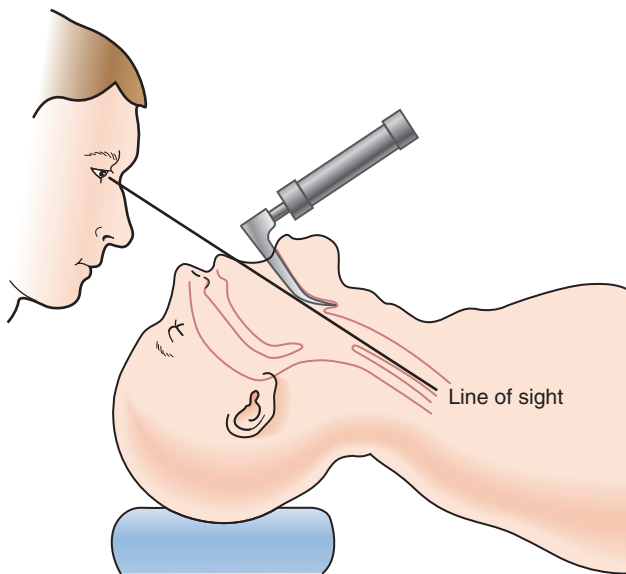


FIGURE E1-1 ■ Line of sight with direct laryngoscopy.



FIGURE E1-3 ■ Cook-Yentis grade IIb laryngeal view with direct laryngoscopy achieves a very high success rate with bougie-assisted intubation.

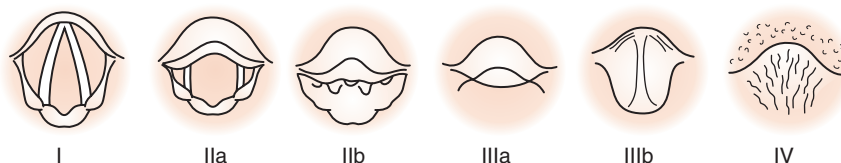


FIGURE E1-2 ■ Lehane-Cormack laryngeal view grading system with the Cook-Yentis modifications, grades I→IV.



FIGURE E1-4 ■ Cook-Yentis grade IIIa view with direct laryngoscopy achieves a respectable success rate with bougie-assisted intubation, especially when compared to blind passing of the endotracheal tube “around the corner.”



FIGURE E1-5 ■ A grade IV view, essentially no view at all of the laryngeal structures. The bougie is not indicated for a grade IV view though in experts’ hands and following failure of other techniques, careful blind passage combined with detection of tip hang-up (carina, main stem bronchus) may allow blinded intubation. This is a last ditch effort maneuver and is not recommended as a routine approach. It is best handled with an SGA, flexible fiberoptic bronchoscopy (FFB), or video-assisted laryngoscopy (VAL).

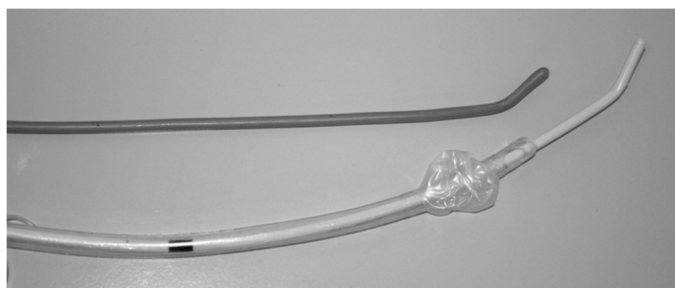


FIGURE E1-6 ■ Two bougie models are shown (tracheal tube introducer). Note the characteristic 30-degree angle. The Coude tip allows manipulation of the bougie underneath the epiglottis to increase its rate of passage through the laryngeal opening.

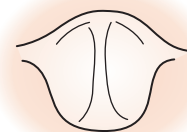


FIGURE E1-7 ■ A grade IIIb view; floppy or overhanging epiglottis may be difficult to navigate around with a variety of airway adjuncts. The bougie may be used to elevate the epiglottis and navigate into the trachea, but the success rate is substantially lower in the grade IIIb setting (30%-50%) compared to a grade IIIa (only leading edge of epiglottis visible, 80%-90%).

ANATOMY

Though the bougie is capable of assisting intubation in nearly all airway situations except when “no view” is possible, it is most commonly used as an adjunct with grade IIb, IIIa, and IIIb laryngeal views. Even when the laryngoscopy reveals a full view (grade I), the bougie may be useful when the hypopharyngeal opening is narrow (OSA, obesity, swelling) and passing the ETT may actually obstruct the view of the glottic opening. In this case, the narrower, more colorful tracheal tube introducer can be passed into the trachea with little visual obstruction taking place. Conversely, the floppy epiglottis is a challenge that may be technically difficult with many different airway adjuncts. The bougie may either be used to elevate the floppy epiglottis or be maneuvered around by virtue of the Coude tip. Though useful, the success rate is often less than 50%, and other airway device alternatives may be needed (intubating laryngeal mask airway [ILMA], VAL, flexible fiberoptic bronchoscope [FFB] (Fig. E1-7).

PROCEDURE

- The bougie is grasped in the intubator’s right hand at the 20- to 25-cm mark.
- It is passed alongside the laryngoscope with the 30-degree angled tip (coude) anteriorly.
- The tip is advanced anterior to the arytenoids and into the larynx (grade IIa, IIb).
- The tip is then advanced underneath the epiglottis and past the vocal cords blindly (grade IIIa).
- The tip lifts the floppy epiglottis and is then advanced blindly past the vocal cords (grade IIIb).
- Following advancement into the trachea to a depth of 22 to 26 cm in an average adult
 - Tip may “bounce” or “click” past the tracheal rings, suggesting tracheal placement.
 - This is a helpful sign but does not guarantee intratracheal placement.
 - Conversely, the lack of “clicks” does not guarantee the position of the bougie, nor does it rule out location within the trachea.
- 10%-50% of bougies passed into a grade III airway may enter the esophagus
 - Grade IIIa: 5%-12% may enter the esophagus
 - Grade IIIb: 30%-50% may enter the esophagus
 - Quickly deploy backup strategy (SGA, FFB, VAL)
 - Some may consider bougie a poor choice in grade IIIb view.
- Tip may be gently advanced farther (28-36 cm) to contact carina/main stem bronchus
 - Tip hang-up provides tactile feedback during blind passage.
 - Detection of carina/bronchus is reassuring to operator.
 - Advancement past 35-40 cm without hang-up strongly suggests the bougie is in the esophagus.

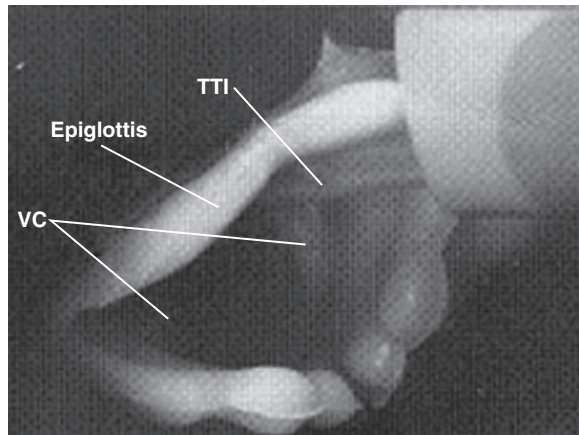


FIGURE E1-8 ■ Endotracheal tube (ETT) being passed over tracheal tube introducer (TTI, bougie) and getting hung up on the epiglottis and arytenoid. Continued advancement should be discouraged. Simply withdraw 1 to 2 cm, rotate ETT counterclockwise about 90 degrees, and re-advance. VC, vocal cord.

- Using hang-up or Cheney's sign lowers the incidence and dangers of passing the ETT into the esophagus.
- Eliminates the delay of verifying the ETT location by insufflation, capnography, auscultation
- Decision time: passing the ETT
 - If time permits, generously lubricate the ETT.
 - Smaller sized ETTs pass over the bougie more easily than larger ones.
 - Maintain tongue displacement with laryngoscopy/hand grasp.
 - Pass the ETT, but do not force the advancement (an assistant should grasp the proximal end of the bougie to stabilize it).
 - Anticipate resistance at 16- to 17-cm depth due to impingement on arytenoid/vocal cord (2 methods to remedy this) (Fig. E1-8).
 - Preemptively advance ETT while rotating in the counterclockwise (CCW) direction to allow ETT to avoid impingement on the glottis.
 - If resistance is encountered, stop and withdraw ETT 2 cm and then rotate CCW and advance the ETT into the airway.
 - If ETT fails to pass, the patient may be ventilated and oxygenated with bag-mask ventilation (move the bougie to the corner of the mouth).
 - Change to a smaller diameter ETT (to ease advancement over the bougie), and assume the glottic opening may be swollen, impeding entry.

AFTER PROCEDURE

Postprocedure Care

- Following advancement of ETT into the trachea, stabilize the ETT in position, and remove the bougie.
- Standard methods of determining the ETT position are required.

Complications

- Inability to pass the bougie underneath the epiglottic edge (grade IIIa) or inability to lift the down-folded or floppy epiglottis (grade IIIb)
 - Depending on the skill and experience of the operator and the condition of the patient, time spent advancing the bougie should be limited so as not to endanger the patient's condition (SpO₂).
 - If unsuccessful, quickly move to another accessory device to secure the airway.

- Infrequent
 - Minor tissue injury, airway trauma
 - Esophageal placement of bougie
 - Esophageal intubation (the hang-up test should eliminate this hazard)
- Serious, rare complications
 - Mucosal laceration, bronchial/carina perforation if extreme force is applied to bougie advancement or the patient's underlying airway anatomy is compromised/diseased

OUTCOMES AND EVIDENCE

The simplicity of the trachea tube introducer makes it an attractive option for assisting with trachea intubation in the situation when a restricted laryngeal view is available with laryngoscopy. A variety of uses for the bougie make it a desirable addition to the difficult airway cart or bag, made accessible at the bedside in the ICU and other remote locations in the hospital. The bougie is a suggested option in the management algorithms offered by anesthesiology societies in the United States, Canada, the United Kingdom, Germany, and many other countries.

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INTUBATING MODEL OF THE SGA FOR EMERGENCY AIRWAY RESCUE (LMA MODEL [FASTRACH] INTUBATING LMA [ILMA] WILL SERVE AS AN EXAMPLE BUT OTHER BRANDS ARE AVAILABLE): BEFORE PROCEDURE

Indications

- Emergency rescue of the airway when tracheal intubation is the goal
 - Failed conventional intubation attempts
 - Failed bougie-assisted intubation
 - Failed VAL intubation
 - May be a substitute for conventional SGA device following its failure to secure successful ventilation/oxygenation

Contraindications

- Inexperienced operator/airway team
- Major risk for regurgitation/aspiration (relative; loss or lack of airway is worse)
- Oral cavity inaccessible/trismus
- Similar to other SGA devices

Equipment

- Equipment for mask ventilation
- Induction medications, topical anesthesia medications, and equipment for intubation

- Disposable or reusable models of the ILMA, ETT, and stabilizing rod
- Lubricating jelly
- Syringe for cuff inflation/deflation
- Tape to secure SGA
- Bite block not needed
- Manometer to measure cuff pressure (<60 cm H₂O)

ANATOMY

The ILMA is similar to other SGA devices that occupy the periglottic area and surround the glottic opening with a cuff. Passing the ILMA into the oral cavity is easier than the comparative standard LMA, since it is designed with an intrinsic curve easing passage into the hypopharynx. The inflatable cuff lies in the hypopharynx and essentially seals the supraglottic region [from the epiglottis down to the cricopharyngeal (upper) sphincter]. The rigid construction of the ILMA is limited by its diameter, so adequate mouth opening is a prerequisite. The sealed ILMA allows positive-pressure ventilation to be delivered. Occasionally, the ILMA will afford effective ventilation if the standard LMA model fails, and vice versa (as could other brands).

In general, placement of the ILMA can be performed in the exaggerated “sniff” position or the other extreme, a neutral cervical spine. In the presence of cervical spine immobility, it is best to maintain stabilization yet remove the front collar to improve oral access. Following cuff deflation, the ILMA is lubricated and then passed along the roof of the mouth across the hard to soft palate, encouraging smooth advancement along the posterior throat so as to minimize getting hung up on the epiglottis or causing its down-folding. The distal tip of the ILMA typically comes to lie in the cricopharyngeal region. Unfortunately, the cuff end may buckle over on itself, come to lie over the glottic opening, or be displaced in a contorted position that impedes effective ventilation and oxygenation (Figs. E1-9 through E1-16).

PROCEDURE

- The ILMA is placed into the airway in a similar fashion as other LMA products. However, the shortened length of the ILMA model and its handle may be simpler to place than the standard LMA model. Placement is augmented by passing it along the hard to soft palate posteriorly into the hypopharynx, posterior to the epiglottis. It too comes to lie with its tip atop the cricopharyngeal area posterior to the arytenoids/glottis. The tip may fold over or under and impede air exchange or be sensed by an incomplete cuff seal (leak). This can be remedied by performing the “in-and-out” or “up-and-

down” maneuver (simply moving the ILMA slightly inward and outward to free up the distal tip). Cuff inflation is followed by positive pressure oxygen delivery. Successful placement allows chest rise, ETCO₂ detection, with no audible air leak to approximately 15 to 25 cm H₂O pressure applied to the ILMA. Always confirm ventilation prior to attempting ETT advancement via the ILMA.

- Two maneuvers are handy to improve success in ILMA placement and intubation.
 - Following ILMA placement, Chandy maneuver #1 involves using the ILMA handle to optimize the positioning of the ILMA within the airway, with the goal of maximizing tidal volume, ETCO₂, and the feel of “bagging.” The ILMA is held in this position in preparation for passing a lubricated ETT. The included LMA brand wire-reinforced ETT is an excellent ETT for passing, but it is suboptimal for long-term use in the ICU airway (if

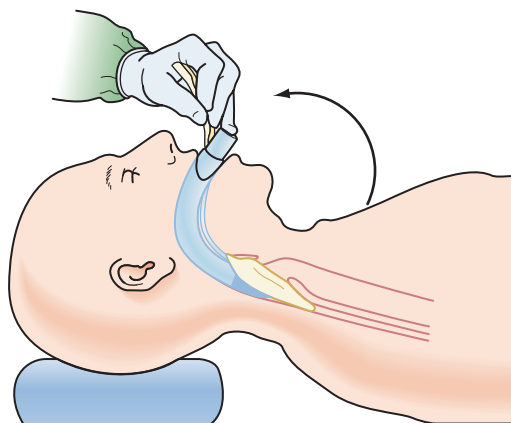


FIGURE E1-10 ■ Swing the mask into place in a circular movement, maintaining contact against the palate and posterior wall of the pharynx. Do not use the handle as a lever.

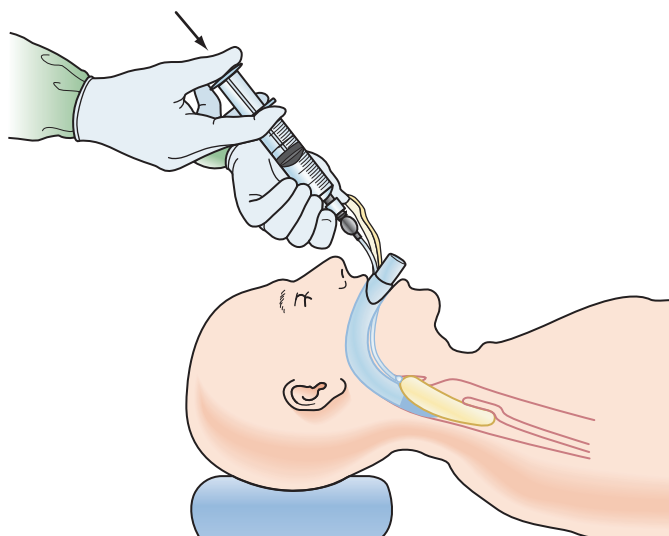


FIGURE E1-11 ■ Inflate the mask, without holding the tube or handle, with approximately 10 to 20 mL of airway to seal the airway. Apply a manual bag or anesthesia circuit and verify ventilation. If no ventilation (leak or resistance), assume misplacement of ILMA or down-folding of the epiglottis. Manipulate the ILMA in an up-and-down or in-and-out maneuver to optimize position. Recheck ventilation, and adjust location of the ILMA to optimize ventilation. Do not attempt passing the endotracheal tube until effective ventilation is ensured.

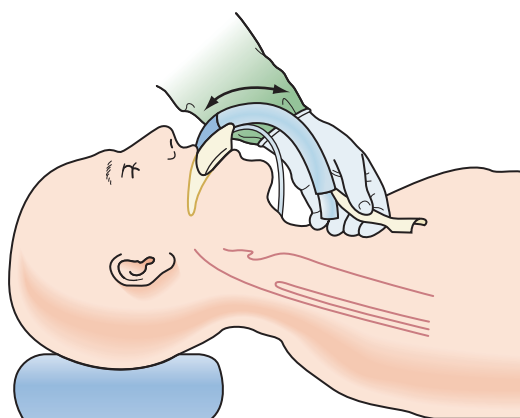


FIGURE E1-9 ■ Deflate the cuff, and lubricate with a water-soluble lubricant on the posterior surface. The lubricated intubating laryngeal mask airway is passed over the hard to soft palate along the posterior pharyngeal wall to the point where gentle resistance is felt.

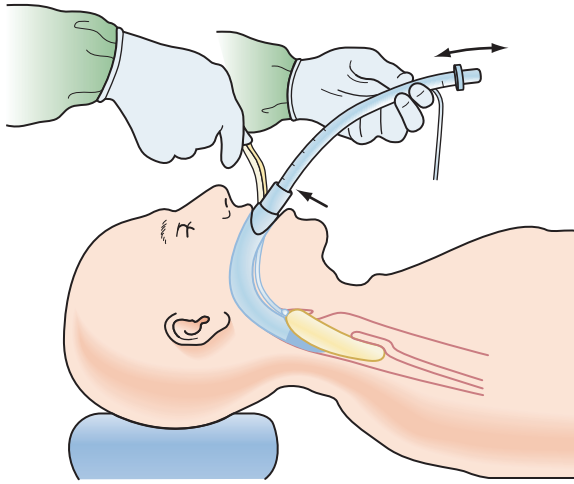


FIGURE E1-12 ■ Hold the ILMA handle while gently inserting the lubricated endotracheal tube (ETT) into the airway shaft. The provided ILMA-ETT is best suited for this, though a well-lubricated standard ETT may be used with fiberoptic guidance or may be used (with proper training and experience) blindly by inserting it “backward,” meaning the concave curve of the ETT faces the nose as it is advanced into the ILMA shaft.

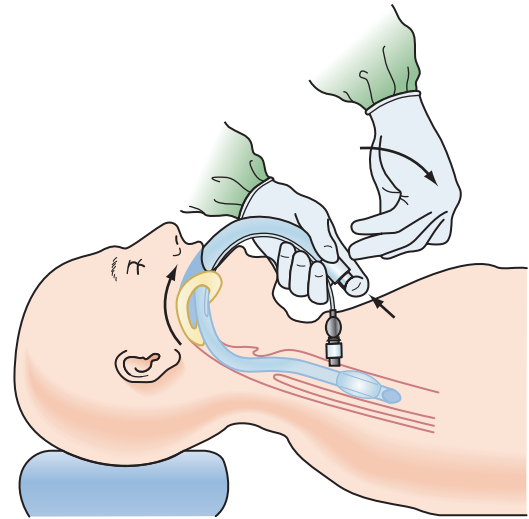


FIGURE E1-14 ■ Remove the ETT connector, and place the provided stabilizing rod onto the end of the ETT. Then ease the ILMA over the existing ETT and rod by gently swinging the handle caudally (keeping the ETT stable in position) until the ETT can be grasped at the level of the incisors.

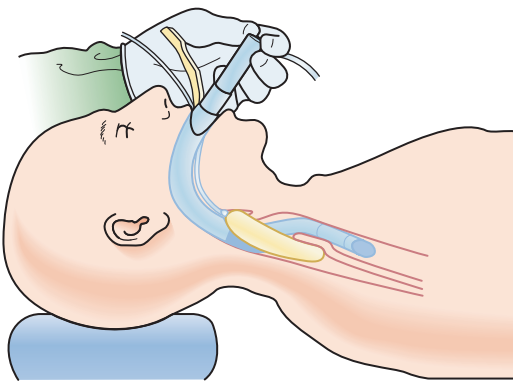


FIGURE E1-13 ■ Advance the ETT, inflate the cuff, and confirm intubation. If unable to pass, ensure adequate lubrication. If resistance is felt, the ILMA may be malpositioned or may have entrapped the epiglottis and thus block ETT advancement. Try the in-and-out maneuver to reposition the ILMA and free up the epiglottis if applicable.

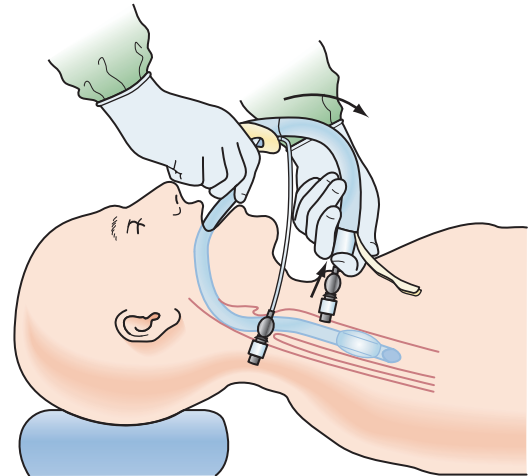


FIGURE E1-15 ■ Remove the stabilizing rod, and gently unthread the inflation line and pilot balloon of the ETT. Replace the ETT connector, and confirm ventilation and position per standard intubation procedures. If the ILMA has been used on a very challenging airway or the patient is unstable, delay removal of the ILMA from the existing ETT until stabilization takes place. Extubation of the airway is possible, so this maneuver should only be performed by those skilled in its execution.

duration of intubation is >24-48 hours, one should consider changing the ETT over an airway exchange catheter to the standard ICU ETT model).

- Once effective ventilation/oxygenation is established, passing an ETT may be the next objective. With the ILMA in the best ventilating position (Chandy #1), Chandy maneuver #2 involves using the ILMA handle to slightly elevate or “lift” the ILMA (handle toward forehead, ILMA distal tip anteriorly) to improve the success rate of passing the ETT into the trachea, based on the ILMA portal being tilted toward the glottic opening and away from the esophagus. This lift increases seal pressure and improves the alignment of the ILMA to the glottic opening and corrects any flexion the mask has undergone following its placement. Malposition or flexion of the mask while in the ventilating position may alter the pathway of the ETT as it exits the ILMA. Generous lubrication of the ETT to ease passage through the ILMA lumen is absolutely essential. Intubation of the trachea

may be performed blindly or with fiberoptic assistance. The skill to successfully intubate the trachea is attained by practice coupled with instruction by an experienced individual. Practicing the technique before an emergency situation arises is in the best interest of patient care.

- Troubleshooting in the event of failure to intubate (typically caused by a down-folded epiglottis, ETT impaction on the periglottic tissues, too large or too small ILMA, or patient is resisting intubation because of inadequate sedation/analgesia/muscle relaxation/anesthesia)
- If resistance is felt approximately 2 cm beyond the black transverse line marked on the ILMA ETT (or 15-16 cm marking on

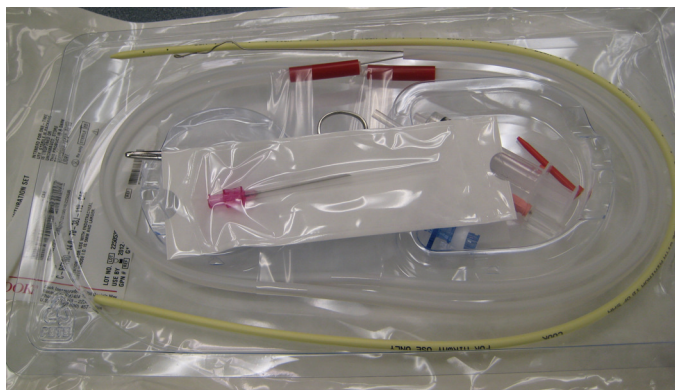


FIGURE E1-16 ■ Cook Critical Care prepackaged retrograde wire intubation kit. Use of the ILMA should be learned prior to its deployment in an emergency airway crisis. Training on a mannequin or humans under elective conditions by a skilled practitioner is best.

a standard ETT), the down-folded epiglottis may be blocking ETT advancement, as may the vestibular wall. Rotation of the ETT may allow passage if impeded by the vestibular wall. A down-folded epiglottis may need to be addressed by performing the “up-and-down” maneuver. This is a partial withdrawal of the inflated ILMA to a maximum of 6 cm, followed by reinsertion. This often frees the epiglottis from its down-folded position. Otherwise, FFB assistance is needed, or a different size ILMA may be tried.

- If the ETT meets immediate resistance at 15 to 16 cm (black mark) or at 4- to 5-cm depth past the black mark, then the ILMA is too large, and downsizing may help.
- If resistance is encountered at 3 cm past the black mark, the ILMA may be too small. If an alternative-size ILMA is not available, external manipulation of the larynx either downward or caudally may assist with passing the ETT. Likewise, ETT rotation may be helpful.
- The ILMA has an “epiglottis elevator bar” to assist in lifting the epiglottis up to afford improved ETT passage into the laryngeal inlet. When using bronchoscopic-guided ETT advancement, using the ETT tip to elevate the bar is best since the bronchoscope typically is not rigid enough to do so by itself.
- Another miscellaneous yet quite important clinical situation that may prohibit intubation is excessive periglottic/glottic edema when viewing with the FFB. Massive airway edema may preclude advancement of the FFB-ETT owing to the inability to clearly identify the glottic opening; caution must be exercised to not advance the FFB tip into unrecognizable tissue planes. Excessive force on the FFB or ETT may lead to tissue injury and thus threaten the current airway patency by inducing further bleeding, edema, or swelling. Attaching a bronchoscopic swivel adapter to the ILMA itself or via the ETT may allow active application of positive pressure to the airway and promote lateralization of the edematous glottic tissues. This is analogous to the use of continuous positive airway pressure (CPAP) in OSA patients. The bronchoscopic adapter is too narrow to allow an ETT to pass through it. To remedy this, an Aintree catheter (bougie-type catheter with a lumen that allows a proper sized FFB to be placed within the catheter) is sized to fit through the adapter and its diaphragm. The Aintree-FFB assembly may be passed through the bronchoscopic adapter, down the ILMA, and used to visualize the glottic opening. Once advanced into the trachea, the Aintree remains within the trachea as the FFB is withdrawn. The ILMA is then removed over the Aintree, and the ETT is advanced over the Aintree catheter in similar fashion to a bougie, tube exchanger, or FFB.

AFTER PROCEDURE

Postprocedure Care

- Following “blind” intubation of the trachea, standard methods to confirm ETT position are pursued (chest auscultation, EtCO₂ detection, ETT misting, chest rise, etc.).
- Following fiberoptic-assisted intubation, the same clinical confirmation of ETT position should be pursued, even though visualization of the ETT within the trachea with FFB is considered failsafe. The caveat here is that FFB confirmation, though failsafe under ideal conditions, may be limited by secretions, edema, soilage, operator inexperience, faulty battery power, and other limitations seen in the ICU airway.
- With the ETT-ILMA assembly in place, the ILMA has to be carefully removed from the patient while leaving the ETT within the trachea. Accidental tracheal extubation during ILMA removal could be disastrous.
- Step-by-step removal of the ILMA is outlined later.
- If one is unfamiliar with ILMA removal, a more experienced team should be summoned to assist with this task. Conversely, if the patient’s clinical condition needs to be stabilized prior to its removal, at a minimum, the air should be removed from the ILMA cuff (leaving the ETT cuff inflated) to reduce the pressure effect on the pharyngeal mucosa.

Complications

- Common
 - As outlined under SGA
 - Inability to establish ventilation/oxygenation
 - Inability to intubate the trachea
 - Esophageal intubation
 - Obstructed advancement of the ETT through the ILMA
- Infrequent
 - Dental damage, mucosal injury
- Serious, rare complications
 - Regurgitation/aspiration (very rare)

OUTCOMES AND EVIDENCE

- The use of the ILMA has revolutionized airway management, especially in the emergency setting. It is an accepted component in the American Society of Anesthesiologists (ASA) airway management algorithm, as well as all other algorithms offered by medical societies throughout the world. The presence of VAL has potentially altered the ILMA’s role as a logical and rational first step toward airway rescue when conventional methods fail or are inappropriate. However, the clinician must be familiar with this device and have it readily available as a backup for VAL difficulties or failures.
- In the elective setting, the ILMA has an excellent track record for a high level of successful ventilation coupled with blind and FFB-assisted intubation. Its successful deployment in the acute care setting in the ICU, the emergency department, or other remote locations outside of the operating room has been well received, though the success rate for both ventilation and intubation is tempered to a more realistic success rate of nearly 8 to 9 out of 10 patient encounters (Hartford Hospital database, TCM). Thus, a backup plan must be in place to deal with ILMA failure and establish effective ventilation/oxygenation and ultimately tracheal intubation, either blindly or with FFB assistance.

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RETROGRADE WIRE INTUBATION: BEFORE PROCEDURE

Indications

- Secure the airway in the elective setting with the patient awake, with adequate local anesthesia topicalization or nerve blocks
 - Trismus, severe temporomandibular joint (TMJ) disease, limited cervical range of motion
 - Known difficult mask ventilation, intubation
- Secure the airway emergently in the setting that mask ventilation/oxygenation is effective
 - Retrograde wire-guided intubation, in the best situation, may require 2 to 5 minutes to complete; hence one must be able to maintain successful ventilation/oxygenation.
- Considered an effective airway rescue in the nonemergent pathway on the ASA difficult airway algorithm (*cannot* intubate, *can* ventilate) when oral or nasal intubation is impossible or failed for a variety of conditions
 - Any reason the patient is a “difficult airway”
 - Massive oral, nasal, or pharyngeal hemorrhage (must be able to locate wire)
 - Trismus (must open at least one fingerbreadth)
 - TMJ abnormalities limiting mouth opening (must open at least one fingerbreadth)
 - Structural deformities of oropharynx, congenital or acquired
 - Mass (cancer, tumor, polyp, or other if not directly in line of wire advancement)
 - Traumatic injuries making oral/nasal tracheal intubation difficult or impossible
 - Maxillofacial injuries
 - Cervical spine instability
- Secure the airway electively when difficult airway factors are known or suspected to exist and intubation by other means may be difficult or impossible.

Contraindications

- Absolute contraindications
 - Transection of trachea with retraction of distal end into the mediastinum

- Fracture or other significant injury of the larynx or cricoid cartilage
- Infection, cancer, mass at site of wire insertion (cricothyroid membrane) or in pathway of wire advancement
- Unfamiliarity with the procedure
- Relative contraindications*
 - Infants and toddlers (<3 years)
 - Bleeding diathesis
 - Patients with massive neck edema, lack of landmarks

Equipment

- Guide wire (suggested >60 cm) matched to appropriate needle size allowing advancement
- 20-, 18-, 16-, or 14-gauge cutting needle on a syringe
- Cuffed 6.0 endotracheal tube
- Hemostat or Kelly clamp
- Alternative: manufactured retrograde wire intubation kit (Cook Critical Care) (see [Fig. E1-16](#))
- Optional: FFB

ANATOMY

The cricothyroid membrane is located between the superior thyroid cartilage and the inferior cricoid ring. The cricothyroid membrane is located just 1.5 to 2 cm below the vocal cords, so care must be practiced when advancing a needle caudad, as the underside of the vocal cords could be impaled. Passing the ETT over the wire or obturator/wire may be met with resistance at the 16- to 17-cm depth, as the ETT tip may impinge on the vocal cords or arytenoids. This is the inherent danger of passing the ETT blindly over the wire or obturator/wire assembly. The location of the distal tip (having met resistance) may or may not be at the position below the vocal cords. This is the challenge of the retrograde wire method; knowing the location of the ETT tip is unknown when the decision is made to remove the wire. If the ETT tip is erroneously positioned above the glottis, then the access to the airway is denied with wire removal; hence, the advantage of using the FFB as an intubation guide ([Fig. E1-17](#)).

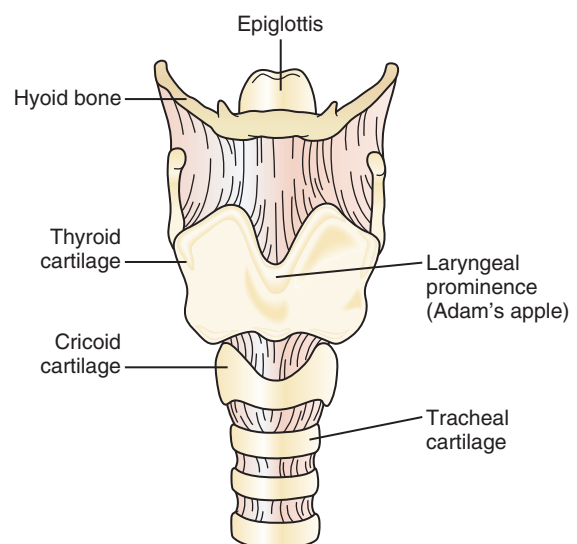


FIGURE E1-17 ■ Anatomic landmarks for access to the cricothyroid membrane.

*Relative contraindications may be overlooked in the emergency situation.

PROCEDURE

- Retrograde tracheal intubation
 - Needle insertion directed cephalad; operator should approach with dominant hand more caudad (e.g., right-handed operator on right side of patient)
 - Puncture cricothyroid membrane with needle directed cephalad (Fig. E1-18). Aspirate air with syringe to locate air column (1-2 mL of saline in syringe; allow bubbles to percolate to verify the air column).
 - Pass the guide wire through needle aimed superiorly so that distal end of wire may be retrieved from mouth (or if desired, nose) of patient. Withdraw needle off wire
 - Pull majority of wire out of the mouth (or naris)
 - Secure distal end of wire by clamping hemostat at level of the cricothyroid membrane (Figs. E1-19 and E1-20).
 - Three choices to pass ETT down the wire into the airway (nasal or oral): (1) wire assisted, (2) wire with obturator to reinforce wire, (3) flexible bronchoscope (loaded with ETT) passed over wire into airway
 - Wire assisted
 - Load lubricated ETT over oral (or nasal) end of wire, passing wire into tube through Murphy's eye.
 - Pull wire relatively taut and straight.
 - Advance ETT over wire into trachea to cricoid area and then, gradually relaxing cricothyroid end of wire, advance ETT to appropriate intratracheal location.
 - Release cricothyroid end of wire, and withdraw wire out of ETT.
 - Confirm ETT position (auscultation/capnography).
 - Wire with obturator to reinforce wire (Fig. E1-21)
 - Pass obturator over wire into airway until resistance is felt.
 - See manufacturer's instructions for Cook retrograde intubation kit.
 - Load lubricated ETT over oral (or nasal) end of wire/obturator.
 - Advance ETT into trachea to cricoid area.
 - Remove wire from cricothyroid membrane end, and then advance obturator distally into trachea.
 - Advance ETT to appropriate intratracheal location.
 - Confirm ETT position (auscultation/capnography).
 - FFB (loaded with smaller sized ETT [6-7 mm]) (Fig. E1-22)
 - Advance wire through the suction portal of the FFB.
 - Grasp wire end from top of FFB.
 - Advance FFB down wire, observing the airway structures as you advance (Fig. E1-23).

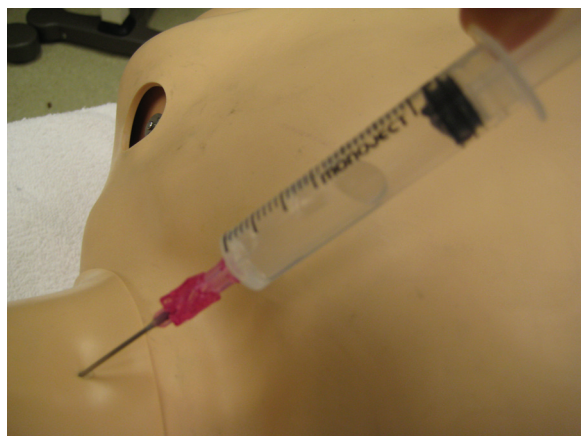


FIGURE E1-18 ■ Puncture of cricothyroid membrane, with air aspiration reflected in bubbling in saline-filled syringe.

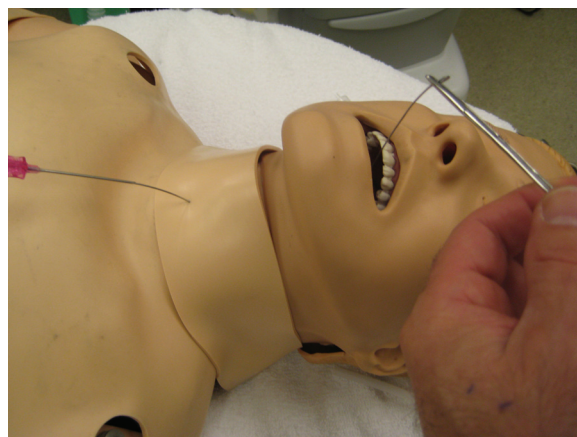


FIGURE E1-20 ■ Advancing the wire from the neck to the oral cavity.

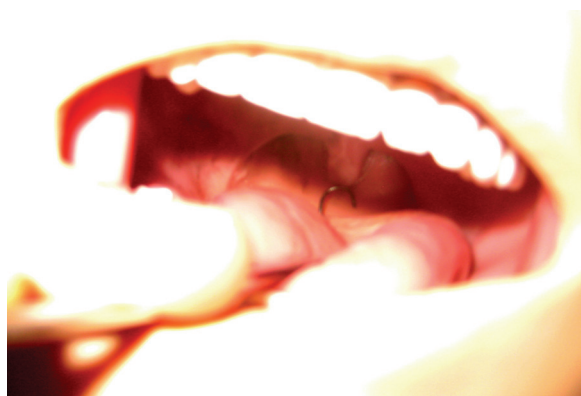


FIGURE E1-19 ■ Locating and retrieving the retrograde wire within the oral cavity.



FIGURE E1-21 ■ Passing the Cook obturator over the retrograde wire to reinforce the wire to allow ease of passing the ETT into the airway.

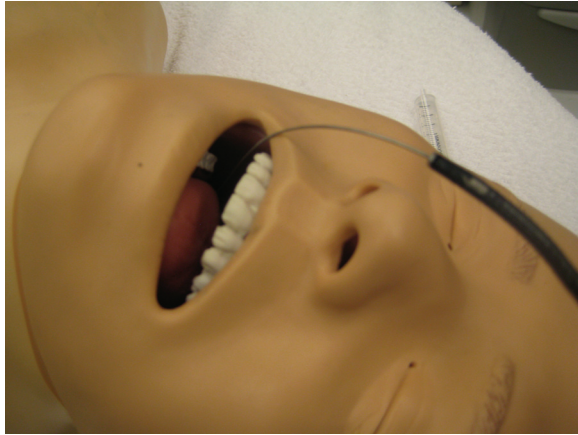


FIGURE E1-22 ■ A better choice than the obturator is the FFB passed over the wire via the suction port of the fiberoptic bronchoscope.

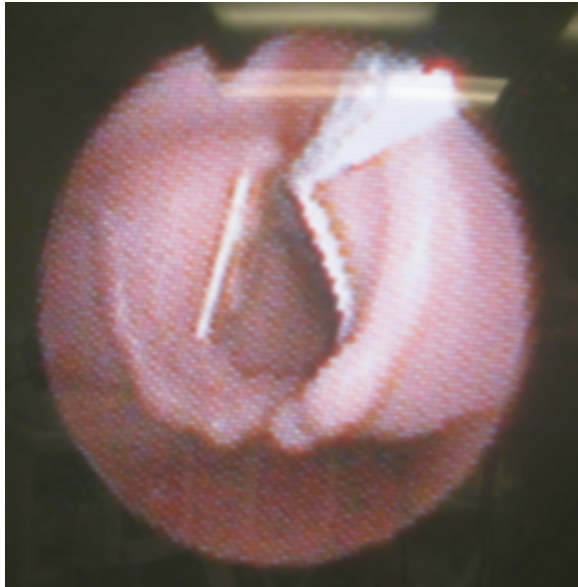


FIGURE E1-23 ■ Retrograde wire seen emerging from glottis.

- Advancing the FFB to distal end of wire will occlude view and appear “pink” (backside of cricothyroid membrane). Correct position may be verified by darkening the room to transilluminate the cricothyroid membrane puncture site (Fig. E1-24).
- Once the FFB is below the vocal cords, the cricothyroid end of wire may be released as fiberscope is advanced to carina and wire and then pulled out of fiberscope.
- Or the wire may be pulled out inferiorly through cricothyroid puncture and fiberscope and advanced into the trachea.
- Advance the FFB tip into distal trachea, and advance ETT into position and confirm.

■ AFTER PROCEDURE

Postprocedure Care

- Following advancement of ETT into the trachea, stabilize the ETT in position.
- Standard methods of determining the ETT position are required.

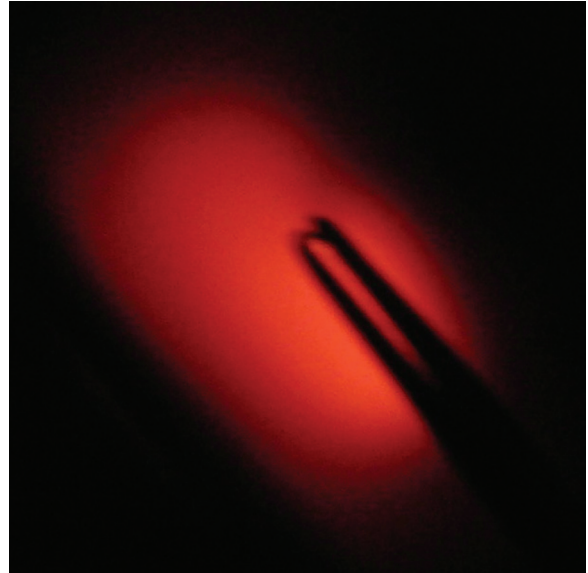


FIGURE E1-24 ■ Flexible fiberoptic bronchoscope (FFB) passed over retrograde wire, with tip of FFB at wire insertion site at the cricothyroid membrane, with transillumination of light from the FFB.

Complications

- Inability to locate wire in oral cavity/nose
 - Use light (e.g., laryngoscope) to assist locating wire
 - Pick up wire with hemostat
- Infrequent
 - Tissue injury when picking up wire with hemostat
 - Hematoma from injury to the cricothyroid artery
 - Subcutaneous emphysema
 - Infection at site of insertion (rare)
 - False tract from passing wire
- Serious rare complications
 - Possible airway obstruction, loss of airway, laryngospasm

■ OUTCOMES AND EVIDENCE

Retrograde intubation, once a prominent adjunct prior to today's many varied airway devices, retains an important position in managing the difficult airway, but it has been relegated to a much less prominent role. It is important for clinicians to maintain the ability, knowledge, and equipment to perform this specialized method of securing the airway. Even in the best of clinical situations and manned by an experienced team, this method remains a relatively time-consuming technique that limits it to the nonemergency pathway, where ventilation/oxygenation is possible with either bag-mask ventilation or SGA or the patient is awake breathing spontaneously.

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NEEDLE CRICOTHYROTOMY WITH TRANSTRACHEAL JET VENTILATION: BEFORE PROCEDURE

Indications

(Similar to cricothyrotomy)

- Impossible or failed oral or nasal endotracheal intubation owing to any of the following
 - Difficult or impossible intubation (CVCI: cannot ventilate, cannot intubate)
 - Massive oral, nasal, or pharyngeal hemorrhage
 - Massive regurgitation or emesis
 - Masseter spasm, clenched teeth, TMJ limitations
 - Structural deformities of oropharynx, congenital or acquired
 - Stenosis/narrowing of upper airway
 - Mass (cancer, tumor, polyp, or other) with partial obstruction
- Airway obstruction (partial but not complete) above cricothyroid membrane
 - Nontraumatic versus traumatic
 - Oropharyngeal edema
 - Mass (cancer, tumor, polyp, or other) (Fig. E1-25)
 - Traumatic
 - Foreign body obstruction
 - Stenosis
- Traumatic injuries making oral or nasal endotracheal intubation difficult or potentially hazardous
 - Maxillofacial injuries
 - Cervical spine instability

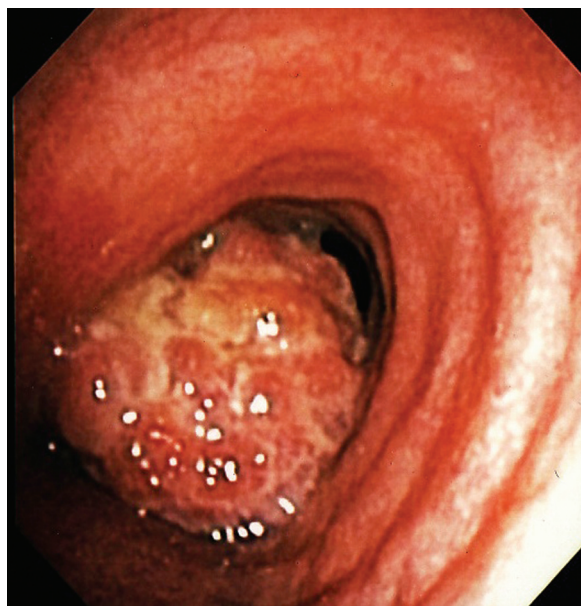


FIGURE E1-25 ■ Classic example of when not to incorporate transtracheal jet ventilation (TTJV). This intratracheal tumor mass occludes more than 85% of the tracheal lumen. Providing high-pressure TTJV supports oxygen transfer into the pulmonary tree, but overpressurization of the thorax will likely occur, because egress of the transmitted pressure may be blocked by the mass and its potential ball-valve effect. Likewise, a glottic or subglottic mass (above the site of needle insertion) may equally disallow egress or relief of the pressure buildup with high-pressure TTJV, thus leading to barotrauma.

Contraindications

- Absolute contraindications
 - Endotracheal intubation can be accomplished easily and quickly, and no contraindications to endotracheal intubation are present.
 - Transection of trachea with retraction of distal end into the mediastinum
 - Fracture or other significant injury of the larynx or cricoid cartilage
 - Lack of egress of pressurized airflow (exhalation, must insure good air in, bad air out) resulting in inability to relieve pressured insufflation from trachea
- Relative contraindications*
 - Infants and toddlers (<3 years)
 - Bleeding diathesis
 - Patients with massive neck edema or lack of landmarks
 - Acute laryngeal disease

Equipment

- Sanders handheld high-pressure ventilator
- 12/14-gauge Jelco IV catheter on a syringe
- Optional: wire-reinforced needle-catheter (e.g., Cook Critical Care)
- Alternatively: ENK oxygen modulator system by Cook Critical Care (low-pressure choice). Requires 15 L/min oxygen supply. Oxygen delivery is derived by finger occlusion of the portals on the plastic assembly. Delivered in similar ratio as high-pressure transtracheal jet ventilation (TTJV). Newer products are being developed that allow more accurate pressure delivery and air egress in the hopes of improving oxygenation, reducing barotrauma, and improving patient safety.

ANATOMY

The thyroid cartilage consists of two approximately quadrilateral-shaped laminae of hyaline cartilage that fuse anteriorly to form the laryngeal prominence. The anterior superior edge of the thyroid cartilage, the laryngeal prominence, is known as the *Adam's apple* and is usually easily seen in men. It is probably the most important landmark in the neck when performing a cricothyrotomy. The cricoid cartilage is shaped like a signet ring with the shield located posteriorly and forms the inferior border of the cricothyroid membrane. The thyroid cartilage forms the superior border of the cricothyroid membrane.

The cricothyroid membrane is a dense fibroelastic membrane located between the thyroid cartilage superiorly and the cricoid cartilage inferiorly; the cricothyroid muscles bound it laterally. The cricothyroid membrane covers an area that is trapezoidal in shape. The average size of the cricothyroid membrane in the adult is approximately 22 to 30 mm wide and 9 to 10 mm high. Palpating a notch, a slight indentation or dip in the skin inferior to the laryngeal prominence, can identify the cricothyroid membrane. The cricothyroid membrane is located approximately 2 to 3 cm below the laryngeal prominence in an adult.

PROCEDURE

- Place the patient in supine position (shoulder roll to extend cervical spine forward if possible).
- Prep neck area if time permits.
- Locate cricothyroid membrane.
- Using a 12- or 14-gauge needle on a syringe, puncture the skin midline and directly over the cricothyroid membrane. (2-3 mL saline in 5- or 10-mL syringe will assist visualizing bubbles).

*Relative contraindications may be overlooked in the true emergency situation, because it is more important to obtain an airway and avoid hypoxemia.

- Direct the needle at a 45-degree angle caudally, and carefully insert it through the upper half of the cricothyroid membrane, aspirating as the needle is advanced. Aspiration of air signifies entry into the tracheal lumen.
- Secure the needle (assign one person to maintain catheter position), and attach Luer-Lok end of high-pressure ventilator.
- Administer low-pressure airflow (5-10 psi initially) bursts of positive-pressure ventilation.
- 6-10 breaths per minute to maximize exhalation time (I/E ratio > 1:5)
- Adjust pressure upward with the goal of visible chest wall excursions and life-sustaining saturation.
- Continue efforts to maintain airway patency to ensure egress of pressurized air (exhalation)
 - Jaw thrust, chin lift, neck extension
 - Oral airway, nasal airway, tongue retraction
 - SGA device, laryngoscopy
- TTJV is short-term oxygen delivery strategy during airway management difficulties.
 - Alternative airway management methods should be pursued.
 - Continue efforts to secure the airway from above if feasible.
 - Pressurization of airway may allow previously failed rescue methods to succeed—i.e., drive airway upward through the glottis, thus revealing an otherwise collapsed, edematous, or unrecognizable airway.
- NOTE: Placing catheter via cricothyroid membrane prior to airway intervention (anticipating difficulty) is acceptable, since placement during a crisis is often hindered by lack of landmarks, suboptimal positioning, and inexperience. If placed but not used, it can be simply removed with little consequence.

AFTER PROCEDURE

Postprocedure Care

- TTJV is considered a short-term “fix” to supplement oxygenation in a life-saving fashion; ventilation (CO₂ exchange) may be limited.
- Continued efforts to secure the airway with advanced techniques (FFB, VAL, SGA) should be pursued.
- Creation of a surgical airway (tracheostomy) is possible with active TTJV taking place.
- Removal of the catheter is quick and with little consequence.

Complications

- Common
 - Kinking of the catheter (use wire-reinforced catheter)
 - Blockage or obstruction of the catheter (redirect or withdraw slightly)
- Infrequent
 - Subcutaneous emphysema of neck, thorax, face
 - Minor bleeding
 - Infection (rare)
 - Incorrect or unsuccessful catheter placement
- Serious, rare complications
 - Damage to the laryngeal cartilage
 - Serious hemorrhage due to severed blood vessel
 - Posterior wall perforation (concerning), but if followed by TTJV, devastating consequences may take place
 - Pressurization of intratracheal airway leading to barotrauma, pneumothorax or worse, tension pneumothorax, pneumomediastinum, pneumopericardium

OUTCOMES AND EVIDENCE

- Patient outcomes after TTJV are related to their coexisting condition

- Recognized as life-saving maneuver in many airway management algorithms
- Lack of training, lack of practice, low frequency of performing procedure make it high risk
- Successful catheter placement may be fraught with incorrect I:E ratio, excessive delivery of breaths (>12/min), lack of pressure egress
- Owing to the emergency nature of the procedure, randomized controlled studies in humans are not possible in the emergency setting.
- Technique used successfully in elective setting with proper equipment, trained and knowledgeable personnel performing TTJV

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NEEDLE AND SURGICAL CRICOTHYROTOMY: BEFORE PROCEDURE

Indications

- Impossible or failed oral or nasal endotracheal intubation due to any of the following
 - Very difficult/impossible intubation (ventilation/oxygenation possible)
 - CVCI airway
 - Massive oral, nasal, or pharyngeal hemorrhage
 - Massive regurgitation or emesis
 - Masseter spasm
 - Clenched teeth
 - Structural deformities of oropharynx, congenital or acquired
 - Stenosis of upper airway
 - Laryngospasm
 - Mass (cancer, tumor, polyp, or other)
- Airway obstruction (partial or complete) that cannot be cleared
 - Nontraumatic
 - Oropharyngeal edema
 - Laryngospasm
 - Mass (cancer, tumor, polyp, or other away from insertion site)
 - Traumatic
 - Foreign body obstruction (above level of insertion)
 - Supraglottic, glottic, or subglottic stenosis/narrowing (above insertion site)
- Traumatic injuries making oral or nasal endotracheal intubation difficult or potentially hazardous
 - Maxillofacial injuries
 - Cervical spine instability

- Elective versus urgent versus emergent
 - Elective: critical airway situation noted prior to induction, patient hemodynamically stable, oxygenation/ventilation adequate
 - Urgent: critical airway situation noted prior to or during induction, patient's hemodynamics and/or oxygenation/ventilation compromised
 - Emergent: critical airway situation during induction, patient hemodynamically unstable and/or oxygenation/ventilation deterioration

Contraindications

- Absolute contraindications
 - Endotracheal intubation can be accomplished easily and quickly, and no contraindications to endotracheal intubation are present.
 - Transection of trachea with retraction of distal end into the mediastinum
 - Fracture or other significant injury of the larynx or cricoid cartilage
- Relative contraindications*
 - Infants and toddlers (<3 years)
 - Bleeding diathesis
 - Patients with massive neck edema, lack of landmarks
 - Acute laryngeal disease (mass, tumor, infection over cricothyroid membrane)

Equipment

- Homemade
 - Guide wire
 - #20 scalpel blade
 - 14-, 16-, or 18-gauge cutting needle on a syringe (depending on wire gauge)
 - Cuffed 6.0 ETT on a dilator (with lumen)
 - Optional: cuffed, nonfenestrated, #4 and #5 tracheostomy tubes
 - Scalpel, #11
 - Trousseau dilator
 - Tracheal hook
 - 4 × 4 gauze sponges
 - Optional equipment: 2 small hemostats, surgical drapes, 1% lidocaine with syringe and needle
- Prepackaged (e.g., Melker Cricothyrotomy, Cook Critical Care) (Fig. E1-26)

ANATOMY

The thyroid cartilage consists of two approximately quadrilateral-shaped laminae of hyaline cartilage that fuse anteriorly to form the laryngeal prominence. The anterior superior edge of the thyroid cartilage, the laryngeal prominence, is known as the *Adam's apple* and is usually easily seen in men. It is probably the most important landmark in the neck when performing a cricothyrotomy. The cricoid cartilage is shaped like a signet ring with the shield located posteriorly and forms the inferior border of the cricothyroid membrane. The thyroid cartilage forms the superior border of the cricothyroid membrane (Fig. E1-27).

The cricothyroid membrane is a dense fibroelastic membrane located between the thyroid cartilage superiorly and the cricoid cartilage inferiorly; the cricothyroid muscles bound it laterally. The cricothyroid membrane covers an area that is trapezoidal in shape. The average size of the cricothyroid membrane in the adult is approximately 22 to 30 mm wide and 9 to 10 mm high. Palpating a notch, a slight indentation or dip in the skin inferior to the laryngeal prominence, can

*Relative contraindications may be overlooked in the true emergency situation, because it is more important to obtain an airway and avoid hypoxemia.

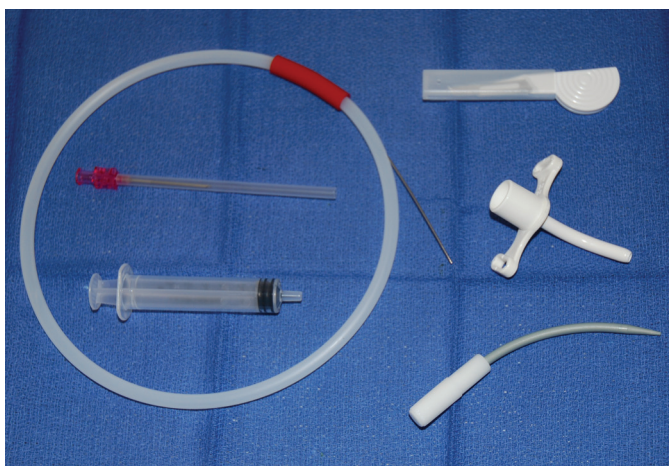


FIGURE E1-26 ■ Prepackaged surgical kit.



FIGURE E1-27 ■ Anatomic outline shows the sternal notch (lower "V"), the straight line (cricoid ring), and the two curved arrows that overlie the cricothyroid membrane, with the outline of the thyroid cartilage above the cricothyroid membrane.

identify the cricothyroid membrane. The cricothyroid membrane is located approximately 2 to 3 cm below the laryngeal prominence in an adult.

PROCEDURE: CONVENTIONAL APPROACH

- Place the patient in a supine position, hyperextended neck with shoulder roll if possible.
- Surgically prep the area using antiseptic solution (if applicable, time permitting).
- Palpate the cricothyroid membrane anteriorly, between the thyroid cartilage and cricoid cartilage.
- Immobilize the larynx—in the right-handed operator, the thumb and long fingers of the left hand are used to grasp the thyroid cartilage.
- Incise the skin—vertical and midline, approximately 2 to 3 cm in length from the depth of the thyroid cartilage, membrane, and cricoid cartilage.
- Prepare subcutaneous tissue—dissect down to the cricothyroid membrane.
- Incise the membrane—transverse, midline, and at least 1.5 cm long to facilitate ETT placement.

- Place tracheal hook on lower edge of thyroid cartilage and lift upward and cephalad.
- Alternatively, place tracheal hook on upper edge of cricoid ring and lift upward and caudad.
- Place ETT or tracheostomy tube—smaller diameter preferred (5.0 to 6.5 mm)
- Inflate cuff and confirm placement using auscultation and/or capnography.
- Secure the tube.
- Optional: FFB evaluation

■ PROCEDURE: STYLET-DILATOR METHOD

- Place the patient in a supine position, hyperextended neck with shoulder roll if possible.
- Surgically prep the area using antiseptic solution (if applicable, time permitting).
- Palpate the cricothyroid membrane anteriorly, between the thyroid cartilage and cricoid cartilage.
- Using a 14-gauge needle on a syringe, puncture the skin midline and directly over the cricothyroid membrane.
- Direct the needle at a 45-degree angle caudally, and carefully insert it through the upper half of the cricothyroid membrane, aspirating as the needle is advanced. Aspiration of air signifies entry into the tracheal lumen.
- Secure the needle, and advance the flexible end of the wire first.
- Once a sufficient amount of the wire is introduced into the trachea, remove the needle.
- Using a 20-blade scalpel, make a deep horizontal puncture.
- Insert the dilator and endotracheal tube assembly onto the wire, and gently advance through the cricothyroid membrane with a continuous downward twisting motion.
- Remove the dilator, inflate the endotracheal cuff, and connect the breathing circuit.
- Secure ETT, auscultate breath sounds, and confirm the return of CO₂.
- Optional: FFB evaluation of airway

■ PROCEDURE: SELDINGER TECHNIQUE—MELKER COOK CRITICAL CARE

- Supine position, hyperextended neck with shoulder roll if possible
- Surgically prep the area using antiseptic solution (if applicable, time permitting).
- Palpate the cricothyroid membrane anteriorly, between the thyroid cartilage and cricoid cartilage.
- Immobilize larynx as described earlier.
- Puncture the skin and the cricothyroid membrane with the puncture cannula with connected syringe.
- Aspiration of air confirms entry into trachea with needle directed caudad.
- Disconnect syringe from needle, pass the wire caudad into airway, remove needle.
- Incise skin 0.5 to 1 cm on each side of the wire guide.
- Insert the dilator together with deflated airway catheter over the wire, through the skin, into the trachea.
- Remove dilator, inflate cuff, and confirm correct tube placement.
- Secure ETT, auscultate breath sounds, and confirm the return of CO₂.
- Optional: FFB evaluation of airway

■ PROCEDURE: SURGICAL APPROACH—RAPID FOUR-STEP OR MODIFIED THREE-STEP

- Supine position, hyperextended neck with shoulder roll if possible
- Surgically prep the area using antiseptic solution (if applicable, time permitting).

- Palpate the cricothyroid membrane anteriorly, between the thyroid cartilage and cricoid cartilage.
- Immobilize larynx as described earlier.
- Incise skin and cricothyroid membrane transversely with scalpel blade.
- Insert a tracheal hook through the incision; secure the cricoid cartilage with the hook.
- Move to a more ventral and caudal position (outward and downward direction with hook).
- Insert smaller-diameter ETT into opening of trachea.
- Three-step technique
 - Midline incision into the skin followed by horizontal division of cricothyroid membrane
 - Advancement of elastic bougie through tracheal space into right mainstem bronchus
 - Advancement of ETT over bougie, removal of bougie
 - Secure ETT, auscultate breath sounds, and confirm the return of CO₂.

■ AFTER PROCEDURE

Postprocedure Care

- Postprocedure care should include the insertion of an orogastric or nasogastric tube in cases of full stomach.
- Revision of the cricothyrotomy may be needed as soon as the patient is stable.
- Most cases have previous laryngeal damage or postobstruction pulmonary edema and will require ventilation in the ICU.

Complications

- Common
 - Kinking of the catheter, wire
 - Blockage or obstruction of the catheter
- Infrequent (potentially life-threatening)
 - Kinking of the catheter
 - Aspiration
 - Creation of false passage into the tissue
 - Subglottic stenosis
 - Laryngeal stenosis
 - Hemorrhage/hematoma
 - Esophageal/tracheal laceration
 - Mediastinal emphysema
 - Vocal cord injury
 - Minor bleeding
 - Infection
 - Incorrect or unsuccessful catheter placement
- Serious rare complications
 - Damage to the laryngeal cartilage
 - Serious hemorrhage due to severed blood vessel
 - False passage, loss of airway
 - Pneumothorax, tension component

■ OUTCOMES AND EVIDENCE

- Patient outcomes after needle cricothyrotomy are related to coexisting conditions.
 - Lowest survival rates are associated with cricothyrotomy undertaken during cardiac arrest (only 6%), compared to 76% for any other reason.
- Most common causes of death are patient comorbidities, followed by failure to achieve an airway, and last, by the procedure itself.
- Owing to the emergency nature of the procedure, randomized controlled studies in humans are not likely to be performed.
- Because cricothyroidotomy is a rarely performed but potentially life-saving procedure of last resort in the patient with a failed airway, clinicians responsible for airway management must retain familiarity with the necessary equipment and relevant anatomy.

- Clinicians responsible for advanced airway management should review the anatomy and practice with the equipment needed for cricothyroidotomy several times per year.
- At the very least, clinicians should know who to call for assistance with gaining surgical access to the airway.
- Immediate access to needed equipment is imperative to optimize patient safety.
- Delay in starting surgical access, lack of equipment, and inexperience with the technique are the most common underlying reasons for poor outcome.
- While an emergency surgical airway may be glamorized to be done rapidly, given common anatomic and positioning restraints (cervical collar, CPR, ongoing BVM, poor positioning, obese thick neck devoid of landmarks), it is the exception that it can be performed accurately in less than 45 seconds. Clinical experience suggests >1 to 3 minutes and well beyond this time frame in many instances.

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ESOPHAGEAL-TRACHEAL COMBITUBE: ALTERNATIVELY, THE RUSCH EASY TUBE (SMALLER—LATEX FREE COMBITUBE LOOK ALIKE AND THE KING LT-LARYNGEAL TUBE-SINGLE LUMEN, ESOPHAGEAL PLACEMENT, ONE SYRINGE FOR DUAL CUFF INFLATION): BEFORE PROCEDURE

Indications

- Emergency airway device in the CVCI pathway
 - Provides rapid control of airway when intubation is impossible and other techniques of securing the airway fail
- Airway management when the patient situation disallows laryngoscopy or bag-mask ventilation due to positioning, confinement
 - Example: trapped in a car after motor vehicle crash and inability to perform laryngoscopy

Contraindications

- Absolute
 - Pediatrics or patients less than 4 feet tall
 - Pediatric sizes unavailable
 - Airway obstruction (supraglottic and below)

- Intact gag reflex
- Recent upper esophageal surgery (i.e., Ivor Lewis esophagogastricectomy)
- Caustic ingestion
- Latex allergy
 - Combitube includes latex in its construction
 - Alternative product: EasyTube, Rusch Medical (latex free); similar in design to Combitube
- Relative
 - Elective/nonemergent situations
 - Example: easy intubation, easy bag-mask ventilation
 - Esophageal pathology (proximal third, upper portion)
 - Example: patient with known esophageal varices; however, if patient is hypoxic and no other airway is possible, benefits clearly outweigh risks. Variceal location tends to be in the lower half of the esophagus.
 - Anatomic alteration of supraglottic area, glottis, hypopharynx
 - Tumor, abscess, foreign body, swelling
 - Emergency short-term use for airway rescue is acceptable.
 - King laryngeal tube
 - Responsive patients with an intact gag reflex
 - Patients with known esophageal disease
 - Patients who have ingested caustic substances

Equipment

- The Esophageal-Tracheal Combitube (Kendall-Sheridan, Argyle, New York) is available in two sizes, 41F (large adult) and 37F. It is a double-lumen soft plastic tube that is inserted into the mouth with or without laryngoscopy and advanced blindly into either the trachea or esophagus (>90% pass into the esophagus). The Combitube has two inflatable cuffs: a smaller distal cuff similar to that of a conventional endotracheal tube and a larger proximal cuff designed to seal the pharynx. Once placed, the practitioner must ventilate the proper conduit to deliver oxygen into the trachea. Understanding the Combitube's design is imperative to its successful use and fosters the ability to troubleshoot difficulties. The Combitube is joined by its recently introduced cousins, the Rusch EasyTube and King laryngeal tube (LT). The Rusch EasyTube is a latex-free alternative that is offered in a large model (similar to the Combitube 41F) and a smaller adult version (35F). The Combitube enters the esophagus in over 95% of cases; ventilation is through lumen #1 (blue connector). End-tidal CO₂ detection, pulse oximetry, and other confirmatory measures must be confirmed for all placements. The occasional placement in the trachea requires ventilation of the lungs through lumen #2 (Fig. E1-28).
- Another airway device that is gaining popularity for in-hospital and prehospital use is the King LT, which is blindly inserted into the hypopharynx with the distal tip inserted past the

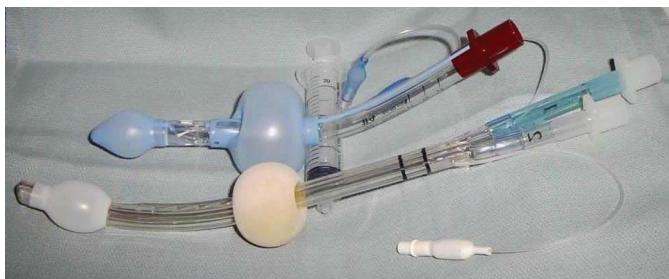


FIGURE E1-28 ■ King laryngeal tube (LT) (upper) and Combitube (lower) are both dual-balloon airway devices. Combitube has a long track record of excellent performance but is being challenged by the smaller sized King laryngeal tube, with its single pilot valve/dual cuff design and single ventilation portal.

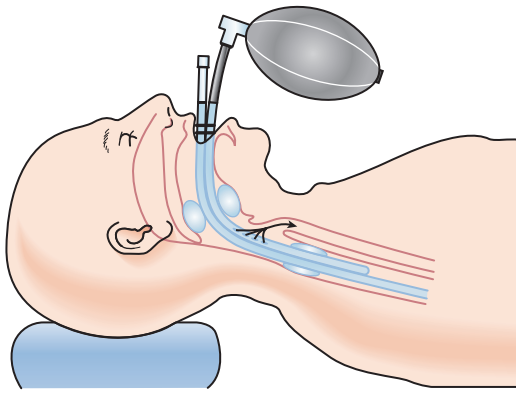


FIGURE E1-29 ■ Combitube in the esophageal position with both balloons inflated. Proper positioning of the eight side ventilation portals allow oxygen delivery into the glottis. If resistance is met when bagging, it is typically caused by two factors: (1) Combitube is positioned too deep, so some or all of the ventilation portals are occluded by esophageal mucosa (solution: withdraw Combitube to a more proximal position); (2) upper inflated cuff has forced the epiglottis downward and is partially or completely obstructing the glottic opening (solution: withdraw Combitube to a more proximal position).

cricopharyngeal opening of the esophagus (not in the trachea). The ventilation portal comes to rest posterior and inferior to the epiglottis in proximity to the open glottis. It has two high-volume low-pressure inflatable balloons similar to the Combitube (one that occludes the esophagus and one that inflates in the posterior oropharynx) yet requires fewer steps, because it is reliant on only a single site of inflation. The distal cuff is designed to seal the esophagus. The proximal cuff is intended to seal the oropharynx. Ventilation is achieved via a 15-mm connector (single portal as opposed to the Combitube's two) for attachment to a standard breathing circuit or resuscitation bag. The patient may breathe spontaneously via the King LT. CO₂ detection is adaptable to all three devices (Fig. E1-29).

ANATOMY

An understanding of basic airway, tracheal, and esophageal anatomy is required to interpret which lumen should be used to ventilate the patient. Also, if ventilation is unsuccessful, it is important to understand that the positioning of the Combitube may not be ideal, and it may have to be advanced or withdrawn slightly.

PROCEDURE: COMBITUBE

- The Combitube is an emergency airway management device for patients requiring rapid control of the airway, particularly when poor laryngoscopic visualization of the larynx makes tracheal intubation impossible.
- Insert appropriate-sized Combitube into patient's mouth, with or without laryngoscopy (the smaller-sized Combitube [37F] may be used in all adults <6 feet, 5 inches tall).
- Advance the Combitube blindly into either the trachea or esophagus.
- Stop advancing once the proximal depth indicator (two black rings) is at the level of the teeth.
- Inflate the smaller distal cuff and the larger proximal cuff that seals the pharynx.
- Ventilate through the proximal (blue, #1) lumen first, because 95% of Combitube placements result in an esophageal position and auscultate the lungs and stomach.

- If breath sounds are not heard but gastric sounds are, the Combitube has likely been placed in the trachea.
- Simply change ventilation to the distal (clear, #2) lumen, and recheck for breath sounds.
- If breath sounds are still not detectable by auscultation, the Combitube has likely been advanced too deeply into the esophagus, and the pharyngeal cuff is obstructing the glottis.
- If this occurs, deflate the pharyngeal cuff, withdraw the Combitube a few centimeters, and recheck for breath sounds.
- Once the appropriate lumen has been selected and ventilation appears adequate, confirm with capnography.

PROCEDURE: KING LARYNGEAL TUBE

The King LT is a supraglottic airway that uses two cuffs to create a supraglottic ventilation seal similar to the Combitube (hypopharynx and esophageal level). The King LT has a single ventilation port (15-mm connector) and a single valve and pilot balloon that simultaneously inflate both the pharyngeal and the esophageal balloons.

- Assuming the operator is familiar with the King LT, lubrication is applied and preoxygenation is completed.
- Sniffing position if possible but not required.
- Hold the King LT at the connector with dominant hand. With nondominant hand, hold mouth open and apply chin lift.
- With the King LT rotated laterally 45 to 90 degrees such that the blue orientation line is touching the corner of the mouth, introduce tip into mouth and advance behind base of tongue.
- As tube tip passes under tongue, rotate tube back to midline (blue orientation line faces chin).
- Without exerting excessive force, advance tube until base of connector is aligned with teeth or gums.
- Inflate via the single pilot valve until sealed (40-80 mL, depending on King LT size).
- Gently ventilate to assess position (free-flowing I/E, large V_T).
- Depth markings give an indication of the distance from the vocal cords to the teeth.
- Confirm proper position by auscultation, chest movement, and verification of CO₂.
- If ventilation is met with high resistance, slowly withdraw device until ventilation improves.
- Intubation may be accomplished with the FFB-Aintree combination (Figs. E1-30 and E1-31).
- The Rusch EasyTube is another alternative to these two products. It is available in two sizes; 41F and 28F, has a single lumen at the distal end, two separate cuffs for inflation as does the Combitube and a latex-free balloon and offers access to the upper airway (via a suction catheter, airway exchange catheter, or flexible bronchoscopy).

AFTER PROCEDURE

Postprocedure Care

- Once patient is stabilized and adequately ventilated and oxygenated, a more definitive airway should be secured.
 - It is an acute emergency airway device.
 - The three products are not intended for extended use in the emergency patient.
 - Intubation of the trachea is favored in most patients, so a plan should be developed to change to an ETT.
 - Changing to an ETT may be performed with the use of conventional and advanced airway devices.
 - If exchange is considered to be dangerous and risky (desaturation, massive edema, poor pulmonary compliance) or it proves to be impossible to identify the glottic opening, securing the airway surgically may be the best (or only) alternative.
 - When the three devices are in the esophageal position, surgical entrance into the trachea is not impeded by the airway device.

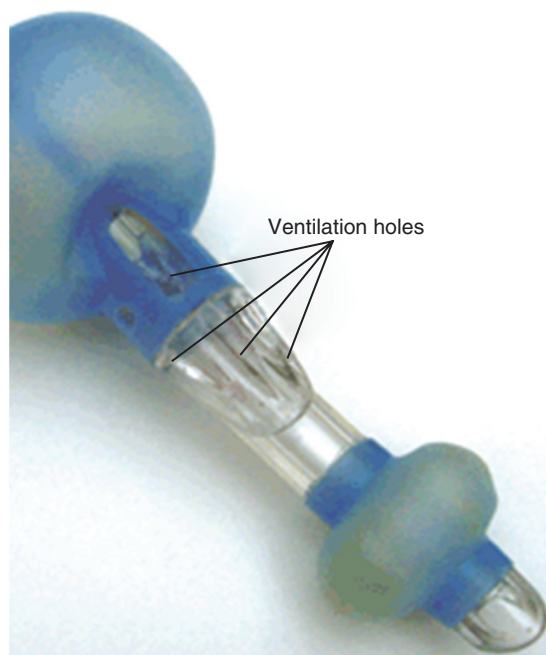


FIGURE E1-30 ■ Close-up view of King laryngeal tube and the ventilation holes that come to lie posterior to the glottic opening. The upper opening will emit an FFB or FFB-Aintree combo to visualize/intubate the trachea. (With permission from Ambu, Inc., Glen Burnie, Maryland.)

Complications

- Common
 - Difficulty maintaining a cuff seal to provide adequate positive-pressure ventilation
 - Regurgitation and aspiration would ideally be limited, but complete protection is not guaranteed.
- Serious, rare complications
 - Lacerations to the esophageal wall or pyriform sinus
 - Can result in subcutaneous emphysema, pneumomediastinum, pneumoperitoneum, and esophageal rupture
 - Ischemia of tongue/airway edema if left in place for long duration

OUTCOMES AND EVIDENCE

These devices, though relatively simple and timely to place, do require complete familiarization with their placement, cuff inflation features, and limitations. The King LT is popular as an elective airway support device as well as a useful rescue airway device in cases of an unexpectedly difficult airway. Anecdotally, clinicians may prefer the King LT based on its smaller size and simplicity with one inflation portal.

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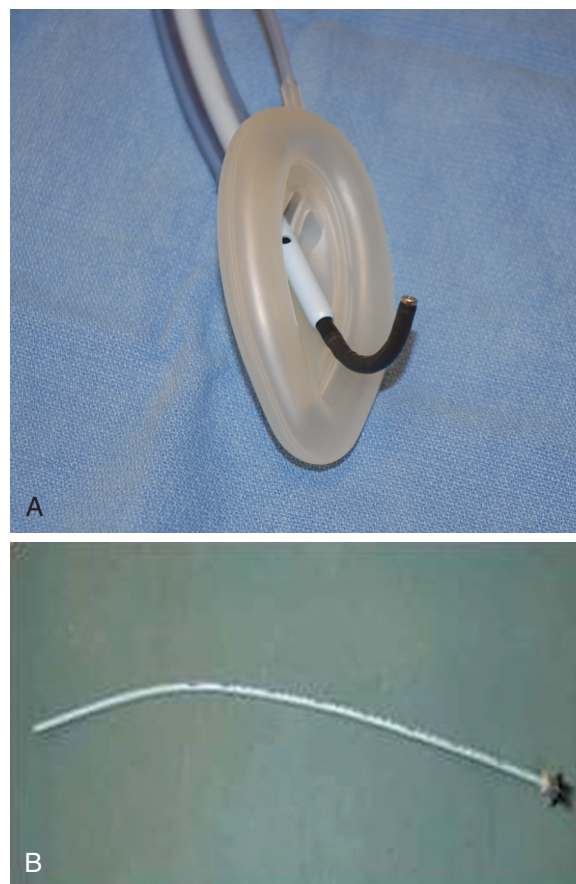


FIGURE E1-31 ■ **A**, The Cook brand Aintree catheter acts as a “jacket” around the flexible fiberoptic bronchoscope (FFB), which is then passed (in this case) via the laryngeal mask airway to assist in visualizing the glottic opening. The Aintree-FFB combo can be passed via the ventilation portal of the King laryngeal tube (LT) to allow passage into the trachea. Following removal of the FFB from the Aintree (which remains in the trachea), the King LT is removed over the Aintree. A lubricated endotracheal tube (ETT) is then passed over the Aintree, as it acts as a bougie. **B**, The Aintree catheter, a 56-cm-long, hollow catheter.

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EVALUATION OF A CUFF LEAK IN THE ICU: BEFORE PROCEDURE

Indications

- Audible cuff leak in an intubated patient may represent a variety of problems
 - Tear/microperforation or macroperforation of ETT cuff
 - Remedy: exchange ETT



FIGURE E1-32 ■ Commercially available pilot balloon repair kit. Blunt needle is inserted into the cut end of the pilot valve line.

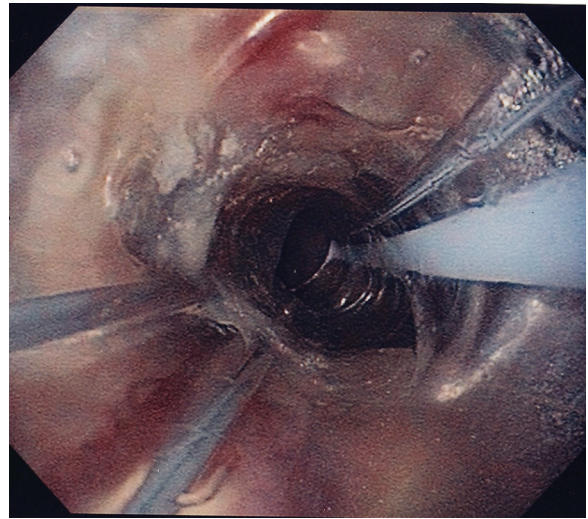


FIGURE E1-33 ■ This patient had a continuous “cuff leak” while supported on mechanical ventilation. The endotracheal tube (ETT) depth was 25 cm at the dentition, yet the ETT tip is just below the vocal cords when viewed with the FFB. The barely visible white vocal cords are “stretched” by the ETT and are located laterally in the picture. In the upper right corner is the bluish edge of the lower portion of the ETT cuff. Distally at the ETT, one can see with the FFB that the posterior wall of the thyroid cartilage is visible (not seen in this picture).

- Broken pilot balloon line
 - Remedy: occlude line perforation, inflate cuff, clamp line with Kelly/hemostat (temporary, low risk)
 - Remedy: cut line, attach new pilot balloon/valve/line assembly, reinflate balloon (less temporary, may perform well long term, low risk)
 - Change ETT (high risk) (Fig. E1-32).
- Incompetent valve/pilot balloon perforation/dysfunction
 - Remedy: cut line, attach new pilot balloon/valve/line assembly, reinflate balloon (less temporary, may perform well long term, low risk)
 - Remedy: inflate cuff, clamp line with Kelly/hemostat (temporary)
 - Remedy: change ETT (high risk)
- ETT cuff/tracheal wall incongruity (tracheomalacia, tracheal softening, tracheitis, overstretched poorly compliant cuff)
 - Remedy: advance ETT/cuff to alternative level in trachea (temporary, low risk)
 - Remedy: change ETT (high risk) or change tracheostomy to larger size, length, or cuff shape/design (moderate or high risk if trach >10 days old)
- Dislocation of ETT (partial or complete extubation of the trachea) is typified by three potential locations within the airway
 - Cuff between vocal cords (partial extubation)
 - ETT tip at level of vocal cords (complete extubation)
 - ETT tip/cuff in hypopharynx (complete extubation) (Figs. E1-33 through E1-35)
- Partial/complete extubation of the airway, masquerading as an ETT with a cuff leak, must be identified
 - It is imperative to check the status of the pilot balloon.
 - If the pilot balloon appears to be intact (holds insufflated air), the ETT tip/cuff location is likely not intratracheal.
 - If the “cuff” leak is erroneously identified as a malfunctioning ETT cuff, and the airway team passes an airway exchange catheter (AEC), the misplaced distal tip of the ETT may allow passage of the AEC to areas external to the trachea (e.g., esophagus, pyriform sinus)

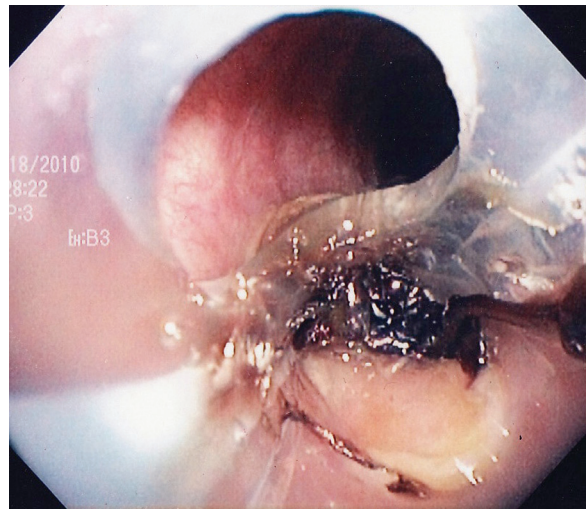


FIGURE E1-34 ■ The ICU physician was called to evaluate an intermittent “cuff leak,” difficulty passing the suction catheter, and waxing/waning oxygen saturation. The pilot balloon was intact and inflated. Flexible fiberoptic bronchoscopic exam found the endotracheal tube (ETT) tip was impaled on the vocal cord, with a view of the subglottic area via the Murphy eye of the ETT. The FFB was passed into the trachea via the Murphy eye, and the ETT was gently advanced into the trachea.

- Two methods are strongly recommended to diagnostically and therapeutically manage the possible ETT tip/cuff dislocation
 - First choice: FFB to diagnose the tip location and therapeutically allow reintubation of the trachea if possible (85% likely at authors’ institution)
 - Second choice: laryngoscopy, preferably VAL versus direct laryngoscopy (DL), so as to allow improved visualization of the airway and possibly improve the margin of safety in this

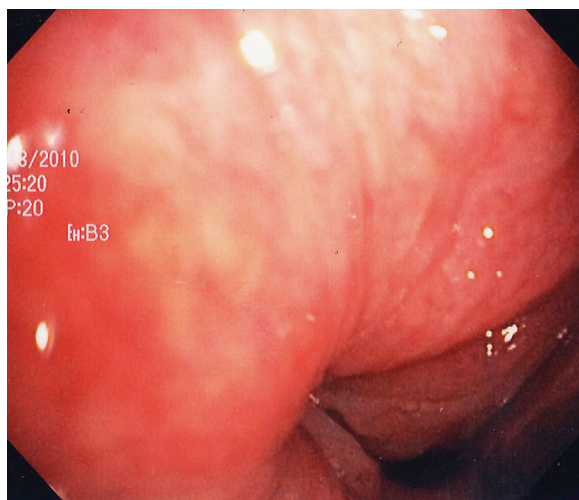


FIGURE E1-35 ■ The intensive care unit team was called to investigate a continuous “cuff leak” in this patient. The pilot balloon was intact; the fiberoptic bronchoscopic (FFB) view of the vocal cords from the tip of the endotracheal tube (ETT) reveals that the ETT tip is well above the glottic opening. The FFB was advanced into the trachea, and the ETT was then returned to the tracheal position.

potentially life-threatening consequence of the intubated ICU patient

- **Caveat:** How reliable is the level of the ETT at the dentition line in determining where the tip is located (based on a database of 245 cases of partial extubation at the authors' institution)?
 - ETT at <20 cm at the dentition line: 55% were above the glottis
 - ETT at >20 cm: 73% at level of glottis or above glottis (hypopharynx)
- **Conclusion:** There appears to be little correlation of ETT markings at the dentition line and the location of the ETT tip.
- Overall, 51% ETT tips were above the vocal cords, 32% were at the level of the vocal cords, and in 17%, the cuff was located between the vocal cords on examination.
- **Caveat:** Is there any difference in the incidence of complications when using FFB versus DL to diagnose and manage a dislocated ETT?
 - Managing this clinical situation with DL alone was fraught with complications such as severe hypoxemia, esophageal intubation, loss of the airway, bradycardia, and cardiac arrest.
 - Diagnostic and therapeutic management with FFB was an overall excellent choice, but it was not without its own problems. The ETT tip that was above the vocal cords was often centralized and easily advanced into the trachea, but approximately 15% to 20% of these cases had the ETT tip abutting the vocal cords, pharyngeal wall, or other tissues that made it very difficult to advance the FFB into the trachea. Several of these ETTs had to be moved more proximal to allow FFB advancement, but this was not always successful.
 - Alternative airway management schema beyond the FFB must be available to rescue the airway in the event difficulty is encountered.

Contraindications

- Absolute
 - Difficult intubation and ETT can be salvaged by some other means than replacing it (e.g., repair of pilot balloon or clearing

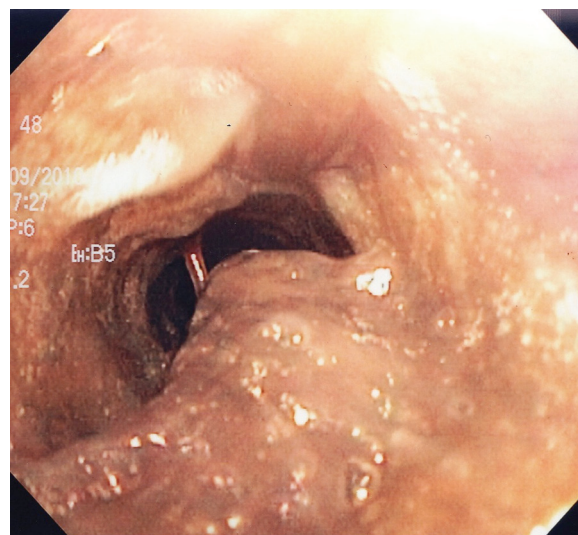


FIGURE E1-36 ■ This patient immediately failed a continuous positive airway pressure (CPAP) trial. Investigation with fiberoptic bronchoscopy (FFB) found significant biofilm accumulation at several levels of the endotracheal tube (ETT) lumen. A choice of exchanging to a new ETT was contemplated, but the patient was a known difficult airway. A catheter with an inflatable cuff (similar to a Fogarty catheter) that had a mesh covering for “traction” was passed and was able to remove 90% of biofilm blockage in less than 90 seconds on two passes.

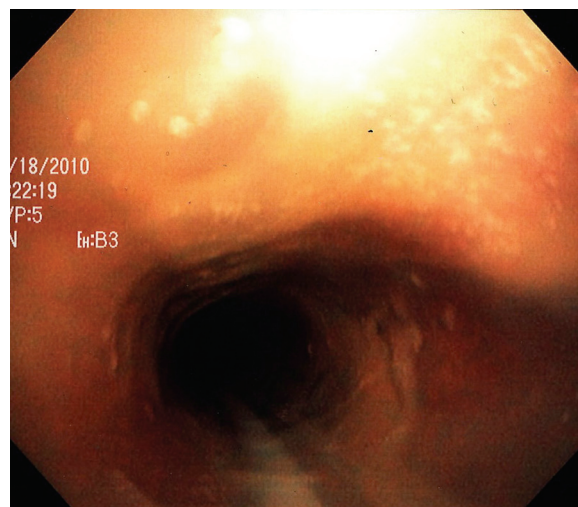


FIGURE E1-37 ■ The same endotracheal tube (ETT) as in Fig. E1-36, following a single pass of the biofilm removal catheter.

of obstructive luminal secretions via the CAM Resqu-Cath) (Figs. E1-36 through E1-38).

- Relative
 - Unprepared
 - Unless the situation is truly emergent, ETT exchange should not be attempted without properly preparing the patient and without having immediate access to difficult airway supplies.
 - ETT is not damaged
 - If the reason for exchange is for “cuff leak,” for example, but the leak is due to supraglottic positioning, not a damaged cuff, then adjustment of the ETT and not ETT exchange is appropriate. However, an overdistended ETT cuff may suffer

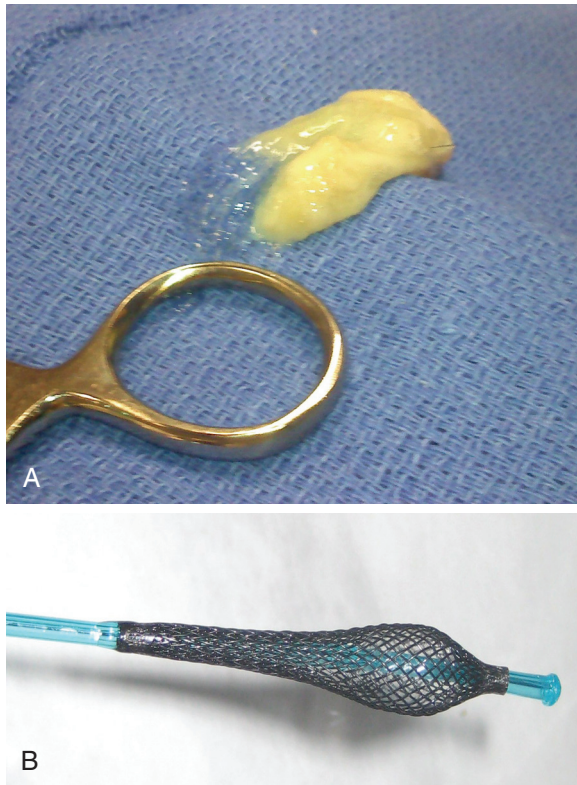


FIGURE E1-38 ■ **A**, A large biofilm plug removed following a single pass of the biofilm removal system. **B**, Close-up of the mesh-covered catheter cuff used to remove the tracheal lumen obstruction of biofilm.

from altered compliance due to stretching. Thus, a new ETT may be advantageous.

Equipment

- Conventional intubation equipment
- Advanced airway rescue devices including FFB, VAL
- Miscellaneous equipment
 - Kelly clamp/hemostat
 - Replacement pilot balloon kit

PROCEDURE

- Place patient on 100% oxygen.
- Review patient history, problem list, medications, level of ventilatory support.
- Assemble conventional and rescue airway equipment including capnography.
- Initiate sedation/analgesia if not already present, with or without muscle paralysis
- Optimize positioning, perform FFB to determine level of the ETT tip if appropriate, and then advance the ETT over the FFB into the trachea.
 - Alternative rescue methods, personnel should be immediately available
- Second choice: examination of the airway (laryngoscopy, video-based preferable)
 - Extra caution when advancing laryngoscope blade into oropharynx, as the tip may puncture the overinflated ETT cuff in the “back” of the throat.
- Consideration should be given to replacing the ETT when its cuff has undergone overinflation and may have altered compliance.

AFTER PROCEDURE

Postprocedure Care

- Reconfirm endotracheal placement with capnography.
- Assess depth of ETT with breath-sound auscultation, bronchoscopy, chest radiograph (delayed).

Complications

- Common
 - Inability to advance new ETT owing to tip imbedded in the upper airway tissues
 - Hypoxemia
- Serious rare complications
 - Loss of difficult airway
 - Most feared and worst outcome
 - Can be reduced by using FFB versus DL
 - Use VAL over DL
 - Ensure airway team has adequate supportive staff and immediate access to advanced airway equipment (including surgical staff)

OUTCOMES AND EVIDENCE

Partial extubation of the airway can be a life-threatening consequence of tracheal intubation in the ICU patient. Misdiagnosis or lack of understanding of this situation may lead to patient morbidity and mortality. Being prepared, as is the case for any ICU airway situation, is in the best interest of patient safety. Running through the differential diagnosis of a “cuff leak” is imperative. The simplest task to complete is to inquire about the characteristics of the cuff leak (duration, amount of air placed in cuff, etc.) and to check its integrity. If the pilot balloon appears intact, it is reasonable to assume the ETT tip cuff is displaced at or above the vocal cords and one should consider FFB for diagnostic and therapeutic management. Again, VAL is invaluable as both a diagnostic and therapeutic option.

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EXTUBATION OF THE DIFFICULT AIRWAY: BEFORE PROCEDURE

Indications

- To optimize the safety of the ICU patient being readied for extubation, with special emphasis on the difficult airway patient
- Known difficult airway
 - Known difficult mask ventilation
 - Known difficult laryngoscopy
 - Known difficult intubation
- Suspected difficult airway
 - Obesity
 - Cervical spine precautions, hard collar, halo vest, limited range of motion
 - Edema, swelling, airway trauma, systemic reaction (sepsis, blood transfusion reaction, anaphylaxis)
 - Massive volume resuscitation

- Evolving head/neck trauma, pathology, injury
- Any limitation to the mouth/oral cavity/oropharynx
- Excessive secretions, bleeding, bandages, alterations to anatomy
- *Difficult extubation* is defined as the clinical situation when a patient presents with known or presumed risk factors that may contribute to difficulty reestablishing access to the airway.
 - The subsequent intolerance of the extubated state poses an increased risk to patient safety.
 - An extubation strategy should be developed that allows the airway manager to (1) replace the ETT in a timely manner and (2) ventilate and oxygenate the patient while the patient is being prepared for reintubation, as well as during the reintubation itself.
 - The practitioner should assess the patient's risk on two levels: the patient's predicted ability to tolerate the extubated state and ability (or inability) to reestablish the airway if reintubation becomes necessary. Weaning criteria and extubation parameters will not be discussed because they vary by locale, practitioner, and the patient's clinical situation.

Contraindications

- Absolute contraindications
 - When the clinical assessment of the patient is suggestive of a high risk for difficulty establishing an airway, and airway management personnel with an expertise of handling such a patient are not present or they are not properly equipped to handle such a patient
 - Patient fails routine accepted extubation parameters for your facility
 - When the full complement of ICU personnel are unavailable for the extubation trial (e.g., nursing staff, respiratory therapy staff, airway team members)
 - When a backup plan/strategy has not been developed or the equipment/personnel to execute such a strategy are not available
- Relative contraindications*
 - Establishing a surgical airway (tracheostomy) would be a better choice.
 - Delaying the extubation trial would be in the patient's best interest.

Equipment

- Conventional airway management equipment
- Advanced airway rescue equipment (difficult airway cart/bag)
 - FFB
 - Advanced VAL equipment
 - Airway exchange catheters
- Nursing staff
- Respiratory therapy staff
- Surgical assistance for a surgical airway (if indicated)
- Sedation/analgesia/muscle relaxant medications
- Postextubation oxygen delivery system
 - Nasal cannula
 - Face mask
 - CPAP, BiPap

ANATOMY

- Patient assessment must be completed prior to decision whether or not to extubate.

- Review of the patient's stay in the ICU, medications, problem list, surgeries, procedures, previous airway interventions, and current clinical condition would be standard to provide needed information to develop an understanding of the patient's current predicament.
- This evaluation would be supported by a clinical assessment of the patient's airway to evaluate inability to tolerate extubation from such causes as
 - Airway obstruction (partial or complete)
 - Hypoventilation syndromes
 - Hypoxemic respiratory failure
 - Failure of pulmonary toilet
 - Inability to protect airway
- Evaluate for potential difficulty reestablishing the airway
 - Difficult airway
 - Limited access to the airway
 - Inexperienced personnel pertaining to airway skills
 - Airway injury, edema formation
- Risk factors for difficult extubation
 - Known difficult airway
 - Suspected difficult airway based on the following factors
 - Restricted access to airway
 - Cervical collar, halo vest, limited range of motion
 - Head and neck trauma, procedures, or surgery
 - ETT size, duration of intubation
 - Head and neck positioning (e.g., prone vs. supine)
 - Traumatic intubation, self-extubation
 - Patient bucking or coughing
 - Drug or systemic reactions
 - Angioedema
 - Anaphylaxis
 - Sepsis-related syndromes
 - Excessive volume resuscitation
- ASA Practice Guidelines have suggested that a preformulated extubation strategy should include
 - A consideration of the relative merits of "awake" extubation versus extubation before the return of consciousness (more applicable to the operating room setting)
 - An evaluation for general clinical factors that may produce an adverse impact on ventilation after the patient has been extubated
 - The formulation of an airway management plan that can be implemented if the patient is not able to maintain adequate ventilation after extubation
 - A consideration of the short-term use of a device that can serve as a guide to facilitate intubation and/or to facilitate ventilation/oxygenation

PROCEDURE

- Suggested three-step patient assessment
 1. Review history, current conditions, medications, mental status as previously stated.
 2. Assess airway; external evaluation supplemented with internal evaluation
 - Conventional laryngoscopy has limited clinical utility in the ICU patient.
 - VAL allows (in most patients) the ability to "see around the corner," thus providing a view of the periglottic airway to determine if the airway is suitable for extubation; also provides valuable information regarding the ease or difficulty of viewing the airway anatomy in the event reintubation needed following extubation.
 3. Develop strategy for extubation, delay extubation or secure via surgical means; extubation choices include
 - Conventional extubation (directly to oxygen source)
 - Extubation over an airway exchange catheter to maintain airway access

*Based on personal preference, experience, and the patient's clinical condition.

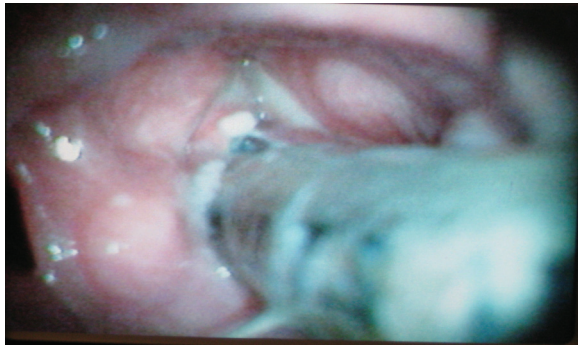


FIGURE E1-39 ■ Laryngoscopic view (GlideScope) of a patient with a known difficult airway who is ready for an extubation trial. The airway was assessed to determine two factors: (1) the ease or difficulty of reintubating the trachea if extubation is poorly tolerated and (2) the status of the periglottic tissues (edema, swelling, and trauma) and whether they are compatible with tolerance of the extubated state. This airway view demonstrated residual edema and swelling, as well as secretion buildup.

- FFB-assisted airway evaluation/extubation
- Transition to LMA until patient is “safe” to lose “airway access” (Fig. E1-39)
- Clinical decision plan for the difficult extubation
 - A variety of methods are available to assist the practitioner to maintain continuous access to the airway following extubation, each with its limitations and restrictions.
 - Though no method guarantees control and the ability to resecure the airway at all times, the LMA offers the ability for fiberoptic-assisted visualization of the supraglottic structures while serving as a ventilating and reintubating conduit but is hampered by a limited time frame.
 - FFB is useful for periglottic assessment following extubation but requires advanced skills and minimal secretions. Moreover, it offers only a brief moment for airway assessment and continuous access to the airway following extubation.
 - Conversely, the AEC allows continuous control of the airway after extubation but without visualization, is well tolerated in the vast majority of patients, and serves as an adjunct for reintubation and oxygen administration. Patient intolerance, accidental dislodgment, and mucosal and tracheobronchial wall injury have been reported but are rare.
 - Carinal irritation may be treated with proximal repositioning, instillation of topical agents to anesthetize the airway, plus explanation and reassurance. Dislodgment may occur because of an uncooperative patient or a poorly secured catheter.
 - Observation in a monitored environment with experienced personnel should be given top priority, as should the immediate availability of difficult airway equipment in the event of extubation intolerance.
- Suggested extubation procedure for the difficult airway patient
 - Acquire advanced airway rescue equipment.
 - Assemble personnel (respiratory therapist, nursing staff, and surgical staff).
 - Prepare circumferential tape to secure the airway catheter after extubation.
 - Discussion with patient/family/airway care team
 - Position patient upright; suction internal and external to ETT.
 - If obese, ramped position recommended
 - Pass lubricated AEC to 23- to 26-cm depth (shorter adults <5 ft tall may require a depth of 20-22 cm).



FIGURE E1-40 ■ Patient on postoperative day 2 following an anterior-posterior 4-level cervical fusion, laminectomy, and discectomy at two levels. She required an “awake” flexible fiberoptic bronchoscopy (FFB) intubation to allow induction of anesthesia. Being a known difficult airway to start with, her airway status only worsened with postoperative swelling and the addition of the halo vest that further restricted cervical movement. She was extubated over an airway catheter but developed rapid deterioration due to stridor, requiring emergency passage of a new endotracheal tube (ETT) over the airway catheter, which was accomplished in less than 20 seconds. A smaller-bore ETT was used (6.0) based on the assumption that airway swelling was the cause of the stridor and a smaller ETT would most likely pass more easily into a swollen airway.

- Remove the ETT while maintaining the AEC in its original position.
- Wipe excess lubrication/secretions from the AEC prior to taping.
- Secure the AEC with tape (circumferential) and mark AEC “airway only.”
- Oxygen: nasal, mask, or humidified oxygen
- Maintain NPO, provide pulmonary toilet.
- Ensure availability of smaller-caliber ETT (6.0) for reintubation if needed.
- Maintain patient in monitored setting with skilled personnel available (Fig. E1-40).
- Clinical judgment and the patient’s cardiopulmonary and other systemic conditions, combined with the airway status, should guide the clinician in establishing a reasonable time period for maintaining a state of “reversible extubation” with the indwelling AEC. [Table E1-1](#) shows a suggested time frame for maintaining the well-tolerated AEC. If significant head/neck and/or laryngeal/periglottic edema precludes extubation, several maneuvers may be implemented to assist in decreasing swelling and edema
 - Raise head of bed as much as tolerated.
 - Maintain even to negative in/out fluid balance.
 - Diurese if volume overloaded (common in ICU).
 - Pretreatment (12-24 hours prior to extubation) with corticosteroids if appropriate (controversial but may reduce postextubation stridor, breathing difficulties, reintubation, and laryngeal edema overall)
- SAFETY NOTICE: administration of oxygen (low flow 1-2 L/min, medium flow 3-6 L/min, or high-pressure “JET” delivery)

TABLE E1-1

Time Frame* for Maintaining the Well-Tolerated Airway Exchange Catheter

| | |
|---|------------|
| Difficult airway only, no respiratory issues or airway swelling | 1-4 hours |
| Difficult airway, no direct respiratory issues, potential for airway swelling | 2-6 hours |
| Difficult airway, cardiopulmonary issues, multiple extubation failures | 2-24 hours |

*Time frame will vary according to patient condition, airway assessment, and tolerance of the presence of the airway exchange catheter.

via the AEC cannot be recommended unless preparing for emergency reintubation (short term only). Without proper egress of insufflated oxygen, even low-flow oxygen may lead to barotrauma leading to life-threatening consequences. Thus, oxygen delivery around, not through the AEC lumen, is recommended.

AFTER PROCEDURE

Postprocedure Care

- Optimize patient positioning, pulmonary toilet, minimize sedation.
- Continuous close observation by trained personnel and immediate access to an experienced airway management team
- Failure to tolerate the extubated state may vary from 2% to 25% of all patients over a variable time line such as 12 to 48 hours.
- The ICU setting is unpredictable. Patients may fail extubation because numerous alterations in the patient's condition can take place unexpectedly (e.g., new-onset dysrhythmia, flash pulmonary edema, acute neurologic changes, systemic reactions).

Complications

- Patient intolerance of AEC (10%)
 - Assure distal tip is not irritating the carina/bronchus.
 - Hand holding, explanation may improve tolerance.
 - Local anesthetic application via AEC
- Infrequent
 - Removing AEC too early and reintubation required later
 - AEC is removed by patient or falls out inadvertently.
 - Inability to reintubate tracheal via AEC (requires alternative strategy)
 - Esophageal intubation if AEC is displaced
- Serious rare complications
 - Possible airway obstruction, loss of airway, laryngospasm, mucosal damage
 - Distal tip of AEC perforated tracheobronchial tree, tip misplacement into the aerodigestive tract
 - Barotrauma due to oxygen insufflation via the AEC

OUTCOMES AND EVIDENCE

The difficult airway patient being readied for extubation warrants a strategy that allows a predictable reintubation in a timely manner, thus, a "reversible extubation." Though regional or national guidelines that outline specific management schema for dealing with this clinical situation are not readily available, this outline offers "safety first" for the patient. Much emphasis is focused on placing the ETT into the trachea, yet the more difficult issue is replacing the ETT in a recently extubated airway, typically under adverse clinical conditions. Patient morbidity and even mortality (i.e., brain injury from anoxia) are real

consequences of extubation of the patient with a difficult airway and should be respected and approached cautiously.

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VIDEOLARYNGOSCOPE-ASSISTED INTUBATION: BEFORE PROCEDURE

Indications

Video-Assisted Laryngoscopy (VAL)

- Routine tracheal intubation
- Emergency tracheal intubation
- Rescue of other failed intubation methods
- Viewing airway structures for educational/training purposes
- Exchange of tracheostomy tube
- Evaluation of airway structures for foreign body, trauma, edema, cuff leak
- Extubation evaluation of airway
- Assistance with advancement of TEE probe, feeding tube, nasogastric tube (NGT), esophageal dilator
- Evaluate ETT position in situ
- Types of VAL blades
 - Conventional angle (20°-30°) versus acute angle (60°-70°)
 - Channeled versus nonchanneled
 - Hybrid
- Advantages of VAL versus conventional DL (Figs. E1-41 and E1-42)
 - Full view of laryngeal inlet in majority of cases
 - Typically transforms laryngeal view 1 to 2 grades lower (better view)
 - Grade III view of the larynx with DL (grade III: no cords visible, only epiglottis visible) improves to grade I or II with VAL
 - Grade IV (no view of any airway structure) often improves to grade II (enough to allow ETT advancement)
 - Improved line of sight of naked eye with DL, as operator must peer via the mouth opening around dentition, tongue, and the like; view is often restricted, even more so when the ETT is passed into the airway

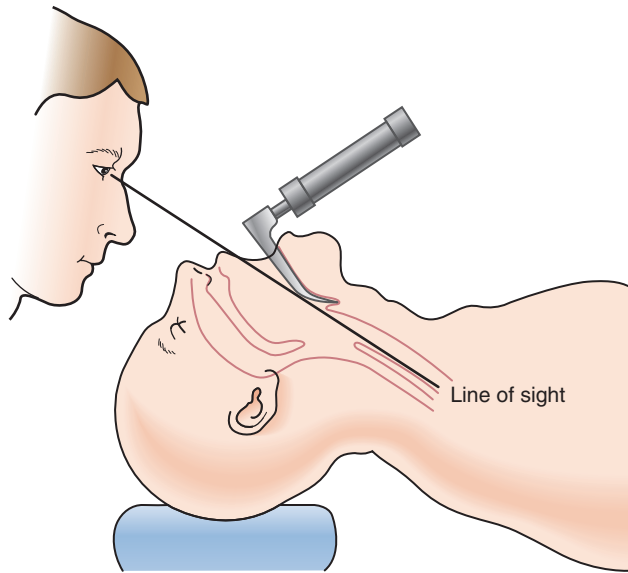


FIGURE E1-41 ■ Line of sight with direct laryngoscopy.



FIGURE E1-42 ■ Lines of sight for direct laryngoscopy (DL) versus videolaryngoscopy (VAL). There is approximately 30 degrees between the two methods that accounts for the ability to “see around the corner” when the laryngeal view is restricted with DL. Several manufacturers offer both conventional and acute angle blades. Conventional angle blades afford gaining experience with a “Macintosh” blade combined with the advantage of video assisted visualization.

Contraindications

- Unfamiliar with its use
- Recent tracheobronchial reconstruction?

Equipment

Five basic choices (not all-inclusive of models available, multiple manufacturers) (Figs. E1-43 through E1-50)

- Channeled VAL devices (groove or channel that is preloaded with ETT to assist with its passing)
 - Pentax AWS, AirTraq



FIGURE E1-43 ■ The Airtraq, a portable yet disposable channeled videolaryngoscopy (VAL) device that offers excellent laryngeal viewing, given its relatively inexpensive cost and simple external design. (With permission from Prodol Meditec S.A., Vizcaya, Spain.)



FIGURE E1-44 ■ The Pentax AWS, a portable, reusable channeled videolaryngoscope (VAL) with a disposable (clear) blade that has an adjustable video screen (black portion in photo) that adapts to various patient positions. An endotracheal tube (ETT) is preloaded into the channel of the blade to ease advancement into the larynx.

- Unchanneled VAL devices (must manipulate ETT freehand into trachea)
 - GlideScope, McGrath, Storz C-Mac, Storz DCI Video Laryngoscope
- Acute angle blade assembly (e.g., 60°-70°, GlideScope, McGrath, Storz)
- Normal angle blade assembly (e.g., 20°-35°, GlideScope, McGrath, Storz)
- Hybrid blade (offering both styles)
- Alternatively, video optical stylet (ETT loaded on stylet, video assisted intubation)
 - Shikani, Levitan, Bonfils

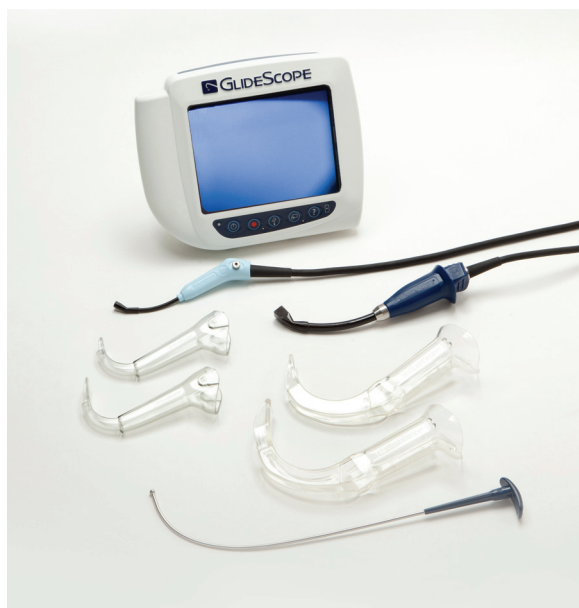


FIGURE E1-45 ■ GlideScope AVL shown with video screen and two of several sizes of disposable video baton blades designed for neonatal to large adult. The optional specially shaped stylet that conforms to the blade's extreme 60 allows the operator improved access to advance the endotracheal tube to the laryngeal opening. (With permission from Verathon, Inc., Bothell, Washington.)

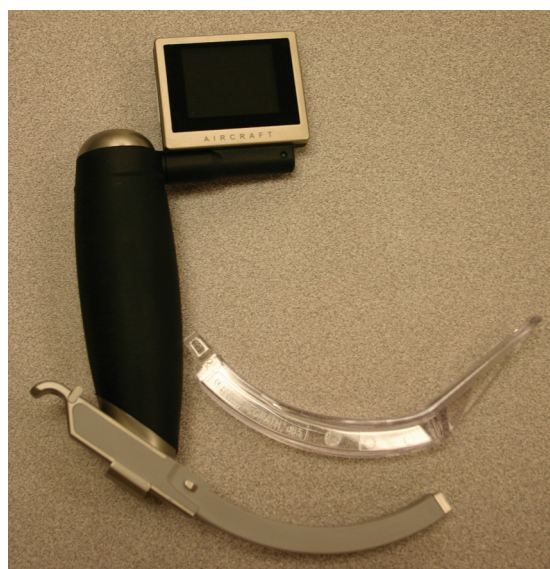


FIGURE E1-46 ■ The McGrath portable videolaryngoscope is easily transported and offers excellent video-quality images but on a smaller screen. To ease placement in patients with restricted oral access (e.g., halo vest, large chest/breasts, short neck), the device features a disposable clear blade and an adjustable video arm that can be disarticulated to allow the blade to be placed into the mouth and then reattached to the handle.

- A variety of manufacturers offer models from disposable models (Airtraq-Prodol, about \$75) to reusable models that range from \$1500 (single device) to \$30,000 (well-stocked cart).
- Reusable models typically offer a disposable blade cover or video baton sleeve to speed its reusability between patient encounters.



FIGURE E1-47 ■ The Levitan FPS Scope is an optical stylet that assists the operator with visualization of the airway structures via the eyepiece. Elevation of the mandible-tongue complex with a manual jaw thrust or combining the optical stylet with direct laryngoscopy allows the stylet-endotracheal tube to be passed underneath the epiglottis and into the trachea.

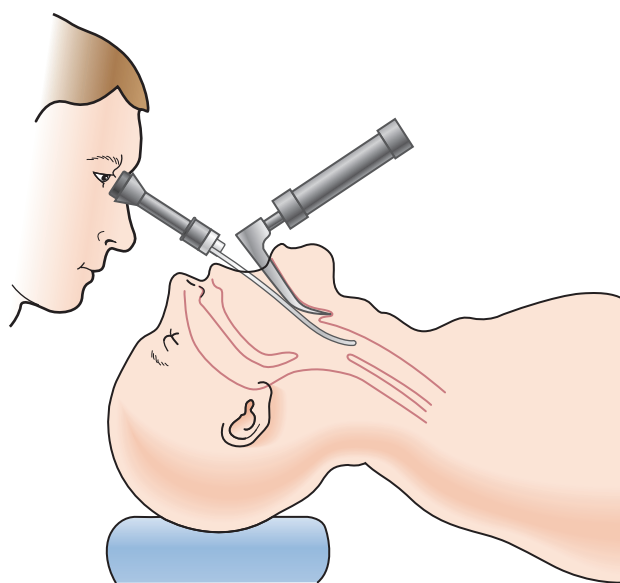


FIGURE E1-48 ■ Combining direct laryngoscopy with the optical stylet to achieve laryngeal visualization.

- Most are easily transportable in an airway cart or bag, attached to an IV pole with wheels.

ANATOMY

Periglottic airway anatomy is typically visualized on a video-based screen, which equates to a much larger view as compared to the restricted view of the operator looking through the patient's mouth. Depending on the VAL device, the quality is excellent overall. Even the disposable model offers good color distinction, reasonable detail, and differentiation of various tissue pathologies. The more expensive models offer excellent quality, color, and detail, and some offer recording capabilities. Secretions, blood, and fogging may impede visualization. Adequate mouth opening is required to allow placement of the

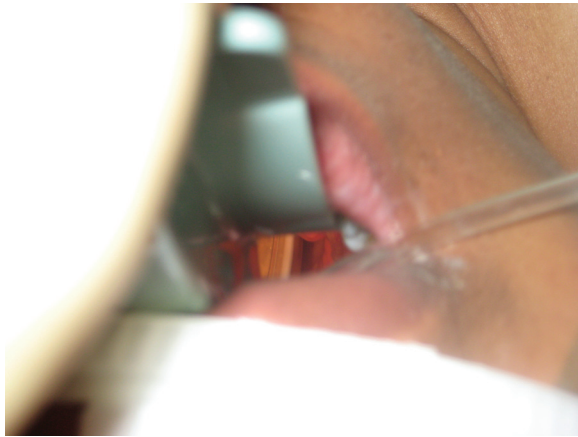


FIGURE E1-49 ■ The view offered by a conventional laryngoscope; limited view of glottis structure owing to dependency of operator's line of sight.



FIGURE E1-50 ■ Same patient as Fig. E1-49 but with videolaryngoscope-assisted view, allowing operator full view of epiglottis, arytenoids, and glottic opening.

blade assembly. Moreover, adequate space between the chest-neck-chin-mouth opening must be present to allow manipulation of the blade into the correct position to view the airway. The McGrath scope offers a disarticulating blade handle that allows placement of the blade followed by attachment of the handle, thus easing its placement in the restricted airway.

■ PROCEDURE

- Because of the variety of devices, the operator must be well versed in the individual device's limitations, indications and contraindications, method of placement, angulation within the oral cavity, video characteristics, and more.
- Because of the bulkiness of VAL's blade, a minimum mouth opening is required to allow device placement into the oral cavity. Further, for the nonchanneled models, adequate space must exist to afford ETT manipulation.
- Use of any of these devices is a four-step process
 - Placement into the oral cavity and advancement into the oro-hypopharynx
 - Optimizing the glottis view
 - Advancing the ETT either via the channel, freehand over a stylet that approximates the curve of the device's blade (nonchanneled), or advancing the ETT-optical stylet assembly to the glottic level and then advancing the ETT into the trachea
 - Smooth and gentle advancement into the mouth is required when manipulating the device, since the operator's attention is



FIGURE E1-51 ■ Videolaryngoscope (VAL) view of a massively swollen airway. No features were discernible via direct laryngoscopy. VAL revealed massive edema but enough detail to allow placement of an endotracheal tube.

typically focused on the “view” and not the patient's dentition or airway tissues.

- Additional caveat for using VAL for airway management (Fig. E1-51)
 - Proper removal of the device to minimize patient injury and avoid extubation
 - Fundamentals of airway management must be practiced, even when use of high-tech equipment is incorporated. VAL may be able to overcome the lack of fundamentals.
 - Proper positioning is an absolute must (e.g., ramping the obese patient)
 - Secretions, vomitus, bleeding impede viewing.
 - Do not use equipment you are not trained to use.
 - Do not try a new technique or device in an emergency (do what you do best).
 - Remove the front of a hard cervical collar (maintain midline stabilization).
 - Secure the head to the bed frame for immobilization with 2-inch tape \pm sandbags; this frees up valuable space that would otherwise be occupied by a colleague trying to maintain a midline position, which could interfere with airway management efforts.
 - If the airway should be secured awake, then do so (FFB, VAL, SGA).
 - Always have a backup plan for any VAL difficulty or failure.
 - VAL is only as good as the person holding it.
 - Do not practice in a cavalier manner just because you have VAL available.
 - The SGA has been displaced by VAL; SGA is an excellent VAL rescue device.
 - Never apply excessive force to the device “to make it fit.”
 - Avoid forcing the advancement of the ETT with VAL (there is no visualization of the ETT until it passes the distally placed video chip).
 - Apply lubrication to the blade as needed, as well as to the ETT, to ease passage.
 - If VAL is your first choice and fails, consider trying DL in some cases.

- An infamous quote regarding the use of VAL: VAL will often make a difficult airway an easy one, but it can make an easy airway a difficult one.
- To review the use of any individual VAL device, please refer to the product's website and review it through educational offerings.
- Review of the technique (which varies with each device) and its indications, contraindications, and limitations is imperative for operator confidence and patient safety.
- Practice on mannequins with proper instruction. Instruction by experienced personnel on the elective, healthy, normal-airway patient is a prerequisite to use in the difficult airway or emergency setting.
- Tip may "bounce."
- 10% to 50% of bougies passed into a grade III airway may enter the esophagus.
 - Grade IIIa: 5% to 12% may enter esophagus
- Tip may be gently advanced farther (28-36 cm) to contact carina/main stem bronchus.
 - Tip hang-up provides tactile feedback during blind passage.
- Decision time: passing the ETT
 - If time permits, generously lubricate the ETT.
 - Smaller sized ETTs pass over the bougie more easily than larger ones.
 - Maintain tongue displacement with laryngoscopy/hand grasp.
 - Pass the ETT, but do not force the advancement (an assistant should grasp the proximal end of the bougie to stabilize it).

AFTER PROCEDURE

Postprocedure Care

- Following advancement of ETT into the trachea and reverifying its position, stabilize the ETT in position, and remove the device.
- Though the video attributes allow observation that the ETT is through the glottis, removing the device may jeopardize its position. Once the device is removed, one is unable to confirm its position without again passing the device. Standard methods of determining the ETT position, such as capnography and chest auscultation, are recommended.

Complications

- Difficulty or failure achieving adequate laryngeal view (2%-10%)
 - Inadequate mouth opening, limited mandibular hinge movement
 - Secretions, blood, vomitus, fogging
 - Power failure (battery, electrical, system failure)
- Difficulty or failure to intubate trachea (2%-10%)
 - Inability to manipulate ETT correctly
 - Operator inexperience
 - Altered/traumatized/edematous/mass/distorted anatomy
 - Unable to pass ETT tip past glottis/cricoid ring: use bougie (through the ETT) for assistance
- Infrequent
 - Tissue injury, airway trauma (palatal or tonsillar pillar wall perforation, pharyngeal wall laceration/perforation)
 - Esophageal placement of ETT
 - Dental damage
- Serious, rare complications
 - Mucosal and tissue laceration/perforation leading to mediastinitis/pharyngeal abscess

OUTCOMES AND EVIDENCE

- The addition of the VAL technology is not new, but the era of lower cost, more accessible models is afoot. DL is now being challenged as a first-line approach to airway management. Whether VAL

replaces DL as the primary method of management is difficult to say, primarily because of economic issues.

- The overall usefulness of video-based visualization of the "easy" airway is questionable except for evaluation and educational purposes. However, its use for the restricted laryngeal view with DL, for the difficult airway (either known or presumed), and for its role as a rescue device for failed DL is without question a welcome addition to our airway arsenal.
- VAL serves a variety of roles in airway management in the ICU setting, well beyond simply tracheal intubation. Extubation evaluation, ETT exchange, rescue of DL failures, plus its use as a primary management choice are but a few.
- The impact VAL imparts on ICU airway management is not currently reflected in the management algorithms offered by anesthesiology societies in the United States, Canada, the United Kingdom, Germany, and many other countries.
- Likewise, its presumed improvement in patient care is intuitive, but it must be proven through research and be evidence-based to warrant its ubiquitous inclusion in ICU airway management as a standard of care. The airway team must use it with caution, practice basic airway fundamentals, and develop a rescue strategy for VAL difficulty or failure, because they will occur regularly, especially in the high-risk ICU patient population.

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ETT EXCHANGE: BEFORE PROCEDURE

Indications

Common Reasons in the ICU Setting

- Dysfunctional ETT (cuff, pilot balloon, narrowed lumen, biofilm, obstruction)
- Change location (nasal-to-oral, oral-to-nasal)
- Change size or type of ETT (7.0→8.0, double-lumen to single-lumen ETT)
- Similar clinical circumstances with tracheostomy tube exchange
- ETT exchange has been mentioned under other headings as it pertains to airway management procedures
- Elective versus urgent versus emergent conditions
 - May affect one's ability to accurately evaluate the airway situation
 - Primary reason to have trained personnel and an appropriately stocked difficult airway cart in the ICU setting

- Time permitting, review current patient medical/surgical history, airway procedures
 - Current ventilator settings
 - Current sedatives, analgesics, vasoactive agents
 - ETT secretion status, ETT patency, reason for exchange (clarify request) and substantiate that it is legitimate given the risks versus benefits.
 - Examine current ETT depth, size, patency, location.
 - Evaluate sedative-analgesic needs, cardiopulmonary response to procedure.
 - Assemble nursing, respiratory therapy, physician assistance as needed.
 - Assure immediate access to difficult airway cart, code cart, resuscitative drugs.
 - An imperative action by the airway team is a preexchange airway assessment. Performed externally and internally, this assessment will allow risk stratification, assessment of airway status, and planning of the exchange procedure. Pre-exchange laryngoscopy affords airway assessment as a segue to improved airway care. Assessment, best performed with VAL, may uncover partial/total ETT extubation masquerading as a “cuff leak” or offer a vital glimpse when there is overwhelming airway edema and secretions that render a high-risk warning for the exchange. In the case of elective ETT exchange—i.e., change of size or location—an alternative may be to delay or abort the exchange or choose to perform a surgical airway. Urgent or emergent exchanges—i.e., cuff perforation, narrowed lumen—may proceed but with a clear understanding of the airway status to optimize procedural planning.
- VAL placement followed by removal and ETT replacement
- Combined VAL+AEC
- Combined VAL+FFB±AEC
- ETT exchange options (nasal to oral, oral to nasal)
 - Similar to above exchange options
 - Safest method for a location change would offer continuous airway access, thus, for example, VAL assessment followed by passing an AEC via the nasally placed ETT, backing out existing ETT above the glottis via the AEC, optimize VAL view, and then freehand ETT advancement. Once the ETT is in position, the AEC may be removed. Conversely, an ETT may be delivered via FFB or DL if visualization is adequate.
 - Maintaining continuous access affords “backtracking” if advancement of the new ETT is disrupted. Either the existing ETT or a new ETT may be readvanced into the airway over the indwelling AEC.
 - Fundamentals of airway management must be practiced, even when use of high-tech equipment is incorporated.
 - Proper positioning is an absolute (e.g., ramping the obese patient).
 - Secretions, vomitus, bleeding impede viewing. Apply suction to optimize view.
 - Assemble equipment and staff and discuss primary and back-up plans.
 - 100% oxygen, suction ETT if applicable
 - Provide appropriate sedatives and analgesics and consider the pro/cons of neuromuscular blocking agents.
 - Prior to the exchange, assign tasks to team members to assure each is aware and comfortable with his or her role in the exchange.
 - Apply liberal lubrication to the blade and ETT to ease passage.
 - Double glove for procedure. If gloves become slippery from lubrication, assistant can remove outer glove(s).
 - “Mind the gap” between the ETT and the airway exchange catheter. An attempt to minimize the gap is imperative. The ETT will pass with less “wobble” and reduce hangup on airway tissues. In some instances, a smaller AEC is the only option (double-lumen tube, existing small-caliber ETT, luminal narrowing or kink). The replacement ETT—e.g., 8-mm ETT—must be advanced over a smaller AEC with an increased risk of ETT hangup, multiple attempts, delay in oxygenation, and other airway and hemodynamic complications. The smaller AEC may “bow” laterally in the airway when force is applied to the advancing ETT. The ETT may veer laterally and impinge on airway tissues, particularly the epiglottis, arytenoid, and vocal cords. Resistance may ensue. This major point promotes two important concepts; minimize the gap and deploy VAL to optimize viewing capabilities.
 - If clinical conditions dictate that a smaller diameter AEC be utilized, the Cook brand Aintree catheter can be used as a “jacket” for the 11F and 14F Cook AEC. Its placement on the AEC will reduce wobble, narrow the gap, and increase the “rigidity” of the AEC.
 - Beware of the depth markings on the AEC and coordinate them with those markings on the ETT. It is imperative that personnel be assigned to stabilize the AEC during removal and replacement of the ETTs. Awareness of the AEC depth is important to minimize distal or proximal migration; both could have devastating consequences.
 - The exchange method with the highest first-pass success rate, fewest attempts, lowest incidence of desaturation, and overall success is combining VAL+AEC, particularly in the known or suspected difficult airway patient.
 - Further, unpublished data from the Hartford Hospital Exchange database strongly suggests that incorporating the larger diameter AEC will markedly improve first-pass success and reduce desaturation and other airway-related complications.

Contraindications

- Inadequate equipment, personnel in high-risk patients
- Delay or abort exchange or alternatively, perform a surgical airway

Equipment

Equipment needs include all contents of the difficult airway cart, capable suction apparatus, and airway exchange catheters (AEC, various diameters) (Figs. E1-43 through E1-50).

ANATOMY

Periglottic airway anatomy has been reviewed in previous sections. The primary concerns for an ETT exchange are access to the oral cavity via the nose or mouth and the patency of the airway in regard to adequate room to place the new ETT across the supraglottic, glottic, and subglottic regions. VAL offers a clear advantage over conventional DL or FFB methods.

PROCEDURE

- Multiple choices exist for ETT exchange. Currently, the safest method would be to maintain continuous access to the airway via an indwelling AEC or placement of both the existing and new ETT across the glottic opening. The latter is occasionally possible when, for example, the existing ETT is small—e.g., 6.0—in a tall male patient (relatively large glottic opening).
- Options for ETT exchange (oral to oral)
 - Blinded ETT removal followed by DL, VAL replacement (maybe required with ETT obstruction or damage)
 - DL placement, ETT removal, and freehand replacement
 - FFB assisted (either passing FFB through glottis with or without existing ETT present)
 - AEC assisted (without the benefit of laryngoscopy to open the airway to provide a pathway for advancement)
 - Combined DL+AEC

AFTER PROCEDURE

Postprocedure Care

- Following advancement of ETT into the trachea and reverifying its position, stabilize the ETT in position, and remove the AEC.
- Standard methods of determining the ETT position, such as capnography and chest auscultation, are recommended. FFB may also be helpful.

Complications

- Passing an AEC into an ETT without knowledge of its relative location—e.g., intratracheal versus supraglottic position in unrecognized extubation masquerading as a “cuff leak”—could lead to esophageal intubation, interruption of oxygen delivery, or loss of the airway. Hence, a preexchange laryngoscopy, preferably VAL based, is recommended.
- Airway related
 - Desaturation, esophageal intubation, regurgitation, aspiration
 - Main stem bronchus intubation, mucosa injury, tracheobronchial wall injury, pneumothorax
 - Loss of airway, need for accessory devices
 - Lip, dental, tongue, pharyngeal injury
 - Tracheobronchial and/or ETT obstruction from distal soilage/secretions
- Hemodynamic related
 - Tachycardia, bradycardia
 - Hypertension, hypotension
 - Dysrhythmia, cardiac arrest

OUTCOMES AND EVIDENCE

- Despite the serious clinical implications of ETT exchange, there is a relative paucity of evidence-based literature regarding best practice for ETT exchange. Maintaining continuous access to the airway is, however, a consistent recommendation. Many serious and potentially life-threatening complications can accompany exchange procedures. Recent evidence suggests patients with a known/suspected difficult airway or poor visualization offered by DL during the preexchange airway assessment may benefit greatly by incorporating VAL+AEC.
- The value of a preexchange airway assessment (VAL) is demonstrated in its ability to diagnose otherwise unrecognized partial/complete tracheal extubation masquerading as a cuff leak.

- Exchanging a double-lumen tube (DLT) to a single-lumen tube (or vice versa) typically is more difficult due to (1) the larger diameter, angled DLT possibly being difficult to place in general, and (2) AEC-assisted exchange often entailing the use of a smaller caliber AEC because the DLT's smaller luminal diameter will not accept the larger AEC.
- The overall usefulness of video-based visualization of the “easy” airway is questionable except for evaluation and educational purposes. However, its use for the restricted laryngeal view with DL, for the difficult airway (either known or presumed), and for its role as a rescue device for failed DL is without question a welcome addition to our airway arsenal.
- VAL serves a variety of roles in airway management in the ICU setting, well beyond simply tracheal intubation. Extubation evaluation, ETT exchange, rescue of DL failures, plus its use as a primary management choice are but a few.

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Advances in ultrasound technology continue to enhance its diagnostic applications in daily medical practice. Constantly evolving, this tool has become useful to properly trained cardiologists, anesthesiologists, intensivists, surgeons, obstetricians, and emergency department physicians. Ultrasound can enable rapid, accurate, and noninvasive diagnosis of a broad range of medical conditions. Patients in the intensive care unit (ICU) present daily diagnostic and therapeutic challenges to the medical team. The availability of ultrasound instrumentation in critical care units has facilitated greatly the evaluation and treatment of patients with a wide spectrum of conditions. Although transesophageal echocardiography (TEE) previously was the principal diagnostic approach using ultrasound to evaluate ICU patients, advances in ultrasound imaging, including harmonic imaging, digital acquisition, and contrast for endocardial enhancement, have improved the diagnostic yield of TTE, which is simpler and safer to perform. Ultrasound devices continue to become even more portable than in the past, and hand-carried devices now are readily available for bedside applications. This chapter discusses the application of bedside ultrasonography in the ICU. The emphasis is on echocardiography and cardiovascular diagnostics. The use of bedside ultrasound to facilitate central line placement and to aid in the care of patients with pleural effusions and intraabdominal fluid collections also is addressed.

USE OF BEDSIDE ULTRASONOGRAPHY IN THE INTENSIVE CARE UNIT

General Indications

Ultrasonography has become an invaluable tool in the management of critically ill patients. Its safety and portability allow for use at the bedside to provide rapid, detailed information regarding the cardiovascular system¹ and the function and anatomy of certain internal organs. It also can be used by the clinician to assess the pleural and intraabdominal spaces and to perform some invasive procedures safely. General indications for performance of echocardiography in the ICU are listed in [Box E2-1](#). [Box E2-2](#) lists major indications for performance of primary TEE in the ICU. Other indications for use of bedside ultrasonography by the intensivist in critically ill patients are listed in [Box E2-3](#).

Technical Aspects

Acoustic Window in a Critically Ill Patient

The practical value of bedside ultrasonography in the management of critically ill patients is now widely accepted despite the inherent limitations of the technique.² These limitations are related mostly to suboptimal imaging conditions that commonly are encountered when performing studies of critically ill patients. The constrained physical environment of the ICU also can compromise the quality of the images obtained. For an ultrasound study to be deemed adequate, a good acoustic “window” is required to allow accurate analysis. Ultrasonography uses the physical principle that sound is reflected from tissue interfaces, allowing a two-dimensional (2D) image of the anatomic structure studied to be constructed.³ Anything hindering the reflection of this acoustic signal—air, bone, calcium, a foreign body, or another interposed structure—interferes with ultrasound transmission and diminishes the overall quality of the examination. In the ICU, many patients are mechanically ventilated. In these patients, adequate

imaging can be limited by pneumothorax, pneumomediastinum, or subcutaneous emphysema.² Other important factors limiting data acquisition in critically ill patients are related to surgical wounds and dressings, tapes, tubing, obesity, and chronic obstructive pulmonary disease. In addition, lack of patient cooperation and the impossibility of moving some patients into the optimal position for the examination contribute to a high prevalence of technically inadequate studies.²

Although ultrasonography permits evaluation of the structure and function of the heart and other important organs and structures, acquisition of data and interpretation of results are fraught with potential traps.⁴ Performing an ultrasound examination requires a thorough knowledge of anatomy and instrumentation, including attention to gain control, grayscale settings, Doppler velocity settings, and transducer placement.

Preparation of the Patient

Before starting an ultrasound examination at the bedside in the ICU, certain important criteria should be fulfilled. The criteria vary depending on the type of examination being performed (transthoracic echocardiography [TTE]; TEE; vascular, abdominal, or thoracic ultrasound) and on certain patient-related factors (e.g., presence or absence of mechanical ventilation, nasogastric tube, or surgical dressings).

An awake patient should be informed about the importance of the ultrasound investigation and should be provided with an explanation of how the clinician will perform the examination.³ These steps are especially important when the examination uses the transesophageal route.

Positioning

Proper positioning of the patient is important for obtaining an adequate image. For performance of TTE and TEE in patients who are not mechanically ventilated, optimal imaging usually is obtained by having the patient in the left lateral decubitus position. Taking the extra 5 minutes to position the patient on his or her left side for TTE often results in much improved image quality and minimizes aspiration risk for TEE. Adequate positioning of the patient varies depending on the structures being assessed for other ultrasound imaging (e.g., pleural space, peritoneal cavity, vascular structures, or bladder). Care must be taken when positioning a critically ill patient in bed, because these patients often have multiple vascular catheters, an endotracheal tube, drains, and other tubes or devices connected to them. When the ultrasound examination is done to localize and mark pleural or abdominal fluid collections for subsequent drainage, it is crucial that the patient remain in the same position used during the marking procedure until the actual drainage of the collection is performed. Risks of perforating surrounding organs (e.g., heart, spleen, liver, lungs, or bowel) and inducing significant morbidity are increased if the drainage is performed in a position different from the one used during marking.

Sedation

To optimize the ultrasound examination, the patient must be cooperative and nonagitated. Noninvasive procedures such as TTE and abdominal ultrasound usually are well tolerated by patients, and additional sedation rarely is needed to perform these procedures. When performing TEE, however, certain precautions need to be taken. Patients should fast (or have their tube feeds stopped) for at least 4

BOX E2-1**General Indications for Performance of an Echocardiographic Examination in the Intensive Care Unit**

Hemodynamic instability
 Ventricular failure
 Hypovolemia
 Pulmonary embolism
 Acute valvular dysfunction
 Cardiac tamponade
 Complications after cardiothoracic surgery
 Infective endocarditis
 Aortic dissection and rupture
 Unexplained hypoxemia
 Source of embolus

BOX E2-2**Major Indications for Performance of Primary Transesophageal Echocardiography Study in the Intensive Care Unit**

Diagnosis of conditions in which the superior image quality is vital (e.g., aortic dissection, assessment of endocarditis and its complications, intracardiac thrombus)
 Imaging of structures that may be inadequately seen by TTE (e.g., thoracic aorta, left atrial appendage, prosthetic valves)
 Echocardiographic examinations of patients with conditions that prevent image clarity with TTE (e.g., severe obesity, emphysema, mechanical ventilation with high level of PEEP, presence of tubes, surgical incisions, dressings)
 Acute perioperative hemodynamic derangements

PEEP, positive end-expiratory pressure; TTE, transthoracic echocardiography.

BOX E2-3**Other Indications for Use of Bedside Ultrasonography by the Intensivist**

Central line placement
 Assessment of pleural effusions and intraabdominal fluid collections
 Urinary bladder scan
 FAST
 Intraaortic balloon counterpulsation
 Ventricular assist devices

FAST, focused assessment of the trauma patient.

hours before the procedure. Topical anesthesia of the oropharynx also is helpful before insertion of the TEE probe, especially in patients who are not endotracheally intubated.³ Even if adequate topical anesthesia is provided, insertion of the TEE probe still can cause significant discomfort and anxiety, so providing adequate sedation and analgesia is important. Frequently used sedative or analgesic agents include intravenous (IV) midazolam, fentanyl, and propofol. Dosing should be titrated according to clinical parameters including arterial blood pressure, minute ventilation, and arterial oxygen saturation.³ Sedative-induced hypotension is a frequent problem in patients with depressed ventricular function or decreased systemic vascular resistance, and occasionally patients may require transient support with IV volume infusion or rarely a vasopressor agent. If the patient is extremely uncooperative and biting, transient paralysis accompanied by increased sedation may have to be used to perform TEE safely.

Monitoring During the Procedure

Most ICU patients are monitored continuously, at least for certain respiratory, cardiac, or hemodynamic parameters. It is essential that

BOX E2-4**Contraindications to Insertion of Transesophageal Echocardiography Probe****Absolute Contraindications**

Esophageal pathologies
 Stricture
 Mass or tumor
 Diverticulum
 Mallory-Weiss tear
 Dysphagia or odynophagia not previously evaluated
 Cervical spine instability

Relative Contraindications

Esophageal varices
 Recent esophageal or gastric surgery
 Oropharyngeal carcinoma
 Upper gastrointestinal bleeding
 Severe cervical arthritis
 Atlantoaxial disease

patients undergoing an ultrasound examination in the ICU be monitored at least with noninvasive recording of blood pressure, pulse oximetry, and electrocardiogram. Even TTE or abdominal ultrasound examinations can be associated with inadvertent pulling of tubes or drains, and anxiety can be encountered during the procedure. Because of its more invasive nature, TEE may induce complications such as increased agitation, respiratory distress, and discomfort during insertion of the probe. These effects can be associated with substantial changes in blood pressure and ventilatory status. Administration of sedatives and sometimes paralytic agents can induce further changes in hemodynamic and respiratory status.^{3,5}

Safety

Performance of ultrasound examinations in the ICU allows procedures that previously required transport to the radiology suite to be performed at the bedside. This is an important advantage to a critically ill patient, because transport out of and back to the ICU is known to be associated with increased risk of complications.⁶ Performance of bedside TTE and of other noninvasive ultrasound examinations is safe and not associated with significant risks to the patient. Performance of bedside TEE also is associated with a low incidence of serious complications (<0.5% in the general population and the elderly).⁵ The reported mortality rate associated with TEE is 0.01% to 0.03%.⁷ Most patients undergoing TEE examinations in the ICU usually are receiving mechanical ventilation and have continuous monitoring of arterial blood pressure, electrocardiogram, and oxygen saturation.⁸ Transient hypotension, typically attributable to administration of sedative medications, usually can be treated with vasopressors or IV fluids or both. The risk of injury to the pharynx or esophagus is greater in anesthetized and endotracheally intubated critically ill patients than in awake patients, because anesthetized patients cannot assist with probe insertion by swallowing and do not resist when insertion is difficult.⁸ Increased difficulty in directing the TEE probe also can be encountered owing to the presence of a nasogastric tube. Coagulopathy and thrombocytopenia, common problems in critically ill patients, can increase the risk of hemorrhage due to mucosal injury during blind insertion of the TEE probe. Daniel et al.⁹ reported significant complications related to TEE in 18 (0.18%) of 10,218 examinations. In 11 studies reporting on 943 patients undergoing TEE, the rate of complications was 1.7%.⁵ Serious complications occurred in only two patients (0.2%). Colreavy et al.⁸ studied the safety and utility of TEE performed by ICU physicians in 255 critically ill patients and showed that TEE was associated with a complication rate of only 1.6%. It is reasonable to conclude that TEE is associated with few complications, given the high severity of illness among ICU patients.⁵ Close monitoring of hemodynamic and oxygenation parameters is essential. **Box E2-4** lists specific contraindications to the insertion of a TEE probe.

BEDSIDE ECHOCARDIOGRAPHY IN A CRITICALLY ILL PATIENT

Echocardiography can provide diagnostic information noninvasively regarding cardiac structure and mechanical function. The supplementary information provided by this technique can help determine the cause of hypotension refractory to inotropic support or vasopressor infusions.³ It also can help in the diagnosis of a wide spectrum of other cardiovascular abnormalities and guide therapeutic management. An adequate understanding of the proper use of echocardiography is a prerequisite for the intensivist. General indications for performance of an echocardiographic examination in the ICU are listed in [Box E2-1](#).

Transthoracic Versus Transesophageal Echocardiography in a Critically Ill Patient

Accurate and prompt diagnosis is crucial in the ICU. The easiest and least invasive way to image cardiac structures is TTE.³ This noninvasive imaging modality is of great value in the critical care setting because of its portability, widespread availability, and rapid diagnostic capability. In the ICU, TTE in certain cases may fail to provide adequate image quality because of different factors that potentially can hinder the quality of the ultrasound signal, as was described previously. The failure rate (partial or complete) of TTE in the ICU has been reported to be 30% to 40%.^{10,11} Improvements have been made in transthoracic imaging (e.g., harmonics and contrast and digital technologies), however, resulting in a lower failure rate of TTE in the ICU (10%-15% in our institution).

TEE is particularly useful for evaluation of suspected aortic dissection, prosthetic heart valves (especially in the mitral position), source of cardiac emboli, valvular vegetations, possible intracardiac shunts, and unexplained hypotension. TEE allows better visualization of the heart in general and especially the posterior structures, owing to the proximity of the probe and favorable acoustic transmission.¹ TTE also has limitations, however. For several areas of the heart and great vessels, TEE may provide limited images. The view of the left ventricular apex often is foreshortened with TEE, and an apical left ventricular clot can be missed. TTE usually is superior for visualization of the apex. Because of interposition of the left mainstem bronchus, the superior portion of the ascending aorta is another important area that may not be well visualized with TEE. With TEE, transducer position and angulation are constrained by the relative positions of the esophagus and heart. The relatively fixed relationship between the position of the probe and the heart often makes it impossible to align the Doppler beam parallel to the flow of interest (e.g., to evaluate the jet of blood resulting from aortic stenosis). In addition, the 2D image planes of TEE often make standard anatomic measurements more difficult to obtain.

As a result of the significantly improved technical quality of TTE, most ICU patients can be studied satisfactorily with this modality. Immediate TEE is still preferable, however, in certain specific clinical situations in which TTE is likely to fail or be suboptimal.¹¹ The major indications for primary TEE in the ICU^{12,13} are listed in [Box E2-2](#). Even when TEE is necessary, data from the TTE examination are often essential for the final clinical interpretation.

Hemodynamic Evaluation Ventricular Function

Left Ventricular Systolic Function. Evaluation of left ventricular performance by echocardiography is often paramount in the ICU. Accurate and timely assessment of systolic function should be an integral part of the medical management of hemodynamically unstable critically ill patients. Global assessment of left ventricular contractility includes the determination of ejection fraction (EF), circumferential fiber shortening, and cardiac output.

The simplest quantitative approach is to measure the mid-left ventricular short-axis dimension at end diastole and end systole for deter-

mination of the percent fractional shortening. Fractional shortening is related directly to EF; normal fractional shortening is 30% to 42%.¹

$$\text{Fractional shortening} = \frac{\text{End-diastolic dimension} - \text{End-systolic dimension}}{\text{End-diastolic dimension}}$$

In the setting of regional wall motion abnormalities, fractional shortening may underestimate or overestimate global ventricular function and must be interpreted in light of what is seen in all of the 2D imaging planes of the ventricle.¹⁴

Global systolic ventricular function also can be assessed quantitatively by fractional area change (normal value is 36% to 64%)¹⁵ and EF (normal value is 55% to 75%) ([Fig. E2-1](#)):

$$\text{Fractional area change} = \frac{\text{End-diastolic area} - \text{End-systolic area}}{\text{End-diastolic area}}$$

$$\text{Ejection fraction} = \frac{\text{End-diastolic volume} - \text{End-systolic volume}}{\text{End-diastolic volume}}$$

These measurements require good image quality, because endocardial border contours must be traced (see [Fig. E2-1](#)). Machine-integrated software computes the data and provides volumes, areas, and the resultant EF (see [Fig. E2-1](#)). In patients with regional wall motion abnormalities, more precise measures of stroke volume can be made by approximating ventricular volumes as a stack of elliptical disks on biplane imaging (modified Simpson's method).^{1,15}

In the critical care setting, endocardial border definition may be suboptimal because of poor image quality.^{10,16,17} In these cases, global ventricular function often is assessed qualitatively by visual inspection alone. This method has been found to be reliable when used by experienced clinicians.¹⁸ By simple visualization of the kinetics and size of the cardiac cavities in real time, an experienced intensivist with a sufficient echocardiographic background can establish a functional diagnosis immediately.

Analysis of regional wall motion includes a numeric scoring system to describe the movement of the different regions of the left and right ventricle (1 = normokinesia; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia; 5 = aneurysmal change).¹⁵ Visualized from the short-axis view of the left ventricle, a complete overview of myocardial areas perfused by the three major coronary arteries can be obtained ([Fig. E2-2](#)). If the TTE examination is technically difficult and the endocardium is poorly visualized, harmonic imaging and possibly contrast, if needed, can dramatically improve endocardial border visualization and subsequent evaluation of global systolic function (as discussed further later in this chapter). For the remaining few technically challenging cases with suboptimal TTE, performance of TEE allows for a more precise evaluation of ventricular function in most critically ill patients because of the higher image quality that can be obtained with this echographic modality.

Left Ventricular Failure in the Intensive Care Unit. In a critically ill patient with unexplained hemodynamic instability, determination of cardiac function is an integral part of the medical management. Echocardiography is valuable in this setting because the clinical examination and invasive hemodynamic monitoring often fail to provide an adequate assessment of ventricular function. In a study by Fontes et al.¹⁹ that compared pulmonary artery (Swan-Ganz) catheterization and TEE, the overall predictive probability for conventional clinical and hemodynamic assessment of normal ventricular function was 98%, whereas for abnormal ventricular function (EF <40%), it was 0%. Several other studies have reported similar results.²⁰⁻²² Assessment of biventricular function is one of the most important indications for performance of echocardiography in the ICU. In a study by Bruch et al.,²³ 115 critically ill patients were studied by TEE. The most common indication for TEE was hemodynamic instability (67% of patients). Of these hemodynamically unstable patients, 20 (26%) were found to have significant left ventricular dysfunction (EF <30%). In a study by McLean²⁴ of the use of TEE in the ICU, the most common

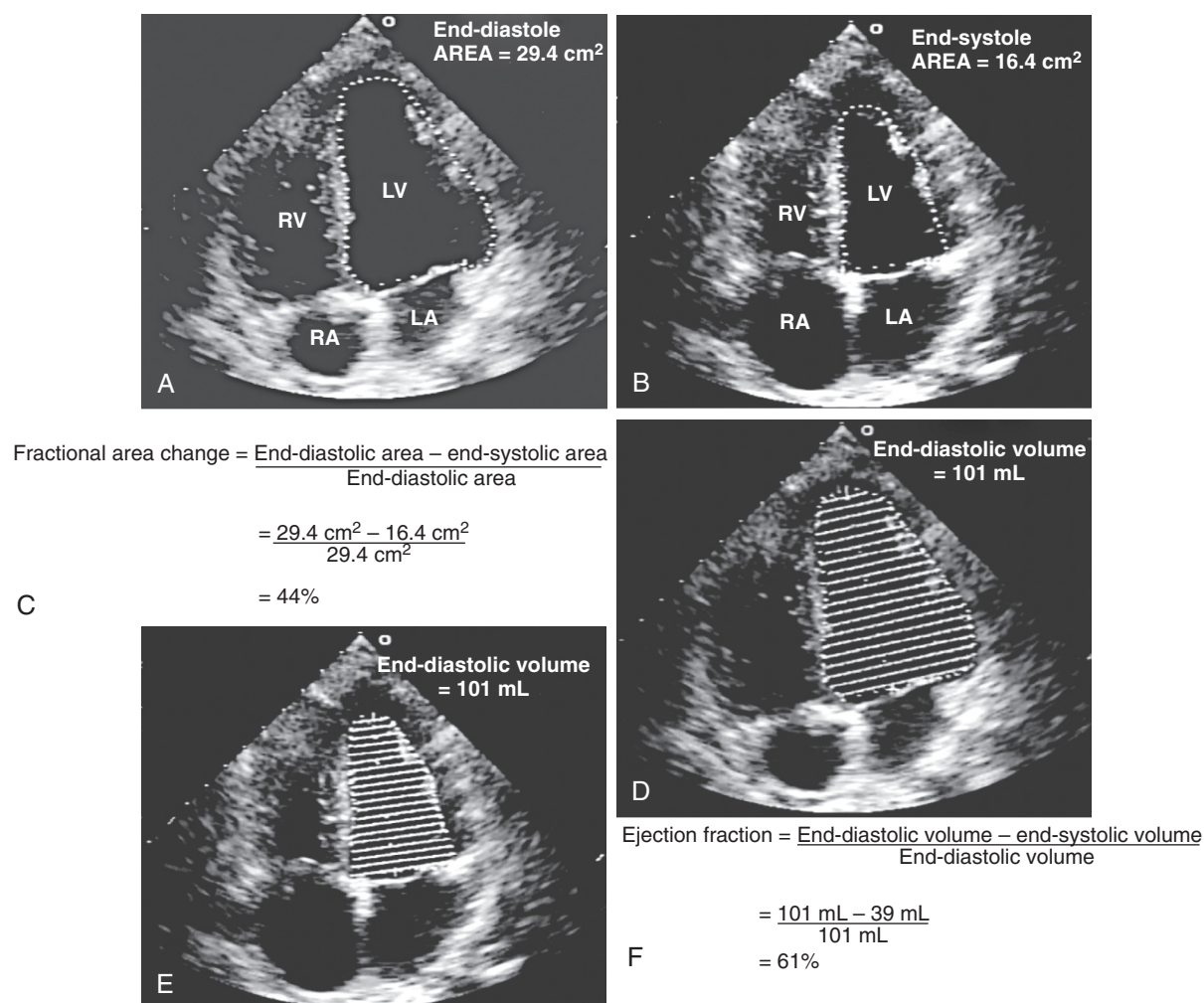


FIGURE E2-1 ■ Fractional area change and ejection fraction calculation. Endocardial contour of the left ventricular cavity is traced at end diastole (A) and at end systole (B) in the transthoracic apical four-chamber view. Machine-integrated software computes the data and gives corresponding end-diastolic and end-systolic areas. Fractional area change can be calculated with these data (C). Normal values are 36% to 64%.¹⁵ Corresponding end-diastolic (D) and end-systolic (E) volumes are computed using the modified Simpson's method. The data are used to calculate the ejection fraction (F). Normal values are 55% to 75%. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

reason to request a TEE was assessment of left ventricular function. In most patients, left ventricular function was assessed adequately by TTE before TEE. In a study by Vignon et al.,¹⁷ TTE allowed adequate evaluation of global left ventricular function in 77% of mechanically ventilated ICU patients. Although TEE was needed for most other indications, TTE was shown to be an excellent diagnostic tool for assessment of left ventricular function in the ICU (Fig. E2-3) even when positive end-expiratory pressure is present.

Several important points should be emphasized: (1) Significant left ventricular dysfunction is common in critically ill patients; (2) ventricular function should be assessed in all patients with unexplained hemodynamic instability, because this information is particularly important for guiding resuscitation and informing decisions regarding subsequent medical or surgical management; (3) it is now possible to obtain adequate information about ventricular function in most ICU patients using TTE, but TEE provides better accuracy in patients with suboptimal imaging by TTE.

Sepsis-Related Cardiomyopathy. Classically, septic shock has been considered a “hyperdynamic” state characterized by normal or high cardiac output. Echocardiographic studies indicate that ventricu-

lar performance often is markedly impaired in patients with sepsis.²⁵⁻²⁷ Parker et al.²⁸ were the first to describe left ventricular hypokinesis in septic shock. They reported that survivors manifested severely depressed left ventricular EF but that adequate left ventricular stroke output was maintained as a result of acute left ventricular dilation.²⁹ Jardin et al.²⁵ studied 90 patients with septic shock and performed daily bedside assessments of left ventricular volume and left ventricular EF using TTE. They observed that left ventricular EF was significantly depressed in all patients, resulting in severe reductions in left ventricular stroke volume. Of these patients, 34 (38%) eventually were weaned from hemodynamic support and showed gradual improvement in left ventricular EF and ultimately recovered. The remaining 56 patients (62%) eventually died (of early circulatory failure or late multiple organ failure). In this subset, the degree of left ventricular dysfunction was less than in survivors but failed to improve over time. The severity of left ventricular dysfunction does not predict outcome. A paradoxical relationship between the degree of left ventricular dysfunction and the likelihood of recovery also has been described by others.^{25,28,30,31} Among patients who survive, left ventricular dilation and systolic dysfunction usually are reversible.

Left ventricular EF might not be a reliable index of left ventricular systolic function in patients with early septic shock because this is a state characterized by low systemic vascular resistance that unloads the left ventricle.²⁵ Normal or supranormal EF in early sepsis might lead clinicians to make the wrong inference about cardiac reserve because left ventricular EF might decrease if afterload is increased by the administration of vasopressor agents.

Left Ventricular Diastolic Function. In the ICU, diastolic dysfunction should be suspected when ventricular filling pressure (pulmonary capillary wedge pressure) is elevated and EF is normal or supranormal.¹ The diastolic properties of the ventricle often are assessed by evaluating Doppler echocardiographic mitral inflow and pulmonary venous flow patterns. Mitral inflow, as measured by pulsed wave Doppler at the tips of the mitral leaflets, is characterized by an early filling phase (E wave) followed by atrial systole, resulting in

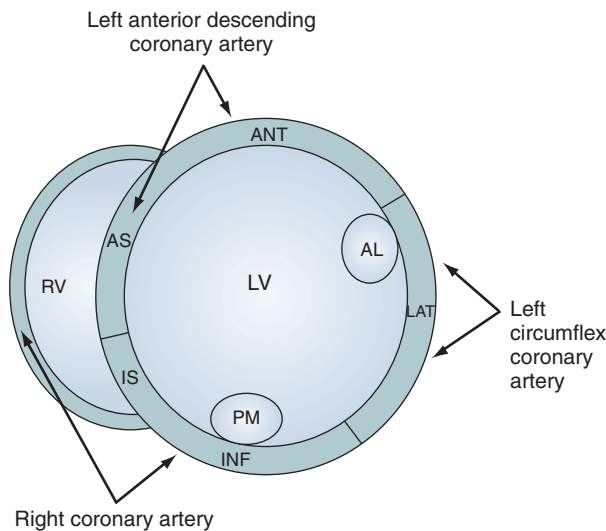


FIGURE E2-2 ■ Transthoracic short-axis echocardiographic view of the left (LV) and right (RV) ventricles at the midpapillary muscle level. In this tomographic view of the heart, areas of myocardium and papillary muscles (AL, anterolateral; PM, posteromedial) supplied by all three major coronary arteries are represented. ANT, anterior; AS, anteroseptal; INF, inferior; IS, inferoseptal; LAT, lateral.

additional filling (A wave) (Fig. E2-4). The transmitral Doppler pattern always should be interpreted in conjunction with pulsed wave Doppler of the pulmonary venous flow, which is characterized by a systolic phase (S), a diastolic phase (D), and an atrial phase (AR) from reversal of flow into the pulmonary veins during atrial contraction (Fig. E2-5). These filling patterns are related to the intrinsic diastolic properties of the myocardium and are influenced by many different factors, particularly left atrial pressure, heart rate, ischemia, ventricular hypertrophy, and valvular pathologies. Only modest correlation has been found between Doppler indices of diastolic function and parameters measured using more invasive means.^{32,33} Integrated interpretation of mitral and pulmonary venous flow patterns may be useful for diagnosing abnormal myocardial relaxation (e.g., owing to hypertensive heart disease, hypertrophic cardiomyopathy, or coronary ischemia) or restrictive pathology (e.g., owing to cardiomyopathy, constrictive pericarditis, coronary artery disease, cardiac transplantation, or dilated cardiomyopathy). Nevertheless, these findings must be interpreted with caution when caring for critically ill patients, given the many different factors that can acutely influence flow patterns in this population of patients.

Right Ventricular Function and Ventricular Interaction. Abnormal right ventricular function often plays an important and sometimes underestimated role in the pathogenesis of critical illness.³⁴⁻³⁶ Based on an echocardiographic definition,³⁷ massive pulmonary embolism and

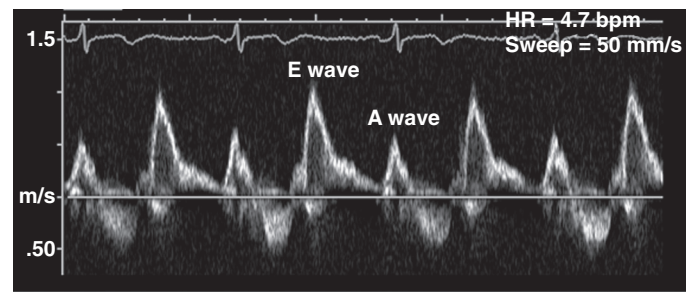


FIGURE E2-4 ■ Normal mitral inflow profile as measured by transthoracic pulsed wave Doppler at the tips of the mitral leaflets. It is characterized by an early filling phase (E wave) followed by atrial systole (A wave), which results in additional filling. These filling parameters are related to intrinsic diastolic myocardial properties and can be influenced by many different factors (see text).

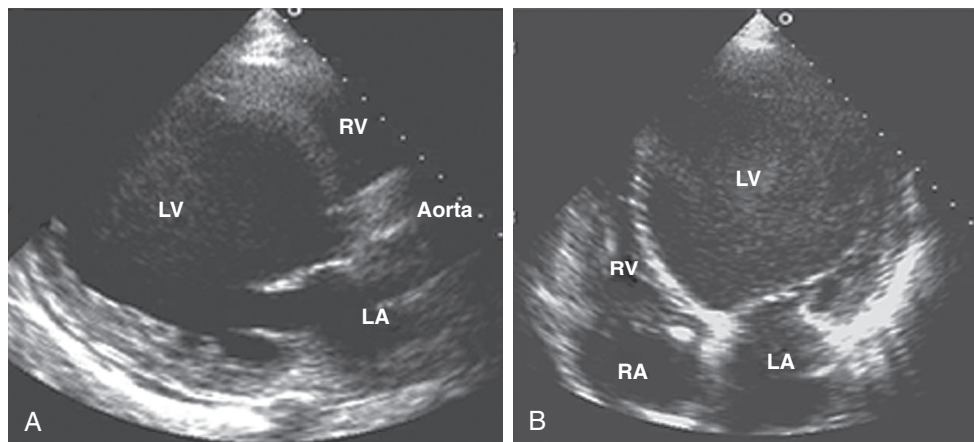


FIGURE E2-3 ■ **Dilated cardiomyopathy.** Transthoracic examination of a severely dilated left ventricle (LV) in the parasternal long-axis (A) and apical four-chamber (B) views. The 65-year-old patient presented with flash pulmonary edema and later was found to have severe diffuse coronary artery disease. LA, left atrium; RA, right atrium; RV, right ventricle.

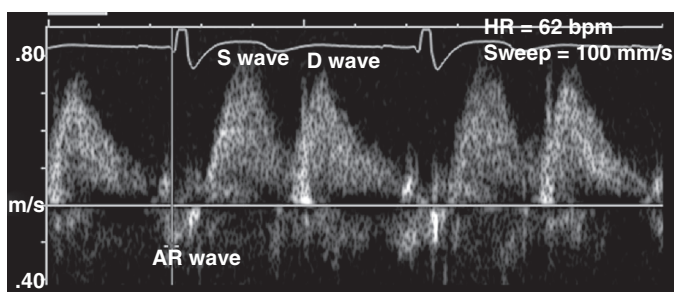


FIGURE E2-5 ■ Normal pulmonary venous flow profile as measured by transthoracic pulsed wave Doppler with the sample volume placed in the right superior pulmonary vein. It is characterized by a predominant systolic wave (S), a diastolic wave (D), and an atrial wave (AR) (from reversal of flow into the pulmonary veins occurring during atrial contraction). The pulmonary venous flow profile always should be interpreted in conjunction with the transmitral Doppler pattern to have a more complete assessment of diastolic function.

acute respiratory distress syndrome are the two main causes of acute cor pulmonale in adults.³⁸ In the critical care setting, right ventricular function also can be altered by any other perturbations that increase right ventricular afterload, such as positive end-expiratory pressure or increased pulmonary vascular resistance (from vascular, cardiac, metabolic, or pulmonary causes). Depressed right ventricular systolic function is also often associated with right ventricular infarction, most commonly in the setting of inferior myocardial infarction. Acute sickle-cell crisis, air or fat embolism, myocardial contusion, and sepsis are other causes of acute right ventricular dysfunction.

Adequate assessment of right ventricular function is important when caring for hemodynamically unstable, critically ill patients, specifically patients with massive pulmonary embolism and acute respiratory distress syndrome, because the diagnosis of concomitant significant right ventricular dysfunction may alter therapy (e.g., fluid loading, use of vasopressors, use of thrombolytics) and provide information about prognosis.^{38,39} Echocardiographic examination of the right ventricle requires primarily an assessment of the size and kinetics of the cavity and septum.^{37,40} Normally the right ventricle appears relatively flat. As it dilates, the apical region of the right ventricle becomes more rounded (Fig. E2-6). In the short-axis view, the right ventricle, which usually has a crescentic shape, becomes oval because of septal displacement and bulging of the right ventricular free wall (see Fig. E2-6).¹ Right ventricular size and function generally are evaluated by visual comparison with the left ventricle. Right ventricular diastolic dimensions can be obtained by measuring right ventricular end-diastolic area in the long axis, from an apical four-chamber view, using either TTE or TEE.

Because pericardial constraint necessarily results in left ventricular restriction when the right ventricle acutely dilates (i.e., there is ventricular interaction), one of the best ways to quantify right ventricular dilation is to measure the ratio between the right ventricular and left ventricular end-diastolic areas, an approach that cancels out individual variations in cardiac size.^{37,40} Moderate right ventricular dilation corresponds to a diastolic ventricular ratio greater than 0.6; severe right ventricular dilation corresponds to a ratio greater than or equal to 1.^{37,40} Right ventricular diastolic enlargement usually is associated with right atrial dilation, inferior vena caval dilation, and tricuspid regurgitation. When pressure in the right atrium exceeds pressure in the left atrium, the foramen ovale may open. Pressure and volume overload of the right ventricle can lead to distortion of left ventricular geometry and abnormal motion of the interventricular septum. With conditions of high strain imposed on the right ventricle (volume or pressure overload or both), the interventricular septum flattens, and the left ventricle appears to have a “D” shape (see Fig. E2-6).^{4,37} This “paradoxic” septal motion also is seen at the interatrial level.

Because the two ventricles are enclosed within the relatively stiff pericardium, the sum of the diastolic ventricular dimensions has to remain constant.⁴¹ Acute right ventricular or left ventricular dilation can occur only if it is associated with an acute and proportional reduction in left ventricular or right ventricular diastolic dimension (i.e., ventricular interaction). With acute right ventricular dilation, septal displacement impairs left ventricular relaxation; the opposite occurs with acute left ventricular dilation. In these situations, the pressure-volume relationships of the left and right heart chambers are altered, and information obtained from a pulmonary artery catheter could be misleading (e.g., high filling pressures are recorded despite normal or even low circulating volume).

Pulmonary Embolism

Hemodynamic instability from acute cor pulmonale as a consequence of massive pulmonary embolism is a relatively common occurrence in critically ill patients. Until more recently, contrast pulmonary angiography generally was regarded as the gold standard for the diagnosis of pulmonary embolism. Angiography is an invasive procedure, however, and carries the risk of major complications in patients with circulatory failure.⁴² Contrast-enhanced helical computed tomography (CT) is an accurate and noninvasive test that has replaced angiography for the diagnosis of pulmonary embolism. Even CT requires transportation of patients to a location outside of the ICU, however, and transport alone is associated with significant risks. Echocardiography is well suited for diagnosis of pulmonary embolism because it can be done within minutes at the bedside. The diagnosis of acute cor pulmonale at the bedside with TTE has good positive predictive value for massive pulmonary embolism.^{43,44} This technique can detect acute right ventricular dilation and dysfunction resulting from a large pulmonary embolism. The finding of right ventricular dilation and dysfunction is not specific for pulmonary embolism, however, because these findings may be observed with a variety of other conditions associated with increased right ventricular strain. In a study by McConnell et al.,⁴⁵ patients with acute pulmonary embolism were found to have a distinct regional pattern of right ventricular dysfunction with akinesia of the mid-free wall but normal motion at the apex by TTE. These findings contrasted with findings obtained in patients with primary pulmonary hypertension who had abnormal wall motion in all regions. Regional right ventricular dysfunction had a sensitivity of 77% and a specificity of 94% for the diagnosis of acute pulmonary embolism; positive predictive value was 71%, and negative predictive value was 96%. The presence of regional right ventricular dysfunction that spares the apex should raise the level of clinical suspicion for the diagnosis of acute pulmonary embolism.

Central pulmonary emboli are present in half of patients with symptoms of pulmonary embolism and acute cor pulmonale on TTE.⁵ Emboli lodged in the proximal pulmonary arteries usually cannot be visualized using TTE.⁵ Because other clinical conditions can produce acute cor pulmonale in the ICU, better visualization of the pulmonary arteries is needed to achieve high accuracy for the diagnosis of pulmonary embolism. This goal can be achieved by using TEE. TEE has good sensitivity for detecting emboli lodged in the main and right pulmonary arteries but is limited for the detection of more distal or left pulmonary emboli.^{5,46,47} If an embolus is visualized, the diagnosis is made. If the study is negative when the index of suspicion for pulmonary embolism is high, however, TEE must be followed up by a more definitive test such as angiography or helical CT. Also, when there is high clinical suspicion for pulmonary embolism but no emboli are visualized using TEE, the potential for nonthrombotic causes of pulmonary embolism (e.g., air or fat emboli) must be kept in mind.

The demonstration of acute cor pulmonale with echocardiography has important prognostic and therapeutic implications.^{48,49} The presence of cor pulmonale with massive pulmonary embolism is associated with increased mortality, whereas the absence of right ventricular dysfunction is associated with a better prognosis.³⁹ There is no consensus on the precise indications for administration of thrombolytics in massive pulmonary embolism complicated by acute cor pulmonale.^{50,51}

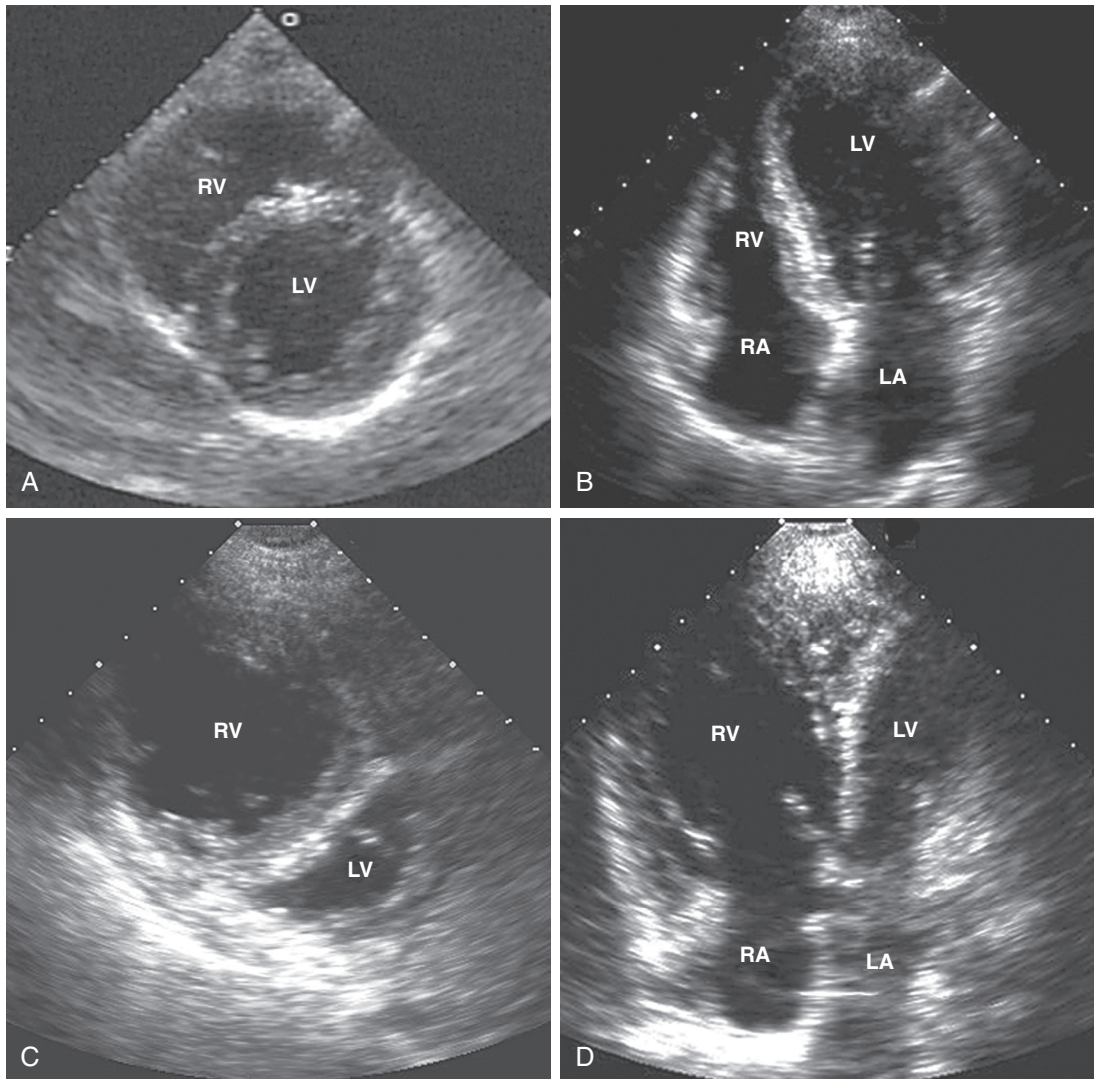


FIGURE E2-6 ■ Severe right ventricular failure and dilation. **A**, Normal transthoracic parasternal short-axis view of the left (LV) and right (RV) ventricles at the midpapillary muscle level. **B**, Normal transthoracic apical four-chamber view of the left ventricle and right ventricle. These pictures of a normal heart depict the relationship between the left ventricle and right ventricle, with the left ventricle being normally larger than the right ventricle and the interventricular septum bulging slightly toward the right ventricle. **C**, Transthoracic parasternal short-axis view of the left ventricle and right ventricle in a patient with severe right ventricular failure and dilation. The right ventricular cavity is seen to be much larger than the left ventricular cavity. Because of the high volume and pressure in the right ventricle, the interventricular septum is bulging toward the left. This gives the left ventricle a characteristic “D” appearance. **D**, Transthoracic apical four-chamber view of the same patient shows the inverse relationship between the left ventricular and right ventricular sizes. The right ventricular dilation can occur only if associated with a proportional reduction in left ventricular diastolic dimension (“ventricular interaction”). This reduction in left ventricular diastolic dimension significantly impairs left ventricular relaxation and changes the pressure-volume relationship of the left heart chambers. LA, left atrium; RA, right atrium.

A safe and reasonable strategy for managing critically ill patients with suspected massive pulmonary embolism is as follows:

1. Initially perform bedside TTE, looking for the presence of regional right ventricular dysfunction as described earlier. If the TTE examination is suboptimal, TEE should be performed.
2. If echocardiography is inconclusive or negative and the clinical suspicion of a pulmonary embolism remains high, a definitive confirmatory radiologic test (preferably helical CT) should be performed.

Assessment of Cardiac Output

Measurement of cardiac output remains a cornerstone in the hemodynamic assessment of critically ill patients. Thermodilution is considered the gold standard approach for determining cardiac output in most ICUs. Measurement of cardiac output using thermodilution requires placement of a pulmonary artery catheter (or at least central venous and arterial catheters); although a useful technique, it is invasive and potentially inaccurate. Unreliable values are particularly

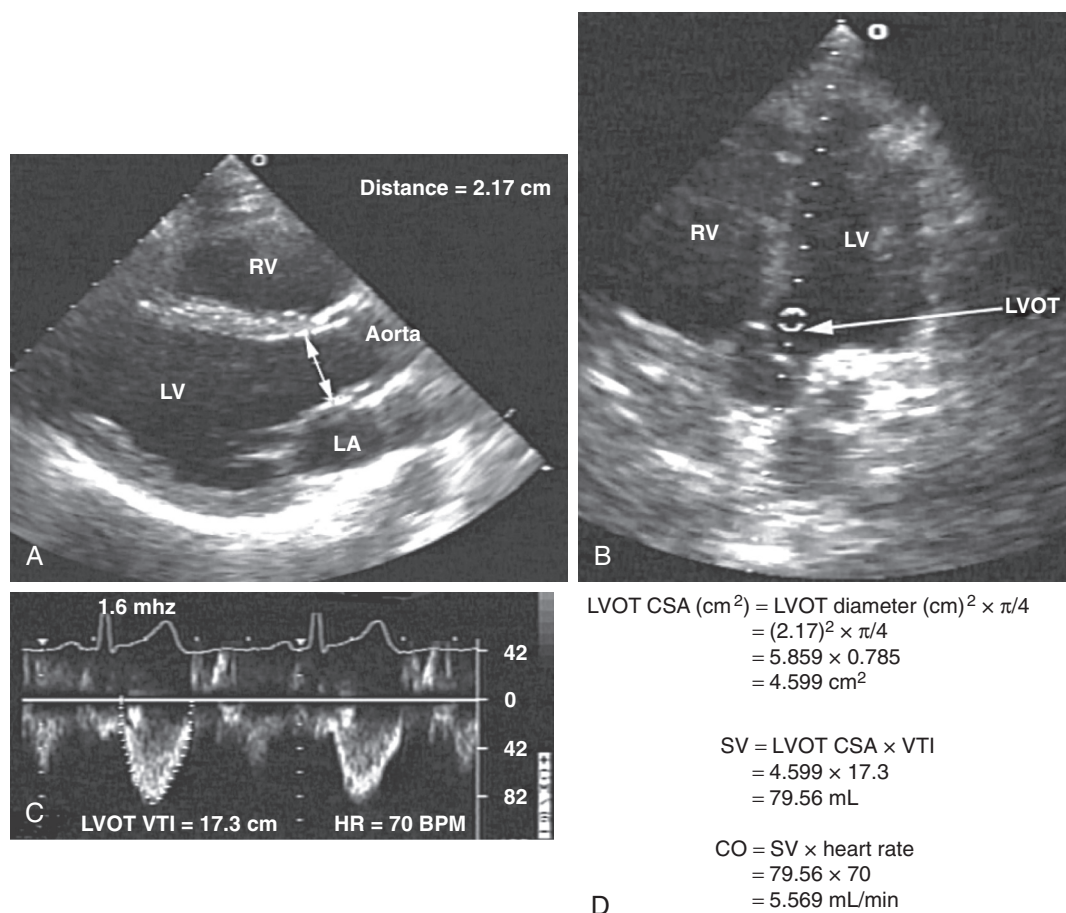


FIGURE E2-7 ■ Calculation of the stroke volume and cardiac output from the left ventricular outflow tract (LVOT). **A**, Left ventricular outflow tract diameter obtained from the transthoracic parasternal long-axis view, just below the insertion of the aortic valve leaflets. In this example, the left ventricular outflow tract diameter is 2.17 cm. **B**, Doppler interrogation (with pulsed wave Doppler) is performed from the apical view with the sample volume being placed in the left ventricular outflow tract, just below the aortic valve. **C**, Spectral Doppler tracing from the left ventricular outflow tract from which the transaortic flow velocity time integral (VTI) is derived. In this example, the VTI is 17.3 cm. **D**, The left ventricular stroke volume (SV) is obtained by measuring the cross-sectional area (CSA) of the left ventricular outflow tract (area [cm²] = left ventricular outflow tract diameter [cm]² × $\pi/4$) and multiplying by the transaortic VTI derived from the spectral Doppler tracing. The stroke volume is obtained by multiplying the heart rate to give the cardiac output (CO). LA, left atrium; LV, left ventricle; RV, right ventricle.

common in the presence of tricuspid regurgitation related to high pulmonary artery pressure. Several methods for determining cardiac output have been described using 2D and Doppler echocardiography. With this technique, stroke volume and cardiac output can be determined directly by combining Doppler-derived measurements of instantaneous blood flow velocity through a conduit with the cross-sectional area of the conduit. Blood flow can be calculated through various cardiac structures, including the pulmonary valve,⁵² mitral valve,^{53,54} and aortic valve.⁵⁵⁻⁵⁸ In the absence of intracardiac shunts, blood flow through these structures should be the same (continuity equation).⁵⁹ Of these methods, the one using the left ventricular outflow tract and aortic valve as the conduit is probably the most reliable and most commonly used. There is excellent agreement with thermodilution in most situations.⁵⁵⁻⁵⁸ The left ventricular stroke volume is obtained by measuring the cross-sectional area of the left ventricular outflow tract (area [cm²] = (left ventricular outflow tract diameter [cm]²) × ($\pi/4$), assuming that just below the aortic annulus, the left ventricular outflow tract is circular) multiplied by the transaortic flow

velocity time integral derived from a spectral Doppler tracing. The stroke volume obtained is multiplied by the heart rate to give the cardiac output: cardiac output = cross-sectional area × velocity time integral × heart rate (Fig. E2-7). With TTE, the left ventricular outflow tract diameter usually is obtained from the parasternal long-axis view, just below the insertion of the aortic valve leaflets. The Doppler interrogation is performed through the aortic valve from the apical view (see Fig. E2-7). With TEE, the left ventricular outflow tract diameter usually is obtained from the five-chamber view of the left ventricle. The transgastric view usually is used to obtain an apical long-axis view of the aortic valve through which Doppler interrogation is performed.⁶⁰ With either TTE or TEE, obtaining an accurate left ventricular outflow tract diameter and Doppler signal is essential to have an accurate cardiac output calculation. Because the measure of the left ventricular outflow tract diameter has a second-order relationship with the cross-sectional area (see previous formula), it is crucial that this measure be determined precisely. For the Doppler signal to be reliable, the Doppler sample must be parallel to the transaortic flow with an angle

of incidence not exceeding 20 degrees to avoid underestimation of transaortic velocity. Using TTE, McLean and coworkers⁶¹ showed an excellent correlation ($r = 0.94$) between cardiac output determined by the left ventricular outflow tract Doppler method and the thermodilution method in critically ill patients. Other studies have shown similar results.⁵⁵ In a study by Feinberg et al.,⁵⁸ cardiac output determined by TEE Doppler imaging was obtainable in 88% of 33 critically ill patients, and there was good correlation ($r = 0.91$) with the thermodilution method. Descorps-Declere et al.⁶⁰ also showed transgastric pulsed Doppler measurement across the left ventricular outflow tract with TEE to be a clinically acceptable method for cardiac output measurement in critically ill patients ($r = 0.975$ compared with the thermodilution method).

Another promising ultrasound-based technology to estimate cardiac output noninvasively in adults uses a small transesophageal Doppler probe to measure blood flow velocity waveforms in the descending aorta combined with a nomogram (based on height, weight, and age) for estimation of aortic cross-sectional area. This minimally invasive esophageal probe can be inserted easily in sedated patients and left in place safely for several days to provide continuous monitoring of cardiac function.^{62,63} Several technical problems can limit the accuracy of cardiac output measurements by esophageal Doppler monitoring,⁶² however, and although initial results are promising,⁶⁴⁻⁶⁶ more studies are needed to make a decision regarding the accuracy of this technique in critically ill patients.

Assessment of Filling Pressures and Volume Status

Adequate determination of preload and volume status is important for proper management of critically ill patients. Invasive pressure measurements to assess left ventricular filling are commonly used at the bedside to make inferences regarding left ventricular preload. These pressure measurements correlate only weakly with left ventricular volume, however.⁶⁷ Data from invasive monitoring using pulmonary artery catheterization may be misleading because ventricular compliance is altered secondary to numerous factors.^{68,69} Differences in diastolic compliance among patients may account for the weak correlation between pressure and volume and may limit the ability to use pressure measurements alone to derive information concerning left ventricular preload.¹⁴ Echocardiography can be helpful for adequately assessing preload. Parameters that can be measured using 2D imaging are left ventricular end-diastolic volume and left ventricular end-diastolic area. Using Doppler interrogation, additional information—mainly transmitral diastolic filling pattern and pulmonary venous flow—can be obtained.

Two-Dimensional Imaging. Echocardiography has been validated for left ventricular volume measurements.¹⁵ Subjective assessment of left ventricular volume by estimating the size of the left ventricular cavity in the short-axis and long-axis views is often adequate to guide fluid volume therapy at the extreme ends of cardiac filling and function. More precise quantitative values are desirable, however, and can be obtained by using endocardial border tracing (as described earlier). The normal left ventricular end-diastolic volume as determined by echocardiography is 80 to 130 mL,¹⁵ and the normal left ventricular end-diastolic volume index is 55 to 65 mL/m².¹⁵ Left ventricular end-diastolic area measured in the left parasternal short-axis view at the level of the midpapillary muscle is commonly used to estimate volume status (Fig. E2-8). The normal values for left ventricular end-diastolic area in the short-axis view are 9.5 to 22 cm².¹⁵

Two-dimensional TTE evaluation of ventricular dimensions has been found to be useful in assessing preload and optimizing therapy of ICU patients.^{25,70} Nevertheless, image quality may be suboptimal and preclude adequate visualization of the endocardial border by TTE. This potential limitation of TTE has been partly circumvented in recent years with the advent of harmonic imaging and contrast echocardiography (see later). In cases in which endocardial border visualization remains suboptimal, TEE is the modality of choice. With TEE, left ventricular volume can be estimated rapidly by subjective assessment of the left ventricular size. Quantitatively, it is estimated

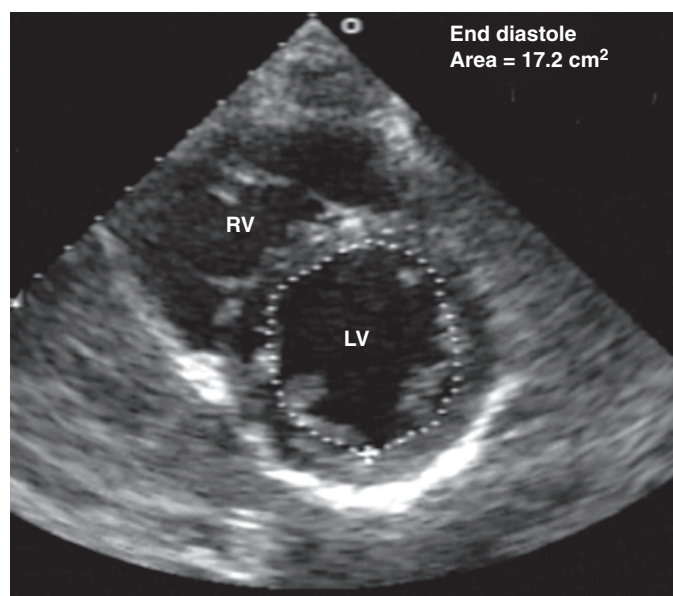


FIGURE E2-8 ■ Calculation of left ventricular end-diastolic area in the transthoracic short-axis view at the level of the midpapillary muscle by endocardial contour tracing. Values of normal left ventricular end-diastolic area in the short axis range from 9.5 to 22 cm².¹⁵ The level of the midpapillary muscle is used because of the reproducibility of the view and because changes in left ventricular volume affect the short axis of the ventricle to a greater degree than the long axis. LV, left ventricle; RV, right ventricle.

most often by determining left ventricular cross-sectional area at the end of diastole, most commonly using the transgastric short-axis view at the level of the midpapillary muscle. This section is used because of the reproducibility of the view and because changes in left ventricular volume affect the short axis of the ventricle to a greater degree than the long axis.¹⁴ The end-diastolic area must be measured consistently from the same reference section. End-diastolic area measured with TEE correlates with left ventricular volume determined by radionuclide studies.⁷⁰

Systolic obliteration of left ventricular cross-sectional area accompanies decreased end-diastolic area and is considered to be a sign of severe hypovolemia (Fig. E2-9). Although a small end-diastolic area generally indicates hypovolemia, a large end-diastolic area does not indicate adequate preload in patients with left ventricular dysfunction. Also, when systemic vascular resistance is low, as in early sepsis, left ventricular emptying is improved because of the lowered afterload. In these situations, it may be difficult to differentiate hypovolemia from low systemic vascular resistance by echocardiography alone, because both conditions are associated with decreased end-diastolic area. Knowledge of left ventricular end-diastolic volume or absolute preload does not allow for accurate prediction of the hemodynamic response to alterations in preload.⁷¹ Tousignant et al.⁷² investigated the relationship between left ventricular stroke volume and left ventricular end-diastolic area in a cohort of ICU patients and found only a modest correlation ($r = 0.60$) between single-point estimates of left ventricular end-diastolic area and responses to fluid loading. Based on the assumption that changes in end-diastolic area occur because of changes in left ventricular volume, the determination of this area and its subsequent degree of variation after a fluid challenge could help better assess preload responsiveness. Studies have shown that changes in end-diastolic area measured by TEE using endocardial border tracing are closely related to changes in cardiac output and are superior to measurements of pulmonary artery occlusion pressure for predicting the ventricular preload associated with maximal cardiac output.⁷³

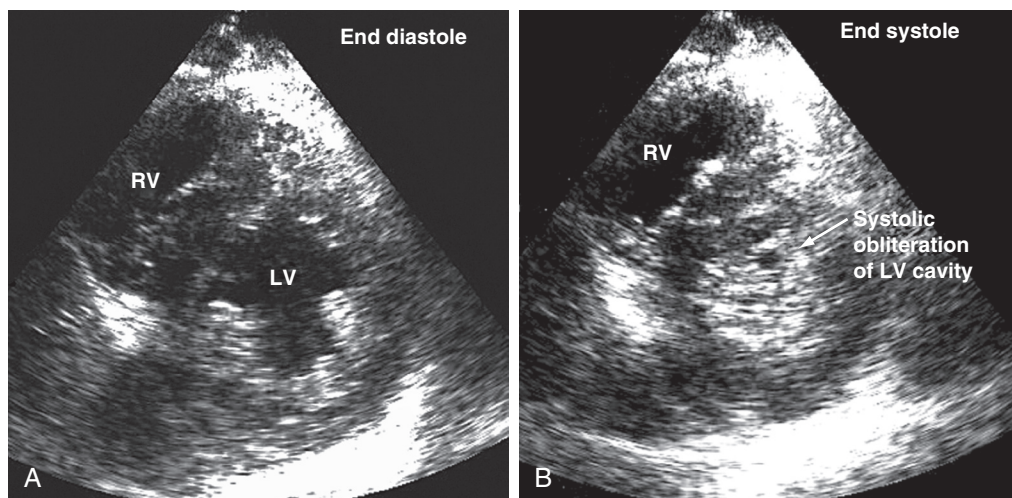


FIGURE E2-9 ■ Systolic obliteration of the left ventricle (LV) in a patient with severe left ventricular hypertrophy and dehydration. This transthoracic parasternal short-axis view shows the left ventricle at end diastole (**A**) and at end systole (**B**). Nearly complete obliteration of the left ventricular cavity is seen at end systole. Systolic obliteration of the cross-sectional area accompanies decreased end-diastolic area and is considered to be a sign of severe hypovolemia. In this case, the patient presented with hypotension and was found to be severely dehydrated because of a viral gastroenteritis. RV, right ventricle.

Circulating volume status also can be assessed by 2D echocardiography by indirectly estimating right atrial pressure; this is often done by assessing the diameter and change in caliber with inspiration of the inferior vena cava (Fig. E2-10). This method has been shown to discriminate reliably between right atrial pressures less than 10 mm Hg or greater than 10 mm Hg.⁷⁴ A dilated vena cava (diameter >20 mm) without a normal inspiratory decrease in caliber (>50% with gentle sniffing) usually indicates elevated right atrial pressure. In mechanically ventilated patients, this measure is less specific because of a high prevalence of inferior vena cava dilation.^{75,76} A small vena cava reliably excludes the presence of elevated right atrial pressure in these patients.^{75,76}

Doppler Flow Patterns. Information obtained by analysis of the Doppler signal at the level of the mitral valve and pulmonary vein offers additional information about preload.^{77,78} These Doppler profiles can be obtained by either TTE or TEE. Transmitral parameters that have been studied include the relation of early to late transmitral diastolic filling (E/A ratio), isovolumetric relaxation time, and the rate of deceleration of early diastolic inflow (deceleration time).¹

A decrease in preload causes a significant reduction in the E wave (early filling flow wave) velocity at the mitral level in conjunction with a decrease of the S wave (systolic flow wave) in the pulmonary vein. In clinical practice, the E/A ratio is easy to assess; the normal value of this ratio is approximately 1.^{1,3} In conjunction with normal left ventricular contractility, a low E/A ratio is usually a characteristic sign of inadequate preload.⁷⁹

Pulmonary venous flow also can be used to assess left atrial pressure. A normal pulmonary venous flow pattern showing a predominance of flow during systole (S phase) compared with early diastole (D phase) usually indicates that left atrial pressure is less than 8 mm Hg, whereas the opposite predominance of flow (in the absence of significant mitral regurgitation) usually indicates elevation of left atrial pressure.¹

Transmitral and pulmonary vein Doppler patterns strongly depend on intrinsic and external factors and are not affected purely by the loading conditions of the left ventricle. It is crucial that interpretation of Doppler parameters be done in conjunction with a global analysis of cardiac function and other available hemodynamic or anatomic variables.

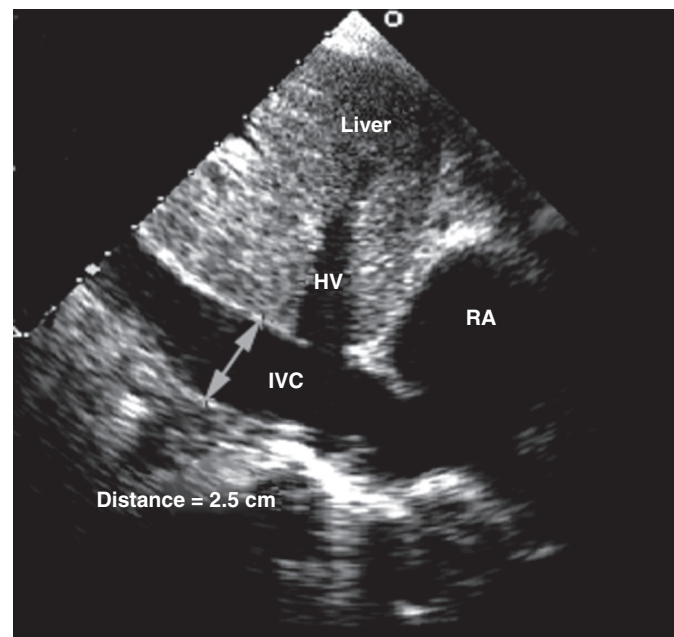


FIGURE E2-10 ■ Indirect assessment of circulating volume status on two-dimensional echocardiography by assessing the diameter and change in caliber with inspiration of the inferior vena cava (IVC). This method has been shown to discriminate reliably between right atrial pressures of less than or greater than 10 mm Hg. A dilated vena cava (>20 mm) without the normal inspiratory decrease in caliber (>50% on gentle sniffing) usually indicates elevated right atrial pressure. A small vena cava reliably excludes elevated right atrial pressure in these patients. In this case, the IVC was dilated at 2.5 cm with minimal respiratory variation in a patient spontaneously breathing. The right atrial pressure was estimated to be approximately 10 to 15 mm Hg. Images were obtained in the subcostal view. HV, hepatic veins; RA, right atrium.

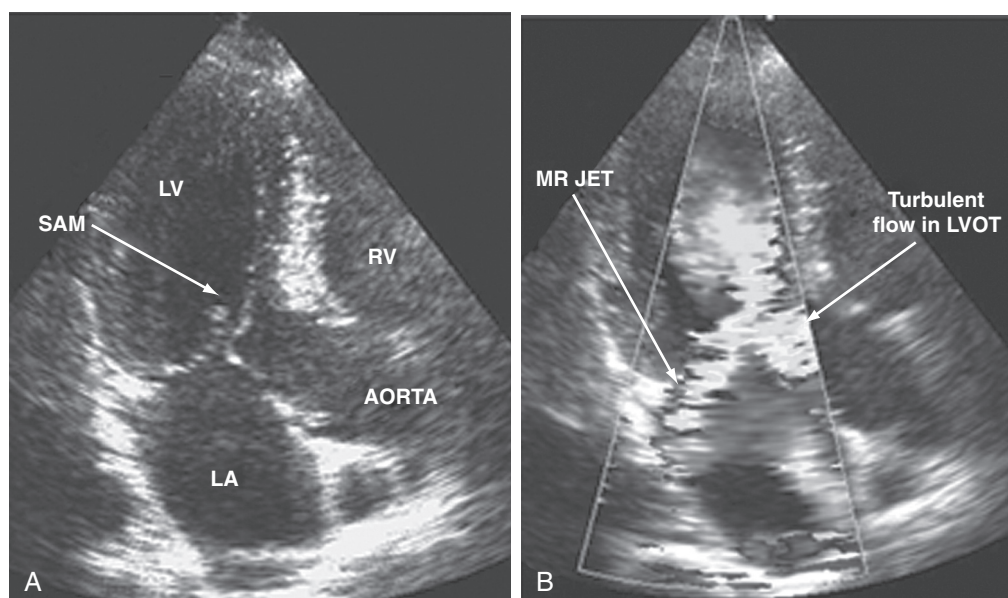


FIGURE E2-11 ■ Systolic anterior motion (SAM) of the mitral valve in a patient with asymmetric left ventricular hypertrophy and dehydration. Two-dimensional transthoracic apical long-axis view shows movement of the anterior leaflet of the mitral valve (arrow) toward the interventricular septum during systole (A). This creates a subaortic dynamic obstruction. The resulting high velocity and turbulence in the left ventricular outflow tract (LVOT) gives a “mosaic” pattern of flow on color Doppler (B). A variable degree of asymmetric mitral regurgitation (MR) also may be present secondary to the systolic anterior motion, as shown in this example. LA, left atrium; LV, left ventricle; RV, right ventricle.

Hypovolemia in the Intensive Care Unit

Precise and rapid assessment of volume status is crucial when caring for hemodynamically unstable ICU patients. Hypovolemia is one of the most common causes of hypotension in the ICU. As was discussed in detail earlier, bedside echocardiography offers a quick and reliable way of estimating volume status by evaluating cardiac dynamics and left ventricular dimensions and area. The finding of end-systolic cavity obliteration is usually a reliable sign of hypovolemia. Other changes in the volume status are usually associated with subtle changes in left ventricular cavity size, so only this extreme is reliable to make the diagnosis of hypovolemia by echocardiography. In general, TTE has good sensitivity for diagnosing the presence of a small hyperdynamic left ventricle, the most typical finding in hypovolemic patients with underlying normal cardiac function, although TEE is useful in the immediate postoperative setting (Video E2-1).

When dynamic left ventricular obstruction is present, cardiac output is low, and even in the presence of marked hypovolemia, pulmonary artery occlusion pressure is high. Paradoxical worsening of hypotension after intravascular volume loading may be the first clue to dynamic left ventricular obstruction in critically ill patients. It is important that this entity be recognized early and that the pathophysiologic process be well understood, because inadequate management of this condition can lead rapidly to worsening of hemodynamic status and death. Dynamic obstruction of the left ventricle can present in different forms. One of these forms is dynamic left ventricular outflow tract obstruction. Although dynamic left ventricular outflow tract obstruction is often seen in association with asymmetric septal hypertrophy, it also can occur in other situations.^{80,81} Dynamic left ventricular outflow tract obstruction is thought to be caused by the Venturi effect. This effect results when excessive acceleration of blood through a conduit produces a decrease in pressure. In the left ventricular outflow tract, such a decrease in pressure leads to a suction phenomenon that draws the anterior mitral leaflet and chordae inward toward

the interventricular septum.⁸² This systolic anterior motion of the mitral valve leads to contact between the mitral leaflet and the septum that creates an obstructive subaortic pressure gradient and distortion of the mitral valve leaflet coaptation (Fig. E2-11).⁸² By 2D echocardiography, the left ventricle appears to be small and hyperdynamic, and there is motion of the anterior leaflet (or chordae or both) toward the septum in systole (see Fig. E2-11). With color Doppler, a “mosaic” pattern of flow is seen in the left ventricular outflow tract, owing to the high velocity and turbulence. Variable degrees of asymmetric mitral regurgitation also may be present (see Fig. E2-11). Continuous-wave Doppler shows the presence of a significant gradient in the left ventricular outflow tract. Dynamic left ventricular obstruction also can be present without systolic anterior motion. In the presence of reduced afterload, dehydration, or significant catecholaminergic stimulation, patients with a small hypertrophied left ventricle (typically seen in elderly patients with chronic hypertension) can develop midventricular obstruction due to hyperdynamic systolic obliteration of the left ventricular cavity (see Fig. E2-9).⁸³ These physiologic factors may predict the development or worsening of left ventricular dynamic obstruction. Interplay of these factors with preexisting ventricular hypertrophy predisposes the patient to develop cardiogenic shock from this combined loss of preload and presence of dynamic left ventricular obstruction. Dynamic left ventricular obstruction has also been described in patients with acute myocardial infarction, mostly in association with apical infarction.^{81,84,85}

In a study by Chenzbraun et al.⁸⁵ in ICU patients, four patients with hemodynamic instability were found to have a small hyperdynamic ventricle on TEE. Of these four patients, three had pulmonary artery occlusion pressure greater than 20 mm Hg. A study by Poelaert et al.²⁰ that evaluated the diagnostic value of TEE compared with pulmonary artery catheterization showed that pulmonary artery catheterization failed to diagnose the presence of hypovolemia in 44% of patients when TEE showed systolic obliteration of the left ventricular cavity, supporting a diagnosis of hypovolemia. TTE and TEE have

been shown to play a key role in making the diagnosis of hypovolemia and left ventricular dynamic obstruction, leading to a dramatic impact on therapy.^{19,21,22,82-85}

Assessment of Pulmonary Artery Pressure

Pulmonary hypertension is common in critically ill patients and is a manifestation of various pulmonary, cardiac, and systemic processes. Pulmonary hypertension is said to be present when systolic pulmonary pressure is greater than 35 mm Hg, diastolic pulmonary pressure is greater than 15 mm Hg, and mean pulmonary pressure is greater than 25 mm Hg.⁵⁹ Many echocardiographic methods have been validated for noninvasive estimation of pulmonary artery pressure.^{59,86} These methods can be helpful in the ICU. Systolic and diastolic pulmonary artery pressures are determined from the tricuspid and pulmonary regurgitation velocities (some degree of regurgitation is essential to be able to obtain a Doppler signal and subsequently determine pulmonary artery pressure). Tricuspid regurgitation is present in more than 75% of healthy adults⁵⁹ and in approximately 90% of critically ill patients.⁸⁷ Peak tricuspid regurgitation velocity, usually obtained by continuous wave Doppler from the right ventricular inflow or the apical four-chamber view position, reflects the pressure difference during systole between the right ventricle and the right atrium (Fig. E2-12).⁸⁸⁻⁹⁰ Peak systolic pulmonary artery pressure is determined from the peak tricuspid regurgitation Doppler velocity using the modified Bernoulli equation⁹¹: $\Delta P = 4 \times (\text{peak tricuspid regurgitation velocity})^2$. To this peak systolic pressure gradient between right ventricle and right atrium is added the estimated right atrial pressure (see previous section) to obtain the peak right ventricular systolic pressure. In the absence of pulmonic stenosis or right ventricular outflow obstruction, peak right

ventricular systolic pressure is equal to systolic pulmonary artery pressure (see Fig. E2-12). Echocardiography also can determine diastolic pulmonary artery pressure by applying the modified Bernoulli equation using the regurgitant Doppler velocity of the pulmonary valve to obtain the gradient between the pulmonary artery and the right ventricle at end diastole. To this is added the estimated right atrial pressure (equivalent to right ventricular end-diastolic pressure in the absence of tricuspid stenosis) to obtain end-diastolic pulmonary artery pressure: end-diastolic pulmonary artery pressure = $4 \times (\text{peak pulmonary regurgitation velocity})^2$ + estimated right atrial pressure. Approximately 70% of critically ill patients have an adequate Doppler signal of pulmonic insufficiency for this calculation.⁹² Tricuspid and pulmonary regurgitation are present at the same time in more than 85% of subjects.⁹³

Assessment of Valvular Function and Integrity

Attention has been drawn to the limitations of the physical examination for the detection of cardiovascular abnormalities.^{94,95} This problem is enhanced in acutely ill patients in the ICU, and many cardiovascular abnormalities may be concurrent with noncardiac illness without being clinically suspected.⁹⁶ Significant valvular abnormalities are a good example of such cardiovascular pathologies that can be present in a critically ill patient without being clinically recognized.⁹⁶ Even in the presence of invasive monitoring, significant valvular pathologies may be missed. Precise evaluation of the valvular apparatus often may be warranted in the ICU. The most common indications for bedside echocardiography for evaluation of valvular apparatus in this patient population are for suspected endocarditis,^{8,24} acute aortic or mitral valve regurgitation,^{97,98} and prosthetic valve dysfunction.¹⁶

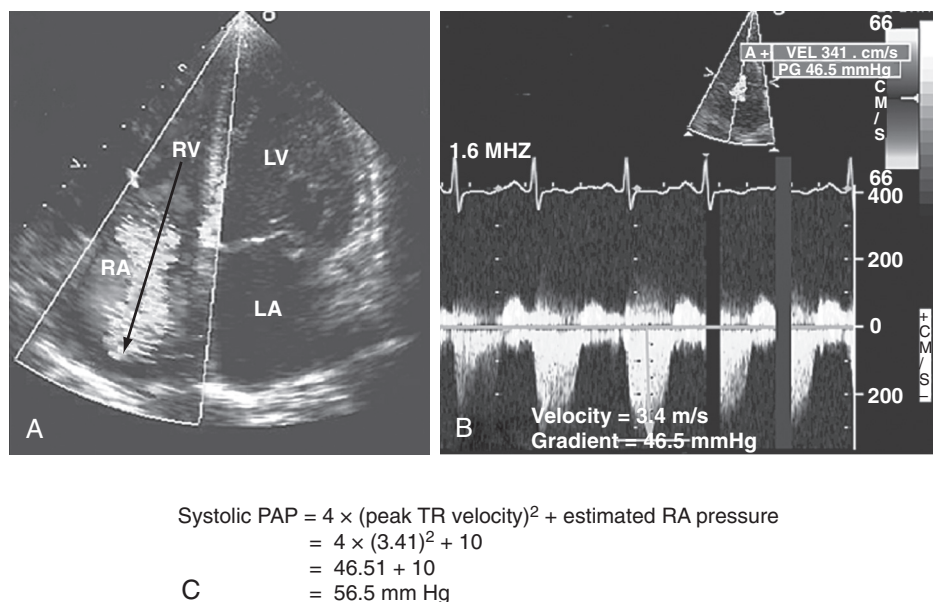


FIGURE E2-12 ■ Calculation of systolic pulmonary artery pressure (PAP). **A**, Color Doppler transthoracic apical four-chamber view showing a significant tricuspid regurgitation (TR) jet from right ventricle (RV) to right atrium (RA). The peak tricuspid regurgitation velocity is measured by placing the continuous wave Doppler in the center of the tricuspid regurgitation jet (arrow). **B**, Spectral continuous wave Doppler profile of the tricuspid regurgitation jet. Peak tricuspid regurgitation velocity (3.41 m/s) and peak systolic pulmonary artery pressure gradient (46.5 mm Hg) can be obtained with this modality. **C**, Peak systolic pulmonary artery pressure also can be determined from the peak tricuspid regurgitation Doppler velocity using the modified Bernoulli equation: $\Delta P = 4 \times (\text{peak tricuspid regurgitation velocity})^2$. To this peak systolic pressure gradient between right ventricle and right atrium is added the estimated right atrial pressure (determined to be 10 in this example) to obtain the peak right ventricular systolic pressure. In the absence of pulmonic stenosis or right ventricular outflow obstruction, peak right ventricular systolic pressure is equal to systolic pulmonary artery pressure. LA, left atrium; LV, left ventricle.

Echocardiography is uniquely suited to the evaluation of valvular heart disease because of its ability to provide information regarding the etiology and severity of valvular lesions. In the ICU, TTE can provide valuable information concerning valvular integrity and function,¹⁶ but it may be suboptimal and not sensitive enough to detect endocarditis, a dysfunctional mitral valve, or prosthetic valve dysfunction. TEE is often warranted. TEE is especially important for the fine detail of mitral valve pathology, such as a torn chordae tendinae and flail scallop (Video E2-2).

Valvular Regurgitation and Prosthetic Valve Dysfunction

In a patient with unexplained hemodynamic instability and a grossly normal TTE examination, performance of subsequent TEE is important to rule out the presence of significant undetected valvular pathology. Common valvular pathologies that can be missed are mitral regurgitation and prosthetic valve dysfunction. In some situations, TTE may provide better imaging than TEE for evaluation of anterior structures such as the aortic valve (native or prosthetic) and for Doppler measurements. TEE is clearly superior to TTE for evaluation of mitral valve pathologies (native and prosthetic). In a study of ICU patients by Alam,¹⁶ TTE compared with TEE was shown either to miss or to underestimate the severity of regurgitation of St. Jude and bioprosthetic valves in the mitral but not in the aortic position.

With acute severe mitral regurgitation, the diagnosis may be clinically difficult because the murmur is often of short duration and low intensity (because of rapid pressure equalization between the left ventricle and the relatively noncompliant left atrium). By TTE, the size of the regurgitant jet in acute mitral regurgitation may appear small and lead to underestimation of severity.⁹⁹ Because of its close anatomic proximity, TEE provides a much more precise evaluation of the degree of mitral regurgitation (Fig. E2-13) and provides crucial diagnostic information regarding the cause for mitral regurgitation. The diagnosis of acute mitral regurgitation represents a medical emergency that may necessitate urgent surgery, so the threshold to perform a TEE when this entity is suspected should be low.^{8,10,97} Also, several investigators have confirmed the superior accuracy, sensitivity, and reliability of TEE over TTE for dysfunction of mitral prostheses, in which ultrasonic shadowing of the left atrium often occurs with the standard transthoracic studies.¹⁰⁰⁻¹⁰³ TEE may be especially useful to detect obstruction of prosthetic valves from thrombus (Video E2-3).

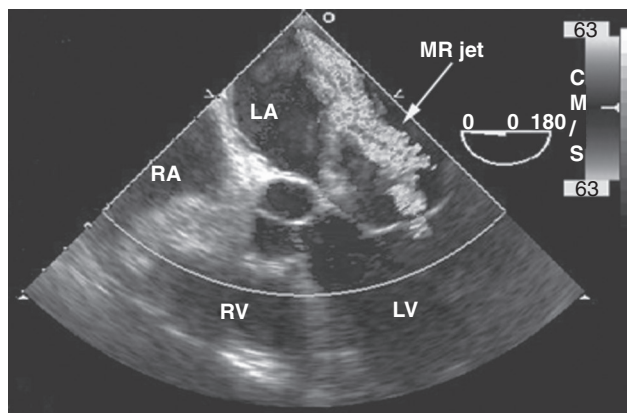


FIGURE E2-13 ■ Severe mitral regurgitation (MR). Transesophageal five-chamber view shows severe mitral regurgitation with a large regurgitant jet (arrow) going far posteriorly in the left atrium (LA). In this case, systolic flow reversal in the pulmonary veins (another echocardiographic sign of severe mitral regurgitation) also was present (not shown on this picture). Because of its close anatomic proximity, transesophageal echocardiography is an excellent tool for the precise evaluation of the degree of mitral regurgitation. LV, left ventricle; RA, right atrium; RV, right ventricle.

Traumatic Valvular Injuries

Traumatic valvular injuries associated with myocardial injury may present as acute regurgitation. Bedside exclusion of major trauma to the aorta, valves, and myocardium is important in the posttrauma context.^{104,105} Valvular injuries may occur as a consequence of blunt or penetrating trauma. Most frequently the aortic valve is injured; less commonly the mitral and tricuspid valves are injured.¹⁰⁶ Valvular dysfunction is usually due to a torn leaflet or rupture of a papillary muscle or chordae.¹⁰⁶ In trauma patients, TEE is the bedside imaging modality of choice to detect these pathologies.^{104,105} In a study by Chirillo et al. assessing the usefulness of TTE and TEE in the recognition and management of cardiovascular injuries after blunt chest trauma, TTE provided suboptimal imaging in 62% of patients, and the bad quality of images obtained was the main cause for the low sensitivity of TTE compared with TEE.

Evaluation of the Pericardial Space

Echocardiography is an essential instrument for the diagnosis of pericardial disease. In the ICU, the most common clinical indication for assessment of the pericardial space is suspected tamponade. The pericardium is a potential space that can become filled with fluid, blood, pus, or uncommonly, air. Presence of fluid in this space is detected as an echo-free space. Pericardial fluid usually is detected easily with TTE. The parasternal long-axis and short-axis views and the apical views usually reveal the effusion (Fig. E2-14). In many critically ill patients with suboptimal TTE image quality, the subcostal view is often the only adequate window available to detect the presence of a pericardial effusion. In these ICU patients with poor acoustic windows and in the post-cardiac surgical setting, TEE may be needed to assess the pericardial space adequately.

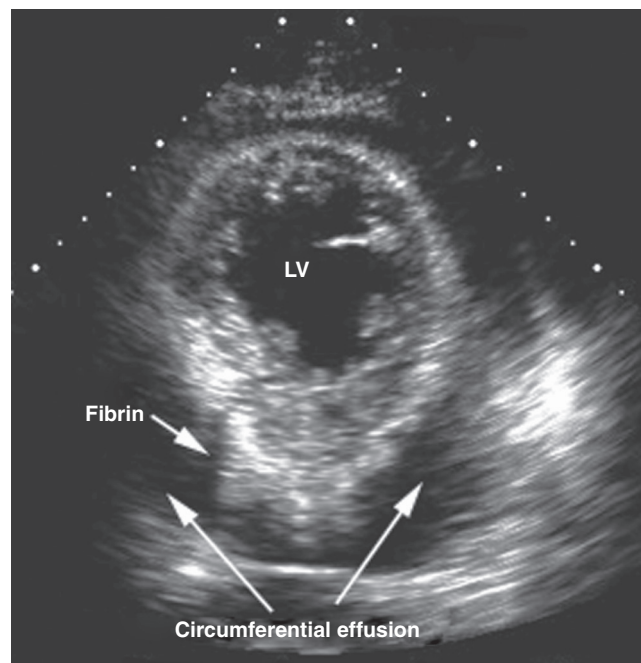


FIGURE E2-14 ■ Large pericardial effusion. Transthoracic parasternal short-axis view shows a large, predominantly echo-free space around the left ventricle (LV). This space represents fluid in the pericardium. In this case, the large circumferential pericardial effusion was bloody at pericardiocentesis. Particulate matter (e.g., fibrin and clots) can be visualized as denser echoes around the heart and floating in the effusion.

In addition to assisting in the diagnosis of pericardial effusion and tamponade, 2D echocardiography can assist in its drainage, as pericardiocentesis can be performed safely under 2D echocardiographic guidance.^{107,108} By determining the depth of the effusion and its distance from the site of puncture, it is possible to optimize the needle placement. Echocardiography also can be used for immediate monitoring of the results of the pericardiocentesis.

Cardiac Tamponade in the Intensive Care Unit

The most common causes of cardiac tamponade in the ICU are listed in **Box E2-5**. Echocardiographic 2D signs of tamponade are a direct consequence of increased pericardial pressure, leading to diastolic collapse of one or more cardiac chambers (usually on the right side first) (**Fig. E2-15**). Usually, collapse of the right ventricular free wall is seen in early diastole, and right atrial wall collapse is seen in late diastole.¹⁴ This latter sign is sensitive but not specific for tamponade. It is, however, specific for a hemodynamically significant effusion if the right atrial collapse lasts longer than one-third of the R-R interval.^{14,109} In the presence of a massive effusion, the heart may have a “swinging” motion in the pericardial cavity. This finding is not always present in cardiac tamponade, because the amount of fluid in the pericardial space may be small but still cause a tamponade physiology, depending on the acuity with which the effusion accumulates and the compliance of the pericardium. In poststernotomy patients, tamponade may be missed by TTE (even in cases in which imaging quality seems adequate) because hematomas causing selective cardiac chamber compression

are often in the form of loculated clots located in the far field of the ultrasound beam in the posterior heart region (even when the anterior pericardium is left open).¹¹⁰ The right atrium and right ventricle may be spared in such cases secondary to postoperative adhesions or tethering of the right ventricle to the chest wall anteriorly.¹¹⁰

Another (indirect) sign of a hemodynamically significant pericardial effusion on 2D imaging is plethora of the inferior vena cava with blunted respiratory changes.¹ The latter sign is less valuable in mechanically ventilated patients, because they often have a stiff, dilated inferior vena cava even in the absence of a pericardial effusion (Video E2-4).

Doppler findings of cardiac tamponade are based on characteristic changes in intrathoracic and intracardiac hemodynamics that occur with respiration. Because of the principle of ventricular interaction, mitral inflow velocity (E wave) decreases after inspiration and increases after expiration. Reciprocal changes occur with respect to tricuspid inflow velocity. With tamponade, the exaggerated inspiratory-expiratory variation of the inflow velocity (E wave) over one respiratory cycle should be greater than 40% on the left and greater than 80% on the right.¹¹¹ In critically ill patients, however, mechanical ventilation, bronchospasm, significant pleural effusion, and respiratory distress can alter intrathoracic and intracardiac hemodynamics and make these Doppler findings less reliable. A significant pleural effusion sometimes causes significant respiratory Doppler variations of the inflow velocities that disappear when the effusion is drained.¹¹² The presence of arrhythmia also makes the Doppler findings difficult to interpret. In some circumstances, echocardiographic signs of tamponade may be subtle or absent, so one must keep in mind that the diagnosis of tamponade remains a clinical one and that the echocardiographic signs must be analyzed in conjunction with the clinical findings.

BOX E2-5

Most Common Causes of Cardiac Tamponade in the Intensive Care Unit

- Myocardial or coronary perforation secondary to catheter-based intervention (i.e., after intravenous pacemaker lead insertion, central line placement, or percutaneous coronary interventions)
- Compressive hematoma after cardiac surgery
- Proximal ascending aortic dissection
- Blunt or penetrating chest trauma
- Complication of myocardial infarction (e.g., ventricular rupture)
- Uremic or infectious pericarditis
- Pericardial involvement by metastatic disease or other systemic processes

Complications After Cardiac Surgery

Bedside echocardiography has proved to be of particular value in the critical care management of patients with hemodynamic instability after cardiothoracic operations.^{7,8,83,113-115} TTE is often severely limited in this group of patients.^{5,8} TEE is the modality of choice in this setting because it provides detailed information that can help determine the cause of refractory hypotension. The most frequent echocardiographic diagnoses encountered in these patients are left ventricular or right ventricular failure, tamponade, hypovolemia, and valvular dysfunction. Schmidlin et al.¹¹⁶ studied 136 patients after cardiac surgery and

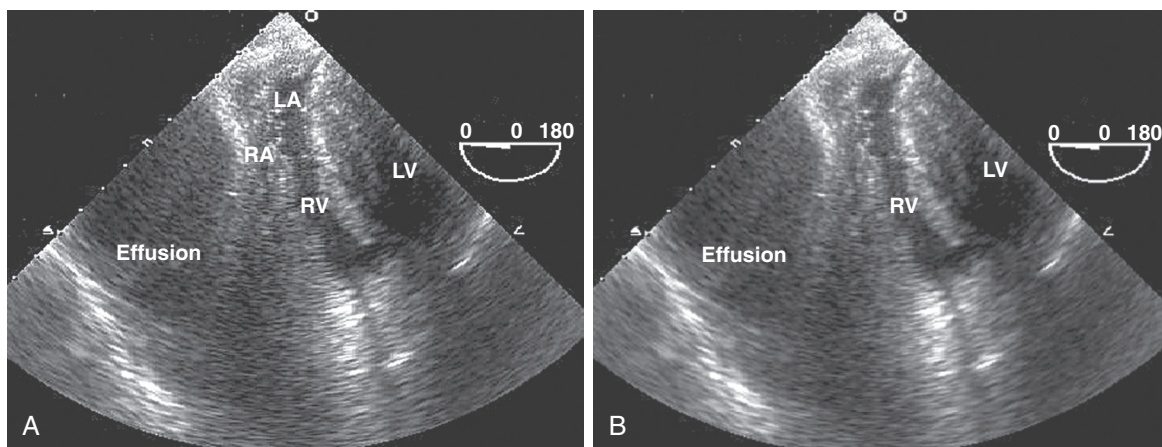


FIGURE E2-15 ■ Cardiac tamponade. Transesophageal four-chamber view (**A**) shows the presence of a large effusion that severely compresses the right atrium (RA) and right ventricle (RV), which appear slitlike. The left ventricle (LV) also is small because of indirect compression and underfilling. Transgastric short-axis view (**B**) of the same patient shows the large pericardial effusion and severely compressed ventricular chambers. This postcardiotomy patient was in profound shock and was brought back to the operating room emergently for reexploration and drainage of the effusion. LA, left atrium.

showed that a new diagnosis was established or an important pathology was excluded in 45% of patients undergoing TEE. A therapeutic impact was found in 73% of cases. The main indications for TEE in this study were control of left ventricular function (34%), unexplained hemodynamic deterioration (29%), suspicion of pericardial tamponade (14%), cardiac ischemia (9%), and “other” (14%). Reichert et al.¹¹³ performed TEE in hypotensive patients after cardiac surgery. Left ventricular failure was found in 27% of patients, hypovolemia in 23%, right ventricular failure in 18%, biventricular failure in 13%, and tamponade in 10%. Comparison with hemodynamic parameters showed agreement on diagnosis (hypovolemia versus tamponade versus cardiac failure) in only 50% of the cases. Echocardiography identified two cases of tamponade and six of hypovolemia that were not suspected based on standard hemodynamic data. In five patients with hemodynamic findings suggesting tamponade, unnecessary reoperation was prevented because TEE ruled out this diagnosis. Costachescu et al.²² also showed the superiority of TEE compared with conventional monitoring with pulmonary artery catheterization in diagnosing and excluding significant causes of hemodynamic instability in postoperative cardiac surgical patients.

Descriptions of the echocardiographic findings of left ventricular dysfunction, tamponade, hypovolemia, and valvular dysfunction were described earlier in this chapter.

Infective Endocarditis

Occurrence of infective endocarditis in patients hospitalized in an ICU is common. It is often in the differential diagnosis of febrile patients in the ICU. Infective endocarditis was the second most common indication for performance of an echocardiogram among centers reporting their experience, as summarized in a review article by Heidenreich.⁵ Nearly all critically ill patients are at risk for iatrogenic infection, bacteremia, and subsequent endocarditis because of the presence of multiple indwelling catheters, severe underlying diseases, malnutrition, and prolonged mechanical ventilation. Classic clinical findings suggesting endocarditis¹⁰⁶ are uncommon in this patient population. Echocardiography is the test of choice for the noninvasive diagnosis of endocarditis. Fowler et al.¹¹⁷ studied patients with *Staphylococcus aureus* bacteremia referred for TEE and showed that endocarditis ultimately was diagnosed in 25%. Only 7% of these patients had physical findings suggesting endocarditis before TEE. Absence of clinical stig-

mata is especially likely if the infection presents acutely. Because the consequences of untreated endocarditis are devastating and often ultimately fatal, it is important that the infection and its complications be recognized promptly and treated appropriately.⁵⁹

The echocardiographic features typical for infective endocarditis are^{59,118} (1) an oscillating intracardiac mass on a valve or supporting structure or in the path of a regurgitant jet or an iatrogenic device, (2) abscesses, (3) new partial dehiscence of a prosthetic valve, or (4) new valvular regurgitation. Sensitivity for the echographic diagnosis of endocarditis is 58% to 62% for TTE and 88% to 98% for TEE.^{119,120} TEE is particularly useful for detecting small vegetations¹²¹ and detecting vegetations on prosthetic valves. TEE also has been shown to be superior to TTE for diagnosing complications of endocarditis such as aortic root abscess, fistulas, and ruptured chordae tendineae of the mitral valve.¹⁶ Among ICU patients, sensitivity of TTE for the diagnosis of endocarditis is often poor because the quality of the transthoracic study is commonly suboptimal. The sensitivity of TEE for suspected infective endocarditis usually is excellent in the ICU (Fig. E2-16). In a study by Font et al.,⁹⁷ a search for vegetations was the indication for 51 (46%) of 112 TEE studies performed for critically ill patients. TEE increased the detection rate by 27% compared with TTE. Suspicion of endocarditis represented 29% of the indications for TEE in a study of ICU patients by Chenzbraun et al.⁸⁵; 9 (27%) of 31 patients with suspected infective endocarditis had a positive study for endocarditis. All positive studies were in patients who had an increased likelihood for infective endocarditis before the examination, as indicated by the presence of fever, positive blood cultures, new-onset murmur, prosthetic valve, or new-onset heart failure (alone or in combination). None of the patients with native valves and no clinical features of endocarditis had a TEE study diagnostic of infective endocarditis, and in none of them was the diagnosis of infective endocarditis made later. The findings from this study indicate that TEE is not useful as a screening procedure for infective endocarditis in septic patients without high clinical likelihood for endocarditis. The clinical probability of endocarditis should guide the use of TEE. Clinical risk factors considered high risk included intracardiac prosthetic material, positive blood cultures (in particular, *S. aureus*), evidence of peripheral emboli, and history of previous endocarditis^{8,16} (Video E2-5).

As concluded by Colreavy et al.,⁸ performance of TEE in the ICU for suspicion of infective endocarditis should be (1) for cases associated with a clinical likelihood of endocarditis and a negative TTE

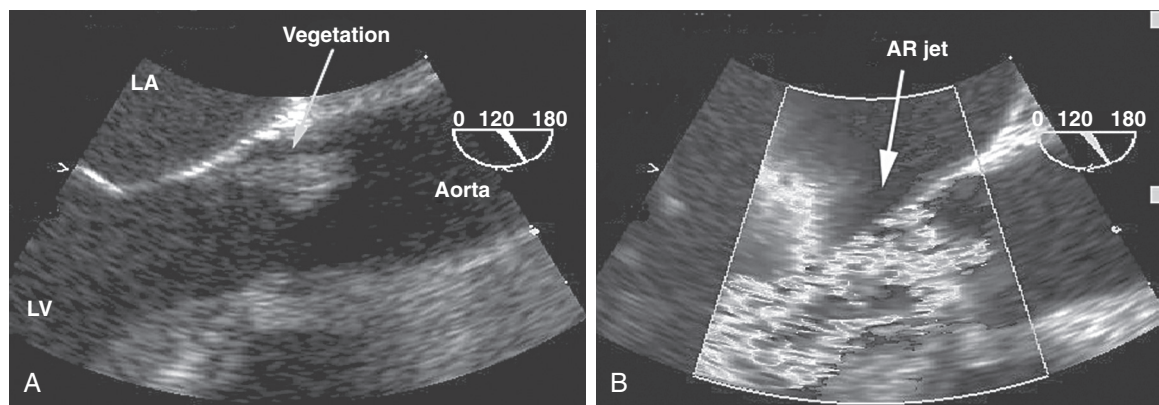


FIGURE E2-16 ■ Infective endocarditis of the aortic valve. A 55-year-old patient was admitted to the ICU with fever, chills, hypotension, and respiratory distress for which he had to be intubated. He had 4/4 positive blood cultures for *Staphylococcus aureus*. Transthoracic echocardiography was performed initially, but the quality was suboptimal, and no definite conclusion could be reached. Subsequent transesophageal echocardiography revealed a large vegetation on the left aortic coronary cusp as seen in the midesophageal view at 120 degrees (**A**). Color Doppler examination (**B**) revealed the presence of associated severe aortic regurgitation (AR). The patient was treated with antibiotics and emergent aortic valvular surgery. LA, left atrium; LV, left ventricle.

examination, (2) for suspected prosthetic valve endocarditis, (3) for assessment of complications in known cases of endocarditis, and (4) for cases of *S. aureus* bacteremia when the source is unknown or blood cultures remain positive despite antibiotic therapy. When assessing a patient for infective endocarditis by echocardiography, one must keep in mind the noninfectious causes of vegetations that may result from tumors, myxomatous degeneration, marantic endocarditis, Lambli's excrescences, valve thrombus, and suture material in patients with repaired native or prosthetic valves.

Assessment of the Aorta

In the ICU, use of bedside echocardiography for assessment of suspected aortic pathologies provides many advantages over CT or aortography: there is no need for IV contrast administration, there may be less time delay, there is no need for transportation of a critically ill patient, and cardiac morphology and function can be evaluated at the same time.³ For many years, aortography has been the gold standard for the investigation of suspected injuries of the aorta.³ The advent of noninvasive modalities such as CT, magnetic resonance imaging (MRI), and TEE with their excellent sensitivity and specificity to diagnose aortic pathologies has decreased the need for aortograms.

Suspected aortic pathologies can be encountered in different ICU settings. The aorta may have to be imaged to rule out dissection, rupture, aneurysm, aortic debris, or aortic abscess. TTE is a good initial imaging modality for evaluation of the proximal aorta (ascending aorta and arch),⁵⁹ but the descending thoracic aorta cannot be adequately assessed and visualized with this modality. Because of the close anatomic relationship between the thoracic aorta and the esophagus, TEE allows optimal visualization of the entire thoracic aorta (Fig. E2-17). As described earlier, there exists a blind spot in the distal portion of the ascending aorta and the proximal portion of the transverse aorta where imaging can be suboptimal.^{122,123}

Aortic Dissection and Rupture

Patients presenting with suspected aortic dissection need emergency diagnosis and treatment. Different noninvasive tests have been advocated for evaluation of suspected aortic dissection, including TEE, CT, and MRI.^{5,124} Nienaber et al.¹²⁴ compared all three modalities and found that they had similar sensitivities (98%). MRI had higher specificity than TEE (98% vs. 77%). A limitation of the study was that

single-plane TEE was used. With multiplane TEE, specificity is improved to greater than 90% (see Fig. E2-17).¹²² TTE was compared with CT and aortography in a multicenter European cooperative study,¹²⁵ and it was shown that TEE was superior compared with both modalities for the diagnosis of aortic dissection (sensitivity 99%). Other studies have confirmed the high accuracy of TEE.¹²⁵⁻¹²⁸ A negative TEE examination for the diagnosis of aortic dissection, even in a high-risk population, has high negative predictive value.¹²⁹ Most centers utilize contrast CT scanning as the first choice for suspected aortic dissection, but TEE is an option in patients who cannot receive contrast, such as those who have advanced renal disease or are too unstable to be transported to the CT scanner (Video E2-6).

Another common indication to perform emergency aortic imaging in the ICU is assessment of patients with blunt or penetrating chest trauma.³ These patients are at high risk of life-threatening aortic injuries such as traumatic dissection and rupture, and prompt diagnosis and treatment are critical. Exclusion of major trauma to the ascending and descending aorta at the bedside is important in this context.¹⁰⁵ The value of TEE on admission for trauma patients with enlarged mediastinum and hemodynamic instability, with or without a combination of several other symptoms (e.g., pleural effusion, decreasing hematocrit, thoracic vertebral fracture), has been stressed by many authors.¹³⁰⁻¹³³ Patients usually have a contained hematoma around the aortic dissection.¹³¹ Transection of the thoracic aorta usually is seen at the level of the ligamentum arteriosum.

Additional helpful features of TEE in evaluating aortic pathologies are the ability to detect or assess extension of dissection into the proximal coronary arteries; the presence of pericardial hematoma or effusion; the presence, severity, and mechanism of associated aortic valve regurgitation; the point of entry and exit between the true and false lumens; the presence of thrombus in the false lumen; and ventricular function.¹⁶ When TEE findings are equivocal or negative in cases of suspected thoracic aortic disease, other imaging modalities such as aortography, CT, or MRI should still be performed.

Assessment for Intracardiac and Intrapulmonary Shunts

In critically ill patients, clinical suspicion for an intracardiac or intrapulmonary shunt most often is raised in the context of unexplained embolic stroke or refractory hypoxemia. In such cases, the presence of

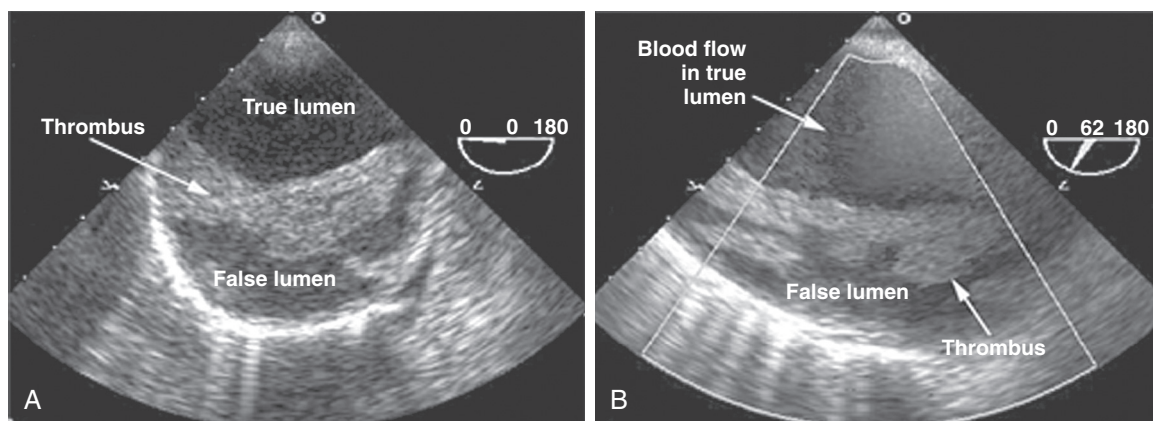


FIGURE E2-17 ■ Dissecting thoracic aortic aneurysm. A 65-year-old patient presented to the emergency department with severe ripping chest pain radiating to the back. The initial electrocardiogram was unremarkable, and the chest x-ray showed a widened mediastinum. The patient underwent transesophageal echocardiography, which revealed the presence of a large dissecting aneurysm of the descending thoracic aorta. The short-axis view (**A**) revealed the presence of a large aneurysm with a true and a false lumen. The false lumen was filled with thrombus (arrow). On the longitudinal view with color Doppler (**B**), blood flow in the true lumen is visualized. The patient was taken emergently to the operating room.

a right-to-left shunt must be excluded. Common origins of right-to-left shunt are atrial septal defect or patent foramen ovale at the cardiac level⁵ and arteriovenous fistula at the pulmonary level.⁵ To be able to detect the presence of such a shunt at the bedside, a contrast study often is needed, because the shunt is usually not well visualized with 2D echocardiography alone. Color-flow imaging increases the detection rate of intracardiac shunt to some extent, but usually only when the shunt is large. Accordingly, a contrast study should be performed routinely as part of a TEE or TTE examination when evaluating a patient with unexplained embolic stroke or refractory hypoxemia in the ICU. For this purpose, agitated saline contrast is usually used. Approximately 0.5 mL of air is mixed with 10 mL of normal saline and is vigorously agitated back and forth between two syringes connected to the patient by a three-way stopcock. After an adequate echocardiographic view of the right and left atrial cavities has been obtained, the agitated saline is forcefully injected IV. After injection, the contrast is seen in the vena cava, right atrium, right ventricle, and pulmonary artery. In the absence of a shunt, only a minimal amount of contrast should be seen in the left-sided cavities, because most of the microbubbles from the agitated saline are unable to pass through the pulmonary capillaries. If an intracardiac shunt is present, such as an atrial septal defect or patent foramen ovale, left-sided contrast is observed immediately after right-sided opacification, and the contrast is seen going through the interatrial septum (Fig. E2-18). Performance of a Valsalva maneuver by the patient during contrast injection increases the sensitivity of the bubble study to detect right-to-left shunting. In mechanically ventilated patients, a maneuver equivalent to a Valsalva may be performed by inducing sudden release of sustained airway pressure previously achieved by inflating the lungs manually. This maneuver reverses the atrial transseptal gradient and may help uncover a patent foramen ovale that would not have been seen otherwise. Right-to-left shunting also can be caused by the presence of pulmonary arteriovenous fistulas. These often are associated with end-stage liver disease (hepatopulmonary syndrome). With this type of shunt, contrast is seen to appear in the left atrium from the pulmonary veins instead of through the atrial septum; this finding is best detected by TEE, which usually permits visualization of all four pulmonary veins. The characteristic of intrapulmonary versus intracardiac shunt is that there is a longer delay (three to five cardiac cycles) between the

appearance of contrast from the right-sided to left-sided cavities in the presence of an intrapulmonary shunt.⁵ Agitated saline is a simple and easy way to use contrast at the bedside.

Other types of intracardiac shunts also can be encountered in the ICU. After myocardial infarction, patients can develop cardiogenic shock due to acute development of a ventricular septal defect and resultant left-to-right shunt. Physical examination and invasive hemodynamic monitoring (pulmonary artery catheterization) sometimes can miss this diagnosis. Echocardiography reveals a disrupted ventricular septum with a high-velocity left-to-right shunt. This kind of shunt usually is well visualized without use of contrast. The diagnosis can be established by 2D and Doppler TTE in approximately 90% of cases.¹³⁴ Penetrating cardiac trauma is often associated with intracardiac and extracardiac shunts, and TEE is becoming the obvious tool for perioperative early identification of occult shunts.¹⁴ Identification of these shunts is paramount in these critically ill patients, because missing them may lead to cardiac tamponade and rapid death. TEE has been shown to be superior to angiography and TTE to visualize these lesions.¹³⁵⁻¹³⁷

Unexplained Hypoxemia

Patent foramen ovale is present in 25% to 30% of healthy individuals.^{59,106} Usually it allows only minimal and intermittent right-to-left shunting. When the right atrial pressure is increased and exceeds left atrial pressure, the patent foramen ovale can widen and significantly increase the importance of the right-to-left shunt, with resultant significant hypoxemia. In a critically ill patient, this increase in right-sided pressure can occur from pulmonary hypertension secondary to acute respiratory distress syndrome or pulmonary embolism, right ventricular failure (from infarction or pulmonary hypertension), or severe tricuspid regurgitation, which is often seen in the ICU for a variety of reasons. In critically ill patients, TEE is in general more useful than TTE for evaluation of patent foramen ovale, atrial septal defect (see Fig. E2-18), and pulmonary arteriovenous fistula¹³⁸ because of the close proximity of the lesion to the ultrasound transducer.

Patients with patent foramen ovale and persistent refractory hypoxemia despite ventilator and hemodynamic manipulation sometimes may need to have catheter-based septal defect closure devices inserted. TEE is crucial to assist in the performance of this procedure.¹³⁹

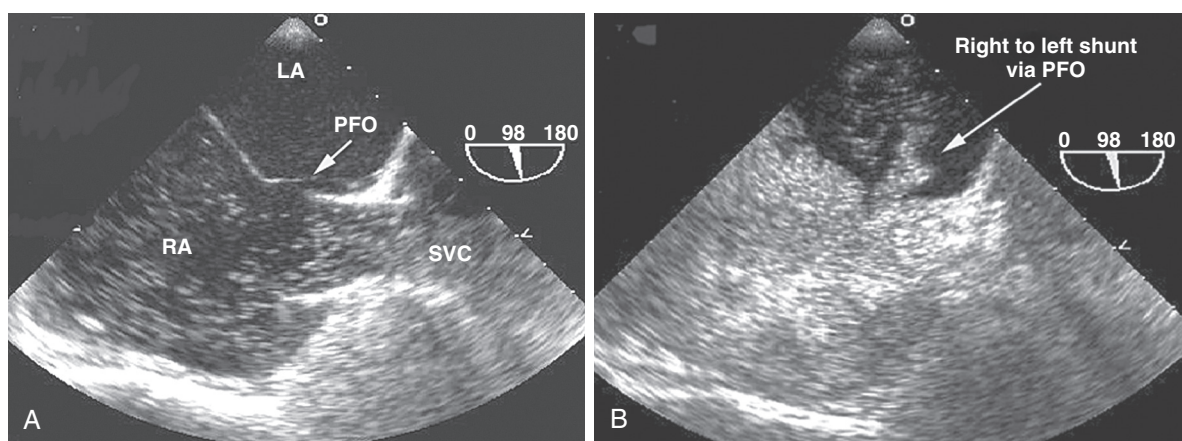


FIGURE E2-18 ■ Positive bubble study shows the presence of a right-to-left shunt via a patent foramen ovale (PFO). Transesophageal echocardiography was performed in a patient hospitalized in the ICU for pneumonia. He presented with refractory hypoxemia that was out of proportion to the underlying minor pulmonary process. Transesophageal echocardiography was obtained (multiplane transducer at 98 degrees) and showed the presence of a patent foramen ovale with a significant right-to-left shunt due to elevated right atrial pressure. Soon after contrast injection (**A**), the bubbles are seen arriving in the right atrium (RA) from the superior vena cava (SVC). A few seconds later (**B**), a complete opacification of the right atrium is reached, and the bubble contrast is clearly seen shunting through the patent foramen ovale from the right atrium to left atrium (LA).

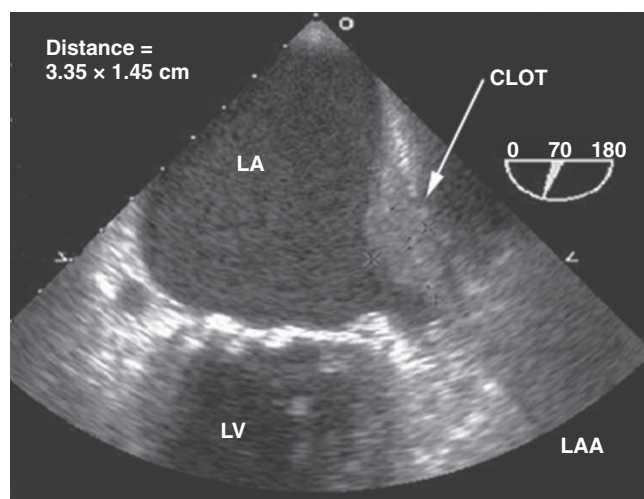


FIGURE E2-19 ■ Large clot in the left atrial wall and left atrial appendage (LAA). A 72-year-old patient hospitalized in the ICU for urosepsis developed rapid atrial fibrillation. She was initially anticoagulated and rate-controlled. Despite resolution of the septic picture, she remained in atrial fibrillation 4 days after its onset. The patient underwent transesophageal echocardiography before undergoing a planned electrical cardioversion. The midesophageal view with multiplane transducer at 70 degrees revealed the presence of a large clot (3.35×1.45 cm) in the posterolateral wall of the left atrium (LA) extending into the LAA. With these findings, the patient's anticoagulation regimen was intensified, and the cardioversion was not performed. LV, left ventricle.

Source of Embolus

In the setting of acute unexplained stroke, echocardiography often is required to determine whether a potential embolic source of cardiac origin is present. TEE is the modality of choice for this purpose. Possible cardiac sources of emboli to the arterial circulation include left atrial or appendicular thrombus, left ventricular thrombus, thoracic atheromatosis, and right-sided clots (right atrium, right ventricle, vena cava) combined with a right-to-left intracardiac shunt (leading to a paradoxical embolus). Cardiac tumors and vegetations are other potential sources of emboli from cardiac origin that must be considered.

When cardioversion is considered for a critically ill patient with atrial fibrillation or flutter, performance of TEE is helpful in evaluating the left atrium and appendage for the presence of thrombus (Fig. E2-19). If no intracardiac clots are documented, cardioversion can be performed with minimal embolic risks.

USE OF CONTRAST AND HARMONIC TECHNOLOGY TO ENHANCE TRANSTHORACIC EXAMINATIONS WITH POOR IMAGE QUALITY IN A CRITICALLY ILL PATIENT

Using standard echocardiographic methods, endocardial delineation is suboptimal in approximately 30% of cases.¹⁴⁰ However, two developments in ultrasound have improved the quality of endocardial border definition: harmonic imaging and IV contrast echocardiography.¹⁴¹ Dramatic improvements in image quality have been achieved with the development of harmonic imaging. This technology exploits the formation of ultrasound signals that return to the transducer at a multiple of the transmitted (fundamental) frequency, referred to as the *harmonic frequency*.¹ Signals are received by the ultrasound transducer at twice the transmitted frequency. This "second harmonic imaging"

results in images with better contrast between the myocardium and cardiac chambers and improved endocardial definition compared with fundamental imaging.¹⁴²⁻¹⁴⁴ Most current ultrasound equipment includes harmonic imaging as a standard feature.

In critically ill patients with poor acoustic windows, endocardial visualization still may be inadequate despite the use of second harmonic imaging.¹⁴⁰ In these patients, contrast agents capable of producing left ventricular cavity opacification with an IV injection can be helpful in delineating endocardial borders. Several contrast agents are currently available that contain albumin microspheres filled with perfluorocarbon gas, allowing for the passage of contrast through the lungs with appearance of contrast in the left ventricle.¹ The chamber is opacified by the contrast agent within 1 minute of administration and allows improved endocardial border detection. The presence of contrast also enhances Doppler signals.¹⁴⁵ Studies have examined the impact of these newer modalities of harmonic imaging and contrast in the ICU. Reilly et al.¹⁴⁶ assessed the benefits of contrast echocardiography for the evaluation of left ventricular function in 70 unselected ICU patients; 22 patients (31%) were receiving mechanical ventilation. Left ventricular EF could not be obtained at all in 23% of patients with standard imaging, but when harmonic imaging was employed, left ventricular EF was unobtainable in only 13% of patients. When contrast imaging was employed, left ventricular EF was measurable in all the patients. Ejection fraction was confidently determined in 56%, 62%, and 91% of patients with standard imaging, harmonic imaging, and contrast imaging. In this study, contrast imaging was safe and dramatically improved the capacity to evaluate left ventricular EF and regional wall motion reliably compared with fundamental and harmonic imaging. Yong et al.¹⁴¹ extended these observations by comparing the results of harmonic and contrast imaging with an independent standard (i.e., TEE) in 32 consecutive critically ill patients who were considered technically very difficult. Estimation of EF was possible in 31%, 50%, and 97% with fundamental imaging, harmonic imaging, and contrast imaging. Quantification of EF by contrast enhancement correlated best with TEE ($r = 0.91$).

In critically ill patients with suboptimal TTE image quality, contrast echocardiography combined with harmonic imaging provides a non-invasive and safe alternative to TEE for determination of regional and global left ventricular function (Fig. E2-20).¹⁴⁰ It is a rapid and simple technique that can be performed at the bedside in the ICU, with positive impact on interpretation of left ventricular function. Before using TEE, this technique should be considered in critically ill patients when TTE is inadequate for the evaluation of left ventricular function.¹⁴⁰

COMPARISON BETWEEN BEDSIDE ECHOCARDIOGRAPHY AND PULMONARY ARTERY CATHETER IN THE INTENSIVE CARE UNIT

Since its introduction into clinical practice in 1970, pulmonary artery catheterization has been the standard hemodynamic monitoring technique for critically ill patients in the ICU.¹⁴⁷⁻¹⁴⁹ Pulmonary artery catheterization provides clinicians with indices of cardiovascular function to assist in therapeutic decision making. Pulmonary artery catheterization can be a useful diagnostic tool, aiding in the management of critically ill patients. Nevertheless, poor interpretation of the data it provides can lead to excessive morbidity and mortality.^{63,147,150,151} Conventional monitoring using a pulmonary artery catheter has been shown to be limited in the evaluation of global ventricular function,^{19,21} and echocardiographic studies have established that pulmonary artery occlusion pressure often does not allow accurate assessment of left ventricular preload.^{26,152,153} The frequent changes in ventricular compliance and loading conditions occurring in critically ill patients can affect systolic and diastolic function. In such cases, conventional monitoring does not enable early detection of acute changes in function, and it does not allow the clinician to discern systolic from diastolic changes.¹⁹

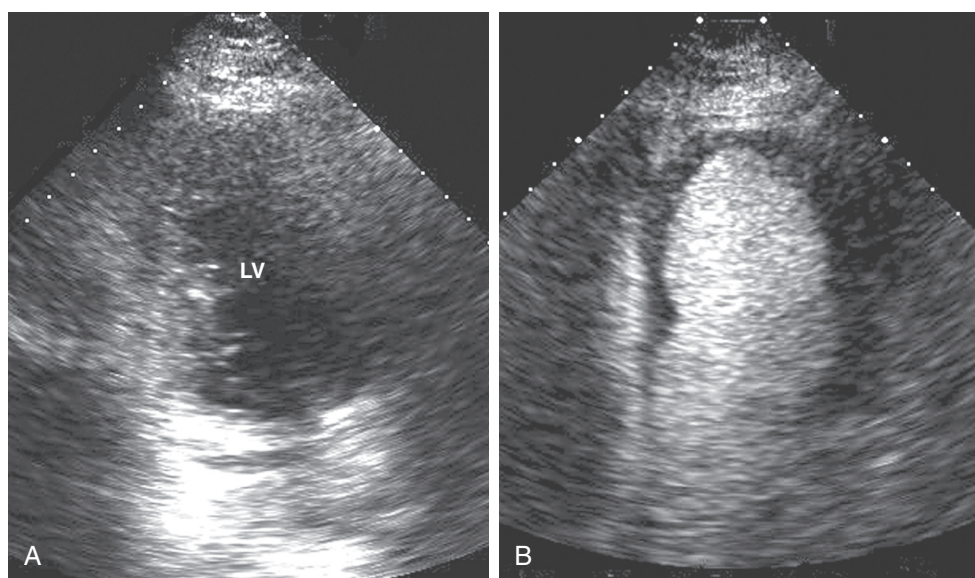


FIGURE E2-20 ■ Use of contrast agent to improve endocardial border delineation in a critically ill patient with suboptimal transthoracic image quality. A suboptimal transthoracic apical two-chamber view (**A**) of the left ventricle (LV) obtained from a ventilated ICU patient with hemodynamic instability. The poor endocardial resolution makes regional and global ventricular function hard to assess. Same transthoracic two-chamber apical view (**B**) in the same patient after contrast injection. A dramatic improvement in endocardial border definition is noted. Contrast echocardiography combined with harmonic imaging provides a noninvasive, safe alternative to transesophageal echocardiography for determination of regional and global left ventricular function.

In critically ill patients, echocardiography, particularly TEE, has the ability to clarify diagnosis and define pathophysiologic process more precisely than pulmonary artery catheterization. In a prospective study of limited scope, Benjamin et al.²¹ found that TEE-derived data disagreed with the pulmonary artery catheterization evaluation of intracardiac volume in 55% of cases and with the pulmonary artery catheterization assessment of myocardial function in 39% of cases. These authors also showed that the post-pulmonary artery catheterization therapeutic recommendations were different from the post-TEE therapeutic recommendations in 58% of patients. In a retrospective analysis of 108 critically ill patients who underwent a TEE, Poelaert et al.²⁰ found that of 64% of patients with pulmonary artery catheterization, 44% underwent therapy changes after TEE (41% in the cardiac and 54% in the septic subgroup). Also, these investigators found that in 41% of patients without pulmonary artery catheterization, TEE led to a change in therapy. They concluded that TEE produced a change in therapy in at least a third of ICU patients, independent of the presence of pulmonary artery catheterization.²⁰

Another significant advantage of echocardiography in the ICU is the speed with which it can be performed relative to pulmonary artery catheterization. In the study by Benjamin et al.,²¹ TEE was performed in 12 ± 7 minutes versus 30 minutes or more for pulmonary artery catheterization insertion. In a study by Kaul,¹⁵⁴ the average time required to place a pulmonary artery catheter and record the data was 63 ± 45 minutes versus 19 ± 7 minutes to perform bedside TEE. Reported complications of pulmonary artery catheterization include pneumothorax, hemothorax, bacteremia, sepsis, cardiac arrhythmias, pulmonary artery rupture, cardiac perforation, and valvular damage.²¹ Compared with pulmonary artery catheterization, bedside echocardiography has a better safety profile, as reported previously in this chapter.

A major advantage of pulmonary artery catheterization versus TEE is that the catheter can more easily serve as a continuous monitoring technique to assess the response to a therapeutic intervention.²¹ This potential advantage may provide little benefit, however, in patients in

whom the information is misinterpreted or inadequate. In some ICUs, TEE has completely replaced pulmonary artery catheterization for assessment of circulatory status of mechanically ventilated patients.³⁸

Despite having multiple limitations, pulmonary artery catheterization still has a role in the ICU and remains a useful diagnostic tool when used by physicians who have extensive experience with it.^{20,155} A combination of invasive pressure monitoring and TEE probably offers the most complete bedside evaluation of morphology and intracardiac hemodynamics and provides a more precise pressure-volume evaluation of left ventricular and right ventricular function and filling.^{20,22}

IMPACT OF BEDSIDE ECHOCARDIOGRAPHY ON DIAGNOSIS AND MANAGEMENT IN A CRITICALLY ILL PATIENT

Echocardiography often provides unexpected diagnoses in critically ill patients. Compared with TTE and invasive hemodynamic monitoring, TEE frequently provides different or additional information. This information often is important for adequate and optimal adjustment of therapy. Several studies have examined the impact of bedside echocardiography, particularly TEE, on the management of critically ill patients. Published studies have reported changes in management after TEE in 30% to 60% of patients,^{17,20,156,157} leading to surgical interventions in 7% to 30%.^{17,98,157,158} Impact varies depending on the type of ICU population being studied. Several studies have reported the clinical impact of urgent TEE in hemodynamically unstable patients.^{157,159,160} In a prospective study of surgical ICU patients by Bruch et al.,²³ echocardiography altered management in 50 (43%) of 115 patients. Alterations in medical management induced by TEE included administration of fluids and initiation or discontinuation of inotropic agents, anticoagulants, or antibiotics. These findings are similar to findings reported in patients in medical or coronary care ICUs.^{10,158} In a retrospective

study done by Colreavy et al.⁸ of a mixed medical and surgical ICU population, TEE findings led to a significant change in management in 32% of all studies performed. In a prospective study by Heidenreich et al.¹⁶¹ of 61 critically ill patients with unexplained hypotension, new diagnoses not made with TTE were made in 17 patients (28%), leading to surgical intervention in 12 (20%). Prospective randomized trials to study the ultimate impact of bedside echocardiography on mortality and morbidity in the ICU are needed. Such studies would be difficult to do, however, given the growing use and importance of this technology in the critical care setting.

OTHER APPLICATIONS OF BEDSIDE ULTRASONOGRAPHY IN THE INTENSIVE CARE UNIT

Central Line Placement

Central venous catheterization is performed frequently in critically ill patients. Placement of a central venous catheter is not without risk and can be associated with adverse events that are hazardous to patients and expensive to treat.¹⁶²⁻¹⁶⁴ Complications can be seen in 15% to 20% of cases.¹⁶⁵⁻¹⁶⁷ As described in a review by McGee and Gould,¹⁶⁸ complications related to central venous line placement are most often mechanical (arterial puncture, local hematoma, hemothorax, pneumothorax), infectious (catheter colonization and related bloodstream infection), and thrombotic. Complications are influenced by patient factors (obesity, coagulopathy, previous failed catheterization), site of attempted access, and operator experience.¹⁶⁹ As previously reported, only approximately 38% to 65% of patients are cannulated on the first attempt using a blind method.^{170,171}

The use of ultrasound guidance during central venous catheterization has been well shown to reduce the risk of complications, mostly so for the internal jugular route. Ultrasound guidance also speeds catheter placement, decreases the number of attempts before successful placement, and improves the overall rate of successful placement. Ultrasound can be used to help localize and define the anatomy of the vein, with subsequent placement of the central venous catheter by the standard use of anatomic landmarks at the site identified by ultrasound, with the knowledge that a vein is present, patent, and of adequate size. Ultrasound also can be used to provide real-time 2D ultrasound guidance to locate the vein and subsequently introduce the needle through the skin and into the vessel. Multiple studies have reported the superiority of ultrasound-assisted cannulation of the internal jugular vein in ICU patients, compared with the external landmark-guided technique.¹⁷⁰⁻¹⁷² Trials looking at ultrasound guidance after failure by the landmark method reported success rates ranging from 33% to 100%.^{169,173-175} A meta-analysis¹⁷⁵ of the literature comparing guidance using anatomic landmarks only versus guidance using ultrasound for the placement of central venous catheters indicates that ultrasound guidance significantly decreases placement failure by 64%, decreases related complications by 78%, and decreases the need for multiple placement attempts by 40%. Data showing superiority of the ultrasound guidance technique are consistent and strong for the internal jugular vein approach but less so for subclavian venous catheterization.¹⁷⁵⁻¹⁷⁷

Some patients can be identified in whom cannulation may be more difficult or in whom consequences of a complication could be more serious.¹⁶⁹ In these patients (Box E2-6), central venous cannulation may be laborious and risky, and ultrasound guidance should be considered. Hatfield and Bodenham¹⁶⁹ showed the benefit of portable ultrasound when central venous access was difficult. As suggested by this study and others,¹⁷⁸ ultrasound guidance is particularly beneficial when used in difficult cases or when a competent operator fails after a few attempts using surface landmarks.

Ultrasound guidance is useful for operators with varying levels of experience.^{169,175} The technique is easy to learn and can be self-taught with some practical assistance from radiologists or other experienced

BOX E2-6

Criteria for Difficult Central Venous Access

Limited access sites for attempts (e.g., local infection, other catheters present)
 Difficult to identify surface landmarks (e.g., local swelling or deformity, severe obesity)
 Previous complications (e.g., pneumothorax, arterial puncture)
 Previous catheterization difficulties (e.g., multiple sites attempted, failure to gain access, >3 punctures at one site)
 Uncorrected coagulopathy (APTT > 1.5x; INR > 1.8; platelets < 50,000/ μ L)
 Patient unable to tolerate supine position
 Known underlying vascular anomalies

APTT, activated partial thromboplastin time; INR, international normalized ratio.

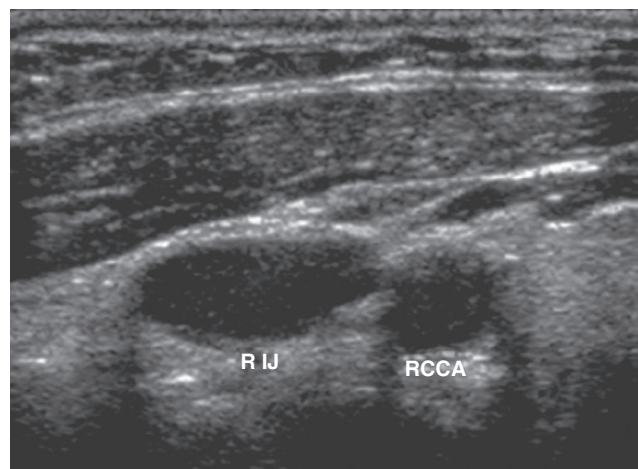


FIGURE E2-21 ■ Transverse view of normal anatomy of the right internal jugular (RIJ) vein and right common carotid artery (RCCA). Ultrasound examination helps determine the anatomic relationship, size, and patency of the vessels. Knowledge of these important vessel characteristics helps determine if the anatomy is suitable for central vein catheterization at a low risk. If the vessel anatomy is normal and the operator is experienced, subsequent venous catheterization can be done by the surface landmark technique or under real-time ultrasound guidance. If high-risk characteristics are identified (see Box E2-6), however, real-time ultrasound guidance (or selection of a different access site) would be preferred. (Courtesy Dr. Kurian Puthenpurayil.)

sonographers.^{169,179,180} Familiarity with the anatomy and equipment is easy to obtain safely at the bedside.

Most large vessels that are catheterized usually can be imaged by ultrasound. Different types of ultrasound modalities can be used to help guide central vessel cannulation, including 2D ultrasound, Doppler transducer, Doppler with the probe in the needle, and fingertip pulse Doppler. With 2D imaging, fluid such as blood in vessels is black because there is nearly complete transmission of ultrasound.¹⁶⁹ Color Doppler mode helps delineate the flow patterns in vessels. Doppler-only equipment that provides no images has shown equivocal results in studies of vascular access.^{176,181}

With 2D imaging, arteries are characteristically small, pulsatile, and difficult to compress with the probe.¹⁶⁹ Veins are usually larger, are nonpulsatile (except in the presence of severe tricuspid regurgitation), are easily compressible, and distend when the patient is placed with the head down or when a Valsalva maneuver is performed.¹⁶⁹

Vessels can be examined in the transverse and longitudinal views. The transverse view permits identification of the vein and arteries based on the sonographic characteristics mentioned earlier and clarifies their positions relative to one another (Fig. E2-21). The transverse and longitudinal views enable the sonographer to monitor in real time the passage of the needle through the skin and the anterior vessel wall.

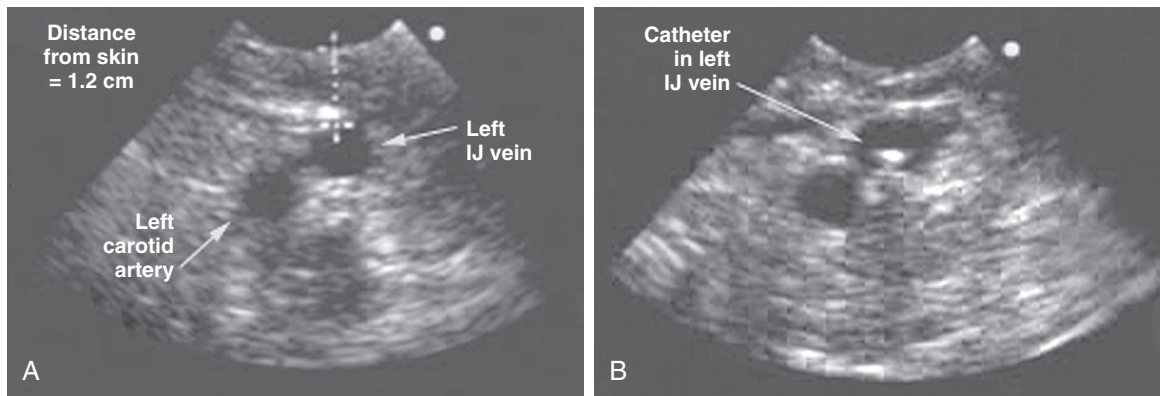


FIGURE E2-22 ■ Transverse view of left carotid artery and left internal jugular (IJ) vein. The distance from the skin to the anterior wall of the vein is measured before insertion of a central venous catheter (**A**). Knowledge of this distance prevents the operator from going too deep with the needle when searching for the vein; this helps decrease the incidence of pneumothorax. After insertion, the catheter position in the jugular vein is confirmed (**B**).

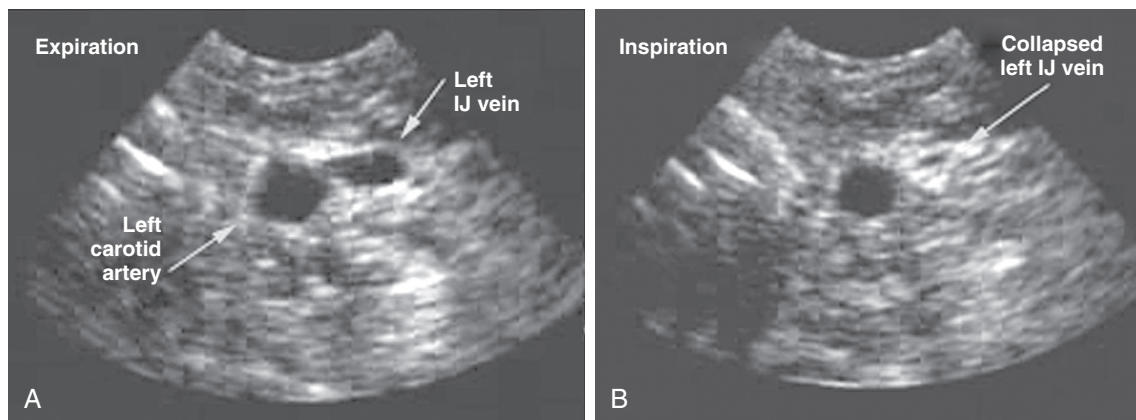


FIGURE E2-23 ■ Transverse view of the left carotid and internal jugular (IJ) vein in a spontaneously breathing patient sitting in bed at a 30-degree angle. The patient was febrile and dehydrated. A near-total collapse of the vein (which is of small caliber) can be appreciated on inspiration (**B**) compared with expiration (**A**).

Ultrasound guidance also ensures detailed and accurate control of the needle (Fig. E2-22).¹⁶⁹

During vessel examination, the sonographer specifically should assess the presence and patency of the vein (Fig. E2-23), the distensibility and compressibility of the vein, the position of the vein relative to the surrounding arteries (Fig. E2-24), and the presence of a thrombus in the vein (Fig. E2-25).¹⁶⁹ Ultrasound identification of certain anatomic characteristics such as small vessel size (<5 mm), intraluminal thrombus, and anterior location of the artery relative to the vein helps the physician identify unfavorable vessel anatomy and choose another catheterization site. A study by Levin et al.¹⁸² showed that 2D ultrasound guidance for the insertion of radial artery catheters was easy to use and increased the rate of success of insertion at first attempt. It was determined to be a useful adjunct to arterial catheter insertion. More studies are needed in the use of ultrasound for cannulation of peripheral arterial conduits.

Assessment of Pleural Effusions and Intraabdominal Fluid Collections

In critically ill patients, atelectasis and pleural effusions are frequent and often are present at the same time. Patients in the ICU are most often supine, and chest x-rays performed in this position offer limited

sensitivity for the diagnosis of pleural effusion.¹⁸³ In many instances, neither atelectasis nor infiltration can be differentiated from pleural effusion. An alternative diagnostic method is needed to provide better results. Decubitus chest radiographs may show if fluid is free flowing, but this approach cannot localize or characterize the effusion precisely. CT of the chest shows the amount and distribution of fluid and is superior to plain lateral decubitus films. CT also can differentiate fluid from atelectasis and reveal information about the lung parenchyma. Chest CT requires transport to the radiology suite, however, which can be hazardous in unstable critically ill patients. Ultrasound examination of the pleural space has proved to be valuable for diagnosis of effusion.¹⁸⁴⁻¹⁸⁸ The value of ultrasound for localizing fluid before catheter drainage or simple thoracentesis is well recognized. Ultrasound is especially valuable for localizing loculated or small effusions before a drainage procedure. In mechanically ventilated patients, blind thoracentesis can be hazardous, especially if the effusion is small or if the patient is on a high level of positive end-expiratory pressure.¹⁸⁹ Lichtenstein et al.¹⁸⁹ evaluated the feasibility and safety of ultrasound-aided thoracentesis in 40 mechanically ventilated patients. No complications occurred in the 45 ultrasound-aided thoracenteses, all performed by ICU physicians.

Basic skill required to detect a pleural effusion may be acquired in minutes and improves with experience.¹⁹⁰ In most instances, the pleural

tap does not have to be done under real-time ultrasound guidance. A critically ill patient first must be positioned adequately on the back or on the side. Scanning of the pleural space is performed with the ultrasound probe. The probe must be oriented upward and downward, laterally and medially, and anteriorly and posteriorly so as to obtain a complete anatomic assessment of the area. The pleural fluid is usually hypoechoic and appears black. The surrounding solid structures (soft tissue, diaphragm) and organs (lung, liver, heart, spleen) are visualized as structures with different degrees of echogenicity around the effusion (Fig. E2-26). The presence of aerated lung causes airy artifacts. Ribs usually yield artifactual anechoic images. When the effusion has been well assessed, one must determine the feasibility of safely doing a thoracentesis. One must check for the absence of interposition of

lung, heart, liver, or spleen during the respiratory cycle¹⁸⁹ to avoid puncturing these organs, which potentially can cause catastrophic complications. When an optimal and safe position for thoracentesis has been determined, the skin should be marked and disinfected, and the patient should remain in the exact same position as was used during the ultrasound examination. Optimally, the puncture should be done within seconds to minutes of the marking.

The same diagnostic and therapeutic procedures described earlier can be applied for intraabdominal fluid collections in a critically ill patient. Evaluation for intraabdominal fluid collection or abscess is restricted to areas that are not impeded by gas-filled structures¹⁹¹ and include the regions around the liver and gallbladder, spleen, kidneys and lateral retroperitoneal areas, and pelvis around the uterus and

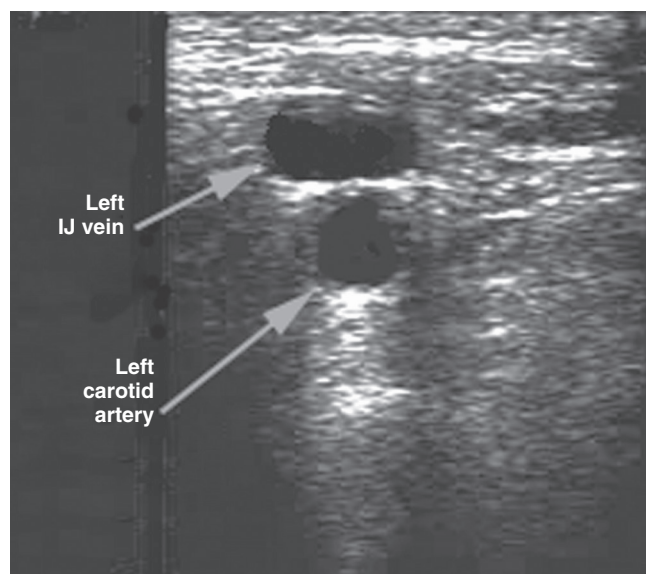


FIGURE E2-24 ■ Transverse view of left internal carotid artery and left internal jugular (IJ) vein. Notice the relative position of the jugular vein directly overlying the carotid artery. This type of anatomy is common on the left side and, when present, significantly increases the risk of procedure failure or arterial puncture.

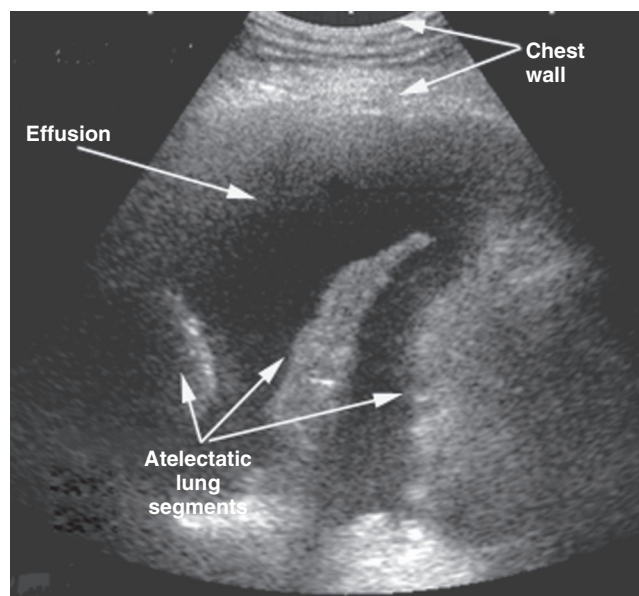


FIGURE E2-26 ■ Transverse view of a right pleural effusion. Collapsed atelectatic lung is well visualized “floating” in the effusion. (Courtesy Dr. Kurian Puthenpurayil.)

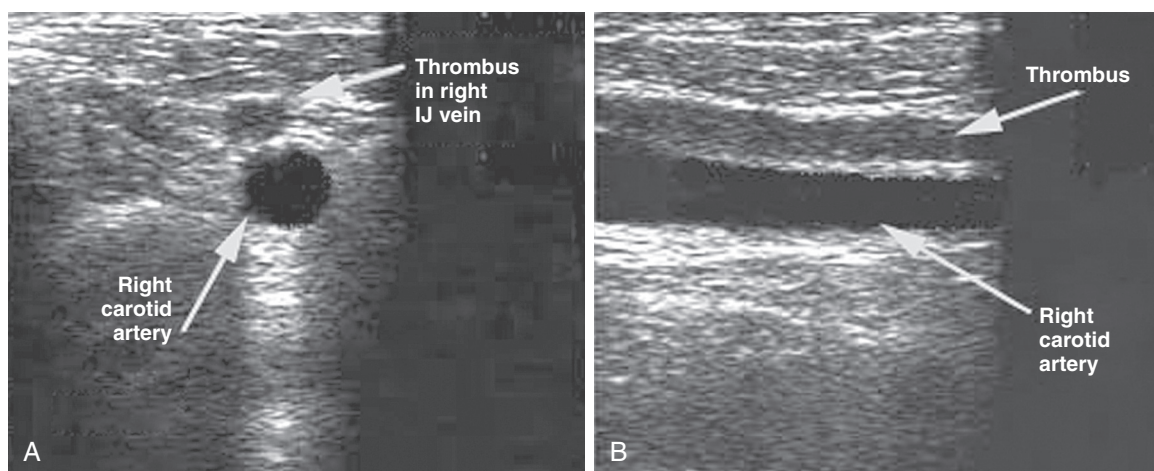


FIGURE E2-25 ■ Transverse (A) and longitudinal (B) views of the right carotid artery and right internal jugular vein. Complete thrombosis of the right internal jugular (IJ) vein can be appreciated. Notice the small caliber of the thrombosed vein and the increased echogenicity of the thrombotic material within it. The vessel could not be compressed by probe pressure.

bladder.¹⁹¹ Fluid that does not change shape with probe pressure or patient positioning most likely represents a loculated collection.¹⁹¹ Echogenic material and diffuse echoes on ultrasound within a fluid collection suggest the presence of particulate matter (e.g., fibrin or clots) and may represent an exudate or blood collection. As with pleural effusions, intraabdominal fluid collections can be percutaneously sampled or drained safely at the bedside under real-time ultrasound guidance (Fig. E2-27).

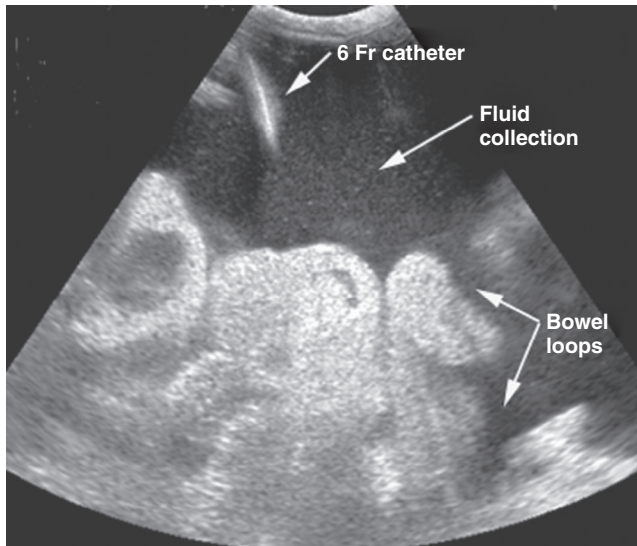


FIGURE E2-27 ■ Transverse view of a left lower quadrant abdominal collection. Echogenic, particulate material can be seen floating in the collection. Loops of bowel also are well visualized. A 6F catheter was inserted under ultrasound guidance to drain the collection, which was found to be chylous. Fluid collection with echogenic material and diffuse echoes on ultrasound are suggestive of particulate matter (e.g., fibrin or clots) and may represent an exudate or blood collection. (Courtesy Dr. Kurian Puthenpurayil.)

Urinary Bladder Scan

Bladder scanning devices are portable units that can provide a measurement of urine volume in the bladder (Fig. E2-28) and avoid bladder overdistention and reduce the need for unnecessary catheterization.^{191,192} Studies have shown that frequent catheterization is a major risk factor for urinary tract infections that can be costly to medical centers.¹⁹³⁻¹⁹⁵ Use of a portable bladder scanning device to reduce the incidence of nosocomial urinary tract infections was described by Moore and Edwards.¹⁹⁶ Bedside ultrasound assessment of volume in the urinary bladder also can be helpful to evaluate oliguria or anuria to rule out obstruction of the urinary catheter.

Focused Assessment of the Trauma Patient

Since the early 1990s, bedside ultrasound has been used in the United States as an additional diagnostic modality for use in determining the presence of intraabdominal injury after blunt trauma.¹⁹⁷ It is performed in the trauma bay during the secondary survey (as described in Advanced Trauma Life Support) or as part of the primary survey in hemodynamically unstable patients.^{191,198-202} The focused assessment for sonographic examination of trauma (FAST) should be done with a specific purpose, usually identification of hemoperitoneum, hemothorax, or tamponade.¹⁹¹ FAST seeks to determine the presence of fluid in four areas: (1) the subxiphoid region in the pericardial sac, (2) the right upper quadrant in Morison's pouch, (3) the left upper quadrant in the splenorenal recess, and (4) the pelvis in the pouch of Douglas or rectovesical space (Fig. E2-29).¹⁹ Because the FAST examination is non-invasive and quickly performed at the bedside, it is ideal for detecting intraabdominal injury in the resuscitation area. It has now been incorporated into the trauma resuscitation algorithm of most level I trauma centers in the United States.^{191,203}

Use of the FAST examination has been shown to diminish the need for more invasive diagnostic measures such as diagnostic peritoneal lavage and subsequent exploratory laparotomy.^{204,205} The FAST examination has been shown to be most accurate when performed for evaluation of hemodynamically unstable patients.^{203,206-208} Studies have suggested that its use as a screening tool for blunt abdominal injury in hemodynamically stable trauma patients may result in underdiagnosis of intraabdominal injuries.^{202,203,209}

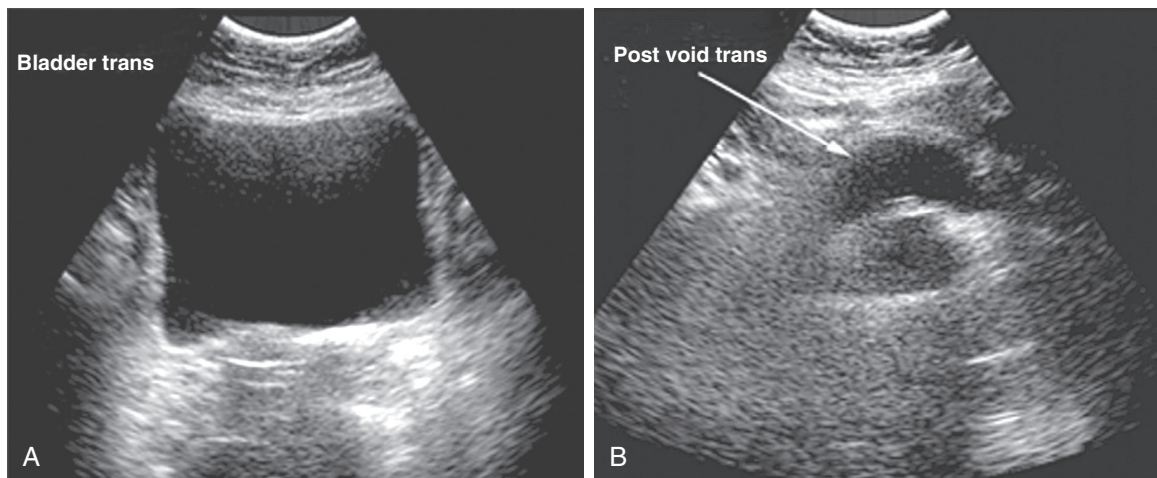


FIGURE E2-28 ■ Urinary bladder. Suprapubic transverse view of a full urinary bladder (A). This “square” appearance of the bladder with a concave superior wall is typical of a moderately full bladder. When overdistended (i.e., in the presence of a low urinary tract obstruction), the bladder is large and adopts a round, globular shape (not shown). Suprapubic transverse view of an empty bladder (B). When empty, the bladder can become small and commonly may be difficult to identify. (Courtesy Dr. Kurian Puthenpurayil.)

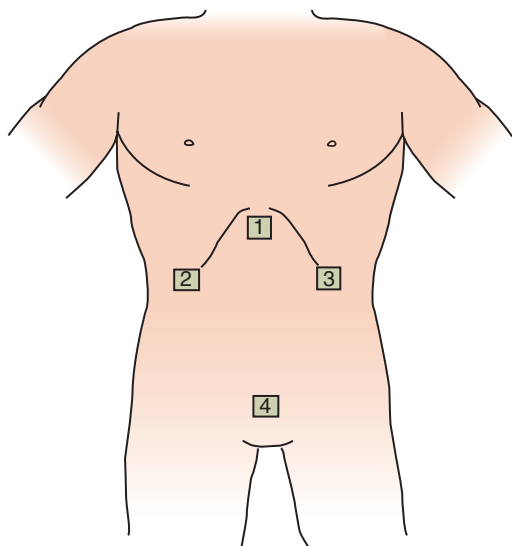


FIGURE E2-29 ■ Focused assessment for sonographic examination of trauma (FAST). The FAST examination seeks to determine the presence of fluid in four areas: (1) the subxiphoid region in the pericardial sac, (2) the right upper quadrant in Morison's pouch, (3) the left upper quadrant in the splenorenal recess, and (4) the pelvis in the pouch of Douglas or rectovesical space.

Intraaortic Balloon Counterpulsation

Bedside TEE may be helpful in different aspects of intraaortic balloon counterpulsation management. Before insertion, TEE can rule out the presence of significant aortic regurgitation, which would represent a contraindication to intraaortic balloon counterpulsation use. After insertion, TEE can confirm the position of the intraaortic catheter in the descending thoracic aorta, ensure correct functioning of the balloon (visualization of inflation and deflation), and rule out the presence of important complications of aortic catheter insertion (e.g., aortic dissection). TEE also may be used for monitoring of the ventricular function while separating the patient from the intraaortic balloon counterpulsation device.

Ventricular Assist Devices

Different complications are likely to occur after ventricular assist device implantation, such as bleeding and hemodynamic instability. Maintenance of ventricular assist device flow is a key indicator of the overall status of the system. In the postoperative period, low ventricular assist device flow is usually due to hypovolemia and right ventricular dysfunction. TEE can be helpful for the diagnosis and monitoring of both of these conditions. Right ventricular failure has been shown to occur in approximately 20% to 25% of patients being supported with an isolated left ventricular assist device.²¹⁰ With prosthetic circulatory support devices, there can be dramatic changes in ventricular volumes and hemodynamic conditions and substantial direct and indirect changes to the contralateral ventricle due to ventricular interactions. TEE can help the clinician monitor and understand these ventricular interactions.²¹¹ It also can help assess adequacy of flow and the patency of the inflow and outflow cannulas to eliminate the presence of a thrombus and collapse or displacement of the cannulas. It also can motivate an urgent return to the operating room if a cardiac tamponade is diagnosed. If hypoxemia supervenes in the ICU, the presence of a patent foramen ovale has to be ruled out. For patients placed on extracorporeal membranous oxygenation support, bedside TEE also can be used to monitor ventricular function during weaning of the circulatory assistance.

Performance of Bedside Ultrasonography by the Intensivist

In acute situations in the ICU, it may be difficult to have a cardiologist or sonographer available on immediate call on a 24-hour basis to perform a bedside ultrasound examination. The value of immediate bedside echocardiography for aiding in diagnosis and management of acute hemodynamic disturbances has been well shown in the literature in the ICU and the emergency department.^{212,213}

Ultrasound technologies are not exclusive to the radiologist or cardiologist. Appropriately trained emergency department physicians, surgeons, anesthesiologists, and ICU specialists have been using ultrasound devices with great success. Anesthesiologists were instrumental in many of the pioneering studies of TEE in the operating room and ICU.^{4,22,214,215} Successful performance of bedside echocardiography by noncardiologist intensivists also has been well shown in the literature.^{8,21,216} A study by Benjamin et al.²¹ showed that a limited TEE examination performed and interpreted by intensivists (after training under the supervision of two cardiologists) is feasible and provides rapid, accurate diagnostic information that can have a dramatic impact on the treatment of critically ill patients.²¹ The safety and utility of performance of bedside ultrasound by the intensivist for various other purposes in the ICU (central venous cannulation, thoracentesis, paracentesis) also have been well shown.^{170-172,189}

With the increasing popularity of ultrasound devices—particularly lightweight, portable, handheld devices—there is controversy regarding the advisability and use of noncomprehensive “goal-directed” examinations performed by clinicians without cardiology or radiology training.¹⁰⁴ Studies with these portable devices that provide basic 2D and Doppler flow imaging showed they can provide important anatomic information²¹⁶⁻²²⁰ but that even in highly skilled hands, they may provide suboptimal imaging or diagnostic capabilities in the ICU.²¹⁸ Inappropriate interpretation or application of data gained by a poorly skilled user may result in adverse medical, ethical, and social consequences.¹⁰⁴ To avoid misusing the technology, adequate training is essential.

The era of a technology-extended physical examination²¹⁹ seems to have arrived, and there seems to be a role for a user-specific, focused ultrasound examination.^{104,221} An examination said to be “targeted,” “focused,” and “limited” may often equate with “incomplete,” “inadequate,” or “inaccurate.” Training must be individualized and tailored to specific needs, and appropriate user-specific application depends directly on the training and expertise of the user.¹⁰⁴ Provided that adequate expert backup is available, the training of intensivists in performing focused or more comprehensive bedside ultrasound examinations is not only feasible but also can be done safely and rapidly and yield information pertinent to the management of critically ill patients. General guidelines in training for TTE and TEE have been developed by the American Society of Echocardiography in association with the American Heart Association and the American College of Cardiology.²²² Since 1996, the American Society of Anesthesiologists and Society of Cardiovascular Anesthesiologists also have developed practice guidelines for perioperative TEE.²²³ The importance of adequate training and subsequent maintenance of competence cannot be overemphasized; inappropriate use or misapplication potentially could temper the acceptance and limit the value of performance of bedside ultrasonography by the intensivist.

Training of intensivists and emergency department physicians in performance of emergency bedside ultrasonography should provide rapid answers to clinical questions that may strongly affect medical and surgical management decisions. As has been mentioned by different authors,^{190,224} training in echocardiography and general ultrasonography should be incorporated into the critical care fellowship, with special emphasis on TEE as part of the training program. It is hoped that critical care and echocardiographic societies will credential such additional training in the near future.

KEY POINTS

1. As a result of improvements in transthoracic imaging, most ICU patients now can be adequately studied with transthoracic echocardiography (TTE).
2. Transesophageal echocardiography (TEE) is particularly useful in the ICU for the assessment of unexplained hypotension, suspected aortic dissection, valvular vegetations, source of cardiac or aortic emboli, prosthetic heart valves (especially mitral), and detection of intracardiac shunts.
3. The use of ultrasound guidance during central venous catheterization has been well shown to reduce the risk of complications, improve rapidity of catheter placement, and improve overall success of the procedure.
4. Successful performance of bedside ultrasonography by intensivists in a limited examination has been shown to be feasible and potentially to provide rapid diagnostic information that can have a dramatic impact on the treatment of critically ill patients.
5. Adequate training and maintenance of competence is crucial for the intensivist to perform bedside ultrasonography safely and efficiently, because inappropriate interpretation or application of data gained by a poorly skilled user may result in adverse consequences.

ANNOTATED REFERENCES

- Benjamin E, Griffin K, Leibowitz AB, et al. Goal-directed transesophageal echocardiography performed by intensivists to assess left ventricular function: comparison with pulmonary artery catheterization. *J Cardiothorac Vasc Anesth* 1998;12:10-5.
This prospective blinded study shows that intensivists can be trained to perform limited-scope, goal-directed TEE rapidly and safely that can yield pertinent data for the management of a critically ill patient.
- Colreavy FB, Donovan K, Lee KY, et al. Transesophageal echocardiography in critically ill patients. *Crit Care Med* 2002;30:989-96.
This retrospective study shows the safety and utility of TEE in the ICU when performed by appropriately trained intensive care physicians.
- Goldhaber SZ. Echocardiography in the management of pulmonary embolism. *Ann Intern Med* 2002;136:691-700.
This article reviews the different utilities and limitations of echocardiography in the management of pulmonary embolism.
- Lichtenstein D, Hult JS, Rabiller A, et al. Feasibility and safety of ultrasound-aided thoracentesis in mechanically ventilated patients. *Intensive Care Med* 1999;25:955-8.
This prospective study done in critically ill patients illustrates that ultrasound localization makes thoracentesis a safe and easy procedure in patients on mechanical ventilation when a few basic rules are followed.
- Yong Y, Wu D, Fernandes V, et al. Diagnostic accuracy and cost-effectiveness of contrast echocardiography on evaluation of cardiac function in technically very difficult patients in the intensive care unit. *Am J Cardiol* 2002;89:711-18.
This article compares use of harmonic imaging alone or in combination with contrast material with TEE in critically ill patients who were considered technically very difficult. It illustrates the significant impact of the use of contrast imaging in the ICU.

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BEFORE PROCEDURE

Indications

- Cannot achieve the goal with peripheral intravenous catheterization
 - Rapid, massive intravascular volume resuscitation
 - Peripheral catheters are often difficult to place in shock states.
- Fast flow rate is required.
 - 3.5-inch, 8.5F introducer catheter has the fastest flow rate.
 - However, a 2-inch, 16-gauge peripheral catheter has a faster flow rate than a 16-gauge centrally inserted triple-lumen catheter
- Cardiopulmonary resuscitation
 - Drug administration is more effective centrally.
- Administration of agents irritating to peripheral veins
 - Concentrated potassium chloride solutions
 - Total parenteral nutrition solutions
 - Chemotherapy agents
 - Vasopressors and inotropes
- Central venous pressure monitoring
- Pulmonary artery pressure monitoring
- Transvenous pacemaker insertion
- Hemodialysis
- Plasmapheresis
- Venous access for frequent blood sampling

Contraindications

- No absolute contraindications if experienced or supervised operator
- Relative contraindications
 - Severe coagulopathy (including thrombocytopenia)
 - Consider a femoral vein central catheter or peripherally inserted central catheter (PICC).
 - Local skin infection
 - Ipsilateral arteriovenous fistula
 - Ipsilateral venous thrombosis
 - Inferior vena cava filter
 - Avoid passing the wire beyond 20 cm during central line insertion to prevent entanglement.

Equipment

- Catheter appropriate for the indication (e.g., single lumen, multilumen, 8.5F introducer)
- Insertion kit, including 10-mL syringes, needles, guidewire, suture material, and local anesthetic
- Sterile saline flush solution
- Sterile fenestrated barrier drape for head-to-toe coverage of the patient
- Four sterile towels
- 2% Chlorhexidine gluconate sterile prep stick
- Sterile gown and gloves for the operator and assistant(s)
- Cap and mask with a face shield or protective glasses for the operator and assistant(s)

- Sterile central line dressing kit
- Shoulder roll (for subclavian vein catheterization)
- Ultrasound (for internal jugular vein catheterization)
- Sterile sheath, gel, and needle guide for ultrasound

ANATOMY

The pertinent anatomy varies depending upon the chosen site of central venous catheterization. All relevant landmarks should be included in the sterile field. For internal jugular venous catheterization, identification of the triangle formed by the two heads of the ipsilateral sternocleidomastoid (SCM) muscle is imperative. It is also important to note the location of the angle of the mandible, the clavicle, and the sternal notch (located between the medial ends of the right and left clavicles). The carotid artery pulse should be located and protected during placement of the needle into the internal jugular vein. For subclavian vein catheterization, the middle portion of the clavicle, insertion point of the clavicular head of the ipsilateral SCM muscle, and sternal notch should be identified. Femoral vein catheterization requires identification of the junction of the middle and distal third of an imaginary line drawn from the pubic tubercle to the anterior superior iliac spine. The ipsilateral femoral arterial pulse should be located as well.

PROCEDURE

- Internal jugular vein (middle approach)
 - Obtain informed consent from the patient or surrogate decision maker.
 - Gather all necessary equipment.
 - Place the patient in the supine position.
 - Position the bed at a comfortable height, with 15 to 30 degrees Trendelenburg.
 - Rotate the patient's head away from the side of insertion.
 - Perform nonsterile ultrasound to confirm patency and depth of the internal jugular vein and the location of surrounding structures.
 - Open the equipment using sterile technique.
 - Wash hands and don a cap, face shield mask, sterile gown, and pair of gloves.
 - Use a 2% chlorhexidine prep stick to prepare the area bounded by the ear lobe, mandible, chin, neck, and sternal notch past the midline, 2 cm inferior to the clavicle, and 2 cm posterior to the sternal head of the SCM muscle.
 - Preparing a wide area is preferred to facilitate conversion to the ipsilateral subclavian approach if the internal jugular approach is unsuccessful.
 - Square off the sterile area with 4 sterile towels.
 - Place the head-to-toe fenestrated sterile drape.
 - Place the ultrasound probe in a sterile sheath with gel and position the correct needle guide on the probe.
 - Find these anatomic landmarks: apex of the triangle formed by two heads of the SCM muscle, sternal notch, clavicle, and carotid pulse.
 - Locate the internal jugular vein with the ultrasound probe, and confirm that the vessel collapses easily with compression and is nonpulsatile.

- Inject local anesthetic into the skin and surrounding region at the proposed insertion site.
- Ensure that all materials needed for catheter placement are in easy reach within the sterile field.
 - Flush all catheter lumens, and then place caps on all ports except the distal port.
- Place the access needle with attached syringe onto the needle guide of the ultrasound probe.
- Advance the needle into the internal jugular vein under direct vision using ultrasound, applying gentle aspiration pressure on the syringe during advancement.
- Confirm the presence of the needle within the vein lumen by ultrasound imaging and by aspiration of free-flowing, nonpulsatile, venous-colored blood.
- Remove the needle from the needle guide on the ultrasound probe.
- If ultrasound is unavailable, insert the needle at the apex of the SCM triangle and advance the needle toward the ipsilateral nipple at a 30- to 45-degree angle while continually applying gentle aspiration pressure on the syringe.
- Place the curved end of the guidewire through the syringe and/or needle into the vein. Never lose control of the distal end of the guidewire.
- Using ultrasound, confirm the presence of the guidewire in the internal jugular vein.
- Remove the syringe and needle over the guidewire.
- Using a scalpel, make a small nick in the skin at the wire insertion site.
- Place a dilator over the wire, and advance the dilator into the soft tissues to establish a tract.
- Remove the dilator, leaving the guidewire in place.
- Place a catheter (single lumen or multilumen) over the wire into the vein:
 - 16 cm for the right internal jugular
 - 19 cm for the left internal jugular
- Remove the guidewire and place a cap on the distal port.
- Aspirate blood via all catheter lumens, and then flush each lumen with sterile saline.
- Secure the catheter to the skin with suture material.
- Place a sterile dressing.
- Clean up and safely discard all sharp objects.
- Order a chest x-ray to check catheter position.
- Subclavian vein (infraclavicular approach)
 - See Video E3-1
 - Obtain informed consent from the patient or surrogate decision maker.
 - Gather all necessary equipment.
 - Place the patient in the supine position with the ipsilateral arm adducted.
 - Place a shoulder roll under the patient, positioned vertically between the scapulae.
 - Position the bed at a comfortable height, with 15 to 30 degrees Trendelenburg.
 - Rotate the patient's head away from the side of insertion.
 - Open the equipment using sterile technique.
 - Wash hands and don a cap, face shield mask, sterile gown, and pair of gloves.
 - Use a 2% chlorhexidine prep stick to prepare the area bounded by the ear lobe, mandible, chin, neck, and sternal notch past the midline, 2 cm inferior to the clavicle, and 2 cm posterior to the sternal head of the SCM muscle.
 - Preparing a wide area is preferred to facilitate conversion to the ipsilateral internal jugular approach if the subclavian approach is unsuccessful.
 - Square off the sterile area with 4 sterile towels.
 - Place the head-to-toe fenestrated sterile drape.
 - Find these anatomic landmarks: midportion of ipsilateral clavicle and sternal notch.
- Inject local anesthetic into the skin and surrounding region at the proposed insertion site.
- Ensure all materials needed for catheter placement are in easy reach within the sterile field.
 - Flush all catheter lumens and place caps on all ports except the distal port.
- Insert the needle with attached syringe into the skin 2 cm inferior to the midportion of the clavicle, directing the needle slightly cephalad toward the clavicle in the direction of the sternal notch.
- "Walk" down the clavicle with the needle until it advances just deep to the inferior surface of the clavicle.
- While applying gentle aspiration pressure on the syringe, continue to advance the needle in the direction of the sternal notch until aspiration of free-flowing, nonpulsatile, venous-colored blood occurs, signaling entry into the subclavian vein.
- Place the curved end of a guidewire through the syringe and/or needle into the vein. Never lose control of the distal end of the guidewire.
- Remove the syringe and needle over the guidewire.
- Using a scalpel, make a small nick in the skin at the wire insertion site.
- Place the dilator over the guidewire, and advance the dilator into the soft tissues to establish a tract.
- Remove the dilator, leaving the wire in place.
- Place a catheter (single lumen or multilumen) over the wire into the vein.
 - 18 cm for the right subclavian
 - 20 cm for the left subclavian
- Remove the wire and place a cap on the distal port.
- Aspirate blood via all catheter lumens, and then flush each lumen with sterile saline.
- Secure the catheter to the skin with suture material.
- Place a sterile dressing.
- Clean up and safely discard all sharp objects.
- Order a chest x-ray to check the catheter position.
- Femoral vein
 - Obtain informed consent from the patient or surrogate decision maker.
 - Gather all necessary equipment.
 - Place the patient in the supine position with the ipsilateral thigh in slight abduction.
 - Open the equipment using sterile technique.
 - Wash hands and don a cap, face shield mask, sterile gown, and pair of gloves.
 - Use a 2% chlorhexidine prep stick to prepare an area bounded by the lateral mid thigh, medial mid thigh, and pubis in the midline, and extending 2 cm superior to an imaginary line connecting the pubis and anterior superior iliac spine.
 - Square off the sterile area with 4 sterile towels.
 - Place the head-to-toe fenestrated sterile drape.
 - Find these anatomic landmarks: pubic tubercle, anterior superior iliac spine, and femoral artery pulse.
 - Inject local anesthetic into the skin and surrounding region at the proposed insertion site.
 - Ensure that all materials needed for catheter placement are in easy reach within the sterile field.
 - Flush all catheter lumens and place caps on all ports except the distal port.
 - While applying gentle aspiration pressure on the syringe, insert the needle at a 90-degree angle into the skin medial to the femoral artery pulse at the junction of the middle and medial third of an imaginary line drawn from the pubic tubercle to the anterior superior iliac spine.
 - Continue to advance the needle until aspiration of free-flowing, nonpulsatile, venous-colored blood occurs, signaling entry into the femoral vein.

- Place the curved end of the guidewire through the syringe and/or needle and into the vein. Never lose control of the distal end of the guidewire.
- Remove the syringe and needle over the guidewire.
- Using a scalpel, make a small nick in the skin at the wire insertion site.
- Place the dilator over the guidewire, and advance the dilator into the soft tissues to establish a tract.
- Remove the dilator, leaving the guidewire in place.
- Place the catheter (single lumen or multilumen) over the guidewire into the vein.
- Remove the wire and place a cap on the distal port.
- Aspirate blood via all lumens, and then flush each lumen with sterile saline.
- Secure the catheter to the skin with suture material.
- Place a sterile dressing.
- Clean up and safely discard all sharp objects.
- Catheter malposition
- Venous thrombosis
- More frequent with femoral vein catheters
- Catheter-related bloodstream infection
- Infrequent
 - Pneumothorax
 - Hemothorax
 - Chylothorax (thoracic duct injury)
 - More common with left internal jugular or subclavian vein catheterization
 - Local nerve injury
 - Entanglement with vena cava filter
 - Tracheal perforation
 - Endotracheal tube cuff rupture
- Serious, rare complications
 - Air embolus
 - Cardiac tamponade

AFTER PROCEDURE

Postprocedure Care

- Obtain a chest x-ray.
 - To confirm the location of the internal jugular and subclavian venous catheter tip at the atriocaval junction
 - To rule out the presence of a hemothorax, pneumothorax, or apical cap
- Inspect the catheter insertion site daily to detect the development of infection.
- Monitor for arrhythmias, as catheter migration may occur.
- Maintain proper local dressing care to minimize complications.
- Access all ports in a sterile manner at all times.

Complications

- Common
 - Cardiac arrhythmias
 - Arterial puncture
 - Hematoma

OUTCOMES AND EVIDENCE

- Femoral vein catheters have a higher incidence of infectious and thrombotic complications compared with subclavian vein catheters.
- Lowest infection rates are associated with subclavian vein catheters.
- Infection of central venous catheters is diminished by judicious attention to sterile insertion technique.
- Antibiotic-treated, noncuffed central venous catheters are associated with a lower rate of device-related bloodstream infection than nontreated catheters but a higher rate when compared to PICCs.
- Use of ultrasound to guide insertion is beneficial in reducing mechanical complications and improving rates of successful cannulation, particularly when accessing the internal jugular vein or when operators are inexperienced.
- PICCs may be more cost-effective and have lower complication rates than centrally inserted venous catheters.
- Deep venous thrombosis due to PICCs may be related to catheter size.

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Arterial Cannulation and Invasive Blood Pressure Measurement

Phillip D. Levin and Yaacov Gozal

Peripheral artery cannulation is one of the most commonly performed invasive procedures in the intensive care unit (ICU),¹ and the resulting arterial line is an integral part of intensive care patient management. Arterial line usage varies according to unit type, patient age, and severity of illness, ranging from approximately 22% of medical ICU patients to over 50% of surgical ICU patients. There are three main indications for arterial line insertion: (1) to allow continuous beat-to-beat monitoring of blood pressure; (2) to provide pain-free, convenient, and repeated access to arterial blood for the assessment of pulmonary and cardiovascular function (including measures of pulse pressure variation and semi-invasive cardiac output measurements using transpulmonary thermodilution); and (3) to provide a source of blood for blood tests as required without the need for repeated venipuncture including continuous measures of blood chemistry (such as continuous glucose measurement). A review of the relevant anatomy, equipment, and techniques for arterial line placement is provided in this chapter along with some of the more common complications.

SITES OF INSERTION

An arterial line can be inserted into almost any palpable peripheral artery. The most common sites in clinical practice are the radial artery (employed in up to 78% of ICU patients^{2,3}), the femoral artery (employed in up to 45%^{2,3}), and the dorsalis pedis artery. Axillary and ulnar artery cannulations are performed somewhat more rarely; brachial and temporal artery cannulation is not recommended. Cannulation of the carotid arteries is absolutely contraindicated for obvious reasons. Each arterial site has advantages and disadvantages.

The Radial and Ulnar Arteries

The radial artery originates in the antecubital fossa at the level of the neck of the radius as a terminal branch of the brachial artery. The artery runs down the length of the forearm laterally. For the distal part of its course it is covered only by fascia and skin and lies above the radius, where it is easily palpated. At the level of the wrist the artery winds laterally around the radius and enters the posterior aspect of the hand. It terminates by dividing into the superficial and deep palmar arches, which are anastomosed with the ulnar artery. The radial artery lies near the superficial branch of the radial nerve in its distal course.

The ulnar artery is the other terminal branch of the brachial artery, also originating in the antecubital fossa at the level of the radial neck. It is usually larger than the radial artery. The ulnar artery runs medially along the length of the forearm. As opposed to the radial artery, for most of its course the ulnar artery lies deep to the muscles of the forearm, becoming superficial only toward the wrist. The ulnar artery lies close to the ulnar nerve in its distal course.

When compared with the ulnar artery, the radial artery is superficial for a longer part of its course, is easily palpated above the radius, and is less closely associated with neural structures. It is, however, a smaller artery. The radial artery is cannulated within a few centimeters of the anterior wrist creases, where it lies conveniently over the radius.

Advantages

Advantages of radial artery cannulation include huge experience and safety, peripheral position, double blood supply to the dependent

territory (by the ulnar artery), and easy compression in the event of bleeding.

Disadvantages

Disadvantages include technical difficulties owing to the small size of the vessel or vasoconstriction (the radial artery pulse may not be palpable when blood pressure is less than 80 mm Hg) and inaccurate blood pressure measurements (when compared with the central circulation).⁴⁻⁶

The modified Allen test has been proposed as a screening tool prior to radial artery cannulation to ensure the presence of adequate distal collateral circulation.^{7,8} The Allen test has, however, been found to have high interobserver variability⁹ and to lack sensitivity and specificity.^{10,11} It is not widely used. Radial artery catheterization for coronary angiography has been compared in patients with normal and abnormal Allen tests with no significant adverse events occurring in patients with an abnormal Allen test.¹² It might be prudent, however, to avoid insertion of an arterial catheter into the radial or ulnar artery when the other artery is known to be absent or occluded.

Positioning for Cannulation

The forearm should be supine and the wrist slightly extended and supported (Video E4-1).

The Axillary and Brachial Arteries

The axillary artery is a continuation of the subclavian artery, beginning at the outer border of the first rib. The artery is surrounded by the cords of the brachial plexus. Its position relative to the other structures of the axilla varies according to the position of the arm. The artery ends at the inferior border of the teres major muscle, where it becomes the brachial artery. The brachial artery runs down the upper arm to the elbow. Initially, it is medial to the humerus, but distally it spirals anteriorly to end as the radial and ulnar arteries approximately 1 cm distal to the elbow. The brachial artery lies near the ulnar and median nerves in its proximal course and near the median nerve in its distal course.

Advantages

The axillary artery is a large artery, and pressure measurements reflect the central circulation.

Disadvantages

The arm position required for axillary artery cannulation may be contraindicated or difficult for some patients. Care should be taken if a long catheter is used, because its tip might be proximal to the origin of the brachiocephalic artery/left common carotid artery. In this case embolic material from the line (i.e., air bubbles or thrombus) could be introduced into the brain. The risk of line infection may also be higher relative to other sites.¹³

Positioning for Cannulation

For axillary artery cannulation the arm should be bent at the elbow and raised above the head (abducted and flexed to 90 degrees). The pulse can then be palpated in the axilla.

The brachial artery is punctured where it is palpable medially on the anterior aspect of the elbow. Generally, cannulation of the brachial

artery is not recommended, because it is associated with specific and potentially severe complications (see later). Despite this, large case series with low complications rates have been published.¹⁴

The Femoral Artery

The femoral artery originates as a continuation of the external iliac artery at the level of the inguinal ligament. At the level of the inguinal ligament, it lies midway between the anterior superior iliac spine and the symphysis pubis. Distal to the inguinal ligament, the artery lies medial to the femoral nerve and lateral to the femoral vein and is superficial, being covered only by fascia, fat, and skin. The femoral artery runs down the thigh and terminates as the popliteal artery in the knee.

Advantages

The femoral artery is a large artery that is easier to locate and puncture than the radial artery. Blood pressure measurements reflect central blood pressure, and the femoral artery is palpable at a lower blood pressure than the radial artery. The femoral arterial line has a lower rate of catheter malfunction and greater longevity (compared with the radial artery).³

Disadvantages

In obese subjects, adipose tissue and skin folds may create difficulties in the approach to the groin. The skin over the puncture site also can be compromised by chronic inflammatory changes or fungal infections, and the artery itself may be very deep and difficult to locate. The insertion site also may be difficult to keep clean and well dressed. The risk of hemorrhage into the retroperitoneal space (which may initially be undetectable clinically) is unique to this site. Hemorrhage (either retroperitoneal or percutaneous) is also a risk when removing femoral artery catheters, particularly in patients with deranged clotting. The femoral artery is a common site for vascular surgery in the leg, and this represents a strong relative contraindication to arterial cannulation.

Position for Cannulation

In a supine patient, assistance may be required in retracting abdominal and thigh adipose tissue to allow access to the groin.

Dorsalis Pedis

The dorsalis pedis artery begins anterior to the ankle as a branch of the anterior tibial artery. The artery runs distally in the foot between the tendons of the extensor digitorum longus and extensor hallucis longus. It terminates as it turns in to the foot toward the sole between the first two metatarsal bones. During its course over the foot the artery is covered only by fascia and skin and is easily palpable.

Advantages

The dorsalis pedis is an easily accessible, compressible small artery.

Disadvantages

This artery is the most distant from the central circulation. Vasoconstriction can affect the quality of the arterial signal. In addition, the distance from the central circulation may result in an artificially elevated systolic pressure reading that is caused by interaction of the arterial pressure wave on smaller and smaller arteries.¹⁵

Position for Cannulation

The foot is placed in a neutral position with slight extension of the ankle.

Additional Considerations

From this discussion of relative anatomy the features of the arteries commonly used for monitoring become clear: all are superficial,

covered only by fascia and skin, easily palpable, and easily compressible. The specific artery chosen for insertion of an arterial line should be influenced by the experience of the operator, ease of palpation, contraindications, and limitations in positioning.

After adequate positioning, the chosen arterial line insertion site should be cleaned and sterilized with a solution containing >0.5% chlorhexidine in 70% alcohol. For femoral or axillary artery insertion maximum sterile barrier precautions should be used—cap, mask, sterile gown, sterile gloves, and full body sterile drapes. For insertion of peripheral artery cannulas, the operator should at the minimum don a cap, mask, and sterile gloves and use a small sterile fenestrated drape at the insertion site.¹⁶ Local anesthesia (approximately 1 mL of 1% to 2% lidocaine *without epinephrine*) should be infiltrated around the insertion site using a small-gauge (24- to 26-gauge) needle. Epinephrine should be avoided as an additive to the local anesthetic in order to prevent arterial spasm.

EQUIPMENT

Before actually inserting the arterial cannula, the monitoring equipment, cables, arterial line setup, and adhesive tape/sutures should all be prepared and checked. Beyond the arterial cannula, the arterial line setup consists of noncompliant tubing; three-way taps (stopcocks), a pressure-transducing device, a flush system, and the monitor. The arterial cannula is connected to a short length of tubing and then to at least one three-way tap. This tap is used for blood sampling and may also be used for zeroing the setup. The three-way tap is, in turn, connected to the pressure-transducing device, which is connected to the monitor. The pressure transducer is also connected to the flush system. The flush system consists of a bag of intravenous fluid under pressure from which all air has been removed. The fluid bag is compressed to a pressure greater than the arterial pressure using a pressure bag or cuff. The flush system maintains a continuous but slow (3 mL/h) flow of fluid through the system and into the artery to maintain cannula patency. The arterial line system may include additional three-way taps, connections to other pressure monitoring sites (e.g., central venous pressure), and damping devices as required.

Sets for Arterial Cannulation and Insertion Technique

A multiplicity of arterial cannulation sets exists, falling into three main groups: sets based on a cannula-sheathed needle (equivalent to the normal intravenous catheter) with or without an additional wire, sets based on the Seldinger technique, and sets used for direct arterial cutdown techniques.

The simplest technique for arterial line insertion employs a 20-gauge catheter-over-needle arrangement. A simple 20-gauge intravenous cannula can be used, although catheters specifically made for arterial puncture are available. Such a catheter is suitable for the smaller arteries (radial or dorsalis pedis). After appropriate positioning, the patient's pulse is palpated with the nondominant hand and the cannula inserted at an angle of 45 to 60 degrees to the skin and into the artery using the dominant hand. The cannula and needle may be advanced until blood flashback is seen in the needle, and then the cannula is threaded into the artery (in a manner similar to intravenous insertion). Alternatively a through-and-through technique can be employed. In this technique, the needle and cannula are inserted directly through both the front and back walls of the artery without seeking blood flashback. The needle is withdrawn partially or fully from the cannula. The cannula is then slowly drawn back until the blood flashback is seen and subsequently threaded into the artery. In the event that blood flashback is not seen, the needle should not be reinserted into the cannula because it may perforate the side or cut off a distal segment.

Occasionally, difficulty may be found in inserting the cannula despite good backflow of blood through it. In this circumstance, the arterial line wire may be of use. The wire fits through the cannula (after the needle has been removed) and may be manipulated into the artery.

The wire need only be inserted a few centimeters beyond the catheter tip (into the artery), and the cannula can then be threaded. As a precondition to wire insertion, good back-flow of blood must be noted through the cannula, and under no circumstances should the wire be inserted with force, because this can lead to perforation or dissection of the artery.

Some cannula-over-needle sets include a wire that is preconnected to the needle/cannula apparatus. These sets are available for both smaller and larger arteries and represent a combination of the guidewire and Seldinger techniques. The artery is punctured by one of the techniques described earlier using the needle and cannula assembly. Blood flashback is seen in the tube housing the wire. Once blood is seen to return, the wire is advanced through the needle while it is still (at least partially) within the cannula and into the artery. The cannula is then advanced over the wire into the artery.

For larger or deeper arteries (femoral and axillary), sets based on the Seldinger technique are available. Using this technique, the artery is punctured with a needle, the wire is inserted through the needle, the needle is removed, and the catheter is inserted over the wire. This differs from the wire technique described earlier, because the wire is inserted through the needle, and then the needle is removed before the cannula is inserted.

Arterial cannulation can be very challenging, especially in patients with severe peripheral vascular disease or low blood pressure. Under these circumstances, additional equipment may be required to help locate the artery. Both Doppler and ultrasound probes may be useful.

The Doppler probe provides an auditory signal corresponding to blood flow. The characteristic arterial pulse form is easily distinguished from venous blood flow. The point of maximal Doppler response lies directly above the artery and may help in directing the needle to localize the artery.¹⁷

By using ultrasound with a high-frequency probe the artery may be visualized. On short axis it is seen as a pulsating echogenic (white) ring on cross section. The arterial catheter needle can also be seen on ultrasound (as a straight echogenic line) and can thus be directed into the artery. Needle insertion can be performed either out of plane using the short-axis image or in-plane using the long-axis view. Two recent meta-analyses demonstrated that use of ultrasound increases the chances of first-time success and decreases the time required for insertion.^{18,19}

Cutdown techniques are rarely required in adults. This issue for pediatric patients is addressed in Chapter 228.

Once inserted, the arterial cannula should be well fixed to the patient to prevent accidental removal and connected to the flush/pressure transduction system. Consideration can be given to using a sterile semipermeable dressing to cover the insertion site with the addition of adhesive tape. Once the presence of an adequate waveform on the monitor has been confirmed, the next step is to zero the system.

Zeroing

The importance of accurate zeroing cannot be overstated—zeroing problems reflect one of the most common sources of error in pressure-transduction systems. Zeroing has two main functions: the first is to equilibrate the monitor, and the second is to correct for the contribution of the fluid column in the pressure-transduction system between the patient and the pressure transducer.

The pressure transducers in use today are rugged, inexpensive, and accurate.²⁰ They convert pressure applied from the artery via the fluid-filled tubing to the transducer into electrical energy. The electrical signal generated by the transducer is then amplified in the monitor to produce a waveform on the screen and a numeric measure of blood pressure. The conversion of mechanical pressure into an electrical signal requires an “excitation voltage” to be provided by the monitor to the transducer. The standard responsiveness of the transducer is 5- μ V/V excitation voltage/mm Hg,²⁰ and atypical excitation voltage is 6 V. Therefore, the pressure transducer produces 30- μ V/mm Hg pressure applied from the artery. Typically, this signal is amplified 1000

times by the monitor, so that for each 100 mm Hg of blood pressure the monitor output is 3 V.²⁰ Before their first use, and periodically during their use, the interaction of the excitation current, the transducer response, and the monitor amplification requires resetting—in the first instance to standardize the system and thereafter to compensate for any drift. This calibration is achieved by zeroing or standardizing the measurement to atmospheric pressure, which thereafter is the zero reference point for further measurement. With current semiconductor equipment, calibration to a mercury manometer is not required.²⁰

The arterial line is zeroed by exposing the pressure transducer to atmospheric pressure, for example, by turning one of the three-way taps such that it is closed to the patient and the transducer is open to room air. The zero procedure is activated on the monitor and the system left untouched for a few seconds until a flat line appears on the arterial monitor tracing and the monitor reads zero. The three-way tap is then closed to air and opened to the patient, and blood pressure can be measured. The zero point (the three-way tap used for zeroing) can be near to the patient or near to the transducer. It is important to consider that the pressure measured by the monitor will represent the patient's arterial pressure plus any contribution made by the column of fluid in the pressure tubing between the patient and the zero point.

To illustrate this point, consider the change in pressure reading if the pressure transducer is lowered by 100 cm to the floor. In addition to the patient's blood pressure acting on the pressure transducer, a column of water 100 cm long is also present and contributes to the pressure reading. The blood pressure reading is in millimeters of mercury, so it will increase by 100/1.36, or by 73 mm Hg. If the pressure transducer is raised relative to the patient, then the pressure recorded by the monitor will decrease in a similar manner. Appropriate zeroing of the pressure transducer can compensate for these differences. Continuing the example above, while the transducer is 100 cm lower than the patient, the three-way tap near the patient's radial artery is closed to the artery and opened to room air. The monitor is rezeroed. Now the zero incorporates the contribution made by the 100-cm column of water in the tubing, and when the arterial pressure is measured again, it will once more be accurate. Although this example is extreme, smaller changes in relative position are common; the transducer is attached to the patient at the level of his shoulder while he is supine. The patient is subsequently repositioned from supine to sitting. His shoulder is raised by 20 cm relative to his femoral artery, and the pressure recorded on the monitor decreases by $20/1.36 = 15$ mm Hg. This change might not cause a change of therapy if arterial pressure is being measured. However, if intracranial pressure (ICP) is being measured, for example, a 15-mm Hg inaccuracy in the measurement could be critical. By convention, for arterial pressure measurement, the zero point is set at the height of the right atrium (i.e., the midaxillary line in the supine patient).

Damping

Another potential source of error in the measurement of blood pressure using the arterial line results from the interaction between the arterial pressure wave and the physical properties of the arterial line setup. This interaction can lead to underdamping (resonance or overshoot) and a spuriously high blood pressure reading or overdamping with a spuriously low blood pressure.

The arterial pulse waveform can be described as a summation of component sine waves with frequencies that are mainly in the range of 3 to 5 Hz. The arterial line set tubing has a natural frequency that is usually greater than 20 Hz. If the natural frequency of the arterial line set is decreased, it can approach the component frequencies of the arterial pulse waveform, and resonance may occur or increase, resulting in underdamping. Resonance/underdamping modulates the pressures measured. The main effect will be an increase in the recorded systolic blood pressure. A decrease in the recorded diastolic blood pressure may also occur while, typically, mean blood pressure will not be affected. Perhaps the most common cause of underdamping is the

use of an excessive length of pressure tubing between the arterial insertion site and the pressure transducer. Underdamping also may be a problem when measuring central arterial pressures and in the presence of severe vasoconstriction.

Overdamping decreases the transfer of energy from the artery to the pressure transducer. Overdamping results from the absorbance of energy by the fluid contents of the arterial set tubing and the tubing wall itself and from the friction between them. Damping is quantified by the damping coefficient (zeta), a measure of the time required for the system to come to rest after activation. Increased damping decreases the recorded systolic pressure and, to a lesser extent, increases the recorded diastolic pressure; mean pressure is affected the least. Damping is increased by the use of compliant, kinked, or partially occluded tubing and by loose connections and leaks (Box E4-1).

To obtain an accurate measure of the blood pressure from the arterial line, the system must be properly balanced. One method to assess balance utilizes the “fast flush test.”^{21,22} This test is performed by activating the flush device for a few seconds and then releasing it. On activation of the flush device, the pressure measured rises to a plateau. After release, the pressure waveform drops abruptly and small sharp waves may be seen (Fig. E4-1). In a balanced system, there should be only one such sharp wave. Figure E4-1, A, shows a system that is underdamped; there are multiple sharp waves after release of the flush. The reason for the underdamping in this case was the use of an

excessive length of pressure tubing. Figure E4-1, B, shows the effect of removing the excess length of pressure tubing. Only one sharp wave follows the flush, indicating that the system is now well balanced. An alternative correction that could have been applied (if the tubing length was required) might have been to increase the damping coefficient with the aid of a dampening device. Using this device is similar in effect to introducing a small air bubble in to the arterial line tubing; however, its use does not incur the risk of air embolus.

Figures for the natural frequency and damping coefficient of an arterial line setup can be approximated from a tracing of the fast flush test.²² The natural frequency of the arterial line setup can be calculated from the cycle length of the sharp waves, whereas the damping coefficient can be calculated from the rate at which the waves decline in amplitude. Figure E4-2 shows an enlargement of the flush release in the underdamped arterial line tracing in Figure E4-1, A, and illustrates the calculation. Based on this tracing, the natural frequency was calculated at 22.7 Hz, while the damping coefficient was 0.34. Removal of the excess tubing (producing the tracing in Fig. E4-1, B) resulted in a natural frequency of 50 Hz, while the damping coefficient was unchanged.

Flush Solutions

To maintain patency and prevent thrombosis of the arterial catheter, it must be continually flushed. Numerous additives have been proposed to achieve this aim, including heparin (the most commonly used), sodium citrate, papaverine, and normal saline. The infusion of heparin through the arterial catheter has been shown to be more effective than normal saline in maintaining patency and/or arterial pressure measurements. However, a recent Cochrane review revealed clinical and statistical heterogeneity in the seven studies and 606 patients included and prevented the definitive demonstration of an advantage to heparin over normal saline.²³ When used, the concentration of heparin in the arterial line flush is usually less than 10 units/mL, with 1 unit/mL being common. Concentrations as low as 0.25 unit/mL, infused at 3 mL/h, are efficacious.²⁴

Sodium citrate (1.4% solution) has been suggested as a flush solution that avoids the potential complications associated with the use of heparin and has been found to be equally effective.²⁵ Papaverine is an additional alternative.^{26,27} Dextrose-containing solutions are not recommended for flushing the arterial line.¹⁶

The use of flush solutions, although beneficial, is associated with potential complications, mainly in their effect on blood test samples obtained through the arterial line as described below. However, infusion of the wrong flush solution—including potassium-containing solutions, x-ray contrast, antibiotics, and others—can also lead to complications.²⁸ Using the wrong solution has been reported in 30% of ICUs.²⁹

COMPLICATIONS

The cumulative experience with arterial lines in patients in ICUs is huge; therefore, there is a considerable body of literature concerning complications. Overall, major complications are rare—15/17,840 (0.084%) in one study.³⁰ Complications are associated with the introduction and maintenance of a cannula in the artery and with its use. Common complications have been collected into series, whereas individual case reports describe a wide spectrum of rarer occurrences. The more common complications are described.

Vascular and Local Complications

Vascular and local complications vary from the clinically mild (small hematoma formation, insignificant bleeding) to catastrophic (permanent ischemic limb damage). A summary of 78 studies concerning the incidence rates for vascular and local complications of radial, femoral, and axillary arterial lines has been published and is summarized in Table E4-1.³¹ Temporary arterial occlusion is common for all sites; the

BOX E4-1

Causes of Underdamping (Overshoot) and Overdamping

CAUSES OF UNDERDAMPING

Central pressure measurement
Long pressure tubing
Marked vasoconstriction

CAUSES OF OVERDAMPING

Air in tubing
Blood clots
Compliant tubing (not stiff-walled pressure tubing)
Kinked arterial catheter
Leaks in system (hole in tubing)
Loose connections

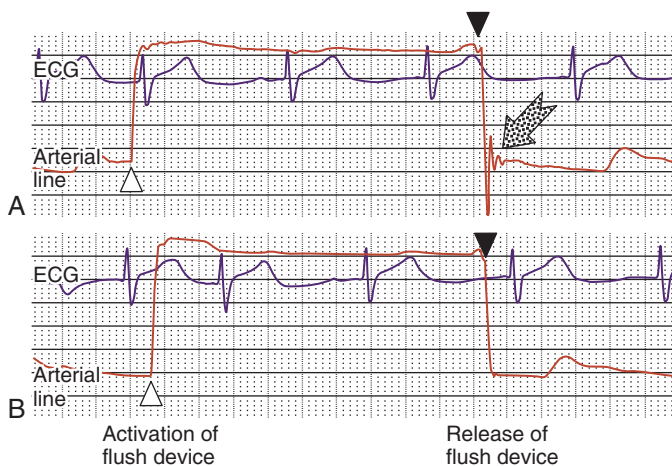
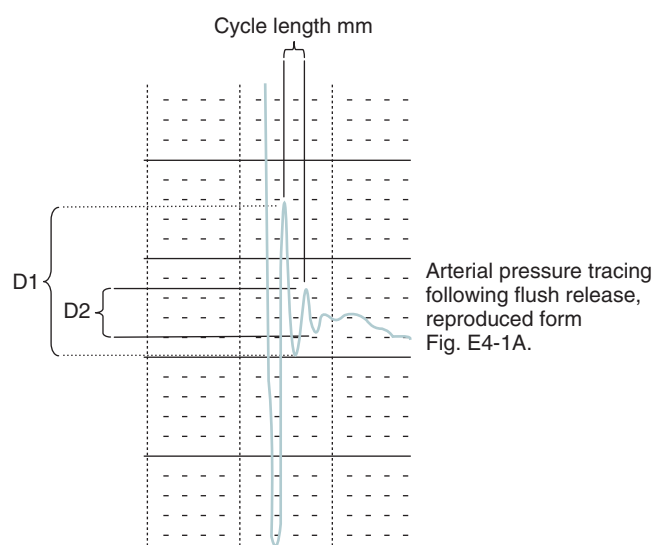


FIGURE E4-1 ■ The fast flush test, electrocardiogram, and arterial line tracings. Tracing A shows underdamping or overshoot with multiple sharp waves following the release of the flush device (speckled arrow). Tracing B shows a balanced system, with only one sharp wave following flush release. The white arrowheads indicate the beginning of the system flush, whereas the black arrowheads represent its termination.



$$\text{Natural frequency} = \frac{\text{Paper Speed (mm/sec)}}{\text{Cycle Length (mm)}} = \frac{25}{1.1} = 22.7 \text{ Hz} \quad (\text{Equation 1})$$

$$\text{Damping Coefficient} = \frac{\left(\ln \frac{D2}{D1} \right)^2}{\pi^2 + \left(\ln \frac{D2}{D1} \right)^2} \quad (\text{Equation 2})$$

A

Inserting values from the figure above:
 $D2 = 2.5 \text{ mm}$ $D1 = 7.8 \text{ mm}$ $D2/D1 = 0.32$,
 And from the graph below, or the calculation, Damping coefficient = 0.34

Graphical representation of (Equation 2) – the relation between $D2/D1$ and the damping coefficient

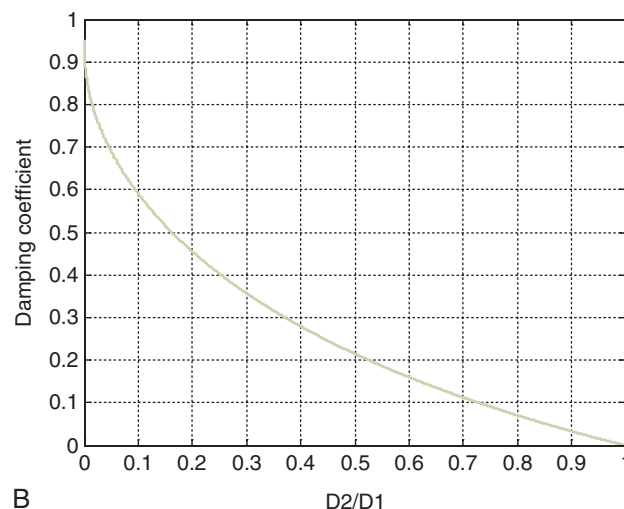


FIGURE E4-2 ■ Calculation of natural frequency and damping coefficient. (Adapted from Gardner RM: Direct blood pressure measurement—dynamic response requirements. *Anesthesiology* 1981;54: 227-236.)

TABLE E4-1 Vascular Complications of Arterial Lines per Site

| SITE | TEMPORARY OCCLUSION | HEMATOMA | BLEEDING | PERMANENT ISCHEMIC DAMAGE | PSEUDOANEURYSM |
|-----------------|---------------------|----------|----------|---------------------------|----------------|
| RADIAL | | | | | |
| % | 19.7 | 14.4 | 0.53 | 0.09 | 0.09 |
| N | 4217 | 2903 | 375 | 4217 | 15623 |
| FEMORAL | | | | | |
| % | 1.45 | 6.1 | 1.58 | 0.18 | 0.3 |
| N | 688 | 461 | 316 | 1664 | 2100 |
| AXILLARY | | | | | |
| % | 1.18 | 2.28 | 1.41 | 0.2 | 0.1 |
| N | 930 | 744 | 711 | 989 | 1000 |

smaller radial artery is at greater risk than the larger femoral and axillary arteries. Arterial occlusion occurs in part as a result of mechanical obstruction of the artery by the cannula and in part by the formation and propagation of thrombus. Despite its high incidence, arterial occlusion is not detrimental in the majority of cases.^{10,31,32} The arteries recannulize rapidly (within a week),^{8,10,32-34} and permanent ischemic sequelae of arterial cannulation are, fortunately, rare.^{31,32} Attempts have been made to correlate a wide variety of factors with increased risk of arterial obstruction, and some of these are summarized in **Box E4-2**. The use of Teflon catheters has been associated with a decreased risk of arterial thrombosis,^{33,35,36} whereas outcome is independent of the age of the patient.^{37,38}

BOX E4-2

Factors Associated with Increased Risk of Arterial Obstruction

Use of smaller arteries (radial and dorsalis pedis vs. femoral or axillary³¹)
 Large catheter size^{33,102}
 Multiple insertion attempts^{33,37}
 Presence of hematoma¹⁰
 Female sex^{10,33,38}
 Preexisting peripheral vascular disease³²
 Prolonged shock³²
 Use of vasoconstrictor drugs³²

Catheterization of the brachial artery is generally not recommended because of potentially severe complications. These include forearm ischemia (secondary to mechanical obstruction of the artery by the catheter and/or thrombus), compartment syndrome (described in case reports³⁹⁻⁴¹), and damage to the median nerve (from either ischemia, direct mechanical trauma, or pressure secondary to a hematoma⁴²). Anticoagulation has been associated with a number of these complications^{39,43,44} and represents a relative contraindication.

Despite the widespread recommendation not to cannulate the brachial artery, its use has been reported in 3% of ICU patients² and up to 20% of operating room patients.¹⁴ Wider experience has been described in other specialties (e.g., angiography, single puncture for blood gases,⁴⁵ and long-term access to the arterial circulation) and provides an indication of potential complication rates. In a study of 10,500 patients undergoing cardiac angiography via the brachial artery, surgical intervention was required for 0.57%, most commonly due to hand ischemia.⁴⁶ The incidence of median nerve damage after cardiac catheterization via the brachial artery is 0.2% to 1.4%,⁴² whereas vascular angiography performed through the brachial artery in 1326 patients was associated with a brachial artery thrombosis rate of 0.28% for men and 1.24% for women.⁴⁷ Long-term cannulation of the brachial artery has been described in a study of 225 transbrachial intrahepatic cannulas (in situ for up to 14 months) and was associated with diminished radial pulses in 88 (39%) patients and ischemic symptoms of the forearm in 16 patients (8%). Brachial artery thrombosis had an incidence of 1.7%.⁴⁸

In clinical practice, the territory supplied by an artery that has been cannulated should be closely monitored. Pain, weakness, changes in sensation, pallor, or decreased temperature all suggest compromised arterial blood flow and should prompt the immediate removal of the arterial cannula. Usually removing the catheter will be sufficient to restore adequate blood flow.

Erroneous Blood Test Results

In 2008 the United Kingdom National Patient Safety Agency reported on two deaths related to erroneous results from blood tests obtained from the arterial catheter. In one of these, the arterial flush solution was changed from 0.9% sodium chloride solution to 5% glucose [*sic*]. Arterial blood glucose evaluations increased, and in parallel the insulin dose increased. After the patient lost consciousness blood was sent to the laboratory, and a glucose concentration of 0.1 mmol/L was detected. The patient never regained consciousness.²⁸ A second similar case report was published in 2013.⁴⁹

As reflected in these cases the most common cause of an unreliable blood test result is either dilution or contamination of the sampled blood with flush fluid. In addition to glucose measurements, removal of inadequate “dead-space” from the arterial line setup before obtaining blood for hemoglobin estimation may lead to a diluted sample and a falsely low hemoglobin level, and if heparin from the flush solution is introduced into a test of the activated partial thromboplastin time (aPTT), this test will be markedly prolonged. Heparin in higher concentration may also artifactually decrease the pH and PCO₂ measurements.^{50,51} If sodium citrate is used in the flush solution and inadvertently introduced into blood samples, then spurious hypocalcemia and a low pH might be reported along with increased glucose.⁵²

The solution to the problem of flush contamination lies in the withdrawal of an adequate deadspace of flush solution and diluted blood before obtaining the blood for testing. The interaction between heparin in the flush solution and the measurement of aPTT is particularly problematic and has been repeatedly studied in an attempt to determine the minimum deadspace volume required to obtain a reliable test result.^{53,54} Five to six times the tubing volume from the artery to the sampling three-way tap (i.e., the deadspace volume) should be withdrawn before the blood for this test to obtain a reliable result.

Whether this deadspace volume should be discarded or returned to the patient depends mainly on maintenance of sterility and speed of

sampling. Sterility can be maintained using a closed system, such that the deadspace blood is maintained in an internal reservoir. Specially designed systems exist with internal reservoirs^{55,56}; however, a simpler double-tap arrangement has also been described.⁵⁷ In this system, an extra three-way tap is added distal (i.e., farther away from the patient) to the sampling port. A syringe is attached to the extra three-way tap. The deadspace blood is drawn into this syringe, and the blood sample is taken from the more proximal (i.e., closer to the patient) tap. After blood sampling, the deadspace blood can be returned.

Blood cultures obtained from the arterial line represent another test in which results might be compromised. The sensitivity of cultures drawn in this way is similar to or slightly higher than that of blood cultures obtained by venipuncture; specificity, however, is lower.^{58,59} The lower specificity presumably reflects introduction of organisms into the culture bottles from the three-way tap or the catheter itself.

Anemia

The ease with which blood specimens can be obtained from the arterial line, and the requirement for frequent testing in critically ill patients, may lead to the removal of considerable volumes of blood. The effect of an arterial line in increasing blood test use was first reported in 1986.⁶⁰ In this study, patients with an arterial line in the ICU had blood drawn 3.4 times per day, leading to blood loss of 41.5 mL per day and a total of 762 mL. This was in contrast to non-ICU patients without an arterial line who had blood drawn 1.1 times per day, 12.4 mL/day, and a total of 175 mL for their whole admission.⁶⁰ Despite efforts to reduce iatrogenic blood loss, similar findings were published in 2015.⁶¹ Among 1894 cardiac surgery patients, the median phlebotomy volume remained high at 332 mL (vs. 118 mL for ward patients).⁶¹ Phlebotomy contributes to the development of anemia among ICU patients and has been implicated as a cause for blood transfusions.^{60,62} Relatively simple steps can reduce the blood loss associated with tests. Such steps include return of deadspace blood (as described earlier),^{55,57} use of pediatric-sized sample tubes,^{63,64} communication with the various laboratories to define the minimal blood volume required for various tests,⁶⁵ and point-of-care testing.⁶⁶ Despite their simplicity, these steps are infrequently employed.⁶⁷

Heparin-Induced Thrombocytopenia

The use of heparin can be associated with a syndrome of thrombocytopenia and thrombotic events usually appearing after approximately 5 days of heparin therapy.⁶⁸ HIT is thought to be mediated by IgG antibodies that develop in response to immunization against the heparin/platelet factor 4 (PF4) complex; these are called HIT antibodies.⁶⁸ The attachment of these antibodies to the heparin/PF4 complex on the platelet surface activates the platelets and induces thrombosis. Both venous and arterial thrombi can occur.⁶⁹ The presence of HIT antibodies does not, however, inevitably lead to thrombotic episodes. For example, up to 50% of cardiac surgery patients develop HIT antibodies, but thrombotic events are relatively rare (2%-3%).⁷⁰⁻⁷² The diagnosis of the HIT syndrome is therefore based on the presence of the antibodies, thrombocytopenia, and thrombotic events.⁶⁸

The overall incidence of this syndrome is reported to be approximately 5%. It is more common in women than men⁶⁸ and in surgical⁷³ as compared with medical^{69,74} or obstetric patients⁷⁵ and is also more common after the use of unfractionated heparin than low-molecular-weight heparin.⁶⁸ A single dose of heparin is sufficient to induce HIT,⁷⁶ and the presence of as little heparin as that found bound to heparin-coated central venous catheters may be sufficient to sustain the immune response.⁷⁷ The development of HIT antibodies has been linked with the administration of heparin in intravascular device flushes⁷⁸⁻⁸⁰ and also with low doses of heparin used in arterial flush solutions.⁸¹

Treatment for the HIT syndrome includes the cessation of administration of all sources of heparin, including those in the line flush solutions. The use of other anticoagulants for thrombotic episodes is recommended. Removing heparin from flush solutions also may be

indicated in the presence of HIT antibodies and thrombocytopenia before any thrombotic events.⁶⁸

After the decline in HIT antibody levels, the short-term use of heparin for certain indications (e.g., cardiac surgery) is considered acceptable.⁶⁸ It is prudent, however, to avoid heparin in the arterial line for patients with a history of HIT until further evidence of the risk of repeated episodes of HIT becomes available.

Infection

A patient may develop a bloodstream infection from the arterial line by one of three main routes. Infections have been introduced via infected equipment, such as reusable transducer domes⁸² or infected flush solutions⁸³; however, with the advent of disposable equipment and improved flush systems, the significance of this route of infection has declined. Two potential routes of infection remain: from the skin puncture site along the catheter and through the three-way taps.^{16,84-88} The predominant organisms associated with arterial line infection are gram-positive cocci (*Staphylococcus aureus* and *S. epidermidis*), although gram-negative rods may also be found.^{34,89,90}

Defining a precise rate of infection for the arterial line is not straightforward, because a multiplicity of definitions of catheter-related bloodstream infections is used in different studies and variables have not been standardized among studies. Clinical, research, and surveillance criteria exist for defining catheter-related infection. Clinical criteria include presence of signs of infection (e.g., fever, increased white blood cell count) associated with an arterial line in place longer than 96 hours with signs of local infection and no other source of sepsis. Whereas these criteria might be useful in clinical practice, they are too broad for research purposes. Surveillance criteria, such as those defined by the Centers for Disease Control and Prevention, include any significant bloodstream infection in the presence of a vascular catheter and no other source of sepsis.¹⁶ This definition overestimates the incidence of catheter-induced bloodstream infection because it includes bloodstream infection from occult sources other than intravascular lines.¹⁶ Research criteria can include the use of arterial line tip cultures (often quantitative or semiquantitative⁹¹) usually correlated to venous blood culture results.^{13,92,93} Combinations of these definitions have been employed.^{34,94}

With regard to arterial line variables, virtually every aspect of line insertion and maintenance (for either central venous or arterial catheters) has been examined for an effect on infection rate. Factors that have been evaluated include type of skin preparation solution used,⁹⁴⁻⁹⁶ insertion site, dressing type and care,^{16,87,88,97,98} arterial catheter length, site of insertion, catheter material, type of flush solution, and frequency of set changes (Box E4-3). Consistency is not found in the results of all these studies, and not all these factors have been standardized from study to study, possibly confounding direct comparisons.

Despite this variability, a meta-analysis reported that the rate of bloodstream infections related to arterial lines was 1.7 infections/1000 catheter-days and that 1.5/100 arterial catheters was found to cause a bloodstream infection.⁹⁹ These rates compared to 2.7 infections/1000 catheter-days and 3.6 infections/100 catheters for unmedicated central venous catheters (CVCs), 0.2 and 0.2 for antiseptic-coated CVCs, and

BOX E4-3

Factors Potentially Associated with a Change in the Infectious Risk of the Arterial Line¹⁶

INCREASED RISK

Cutdown technique versus percutaneous insertion⁹²
Duration of cannulation >96 h^{13,89,92,93,103}
Axillary artery site¹³
Frequent arterial line set changes¹⁰⁴

DECREASED RISK

Teflon catheters (vs. polyvinyl chloride)¹⁰⁵
Heparin (in central venous pressure and pulmonary artery catheters)¹⁰⁶
Use of chlorhexidine-containing skin preparation solutions^{94,95}
Factors not associated with a change in infectious risk
Femoral versus radial artery insertion site^{37,89}
Dorsalis pedis versus radial artery insertion site³⁴
Duration of catheterization >96 h^{37,90}
Systemic antibiotic prophylaxis before insertion⁹²

2.5 and 4.3 for antibiotic-coated CVCs.⁹⁹ The implication is that the infection rate associated with arterial catheterization is higher than generally assumed and may be higher than for the newer types of CVCs.

The Centers for Disease Control and Prevention summarized these diverse findings into these recommendations: use the radial, brachial, or dorsalis pedis sites rather than femoral or axillary arteries; use a minimum of cap, mask, sterile gloves, and a small sterile fenestrated drape for peripheral artery insertion and full sterile barrier precautions for axillary and femoral sites; use >0.5% chlorhexidine in 70% alcohol for skin preparation; do not change arterial catheters routinely; change the pressure monitoring sets and transducers every 96 hours; do not use dextrose in the flush solution.¹⁶ Despite these recommendations, and particularly the requirement for sterile precautions, less than half of physicians replying to a web-based survey adhered to them, indicating a need for education surrounding arterial catheter insertion.¹⁰⁰

In clinical practice, it is unlikely that an arterial cannula present for less than 96 hours is the cause of an infection. If the arterial line has been present for more than 96 hours, and no other source of sepsis is identified, strong consideration should be given to removing or replacing the arterial catheter. The presence of redness or pus at the arterial cannula introduction site should further increase the index of suspicion of an arterial line-related infection.

Finally, in view of these potential complications, the benefit of arterial cannulae in the ICU has begun to be questioned. Needless to say, there are no randomized controlled studies showing mortality benefit or harm from arterial cannulation. A recent retrospective study in a well-defined but limited population of hemodynamically stable patients with respiratory failure showed no difference in 28-day mortality.¹⁰¹ This study has led to calls to reassess the necessity for arterial cannulation in the ICU population in a similar manner to the assessments performed on pulmonary artery catheters.

KEY POINTS

Insertion Site and Equipment

1. The common sites of arterial line insertion are the radial, femoral, and dorsalis pedis arteries. These arteries are superficial; covered only by skin, fascia, and fat; and are easily compressible.
2. The arterial line can be inserted using a simple catheter-over-needle arrangement (with or without a guidewire) or a set based on the Seldinger technique.

3. Guidewires should only be used when back flow of blood is present to avoid arterial damage.
4. Doppler or ultrasound can be helpful for difficult line insertion.
5. Errors in pressure measurement can arise from incorrect zeroing, overshoot, or damping.
6. When zeroing, the height difference between the arterial puncture site and the transducer must be taken into account.

KEY POINTS—cont'd

7. Overshoot and damping affect the systolic blood pressure more than the diastolic or mean pressure.
8. The fast flush test can be used to assess underdamping or overdamping.
9. Low-concentration heparin is the most common arterial line flush solution. Sodium citrate, papaverine, and saline have been used.

Vascular and Local Complications

1. Arterial obstruction is very common after catheter insertion although rarely detrimental.
2. Obstruction may be mechanical from the catheter or result from thrombosis.
3. Small arteries, female gender, and shock are risk factors for thrombosis.
4. Pain, weakness, changes in sensation, pallor, or decreased temperature should prompt immediate catheter removal.

Erroneous Blood Tests

1. The majority of blood tests obtained from the arterial line will be accurate.
2. The type of flush solution used may interfere with certain tests.
3. Particular care should be taken when interpreting the activated partial thromboplastin time and blood culture results in samples drawn from the arterial line.

4. Five to six times the deadspace volume might be required for accurate tests, which may be reinfused with appropriate precautions.

Anemia, Heparin-Induced Thrombocytopenia, and Infection

1. Anemia can result from the volumes of blood drawn from the arterial line. Simple steps can reduce this blood loss.
2. Heparin-induced thrombocytopenia (HIT) is a syndrome defined by thrombocytopenia and thrombotic events in the presence of heparin/platelet factor 4 (PF4) complex antibodies.
3. Even very small doses of heparin can induce or maintain HIT. All sources of heparin should be removed if HIT is suspected, including from arterial line flush.
4. The rate of bloodstream infections related to the arterial line has been estimated to be 1.7 per 1000 catheter-days, whereas 1.5 in 100 arterial catheters causes infection.
5. Insertion technique, duration of cannulation, site, insertion site, and frequency of set changes have all been related to an increased infection risk.
6. Comparisons of studies relating to infectious risk are difficult owing to differing definitions of infection and study methodology.
7. The Centers for Disease Control and Prevention recommends: Use a >0.5% chlorhexidine in 70% alcohol solution for skin cleaning, do not change arterial catheters routinely, change the pressure monitoring sets and transducers every 96 hours, and do not use dextrose-containing flush solution.

ANNOTATED REFERENCES

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BEFORE PROCEDURE

Indications

- Need for continuous monitoring of pulmonary artery (PA) and right atrial (RA) pressures, cardiac output, and mixed venous oxygen saturation (SvO₂) providing that
 - The data collected will help in the management of the patient
 - The same measurements cannot be reliably obtained by a less invasive method

Contraindications

- Absolute contraindications
 - Tricuspid or pulmonary valve endocarditis
- Relative contraindications:
 - Tricuspid or pulmonary valve mechanical prosthesis
 - Right heart mass (thrombus and/or tumor)
 - Complete left bundle branch block (risk of complete heart block)

Equipment

- Sterile gowns, gloves, and masks
- 8F to 9F gauge introducer
- Sterile saline solution for flushing
- Volume-limited syringe for pulmonary artery catheter (PAC) balloon
- Pressure monitor transduction system and connector tubing

ANATOMY

The inflated balloon of the PAC facilitates the catheter progression through a branch of the PA. The distal lumen of the PAC measures the pressure downstream. It is assumed that there is a continuous column of blood between the distal lumen and the left ventricle (LV), and therefore the PA balloon-occluded pressure (PAOP) is equal to left ventricular end-diastolic pressure (LVEDP). PAOP reflects the pressure where the nonflowing blood (in the obstructed vessel) joins the blood flowing from the nonoccluded branches of the pulmonary artery. PAOP is actually intermediate between pulmonary capillary pressure and left atrial (LA) pressure. There are conditions, however, in which this theoretical continuous column of blood is interrupted, and in these circumstances PAOP no longer reflects LVEDP.

PROCEDURE

See Video E5-1.

- Check the patient's electrocardiogram (ECG), coagulation profile, and serum electrolyte panel. One should consider correcting major clotting disorders. If the patient already has a temporary pacemaker, it may be better to place the catheter under radiographic guidance to avoid dislodging the pacemaker.
- Inflate the catheter balloon as a test prior to catheter insertion.
- Connect the distal lumen to the pressure-monitoring system, and flush all lumens with sterile saline solution.
- Zero-reference the pressure transducer to the mid-chest position.

- Slide the protective sleeve onto the catheter to maintain sterility for further manipulations.
- Place sterile field.
- Give local anesthesia.
- Insert introducer into a central vein, preferably the internal jugular or subclavian, using the Seldinger technique.
- Pass the catheter through the hemostatic valve of the introducer.
- Inflate the balloon once the catheter tip has passed about 15 cm.
- Advance the catheter for another 15 cm. It should pass into the right ventricle (RV) and give an RV pressure waveform (Fig. E5-1).
- Advance the catheter further to pass into the PA and finally to obtain a PAOP waveform.
- Once a PAOP waveform has been obtained, deflate the balloon to return to the PA waveform.
- Once the catheter is in place, check the position with a chest radiograph. In the vast majority of cases, the tip is in the right lung. The tip should be within 2 cm of the cardiac shadow.
- All pressures should be measured at end expiration, when alveolar pressure should be closest to atmospheric pressure.

Procedural Precautions

- Always have the PA trace displayed on the monitor.
- Never withdraw the catheter without first deflating the balloon.
- Do not insert large lengths of catheter without observing a pressure change, because this maneuver may lead to looping and knotting of the catheter.
- There may be difficulties in reaching the RV or PA owing to RA or RV dilatation, tricuspid regurgitation, or abnormalities of the central veins. An option may be to advance the catheter with the balloon partially deflated during inspiration, repositioning the patient in a head-up or right lateral position, or flushing the catheter with iced saline to make it more rigid.
- If the PAOP trace is obtained when the balloon is inflated with less than 1 mL of air, or if there is a progressive elevation of pressure when the balloon is inflated ("overwedging"), the catheter tip is too advanced and should be withdrawn by a few centimeters to decrease the risk of PA rupture/infarction.

AFTER PROCEDURE

Postprocedure Care

- The PAC can be kept in situ for several days but should be removed as soon as it is no longer required for patient care.
- Balloon rupture can be identified by failure to wedge and failure of the syringe plunger to spontaneously deflate the balloon.

Interpretation of Measured Pressures

See also Table E5-1.

- The PA waveform has a systolic and diastolic pressure with a dicrotic notch corresponding to closure of the pulmonary valve.
- The PAOP, like the central venous pressure (CVP), has a venous waveform with a, c, and v waves corresponding to LA contraction, closure of the mitral valve, and passive LA filling, respectively.
- The a wave coincides with the point of maximal filling of the LV and is, therefore, the value that should be used for measurement of

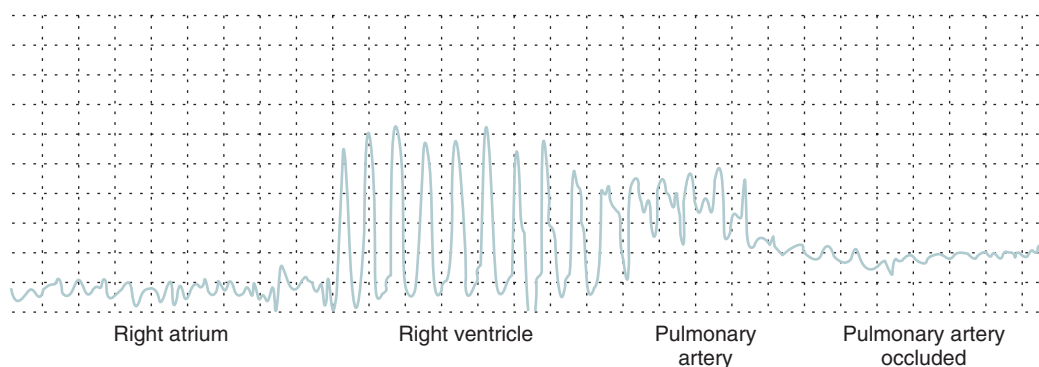


FIGURE E5-1 ■ Pressure traces as the pulmonary artery catheter is advanced.

TABLE E5-1

Interpretation of the Measured Pressure Variables

| CVP/RAP | PAP | PAOP | INTERPRETATION |
|-------------|------------|------------|---|
| Low/normal | Low/normal | Low/normal | Normal |
| Low/normal | High | High | Left heart failure (good right heart function) |
| Normal/high | High | Low | Pulmonary hypertension (e.g., COPD, ARDS, pulmonary embolism) |
| High | High | High | Hypervolemia (high CO) Global heart failure (low CO) Tamponade (low CO) |

COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; CO, cardiac output.

LVEDP. A large-amplitude a wave with an increase in measured PAOP suggests LV ischemia and decreased ventricular compliance.

- A large v wave on the PAOP trace represents mitral regurgitation or an acute volume load to the LA, as occurs with septal rupture. The PAOP level should be measured without consideration for this v wave.
- The RA pressure waveform can look like an RV waveform if there is significant tricuspid regurgitation.
- In cardiac tamponade, RA pressure and PAOP are high and similar as they equilibrate with pericardial pressures.
- A “dip-and-plateau” waveform may be seen in the RV pressure tracing in constrictive pericarditis, restrictive cardiomyopathy, RV infarction, and massive pulmonary embolism. This pattern is due to impaired ventricular filling during diastole.

Measurement of Cardiac Output with the PAC

- Cardiac output is measured using thermodilution.
- Measurement is based on the *indicator dilution principle*: when an indicator substance is added to a stream of flowing blood, the flow rate is inversely proportional to the mean concentration of the indicator at a downstream site. In the case of thermodilution, the indicator used is temperature, using either a bolus of cold injectate (cold thermodilution) or a thermal filament to generate heat (warm thermodilution).
- The old technique included a 10-mL bolus of room temperature 5% dextrose solution or saline injected over 4 seconds through the proximal port of the PAC. The thermistor proximal to the balloon then recorded the temperature change in the PA, and a temperature

time curve was displayed. The average of at least three curves was then obtained.

- Modern catheters provide a semicontinuous method in which a thermal filament is mounted on the PAC 14 to 25 cm from the tip. The filament intermittently generates pulses of heat, and the temperature change is recorded by the thermistor in the PA. These pulses of heat are pseudorandom to minimize the influence of other sources of temperature change such as infusions or respiratory fluctuations. The cardiac output is updated every 30 to 60 seconds and is time-averaged over the previous 3 to 6 minutes.

Complications

Complications that are unique to the PAC and not just due to insertion of a central venous catheter can be divided into those caused by placement and the longer term complications due to its presence:

- Placement
 - Common
 - Arrhythmias, most commonly premature atrial or ventricular contractions that are self-limiting and can occur on insertion or withdrawal of the catheter
 - Rare
 - Knotting of the catheter; a knot generally can be removed by placing a guidewire through the PAC to undo the loop or by pulling the loop tight against the introducer sheath and removing the whole unit.
 - Tricuspid pulmonary regurgitation or chordae tendineae rupture can occur if the catheter is withdrawn with the balloon inflated.
- Presence of the catheter
 - Common
 - Arrhythmias, most commonly premature atrial or ventricular contractions that are self-limiting and can occur on insertion or withdrawal of the catheter
 - Catheter-related infections
 - Rare
 - Pulmonary infarction due to catheter-related thromboembolism, obstruction of the pulmonary blood flow by the catheter tip, or prolonged inflation of the balloon. Usually without any consequences.
 - Endocarditis
- PA rupture occurs in less than 0.1% of cases, associated with a mortality of greater than 30%. Warning signs include hemoptysis, with shadowing on the chest radiograph. Diagnosis is confirmed by pulmonary angiography. Treatment consists of embolization or thoracotomy. Factors increasing the risk of rupture include pulmonary hypertension, advanced age, hypothermia, coagulation disorders, and distal positioning of the catheter.

OUTCOMES AND EVIDENCE

- Benefits of bedside PAC remain controversial, and insertion of a PAC cannot, per se, improve patient survival.
- Pulmonary artery catheters should not be inserted routinely but only in patients in whom the data collected will help in the patient's management and the same measurements cannot be obtained by a less invasive method.
- To be beneficial, data from the PAC must be collected, interpreted, and applied correctly.

SUGGESTED READING

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■ BEFORE PROCEDURE

Indications

- Emergency reestablishment of an organized electrical rhythm
 - Hemodynamically unstable polymorphic ventricular tachycardia
 - Ventricular fibrillation
 - Pulseless ventricular tachycardia
 - Narrow or wide QRS complex tachycardia (ventricular rate >150) associated with hemodynamic instability, chest pain, or pulmonary edema
- Elective reestablishment of sinus rhythm
 - Atrial fibrillation
 - Atrial flutter
 - Hemodynamically stable ventricular tachycardia unresponsive to medical treatment
 - Others

Contraindications

- Specific advance directives (e.g., do not attempt resuscitation for cases of ventricular fibrillation)
- Digitalis toxicity–associated tachycardia
- Sinus tachycardia caused by various clinical conditions
- Rhythms not responsive to electric shock (e.g., multifocal atrial tachycardia)
- Atrial fibrillation or atrial flutter without proper anticoagulation or exclusion of atrial thrombi

Equipment

- Automated external defibrillator or manual defibrillator
- Proper age-adjusted pads or paddles

■ ANATOMY

The heart is located behind the sternum. Its base is at the level of the third intercostal space immediately to the right of the sternum, and its apex is at the level of the fifth intercostal space inferior, and usually just medial to the nipple. External cardioversion or defibrillation is attempted by delivering one or more electric shocks through the chest cavity for the purpose of passing an electric current of sufficient energy through the heart muscle to fully depolarize the atria (e.g., atrial fibrillation or atrial flutter) or the ventricles (e.g., ventricular fibrillation or ventricular tachycardia). Cardioversion should enable the natural or artificial cardiac pacemaker to resume control of the cardiac rhythm. Electrodes (paddles or pads) can be positioned on the anterior chest wall, with one electrode below the right clavicle lateral to the sternum and the other electrode below the breast tissue along the midaxillary line. Electrodes (e.g., pads or paddles that are more difficult) can also be positioned in an anteroposterior position, with the anterior electrode placed over the precordium and the posterior electrode at the right infrascapular location. For internal cardioversion or defibrillation, specially designed paddles are applied directly to the epicardial surface of the ventricles.

■ PROCEDURE

See Videos E6-1 and E6-2.

- For external elective cardioversion, many of the following steps may have to be shortened or circumvented in hemodynamically unstable patients (especially if unconscious), requiring rapid termination of life-threatening arrhythmia (e.g., ventricular fibrillation or pulseless ventricular tachycardia as part of cardiopulmonary resuscitation).
- Admit the patient to an appropriately equipped hospital area with the capability for monitoring cardiac rhythm, oxygenation, and vital signs, along with airway management and cardiopulmonary resuscitation.
- Fast the patient overnight or for at least 6 to 8 hours.
- Establish vascular access.
- Obtain an electrocardiogram.
- For sedation, consider using a short-acting anesthetic agent (e.g., midazolam, propofol, or etomidate) under the care of an anesthesiologist or similarly privileged anesthesia provided and adequate supportive personnel. An alternative to anesthesia is moderate sedation, in which the patient maintains consciousness but in a somnolent state. This has the advantage that it can be given by trained physicians without an anesthesiologist present.
- Attach monitor leads to the patient, and ensure proper display of the patient's rhythm.
- Place electrodes properly separated (as described under Anatomy). Apply coupling gel if using paddles; avoid smearing the gel over the chest wall to prevent current traversing superficially through the chest. In patients with permanent pacemakers or implantable cardioverter-defibrillators, place electrodes away from the device generator to avoid device malfunction. Consider reevaluating pacing thresholds in patients with permanent pacemakers and interrogation of implantable cardioverter-defibrillator function after cardioversion.
- Engage the synchronization mode, and identify markers on the R waves indicating adequate R-wave recognition. If necessary, adjust the gain of the monitor until markers appear on each R wave.
- Select the energy level to deliver the necessary current based on the patient's waveform, age, and arrhythmia. Organized rhythms with a simple reentry circuit (e.g., atrial flutter and monomorphic ventricular tachycardia) usually require less current than more complex rhythms (e.g., atrial and ventricular fibrillation).
- Press the charge button on the unit or paddles.
- If using paddles, apply approximately 12-kg pressure to each paddle.
- Press the discharge button on the unit or paddles simultaneously.
- Check the monitor. If the arrhythmia persists, increase the energy level according to the protocol for the specific rhythm.
- Reset the synchronization. Most units default to the unsynchronized mode (allowing immediate defibrillation if ventricular fibrillation ensues).
- Repeat the shock until the conversion of the arrhythmia or completion of the protocol.
- Deliver unsynchronized shocks only for ventricular fibrillation or pulseless ventricular tachycardia.

AFTER PROCEDURE

Postprocedure Care

- Obtain an electrocardiogram.
- Assess hemodynamic and respiratory status.
- Observe the patient until the recovery from anesthesia or sedation is complete.
- Consider hospital discharge if the procedure was elective.

Complications

- Cardioversion and defibrillation are relatively safe procedures with infrequent complications that may include
 - Induction of ventricular fibrillation if the electric shock is improperly synchronized

- Transient conduction abnormalities
- Myocardial dysfunction (after high-energy and repetitive delivery of electric shocks)
- Release of cardiac enzymes
- Pulmonary edema
- Embolization of thrombi formed within the cardiac chambers (e.g., atrial fibrillation and flutter)
- Respiratory depression associated with anesthesia or sedation

OUTCOMES AND EVIDENCE

- Sinus rhythm will be restored in a high percentage of patients.
- Underlying conditions may predispose certain patients to a recurrence of arrhythmias.
- Early defibrillation of ventricular fibrillation is associated with improved survival.

SUGGESTED READING

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BEFORE PROCEDURE

Indications

- Treatment of symptomatic bradycardia
 - Sinus bradycardia
 - Second-degree or third-degree atrioventricular block
- Prophylaxis
 - Bradycardia-induced ventricular tachyarrhythmias (e.g., torsades de pointes)
 - Increased risk of advanced atrioventricular block (e.g., acute myocardial infarction, infective endocarditis, surgery in patients with underlying conduction defects)
- Overdrive pacing for termination of tachyarrhythmias
 - Supraventricular tachycardia
 - Ventricular tachycardia
- Improving hemodynamic function
 - Sequential atrioventricular pacing

Contraindications

- Specific advance directives (e.g., do not attempt resuscitation for cases of pulseless electrical activity)
- Asymptomatic bradycardia
- Severe hypothermia (risk of ventricular fibrillation)

Equipment

- Pacing catheter with pulse generator
- Transcutaneous electrodes with pacing unit (integrated with current cardioverter-defibrillators)

ANATOMY

The heart is located behind the sternum. Its base is at the level of the third intercostal space immediately to the right of the sternum, and its apex is at the level of the fifth intercostal space inferior, usually just medial to the nipple. Transcutaneous pacing can be performed by delivering electric impulses through the chest cavity to “capture” and drive the electrical activity of the heart. Electrodes can be placed on the anterior chest wall, with one electrode below the right clavicle lateral to the sternum and the other electrode below the breast tissue along the midaxillary line. Electrodes can also be placed in an anteroposterior configuration, with the anterior electrode placed over the precordium and the posterior electrode at the right infrascapular location. For transvenous pacing, the pacing catheter can be advanced through the brachial (antecubital), femoral, internal jugular (preferably right), subclavian (preferably left), or the right subclavian via supraclavicular access (experienced practitioner).

PROCEDURE

Transvenous Temporary Pacing

See Video E7-1.

- Admit the patient to an appropriately equipped hospital area with the capability for monitoring cardiac rhythm, oxygenation, and

vital signs, along with airway management and cardiopulmonary resuscitation.

- Obtain a 12-lead electrocardiogram (ECG).
- Attach monitor leads to the patient, and ensure proper display of the patient's rhythm.
- Perform the procedure under fluoroscopy if available and time permits; otherwise use the ECG and rhythm to guide placement.
- Establish vascular access under local anesthesia and full sterility, advancing a proper-size introducer sheath.
- Select pacing catheter contingent on approach. Catheters for use under fluoroscopy are semirigid (usually made of woven polyester) to facilitate maneuvering into position. Catheters designed for blind placement have a balloon at the tip to be floated into position. Transvenous pacing can also be accomplished using multipurpose pulmonary artery catheters built with up to five electrodes for right atrial and right ventricular pacing.
- Blind placement using a balloon-tipped catheter can be guided by the ECG. A V_1 lead of a conventional ECG is connected to the distal pole (cathode) of the pacing catheter and used to monitor a unipolar intracavitary electrogram. The catheter is floated, seeking the display of a right ventricular intracavitary electrogram point at which the balloon can be deflated, and the catheter advanced a few centimeters to position its tip in the right ventricular apex. Endocardial contact is confirmed by the development of an “injury” current characterized by prominent ST-segment elevation. The pacing electrode is connected to the pulse generator and used in the unipolar or bipolar configuration.
- Another, more practical, approach (that is preferred in emergency situations) is to advance the pacing electrode into the right ventricle and turn the pulse generator on in the asynchronous mode at a rate that exceeds the native rate. The pacing current is set between the default and maximum output, and the pacing electrode is maneuvered until capture occurs.
- A defibrillator should be available during insertion and afterward because life-threatening ventricular tachyarrhythmias may develop, especially if the pacing lead moves within the ventricular cavity.
- Leave a sterile sleeve around the catheter (available with most introducer kits) to facilitate subsequent repositioning if required.
- Obtain an anteroposterior and lateral chest x-ray to verify proper placement and exclude complications.
- Set pacing options as follows:
 - Determine the pacing threshold, and set the pacing output. For this purpose, set the pacemaker rate to exceed the spontaneous heart rate by 10 to 20 beats/min and the output to a level expected to capture 100% of the beats (i.e., 6 mA). Capture is verified on the ECG by identifying the presence of a spike (pulse) followed by a wide QRS complex. The output is reduced gradually until beats are no longer captured and then increased again to identify the minimal level at which 100% of the beats are paced; this is the threshold output. This threshold level should be less than 1 mA for ventricular pacing and less than 2 mA for atrial pacing in the unipolar and the bipolar configurations; otherwise, the lead must be repositioned. The output is set at about three times the threshold level for reliable capture.
 - Set sensitivity (range: 0.5–20 mV), allowing the native R wave to inhibit the pacemaker impulse when the generator is set in synchronous mode. The output is first set to its minimal level

(e.g., 0.1 mA) and the pacing rate to a value below the spontaneous heart rate. Starting from the maximal sensitivity (the lowest value; i.e., 0.5 mV), gradually decrease the sensitivity (increasing its value) until the unit stops sensing the R wave. For reliable inhibition, the sensitivity is set at about three times the sensitivity threshold (e.g., if the threshold is 3 mV, the level is set at 1 mV).

- The pacing rate for bradyarrhythmias is set according to physiologic needs, usually between 60 and 75 beats/min. Higher rates (800 beats/min) are available for overriding the pacing of ventricular or supraventricular tachyarrhythmias.
- Sequential atrioventricular pacing requires the placement of an additional lead or the use of a multipurpose pulmonary artery catheter along with a dual-chamber pulse generator. The individual chamber specifications for dual-chamber generators are similar, with the option of setting the AV pacing interval between 20 and 300 msec.

Transcutaneous Temporary Pacing

See Video E7-2.

- Transcutaneous pacing is noninvasive and can be used in emergency settings with ease and minimal delay while preparing for more definitive therapy. Alternatively, it can be used prophylactically.
- Pacing is limited to the ventricles (with minimal capability for atrial pacing), capture is not always attained, and tolerability may be poor.
- Place electrodes on the anterior chest wall or in an anteroposterior configuration as described under Anatomy. Place the negative electrode (i.e., cathode) anteriorly, close to the heart (typically over the palpable cardiac impulse or centered on a V_3 lead) to minimize the capture threshold. Place the positive electrode (i.e., anode) over the upper right region of the chest or the posterior chest wall between the bony spine and the inferior border of either the left or right scapula.
- Determine the pacing threshold as for transvenous pacing (described earlier), bearing in mind that the pacing threshold is much higher (20 to 140 mA), particularly in patients with emphy-

sema and pericardial effusion and in patients undergoing positive pressure ventilation. The pacing output is set 5 to 10 mA above the threshold. Pulse generators are designed to deliver high current levels (200 mA) with a longer pulse duration (20 to 40 msec) to facilitate capture and minimize patient discomfort.

- Ensure that capture occurs by demonstrating coincident pulse generation; do not rely on the ECG capturing artifacts from the skeletal muscle activity.

AFTER PROCEDURE

Postprocedure Care

- Obtain an ECG.
- Assess hemodynamic status.
- Monitor native and paced rhythms.
- Establish etiology, and institute definitive treatment.

Complications

- Pacemaker malfunction, defined as the failure to sense, capture, or both
- Ventricular dysrhythmias at the time of insertion
- Myocardial perforation with risk of cardiac tamponade
- Diaphragmatic stimulation
- Complications related to the vascular access (e.g., phlebitis, pneumothorax, arterial puncture, brachial plexus injury, pulmonary embolism, and sepsis)

OUTCOMES AND EVIDENCE

- Effective in pacing at the desired heart rate
- Transvenous pacing is more effective than transcutaneous pacing (lower capture rate)
- Lack of effectiveness for treatment of cardiac arrest due to asystole or pulseless electrical activity
- Temporary measures pending the resolution of the rhythm abnormality or permanent definitive pacemaker placement

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■ BEFORE PROCEDURE

Indications

- Postcardiotomy failure (left ventricular assist device [LVAD])
 - Elevated left atrial pressure (LAP) and cardiogenic shock despite inotropic support and intraaortic balloon pump (IABP)
 - LAP >25 mm Hg
 - Cardiac index (CI) <2 L/min/m²
 - Severe left ventricular (LV) dysfunction on echocardiogram
 - Intractable ventricular arrhythmias
 - Ongoing myocardial ischemia despite revascularization
- Postcardiotomy failure (bilateral ventricular assist device [BiVAD])
 - Evidence of an elevated central venous pressure (CVP; >9 mm Hg) despite pulmonary afterload reduction
 - Evidence of severe right ventricular (RV) dysfunction on echocardiogram
 - Inability to provide adequate blood flow to fill the LVAD (if an LVAD is in place)
- Bridge to cardiac transplantation
 - Failure of optimal medical therapy that increases the risk of compromised life or end-organ function while awaiting cardiac transplantation
 - CI <2 L/min/m²
 - Mixed venous oxygen saturation <50% on optimal medical therapy
 - Ventricular arrhythmias
 - Severe symptoms at rest
 - Need for multiple inotropic agents
 - Lack of response to diuretic medications, with a rising creatinine
 - Pulmonary artery hypertension
 - Cool and constricted extremities reflective of poor perfusion
 - Low blood pressure, resting tachycardia, rales, and/or distended neck veins
 - Laboratory evidence of prerenal azotemia, hepatic dysfunction, or coagulopathy
 - Requirement for supplemental oxygen
- Bridge to bridge: in conditions of cardiogenic shock when indications for cardiac transplantation are not yet met but are potentially attainable
- LVAD versus BiVAD
 - Biventricular assist devices should be considered for
 - Intractable ventricular tachycardia or fibrillation
 - Cardiogenic shock requiring resuscitation with extracorporeal membrane oxygenation (ECMO)
 - Cardiogenic shock with multiorgan failure
 - Pulmonary edema despite maximal medical therapy
 - Chronic RV failure with ascites, low pulmonary artery pressure, severe hepatic or renal dysfunction, and tricuspid insufficiency
 - Severe acute respiratory distress syndrome
 - Giant cell myocarditis
 - Large anterolateral myocardial infarction with involvement of the anterior right ventricle
 - RV infarction

- Destination therapy
 - Indicated for patients who meet the above criteria for bridge to transplantation LVAD candidacy but who are not eligible for transplantation based upon age, obesity, renal dysfunction that will not tolerate immunosuppressive agents, or other comorbidities suggesting that the risk of transplantation is unacceptable
- Patients with advanced heart failure (HF) symptoms (New York Heart Association [NYHA] class IIIB or IV) who meet at least one of these criteria
 - Continued failure despite optimal medical management for at least 45 of 60 days
 - NYHA class III or IV status for at least 14 days and dependent on IABP for 7 days and/or inotropes for 14 days
 - Treated with angiotensin-converting enzyme (ACE) inhibitors or beta-blockers for at least 30 days and found to be intolerant of these medications
 - Maximal oxygen consumption (VO₂ max) ≤14 mL/kg/min or ≤50% predicted VO₂ max with exercise testing (unless testing is contraindicated because of class IV status)

Contraindications

- Postcardiotomy failure
 - Sepsis
 - “Stone heart” or lack of any innate cardiac function
 - Age >70 years
 - Condition in which recovery is not anticipated and the patient is not a candidate for cardiac transplantation
- Bridge to transplantation
 - Patient is not a candidate for cardiac transplantation
 - Sepsis
 - End-organ damage is not likely to recover
 - Severe impairment of neurologic function
 - Severe chronic obstructive pulmonary disease
 - Procoagulation abnormalities, with previous venous or arterial thrombosis despite anticoagulation therapy
 - Pregnancy
 - Inability or refusal to receive blood transfusions
 - Technical obstacles that pose an inordinately high surgical risk
- Destination therapy
 - Same as for transplantation, other than the requirement for cardiac transplantation candidacy
 - Lack of social or family support that allows for home discharge
 - Inability to comprehend plans for postoperative LVAD training
 - Expected need for prolonged biventricular support
 - Severe symptomatic peripheral vascular disease
 - Intolerance to anticoagulant or antiplatelet therapies or any other peri- or postoperative therapy the patient will require based upon his or her health status
 - Psychiatric disease, irreversible cognitive dysfunction, or psychosocial issues likely to impair compliance with protocols and LVAD management

Equipment

- Postcardiotomy
 - IABP
 - ABIOMED AB/BVS 5000 (LVAD and BiVAD)
 - Tandem Heart
 - Thoratec CentriMag (LVAD and BiVAD)
 - Thoratec PVAD (LVAD and BiVAD)
- Bridge to transplantation
 - Thoratec PVAD (LVAD and BiVAD)
 - Heartmate II
 - Heartware HVAD
 - DuraHeart
 - Levacor
 - CardioWest Total Artificial Heart
- Destination therapy
 - Heartmate II
 - Heartware HVAD

PROCEDURE

- Intraoperative preparation and evaluation
 - Lines: arterial, venous, Swan-Ganz (continuous cardiac output type for continuous-flow LVADs)
 - Preoperative echocardiogram assessment
 - LV thrombus
 - Interatrial septal defect or patent foramen ovale (PFO)
 - Aortic insufficiency
 - Tricuspid insufficiency
 - Right ventricular function
 - Hemodynamic control
 - Management and preservation of perfusion pressure for right ventricle and coronary arteries utilizing α -agonists
 - Preoperative thromboelastogram to assess coagulopathy and the need for transfusion products
 - Cautious volume management
 - Cannulation for cardiopulmonary bypass
 - Distal ascending aortic site for inflow
 - Standard two-stage venous cannula for drainage (for standard LVAD)
 - Biatial cannulation for BiVAD or if tricuspid repair or PFO closure is required
 - Apical LV cannulation achieved for LVAD
 - Apical cannulation performed according to protocol dictated by each individual VAD brand
 - Preperitoneal pocket required for some LVADs; otherwise, a subcostal tunnel is created as needed
 - Aortic outflow graft sewn end-to-side for outflow
 - RVAD cannulation via the right atrial appendage
 - RVAD return to the pulmonary artery via arterial cannula
- Closure of pericardium preferred
- Adequate chest tube drainage from mediastinum and pleural spaces

AFTER PROCEDURE

Postprocedure Care

- Hemodynamic and volume control
 - Blood pressure maintenance is critical for RV function.
 - Adequate inotropic support is needed for the right ventricle.
 - Appropriate blood product replacement should be given, guided by thromboelastogram.
 - Adequate blood pump flow is determined by adequate CI (at least 2.4 L/min/m²).
 - In most cases, decompression of the LV should not be so great as to cause right-to-left interventricular septal shift. Mitral regurgitation should be reduced and the aortic valve open occasionally.
 - CVP should be maintained between 8 and 12 mm Hg.

- Intensive care unit management
 - Maintain positive pressure ventilation until mental status and pulmonary function allow for extubation.
 - Remove chest tubes as soon as possible.
 - Begin anticoagulation for the ventricular assist device (VAD) with heparin after 24 hours (if bleeding is less than 50 mL/h), and convert to warfarin when the patient is taking oral fluids.
 - Broad-spectrum antibiotics should be continued for 4 to 5 days.
 - Active physiotherapy should be carried out, with emphasis on pulmonary toilet and incentive spirometry.

Complications

- Common
 - Bleeding: mediastinal, wounds, driveline sites, gastrointestinal
 - RV dysfunction
 - Infection: driveline-associated (especially at exit site), pulmonary, urinary tract
- Infrequent
 - Neurologic events
 - Arrhythmias
 - Hemolysis
 - Psychiatric
- Serious, rare complications
 - Device malfunction

OUTCOMES AND EVIDENCE

Successful clinical evaluation of the Thoratec PVAD led to U.S. Food and Drug Administration (FDA) approval for bridge to transplantation (BTT) indication in 1992. Twenty-four patients (62%) required support with an LVAD alone, and 15 (38%) required BiVAD support. Survival from support to successful outcomes was 70% for BTT and 67% for postcardiotomy recovery.

The HeartMate II (Thoratec Corporation, Pleasanton, California) is a continuous-flow rotary pump with an axial design, which is representative of the second generation of LVAD technology in clinical use in the United States. Successful clinical evaluation of the Thoratec pVAD led to FDA approval for BTT indication in 1992. Of the 133 patients receiving support with the HeartMate II device, the principal efficacy outcomes were observed in 100 patients (75%). The median duration of support was 126 days (range, 1-600). The survival rate during support was 75% at 6 months and 68% at 12 months. There was significant improvement in distance walked between baseline and 6 months, with over 50% of patients experiencing an improvement in the 6-minute walk distance to over 200 meters.

In 1998, the National Heart, Lung, and Blood Institute funded the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial. REMATCH was a pivotal trial designed to assess morbidity, mortality, and functional outcomes in a homogeneous cohort of patients with advanced heart failure ineligible for cardiac transplantation. Survival rates at 1 year (52% vs. 25%, $P = 0.002$) and 2 years (23% vs. 8%, $P = 0.09$) were superior (significantly) in the VAD patients compared with the survival rates in those patients randomized to medical therapy.

Following the original REMATCH publication, Park and colleagues analyzed the outcomes of the trial, based upon the era of enrollment. Despite more high-risk characteristics, patients enrolled in the latter half of the study had significantly higher 1- and 2-year survival rates than those enrolled during early experience with the VAD. A similar improvement in survival outcomes was seen in the postapproval registry, with a 56% 1-year survival rate. Improved outcome with VAD use and experience is a consistent observation, which was also evident in the continued access protocol cohort versus primary cohort in the HeartMate II BTT trial. Demonstration of improved survival outcomes in patients with preimplant risk profiles similar to or worse than those enrolled in the initial randomized trial suggests that refinement of pre- and postoperative management and greater experience with mechanical circulatory support are important

factors in determining survival and functional improvements after VAD implantation.

The HeartMate II DT Pivotal Trial evaluated 200 patients with NYHA class IIIb-IV symptoms, ejection fraction (EF) <25%, and VO_2 max ≤ 14 mL/kg/min or treatment with intravenous inotropic agents for at least 14 days or an IABP for 7 days. The patients were randomized

to receive a HeartMate II (n = 134) or a HeartMate XVE (n = 66). There was a greater than fourfold increase in the percentage of HeartMate II patients who successfully reached the primary endpoint (46% vs. 11%, $P < 0.001$). Patients randomized to the HeartMate II had 1- and 2-year survival rates of 68% and 58%, compared with 55% and 24% in patients who received the HeartMate XVE.

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■ PREPROCEDURE

Indications

- Pericardial tamponade
 - Pericardiocentesis is the first treatment option in patients with overt tamponade because only the removal of fluid allows normal ventricular filling and restores adequate cardiac output.
 - If the patient is hemodynamically stable, the procedure should be performed within 12 to 24 hours from diagnosis, after obtaining laboratory results including the blood counts.
- Pericardial effusion without hemodynamic compromise
 - Persistent (more than 1-week treatment) large pericardial effusion (>20 mm anterior plus posterior space in echocardiography in diastole).
 - Suspected bacterial or tuberculous pericarditis
 - Elective pericardiocentesis is warranted in patients with suspicion of purulent pericarditis.
 - Purulent pericarditis should be managed aggressively, as death is inevitable if untreated, whereas with comprehensive therapy 85% of cases have been reported to survive the episode and have a good long-term outcome.
 - Treatment consists of systemic antibiotic therapy and complete evacuation of the effusion. Surgical drainage usually is required, because percutaneous drainage alone is not able to completely evacuate the effusion, which is often rich in fibrin and can be loculated and associated with dense adhesions. An alternative and less invasive method, which can be used to completely evacuate purulent effusions, thus controlling sepsis and avoiding the evolution to constrictive pericarditis, consists of pericardial drainage associated with intrapericardial infusion of streptokinase. Fibrinolytic therapy can enhance the removal of material that would otherwise be too viscous or particulate to be removed by tube drainage. This treatment should be considered before undertaking surgery.
- Suspected neoplastic effusion
- Pericardiocentesis for diagnostic purpose in mild or moderate effusions (<20 mm) should be confined to selected cases.
 - Pericardiocentesis with a diagnostic purpose (except in cases of suspected neoplastic, tuberculous, or purulent pericarditis) is not justified in the majority of cases for the following reasons: (1) low diagnostic power; (2) the underlying pathology is often already known or identifiable by different non-invasive tests; (3) viral pericarditis is usually self-limiting, and it only requires an antiinflammatory treatment; (4) high procedural risk.

Contraindications

- Urgent pericardiocentesis or drainage of pericardial effusion is indicated for each patient with established diagnosis of cardiac tamponade and hemodynamic shock.
- Aortic dissection and postinfarction rupture of the free wall are contraindications to pericardiocentesis and indications for urgent surgical drainage. Only when surgical management is not immediately available or the patient is too unstable, pericardiocentesis and

controlled pericardial drainage of very small amounts of the hemo-pericardium can be attempted to temporarily stabilize the patient in order to maintain blood pressure at ~90 mm Hg.

- Relative contraindications include uncorrected coagulopathy, anticoagulant therapy, and thrombocytopenia (PLTc < 50,000/mm³), and small, posterior, and loculated effusions.
 - The alterations of coagulation can be corrected using:
 - Fresh frozen plasma or platelets (may be time consuming)
 - Recombinant human factor VIIa, which may be effective in a shorter time.
 - Vitamin K + prothrombin complex concentrate

Equipment

- Echocardiography
- Multiangle bracket, to be assembled on the probe, (biopsy starter kit for GE 3S, 3S-RS, M3S, and M4S transducers [CIVCO USA, Kalona, IA])
- Needle-guide kit with sterile sheath and sterile echo-gel (Ultra Pro II needle guide [CIVCO USA, Kalona, IA])
- 14- to 16-gauge Teflon-sheathed needle (technique A)
- 18-gauge, 9-cm needle on a syringe for apical approach (technique B)
- 18-gauge, 15-cm needle, included in the PeriVac set (Boston Scientific USA, Marlborough, MA) for subxiphoid approach
- J-tipped guidewire
- 6F to 8F dilator
- Drainage catheter: pigtail angiocatheter 6F to 8F or pericardiocentesis set (PeriVac)
- Disposable flushing system to maintain the patency of the system

■ ANATOMY

The pericardium is a fibroserous sac that contains the heart and the origin of the main vessels. The pericardium is composed of two layers, the visceral pericardium, a monolayer membrane of mesothelial cells that is adherent to the epicardial surface of the heart, and the fibrous parietal layer that surrounds most of the heart. The pericardial space normally contains 25 to 50 mL of fluid in adults. If the amount of fluid increases, the pericardium is not immediately distensible, even though stress relaxation may occur within minutes from the beginning of the increase in pericardial pressure. If the fluid accumulates slowly, over weeks or months, the pericardium can increase in size to a maximum capacity of 1 to 2 L. The heart, and therefore the pericardium, is located at the center of the mediastinum, partially covered by the lungs; by the sternum and by the costal cartilages of the third, fourth, and fifth ribs; and by intercostal muscles. About two-thirds of the heart is located on the left side of the chest. The heart rests on the diaphragm. The pericardium is innervated by the vagus nerve, by the left recurrent laryngeal nerve, by the esophageal plexus, and it also has rich sympathetic innervation from the stellate and first dorsal ganglia and the cardiac, aortic, and diaphragmatic plexuses. When performing pericardiocentesis, close attention should be paid to avoid damaging the internal thoracic artery, which runs behind the sternal end of the costal

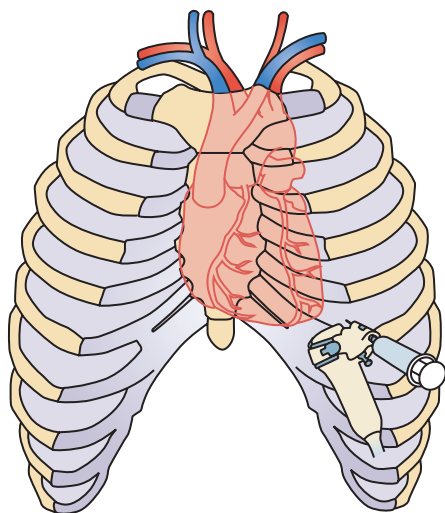


FIGURE E9-1 ■ Projection of cardiac area on the anterior thoracic wall.

cartilages, and the vascular bundle at the inferior margin of each rib (Fig. E9-1).

■ PROCEDURE

Echo-Guided Technique (A)

- Perform a two-dimensional and Doppler study to assess the size, distribution, and hemodynamic effect of the effusion.
- Place the patient in a semi-reclining position, at an angle of about 30 degrees, and slightly rotated leftward to enhance fluid collection in the infero-anterior part of the chest.
- Ensure that a central venous catheter is in place. The catheter is essential for monitoring right atrial pressure and permitting the rapid infusion of fluids and drugs as indicated.
- Continuous arterial pressure monitoring is indicated to detect the presence of pulsus paradoxus and to rapidly detect and correct sudden hemodynamic instability.
- Medical management:
 - In the unstable patient with hypotension and tachycardia, during preparation for pericardiocentesis, measures aimed to stabilize the patient should be instituted. Intravenous fluid administration is the best treatment option before and during drainage. In stable patients without low systolic blood pressure (>100 mm Hg) this treatment is not useful, and it could be dangerous reducing the cardiac output.
 - Intravenous administration of diuretics is contraindicated and could be fatal in patients on the edge of their compensatory mechanism in tamponade.
 - Both dopamine and dobutamine improved hemodynamics in cardiac tamponade; dobutamine has greater beta activity and therefore it may be considered preferable. However, the usefulness of inotropes is generally limited because endogenous adrenergic stimulation is already enhanced under tamponade conditions, and ejection fraction is preserved, but stroke volume is critically depressed.
 - Packed red cell units should be readily available before starting nonemergency procedures.
- Respiratory management
 - Pulse oximetry and supplemental O₂ should be warranted.
 - Influence of respiratory parameters: spontaneous versus mechanical ventilation and PaCO₂ levels significantly influence the evolution of pericardial tamponade. Pericardial pressure decreases 3 to 6 mm Hg when PaCO₂ decreases to 24 mm Hg; conversely, pericardial pressures increase 2 to 4 mm Hg when

PaCO₂ reaches 57 mm Hg. Increased intrathoracic pressures during the inspiratory phase of mechanical ventilation can decrease cardiac output up to 25% in patients with tamponade. To avoid further haemodynamic compromise, patients with suspected cardiac tamponade should not receive positive-pressure ventilation unless absolutely necessary.

- After appropriate disinfection of the operative field, local anesthesia of the skin is obtained by injecting with 2% lidocaine subcutaneously.
- The trajectory of the needle is defined by the angle between the probe and the chest wall. Ultrasound does not cross aerial spaces. Therefore, if cardiac structures are identified, there is no lung tissue interposed between the probe and the pericardium.
- The proper landmark for needle insertion corresponds to the area where the pericardial space is closest to the probe and the fluid accumulation is maximal; this site is para-apical more often than subxiphoid. The subcostal route is less frequently used because it requires a longer path to reach the fluid. It passes anterior to the liver capsule and is directed toward the right chamber of the heart.
- The optimal needle trajectory should be transfixed in the operator's mind and then a 14- to 16-gauge Teflon-sheathed needle with an attached saline-filled syringe is advanced in the direction of the fluid-filled space.
- Para-apical approach: insert the needle at 3 to 5 cm from the parasternal border (to avoid the internal thoracic artery), and close to the superior edge of the rib (to avoid the intercostal artery).
- Subxiphoid approach: direct the needle posteriorly until the tip passes posterior to the bony cage. Press the hub of the needle toward the diaphragm and advance the needle with a 15-degree posterior tilt, either directly toward the patient's head or toward the right or left shoulder.
- When fluid is aspirated, the needle should be advanced approximately 2 mm farther. The sheath should be advanced over the needle and the steel core withdrawn.
- If bloody fluid has been aspirated or if the position of the sheath is questionable, the position of the catheter can be confirmed by injecting 5 mL of agitated saline through the sheath. The bubbles in the solution provide a contrast effect that can be observed by two-dimensional echocardiography. Thus, if contrast agent appears in the pericardial space, the procedure can be continued.
- A guidewire should be advanced through the sheath, and then the sheath should be removed over the guidewire.
- A small incision should be made at the entry site, followed by introduction of a dilator (6F to 8F) over the guidewire. Predilatation of the chest wall passage facilitates subsequent insertion of the introducer sheath-dilator (6F to 8F).
- The guidewire and the dilator should be removed and only the sheath left in the pericardial sac. A pigtail angiocatheter should be inserted through the introducer sheath and the fluid aspirated.

Real-Time Echo-Monitored Procedure (B)

(This is the technique preferred by the authors.)

See Video E9-1.

- A different approach utilizes a needle carrier mounted on the transducer to advance the needle to the pericardial space under continuous visualization.
- Patient's preparation and supportive management are the same as those described earlier.
- Mount the bracket on the probe to support the needle-guide kit and to allow a real-time echo-monitored procedure. The bracket supports the needle with different angles, and the operator can choose between a closer angle for the subcostal approach and a wider angle for the apical approach (Fig. E9-2).
- Cover the probe with the sterile sheath and mount the needle-guide kit on the sheathed probe (Fig. E9-3).
- Once the optimal position is found and the pericardiocentesis procedure is started, the echocardiography probe should not be

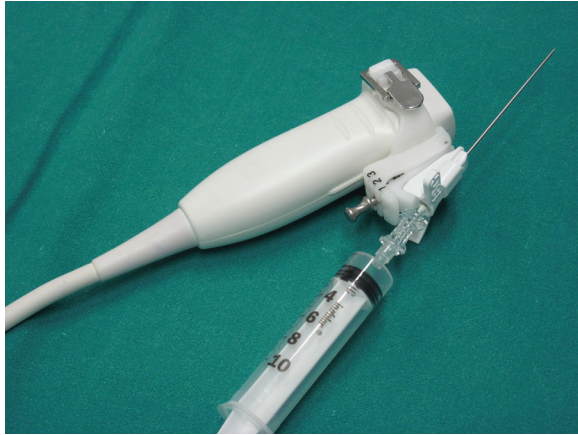


FIGURE E9-2 ■ Echocardiographic probe with bracket, needle guide, and syringe.



FIGURE E9-3 ■ After bracket is mounted, probe is protected by sterile wrap.

more mobilized to avoid tearing the tissue. The execution of the technique with two operators can be useful to minimize this risk; one can firmly hold the probe, and the other can advance the needle. The needle (SDN 18-gauge, 9-cm Cook for apical approach, or the needle included in the PeriVac set for subxiphoid approach) is connected to a syringe for constant gentle aspiration and is slowly introduced through the tissues until there is echographic visualization of the tip (Fig. E9-4, A-C).

- When the needle tip is observed on the echo screen in the pericardial space and fluid is freely aspirated, the syringe is disconnected, and a J-tipped guide is inserted (Fig. E9-4, D).
- The technique is summarized in Figure E9-5.
- Remove the needle and make a small skin incision at the site of insertion.
- The drainage catheter (a pigtail angiocatheter 6F to 8F or pericardiocentesis set [PeriVac]) is subsequently introduced along the guidewire, according to the Seldinger technique, after introducing a 6F to 8F dilator over the guidewire.
- Completely aspirate the pericardial effusion by syringe suction, and connect the catheter to a disposable flushing system that infuses saline solution at a rate of 3 mL/h to maintain the patency of the system.

- In patients with very large pericardial effusion (>1 L), quick emptying of the pericardial sac may cause (in very rare cases) an acute pulmonary edema. In these patients, it may be advisable to limit aspiration to 1 L every 24 hours.

AFTER PROCEDURE

Postprocedure Care

- After the procedure, perform a chest radiography to exclude the presence of pneumothorax or pneumopericardium.
- Repeat aspiration by syringe every 4 to 6 hours.
- Remove the catheter once the drainage has decreased to less than 25 to 30 mL in 24 hours.
- Pericardial drainage for 24 to 72 hours is sufficient to avoid recurrence of pericardial tamponade in the majority of cases.
- It is important to empty the pericardial sac as completely as possible, leaving the catheter in place up to 72 hours (or more) if the fluid has a rate of accumulation greater than 30 mL in 24 hours.
- The omission of extended catheter drainage is an important independent predictor of recurrence.
- Reaccumulation of pericardial fluid is common in patients with malignant pericardial effusions (40%-70% recurrences rate without specific treatment). In these patients, several measures have been suggested to prevent recurrence of tamponade. These approaches include (1) complete evacuation of the fluid, (2) prolonged pericardial drainage, and (3) systemic antineoplastic treatment as baseline therapy. Other suggested measures are intrapericardial instillation of sclerosing and cytotoxic agents tailored to the type of tumor, radiation therapy in patients with radiosensitive tumors (i.e., lymphomas and leukemias), and pericardiectomy.
- Perform a complete echocardiographic study in all patients before removing the catheter and before the discharge from the ICU or coronary care unit.

Complications

- Common
 - Puncture of cardiac chambers (1.5%)
 - Pneumothorax (1%)
 - Pleuropericardial fistulas (0.8%)
 - Arrhythmias (usually vasovagal bradycardia)
- Infrequent
 - Laceration of coronary arteries or intercostal vessels
 - Bacteremia
 - Pneumopericardium
- Serious, rare complications
 - Death (0.1%-0.5%)
 - Chamber laceration requiring surgery

In a series of 53 pericardiocenteses performed under continuous echocardiographic visualization (technique B), no major complications occurred, no perforations or ruptures of cardiac chambers were reported, and the incidence of minor complications was 3.7%.

OUTCOMES AND EVIDENCE

- Randomized studies comparing different techniques do not presently exist.
- Pericardiocentesis-related mortality and serious complications are low when the procedure is performed by trained professionals following consolidated techniques.
- Percutaneous pericardiocentesis has been performed for many years using the blind subxiphoid approach. This technique is associated with high incidence of morbidity and mortality, and using electrocardiographic needle monitoring does not lead to significantly better outcomes. Accordingly, blind approaches are no longer justified.

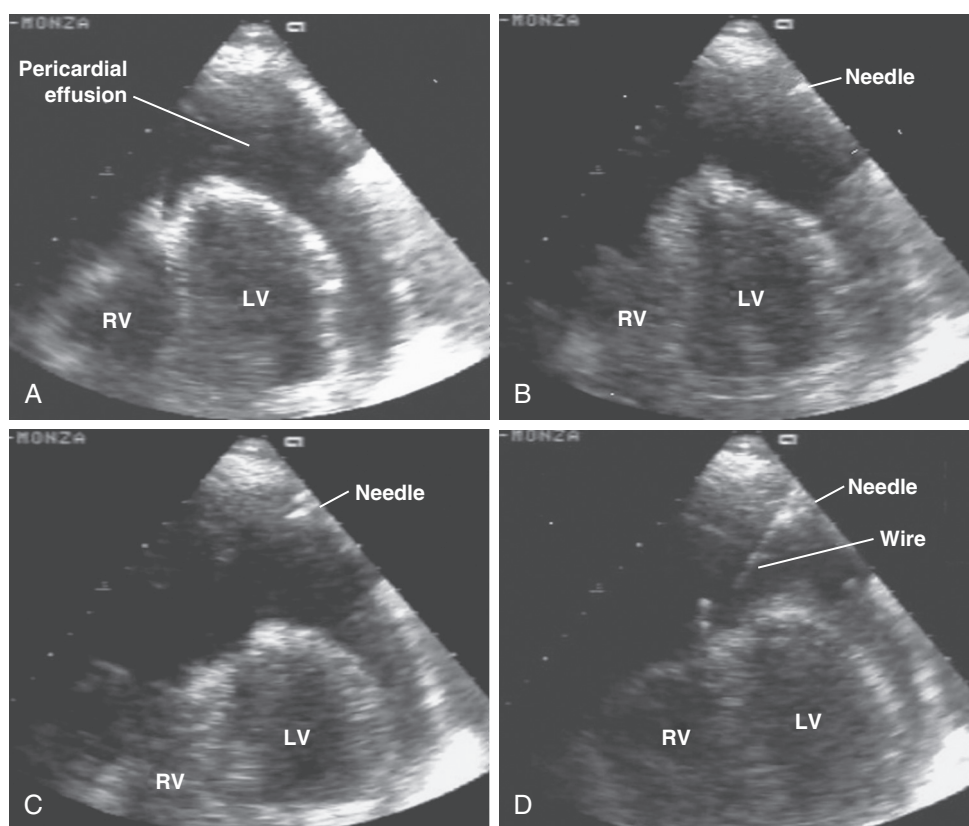


FIGURE E9-4 ■ Two-dimensional echocardiographic image (apical four-chamber view) during needle introduction through tissues. **A**, Detection of pericardial effusion. **B**, Visualization of needle tip. **C**, Needle is advanced through tissues. **D**, Needle enters pericardial space and guidewire is introduced. LV, left ventricle; RV, right ventricle. (From Maggiolini S, Bozzano A, Russo P, et al: Echocardiography-guided pericardiocentesis with probe-mounted needle: report of 53 cases. *J Am Soc Echocardiogr* 2001;14:821-824.)

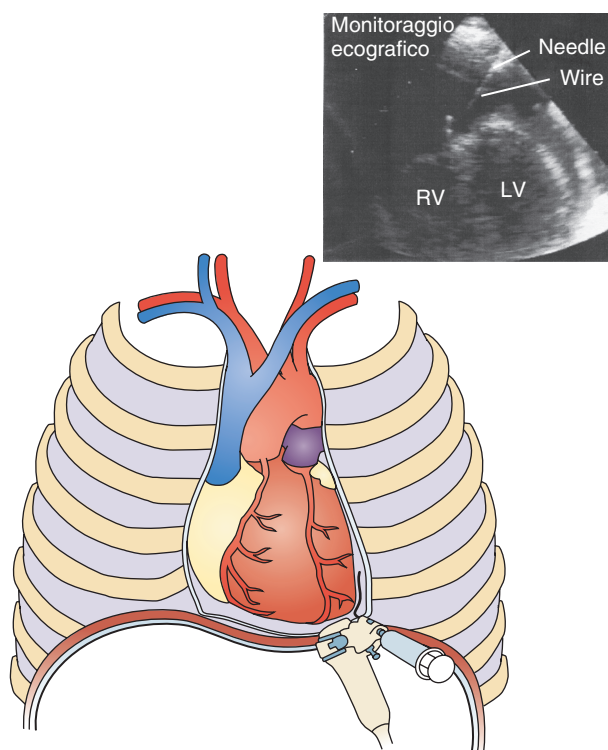


FIGURE E9-5 ■ Representation of pericardiocentesis using the apical approach. The pericardial needle is continuously monitored by apical four-chamber echocardiographic view while entering the pericardial space. When the pericardial effusion is reached, a guidewire is introduced in the pericardial space.

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■ PARACENTESIS: BEFORE PROCEDURE

Indications

- Paracentesis is the insertion of a needle or catheter into the peritoneal cavity for the purpose of aspirating peritoneal fluid. It is most often indicated for diagnostic or therapeutic evacuation of ascites.
- Diagnostic indications
 - New-onset ascites: fluid evaluation to help determine etiology, differentiate transudate versus exudate, detect the presence of cancerous cells, or address other considerations
 - Differentiate between suspected spontaneous or secondary bacterial peritonitis
- Therapeutic indications
 - Respiratory compromise secondary to ascites
 - Abdominal pain or pressure secondary to ascites (including abdominal compartment syndrome)

Contraindications

- Absolute contraindication
 - Acute abdomen that requires surgery
- Relative contraindications
 - Inadequate volume of ascites on imaging (e.g., ultrasound)
 - Uncorrected hypovolemia
 - Severe uncorrected thrombocytopenia (platelet count < 20,000/ μ L) or coagulopathy (international normalized ratio [INR] > 2.0)
 - Pregnancy
 - Distended urinary bladder
 - Abdominal wall cellulitis
 - Distended bowel
 - Intraabdominal adhesions

Equipment

- Ultrasound machine
- Local anesthetic
- Chlorhexidine prep
- Sterile towels, gloves
- 18- or 20-gauge, 2- to 3-inch needle
- 20- to 50-mL syringe
- 14- to 16-gauge cannula-over-needle
- 8.5F 40-cm polyurethane pigtail catheter with guide wire
- 2-0 polypropylene suture

■ ANATOMY

The site for paracentesis is in the abdomen, lateral to the rectus muscle in the lower quadrant midway between the umbilicus and the anterior superior iliac spine, avoiding prior surgical incisions. Ultrasound guidance is recommended to identify the site of the largest volume of ascites and reduce the chance of injury to the intestines.

■ PROCEDURE

See Video E10-1.

- The patient should be supine. Bedside ultrasonography can be a valuable aid for localizing the largest collection of ascites and

avoiding injury to the bowel and should be employed routinely. The patient should void or have a urinary bladder drainage tube inserted before the procedure. The area is cleansed, draped, and anesthetized.

- When a small volume of ascitic fluid is needed for diagnostic studies, an 18- or 20-gauge, 2- to 3-inch needle attached to a 20- to 50-mL syringe is inserted into the abdomen lateral to the rectus muscle in the lower quadrant, midway between the umbilicus and the anterior superior iliac spine, avoiding prior surgical incisions. The skin is retracted caudad while inserting the needle. When fluid is aspirated, the needle is stabilized, and the fluid sample is obtained by syringe. After removal of the needle, the skin is released, causing the entrance and exit needle sites to form a “Z-track” that reduces the chance of ascitic fluid leakage.
- For large-volume paracentesis, a 14- to 16-gauge cannula-over-needle is employed. Once the fluid is aspirated into the syringe, the needle is removed, leaving the plastic catheter in place, which is attached to plastic tubing and a vacuum canister. Usually, 4 to 6 L of ascites can be safely removed, although larger volumes have also been obtained.
- If it is necessary to place a catheter into the peritoneal cavity, a guide wire should be inserted into the peritoneal cavity through the needle; an 8.5F 40-cm polyurethane pigtail catheter should be guided into the peritoneal cavity over the wire and sutured in place.
- The aspirated fluid should be submitted for a cell count, absolute polymorphonuclear neutrophil count, albumin, total protein concentration, Gram stain, and cultures. Optional studies, based on clinical suspicion, may include glucose concentration, amylase concentration, lactate dehydrogenase concentration, bilirubin concentration, and cytology.

■ AFTER PROCEDURE

Postprocedure Care

- The patient should be closely monitored for complications (see later), especially bleeding and peritonitis.
- If a pigtail catheter is left in place, it should be attached to a collection bag and monitored for bleeding or the drainage of succus.

Complications

- Common
 - Hypotension
 - Hypotension after paracentesis in cirrhotic patients can be associated with a worsening of arteriolar vasodilation.¹ In the first few hours after large-volume paracentesis, there is a reduction in the plasma levels of renin and aldosterone, an increase in the atrial natriuretic peptide concentration, a reduction in the cardiac filling pressures, and an increase in the cardiac index.
 - However, after 12 to 24 hours, these changes reverse, reflecting effective hypovolemia. Infusion of intravenous colloids, specifically albumin, has been shown to attenuate the hemodynamic consequences of paracentesis and the associated neurohumoral alterations.² However, no large randomized study has shown that routine expansion of plasma volume with a colloid solution confers a survival advantage.

- Infrequent
 - Bleeding
 - The incidence of significant hemorrhage from this procedure is about 1%, despite the fact that over 70% of patients have clotting parameter abnormalities.³ Therefore, it is usually unnecessary to normalize the prothrombin time before proceeding.⁴
- Serious complications (e.g., bowel perforation) are rare (0.1%)³
 - Peritonitis
 - Bowel injury
 - Injury to the bladder
 - Injury to the epigastric vessels

OUTCOMES AND EVIDENCE

- Determining the etiology of ascites is based on the patient's history, physical examination, liver function tests, ultrasonography, and ascitic fluid analysis. Abdominal paracentesis and ascitic fluid analysis should be an early step in the workup of patients with new-onset ascites. Paracentesis is also important to diagnose infection of the ascitic fluid (i.e., peritonitis).
- Development of ascites is a common complication of cirrhosis, being more frequent than either encephalopathy and variceal hemorrhage in these patients. The median survival of cirrhotic patients with ascites is 2 years.⁵ Other causes of ascites besides cirrhosis include malignancy, heart failure, tuberculosis, renal failure, and pancreatic disease.
- The mainstays of treatment of ascites secondary to cirrhosis involve dietary sodium restriction (2 g/d) and oral diuretics (e.g., spironolactone and furosemide).
 - The underlying etiology of liver disease should be corrected when possible, and ethanol consumption should be strongly discouraged. Abstinence from ethanol can normalize portal venous pressures in some patients with early ethanol-induced liver disease.⁶
 - Patients with early cirrhosis and diuretic-responsive ascites should not be managed by serial paracentesis; rather, medical management should be employed. In the majority of patients, ascites can be controlled with medical management.
 - In 5% to 10% of patients, ascites becomes resistant to medical treatment. The standard of care for the management of refractory ascites is therapeutic paracentesis. This can be performed as often as every 2 weeks to control symptomatic ascites.
 - Other options for managing refractory ascites include transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation. In a randomized trial of 60 patients comparing TIPS with repeated therapeutic paracentesis, the probability of survival without liver transplantation at 2 years was 58% in the TIPS patients as compared with 32% in the paracentesis patients.⁷ A smaller study of 25 patients randomized to TIPS or paracentesis demonstrated the opposite: mortality was higher in the TIPS group.⁸
 - Surgical portosystemic and peritoneovenous shunts have fallen out of favor because of the high incidence of morbidity and mortality and the development of hepatic encephalopathy.
 - For patients with tense ascites, large-volume paracentesis rapidly relieves intraabdominal pressure. A single 4- to 6-L paracentesis can be performed safely and often does not require an infusion of colloids.⁹ However, paracentesis does nothing to correct the etiology of the ascites, and ascites will recur if sodium restriction and diuretics are not instituted or fail. Referral for liver transplant evaluation should be considered for eligible patients with cirrhosis and refractory ascites.
 - Infection of ascitic fluid often occurs in cirrhotic patients. When there is no surgically correctable etiology (e.g., perforated viscus), the term *spontaneous bacterial peritonitis* is used. This diagnosis is made when there is a positive ascitic fluid culture or an ascitic fluid polymorphonuclear (PMN) cell count greater

than 250 cells/mm³ in the correct clinical scenario without any evidence for an intraabdominal, surgically correctable etiology. The infection is usually monomicrobial. Polymicrobial infection suggests secondary peritonitis. Consideration of the diagnosis mandates paracentesis and evaluation of the ascitic fluid; a clinical diagnosis without paracentesis is inadequate.

DIAGNOSTIC PERITONEAL LAVAGE: BEFORE PROCEDURE

Indications

- With the widespread use of focused abdominal sonography for trauma (FAST), the indications for diagnostic peritoneal lavage (DPL) are decreasing.
- Patients who have sustained blunt trauma and have no overt signs of acute abdominal injury or bleeding but require an evaluation to rule out intraabdominal hemorrhage or hollow viscus injury
- Patients who are not candidates for computed tomography (CT) (e.g., because of hemodynamic instability) or when FAST is unavailable or yields equivocal results

Contraindications

- The only absolute contraindication to performing a DPL is the clinical condition of the patient mandating immediate laparotomy.
- Relative contraindications include previous abdominal surgery, cirrhosis, obesity, and coagulopathy.
- In patients with pelvic fractures or pregnancy, a supraumbilical incision should be performed.

Equipment

- Local anesthetic
- Chlorhexidine prep
- Sterile towels, gloves
- 10-mL syringe
- 8F to 9F 25-cm lavage catheter
- 2-0 polypropylene suture

ANATOMY

DPL should be performed in the midline of the abdomen immediately below the umbilicus, or above the umbilicus in patients with a pelvic fracture, suspected pelvic hematoma, or pregnancy. Prior surgical incisions should be avoided if possible.

PROCEDURE

- The patient should be in the supine position. Gastric and bladder decompression tubes should be inserted to minimize the risk of injury to these organs. The periumbilical skin should be prepped and draped sterilely. Local anesthesia is injected into the site.
- DPL can be performed with an open, semiopen, or closed technique.
 - The open technique employs a midline infraumbilical abdominal incision 2 to 5 cm in length; the incision should be supraumbilical if the patient has a pelvic fracture or is pregnant. A small incision is made in the midline abdominal fascia and peritoneum. An 8F to 9F 25-cm lavage catheter with side holes is inserted under direct visualization toward the pelvis.
 - The closed method uses a Seldinger technique. A 16-gauge, 3-inch needle is inserted through a skin puncture and into the peritoneal cavity. A guide wire is passed through the needle into the peritoneal cavity. The lavage catheter is inserted over the wire.
 - The semiopen technique involves incising the skin and fascia and then using a guide wire technique for inserting the catheter into the peritoneal cavity.

- Once the catheter is placed, aspiration should be attempted with a syringe.
- If 10 mL of blood is aspirated, the DPL is considered positive, and appropriate surgical intervention should be undertaken.
- Otherwise, 1 L of crystalloid solution is infused (10 mL/kg in pediatric patients) and then retrieved by gravity and sent to the laboratory for analysis.
- In general, the DPL is considered positive in blunt-trauma patients if
 - Red blood cell (RBC) count is greater than 100,000/mm³
 - White blood cell (WBC) count is greater than 500/mm³
 - Amylase concentration is greater than 100 IU/L
- Other positive findings include the presence of bile or food particles or the drainage of lavage fluid from the bladder drainage catheter, gastric tube, or thoracostomy tube.
- The sensitivity and specificity of the test are dependent on the threshold criteria for determining a positive test result.
- If the lavage is negative but there is a high index of suspicion for intraabdominal pathology, the DPL catheter can be left in place for repeat lavage to rule out delayed hemoperitoneum or intestinal perforation.

AFTER PROCEDURE

Complications

- Infrequent
 - Bowel or vascular injury occurs in less than 1%.¹⁰
 - Bladder injury
 - Bleeding (cause for a false-positive DPL result)
 - Wound infection

OUTCOMES AND EVIDENCE

- Evaluation of the abdomen is a critical component in the assessment of injured patients. Failure to identify intraabdominal injury results in preventable morbidity and mortality in trauma patients. The physical examination for abdominal injury is often hampered by alterations of the sensorium by substances (e.g., ethanol and illicit drugs), injury to the central nervous system, or pain from other injuries. Moreover, a significant amount of blood can be present in the peritoneal cavity without obvious abdominal distention or peritoneal signs.
- DPL, CT, and ultrasonography have emerged as the main diagnostic modalities to evaluate trauma patients and currently have complementary roles. DPL was introduced by Root and colleagues in 1965 for the evaluation of abdominal trauma.¹¹
 - In the era before CT and ultrasonography, DPL was the first well-established method to identify hemoperitoneum in trauma patients.
 - DPL is primarily useful in diagnosing hemoperitoneum from blunt, solid-organ injury, but it can also be helpful for the diagnosis of hollow viscus injury.
- For *hemodynamically stable* patients with an equivocal abdominal examination, associated neurologic injury, or painful injuries, abdominal CT is recommended as the diagnostic modality of choice and has all but eliminated the need for DPL in these patients.
 - CT is also the preferred diagnostic method for determining whether nonoperative management of a solid-organ injury is appropriate.
 - Furthermore, in stable patients with a positive DPL, a follow-up abdominal CT should be considered. Thus, CT and DPL play complementary roles in evaluating stable patients following blunt abdominal trauma.
- For *hemodynamically unstable* patients, FAST and DPL are the preferred tests, with FAST rapidly gaining acceptance over DPL in many trauma centers as the preferred initial diagnostic modality.

- FAST and DPL are used to rule out hemoperitoneum as the cause of hemodynamic instability.
- In contrast to DPL, FAST can be used to identify pericardial tamponade.
- These tests can be performed expeditiously, and ongoing efforts at resuscitation and evaluation can occur simultaneously with the performance of the test.
- Since resuscitation is difficult during CT, CT is contraindicated when patients are hypotensive or hemodynamically unstable.
- DPL is also useful in certain clinical scenarios. Consider, for example, a head-injured patient needing an emergency craniotomy: DPL can be performed in the operating room at the same time as the craniotomy without interfering with the neurosurgical procedure.
- Controversy exists regarding the best way to manage blunt trauma patients with isolated evidence of free intraabdominal fluid by CT but without evidence of solid-organ injury.
 - In a review of the literature, isolated free fluid was observed in 2.8% of over 16,000 blunt trauma patients studied with CT.¹² Of these, only 27% underwent a therapeutic laparotomy, so some experts recommend serial abdominal examinations, whereas others recommend surgical exploration to rule out hollow viscous injury.
 - DPL can be useful in the evaluation of patients with suspected perforated viscus. Very early after bowel perforation, the WBC count in the lavage fluid may be low; however, within a few hours after injury, the degree of inflammation is usually sufficient to increase the WBC count in the lavage fluid to greater than 500 cells/mm³. The presence of bile, amylase, bacteria, or food particles in the lavage fluid also confirms intestinal perforation.
- The use of DPL in the evaluation of hemodynamically stable patients with penetrating abdominal wounds remains controversial.
 - A significant number of missed injuries remain undetected by this method. For example, Kelemen et al.¹³ reported a 21% false-negative rate for stable patients with abdominal gunshot wounds. Using a low RBC threshold (1000/mm³) has been described in an attempt to overcome this shortfall.¹⁴
- False-positive DPL leading to unnecessary laparotomy may occur in as many as 30% of cases.^{10,15} This problem can be reduced by using CT as a complementary test in stable patients. The false-negative rate (i.e., failure to diagnose hemoperitoneum) is low. However, DPL is unable to detect retroperitoneal injuries (CT is the preferred test to detect retroperitoneal injuries for the stable patient) and is insensitive for detecting early hollow viscous and diaphragmatic injuries.
- One of the major problems with DPL is that the test is too sensitive. Only about 30 mL of the blood in the peritoneal cavity is necessary to produce a positive DPL. In this era of selective management of solid-organ injuries, a significant number of nontherapeutic laparotomies would be performed on the basis of these DPL results unless the diagnostic evaluation includes other modalities as well.
- Proponents of the open technique argue that it is safer, whereas proponents of the closed and semiopen methods argue that these approaches are more expeditious and can be safely performed by appropriately trained individuals.
- A large meta-analysis that aggregated the results from 1126 patient trials showed that the incidence of major complications is not different for the diverse DPL techniques.¹⁶
- Failure to properly place the catheter and technical difficulties were more likely to occur with the closed method, whereas the procedure time was shorter with the open method (17.8 vs. 26.8 minutes, respectively).
- Sensitivity, specificity, and accuracy were not different between the various methods of catheter insertion.

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DIAGNOSTIC PERITONEAL LAVAGE

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■ BEFORE PROCEDURE

Indications

- Pleural effusion is not explained by the clinical presentation
- Massive pleural effusion with impending respiratory failure
- Suspected pleural space infection
- Suspected complication of pneumonia (empyema)
- Suspected hemothorax

Contraindications

- Absolute
 - Lack of expertise
 - Severe uncorrectable coagulopathy (platelet count < 25,000 cells/ μ L; international normalized ratio [INR] > 2.0)
 - Azotemia (creatinine > 6 mg/dL)
 - Uncooperative patient
- Relative
 - Operator-dependent and of technical nature
 - Lack of image guidance to determine the safety of the puncture site

Equipment

- Diagnostic thoracentesis
 - Iodophor- and chlorhexidine-containing antiseptic
 - 10- and 30-mL sterile syringes
 - 21-gauge needle
 - 21-gauge spinal needle may be needed for obese patients
 - 1% lidocaine for use as local anesthetic
- Therapeutic thoracentesis
 - Commercially available catheter-over-needle system

■ ANATOMY

The pleura is a serous membrane that covers the lung parenchyma, mediastinum, diaphragm, and rib cage. The pleura is divided into the visceral and parietal pleura. The visceral pleura covers the lung parenchyma, as well as the interlobar fissures. The parietal pleura lines the inside of the chest wall and the diaphragm. As pleural fluid forms, separation of the visceral and parietal pleural occurs, creating a space for a needle to be placed safely. Free-flowing pleural fluid will collect through gravitational effects in dependent areas. Thus, if a patient is sitting upright, pleural fluid will collect along the diaphragm and the costophrenic and cardiophrenic angles. In contrast, in a supine patient, pleural fluid will collect along the posterior aspects of the lung.

The parietal pleural receives its blood supply from the systemic capillaries of the intercostal arteries supplying the costal pleura, whereas the mediastinal pleura is supplied by the pericardiophrenic artery. The diaphragmatic pleura is supplied by the superior phrenic and musculophrenic arteries. The bronchial arteries likely supply the visceral pleura. The intercostal artery, vein, and nerve travel below the ribs. It is important to understand that the neurovascular bundle is not protected by the phalange of the rib within the first 8 to 10 cm from the origin of the vessels and nerves from the spine. Performing a

thoracentesis near the spine increases the risk of intercostal artery laceration and hemothorax.

■ PROCEDURE

See Video E11-1.

- Obtain informed consent.
- Place patient in a sitting position if hemodynamically stable, or move the patient to the edge of the bed, with the head of the bed elevated to a 30- to 45-degree angle.
- Perform thoracic ultrasonography, and mark the puncture site.
- The upper margin of the rib immediately below the access area should be defined by palpation (may be impossible with obesity).
- The area should be disinfected with an iodophor- or chlorhexidine-containing antiseptic.
- Use 1% lidocaine without epinephrine for local anesthesia.
- Perform the procedure under sterile conditions at this point.
- Inject lidocaine subcutaneously into the periosteum of the rib and the parietal pleura, ensuring that the upper margin of the rib is identified and anesthetized.
- The upper margin of the rib should be identified with a 21-gauge needle before placing a thoracentesis catheter for a therapeutic procedure.
- Accessing the pleural space over the upper margin of the rib (should be identified) places the needle at a greater distance from the intercostal vessels and nerves.
- Always maintain the needle angle perpendicular to the patient.
- Once the pleural fluid is aspirated, retract the needle outside the pleural space.
- Place a 30- to 60-mL syringe onto the needle, and advance into the pleural space to collect the specimen.
- If therapeutic thoracentesis is desired, withdraw the needle after the pleural fluid is clearly aspirated.
- If fluid cannot be obtained with a small-gauge needle, no attempts at placing a thoracentesis catheter should be made.
- Insert the catheter-over-needle system under continuous application of suction until the pleural fluid is aspirated.
- Once the pleural fluid is obtained, advance the catheter system another 1 cm to place the catheter with its maximum diameter in the pleural space.
- Without advancing the needle, strip the catheter into the pleural space, and remove the needle.
- To prevent air entry into the pleural space, turn the thoracentesis stopcock off as related to the patient.
- Finally, connect the drainage tubing and collection bag to the thoracentesis catheter.
- To prevent the development of excessively negative pleural pressures in ventilated patients, draining large amounts of pleural fluid is not recommended unless pleural manometry is performed.

■ AFTER PROCEDURE

Postprocedure Care

- A postprocedure chest radiograph should be performed on all ventilated patients.

- Monitor for signs of tension pneumothorax and hemothorax
 - Hypotension
 - Worsening lung compliance in ventilated patients
 - Tube thoracostomy is required for all patients who develop a pneumothorax on mechanical ventilation.

Complications

- Common
 - A cough due to lung reinflation
 - Anterior chest pain in the setting of an unexpandable lung
 - Pain at the puncture site
 - Seroma or hematoma at the puncture site
 - Pneumothorax (up to 30% for non-image-guided procedures)
- Infrequent
 - Pneumothorax with image guidance reported between 0% and 3%
 - Inadvertent puncture of subdiaphragmatic structures (e.g., liver and spleen)

- Hemothorax
- Serious, rare complications
 - Pneumothorax
 - Tension pneumothorax
 - Intercostal artery laceration
 - Hemothorax
 - Reexpansion pulmonary edema
 - Hypotension

OUTCOMES AND EVIDENCE

- Feasibility and safety of ultrasound-guided thoracentesis in mechanically ventilated patients are strongly supported by the literature.
- Clinically directed thoracentesis should not be performed in mechanically ventilated patients.
- Bedside ultrasonography is the preferred modality for diagnosis of pleural effusion in the critically ill patient.

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BEFORE PROCEDURE

Indications

- Most commonly undertaken to treat one of the following conditions
 - Pneumothorax
 - Pleural fluid collection
 - Hemothorax
 - Simple effusion
 - Empyema
- Can be both a diagnostic and a therapeutic maneuver

Contraindications

- In an emergent situation (i.e., tension pneumothorax), there are no contraindications.
- In a nonurgent situation, caution should be exercised in the presence of
 - Known or suspected adhesions
 - Prior chest surgery or trauma
 - History of pleural space infection
 - Intrinsic parenchymal disease
 - Complex, loculated air or fluid collection(s)
 - Typically noted on imaging studies
- In situations where insertion is not emergent and is anticipated to be difficult, consideration to placement by a skilled operator (surgeon) or under image guidance (computed tomography [CT], ultrasound) is recommended.

Equipment

- Chest tube of appropriate size and configuration (Fig. E12-1)
 - In general, larger tubes are required to drain blood, pus, or viscous fluid, and smaller tubes (i.e., pigtail catheter) may suffice for a simple effusion or pneumothorax.
 - Sizes range from 20F to 40F for adults and 6F to 26F for pediatric patients.
 - Straight tubes most commonly placed in the emergency department or intensive care unit.
 - Right-angled tubes are available but typically are placed by surgeons in the operating room.
- Commercially available collection system (Fig. E12-2)
 - Includes the following components
 - Plastic connector of at least 0.25-inch diameter to connect the chest tube to the accessory tubing (a Y connector may be used in the case of multiple chest tubes, but caution is advised because these are prone to occlusion and subsequent drainage failure).
 - Accessory tubing (generally 0.5 inch in diameter and 6 feet long)
 - Drainage system (composed of a trap, water seal, and manometer compartments)
- Wall vacuum source with connection tubing
- Prepackaged chest tray
 - At a minimum, should contain a scalpel and a clamp (large Kelly clamp or hemostat)

- Skin antiseptic
- Sterile drapes
- Sterile gown and gloves, mask, and cap
- Local anesthetic
- Intravenous narcotic and/or sedative
- Suture material (commonly 0 silk)
- Gauze
- Tape

ANATOMY

Entry into the pleural space should generally be gained via a location based on ease of access, safety, and avoidance of complications. The American College of Surgeons Committee on Trauma recommends drain insertion between the anterior and posterior axillary lines at a level with or just above the fifth intercostal space (nipple level). In this location, the chest wall is thinnest, and the operator can avoid the pectoralis major muscle and breast parenchyma (anteriorly), the latissimus dorsi muscle (posteriorly), the axillary vessels/brachial plexus (superiorly), and the diaphragm/intraabdominal contents (inferiorly). Within the intercostal space, coursing along the inferior surface of each rib is the neurovascular bundle. Insertion of the tube over the superior aspect of the rib is recommended so that injury to these structures can be avoided (Fig. E12-3). From superficial to deep, one will first encounter skin, followed by a variable amount of subcutaneous tissue, the superior surface of the rib, the intercostal space with its musculature, and finally the parietal pleura. The pulmonary parenchyma and mediastinal structures are deep to the parietal pleura, so it is important to avoid overzealous insertion of the chest tube. In some instances (e.g., a loculated collection), specialized placement may be required, and the assistance of a surgeon or insertion under image guidance is encouraged.

PROCEDURE

See Video E12-1.

- If nonemergent, perform a “time-out” to verify the indication(s), review the relevant imaging and coagulation studies, and confirm the correct patient and laterality.
 - A procedural checklist may be helpful and has been shown to reduce errors and decrease complications.
- Obtain necessary equipment (see earlier), and fill the water seal compartment of the collection system with water.
- Position as follows
 - Supine or slight elevation of the head of the bed
 - Ipsilateral arm behind the head or abducted
 - Bed at comfortable height for the operator
 - Ensure adequate lighting.
- Practice aseptic technique, and apply Universal Precautions.
- Prep the area broadly with skin antiseptic.
- Drape widely such that anatomic landmarks (e.g., the nipple) are visible.
- Plan the skin incision to overlie the rib just inferior to the chosen intercostal space (i.e., if entering the fifth interspace, place the incision along the superior aspect of the sixth rib).
- Consider premedication with a narcotic or anxiolytic.



FIGURE E12-1 ■ Standard chest tube (*top*) with trocar (*middle*) and angled chest tube (*bottom*) without trocar.

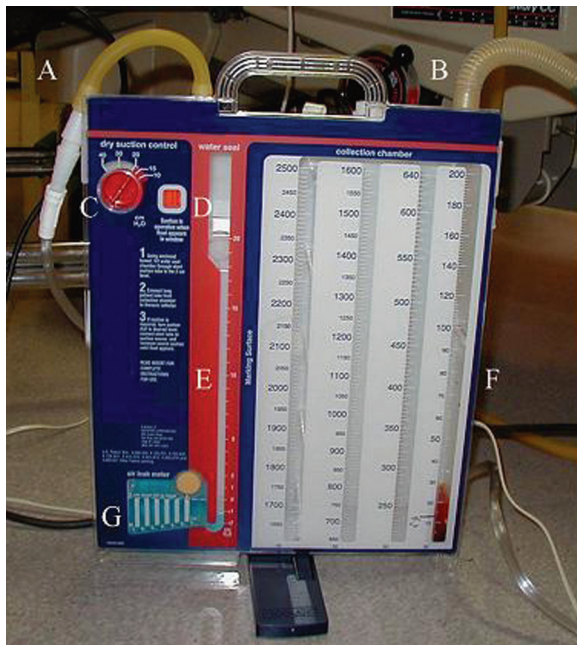


FIGURE E12-2 ■ Modern chest drainage system. **A**, Accessory tubing to wall suction. **B**, Accessory tubing to chest tube/patient. **C**, Suction control. **D**, Float indicating suction is operative. **E**, Water seal chamber. **F**, Collection chamber. **G**, Air leak meter.

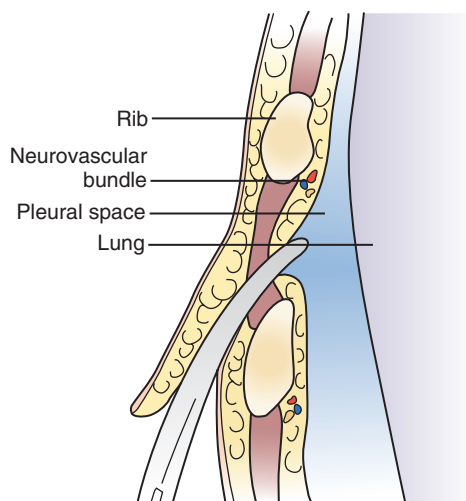


FIGURE E12-3 ■ Use of Kelly clamp to enter pleural space.

- Inject local anesthetic (apply aspiration at all times)
 - First anesthetize the skin.
 - Then angle the needle slightly cephalad to anesthetize the periosteum of the rib and the deeper tissues.
 - Several passes may be required to cover an area 1 to 2 cm in diameter.
 - If air or fluid is aspirated, retract the needle while aspirating it until it ceases and then inject additional local to anesthetize the parietal pleura.
- Make an incision large enough to accommodate the operator's index finger and chest tube at the same time.
- Bluntly dissect (with index finger and/or Kelly clamp) along an oblique path angled superiorly to the chosen intercostal space, with care taken to remain on the superior border of the rib (see Fig. E12-3).
- If the patient is on a ventilator, hold respirations temporarily.
- Gently enter the pleural space with the tip of the clamp.
 - Avoid excessive clamp insertion to minimize injury to deeper structures.
 - Typically will feel a pop and get return of air and/or fluid
- Open the clamp slightly to sufficiently enlarge the opening into the pleural space.
- Insert index finger to confirm entry into the pleural space.
 - Should be able to palpate parietal pleura and, at times, the lung
 - Note the presence of any adhesions (seen in up to 15% of cases).
- We recommend discarding the chest tube trocar and grasping the end of the tube with the Kelly clamp to facilitate safer insertion.
- Insert index finger alongside the chest tube, and guide the tube into the pleural space away from the lung parenchyma.
 - Though it is recommended to direct the tube anteroapically for a pneumothorax and posterobasally for fluid, exact location within the pleural space is probably not important in most cases.
 - Ensure that the last drainage hole is well within the pleural space.
- Connect the tube immediately to the collecting system.
- If suction is desired, adjust the wall vacuum source to provide slow, consistent bubbling.
 - Typically, the collection system is set initially to -20 cm H_2O suction.
- Secure the tube to the skin at the exit site with sutures (avoid a purse-string stitch).
- Cover the wound with dry gauze and tape.
- Obtain a chest x-ray to document proper placement, evaluate expansion of the lung, and assess for residual pleural fluid or air.

AFTER PROCEDURE

Postprocedure Care

- Daily assessment
 - System must remain upright and should be kept below chest level.
 - The accessory tubing should be in a straight or coiled position and not kinked.
 - Be certain the water level in the system is maintained.
 - If suction is being used, verify the proper setting and confirm that it is functional (the float should be visible in the window).
 - Note the amount of drainage, presence of bubbling, and respiratory variation.
- Troubleshooting
 - Observation of synchronous water seal and motion with respiration suggests the tube is still functioning in the pleural space and that all connections are tight.
 - If the tube is not functioning and occlusion of the drainage holes is suspected
 - Disconnect and flush with normal saline
 - Consider fibrinolytics (particularly if a parapneumonic effusion is present)

- If an air leak within the system is suspected
 - Sequentially clamp the accessory tubing with distal suction applied. The leak will cease when a clamp is placed proximal to the site, and the problem can then be addressed.
 - If the accessory tubing or the connections are not the problem, check the insertion site. If the skin incision is too large, the leak may be audible and can readily be addressed with an additional stitch. Also, be certain the last drainage hole has not migrated out of the pleural space.
 - If neither of the above identifies the problem, a major airway injury or bronchopleural fistula may be to blame.
- Removal
 - Should be performed once the indication for tube thoracostomy has resolved
 - Will vary somewhat according to the patient population and the indication for insertion
 - For simple pneumothorax, hemothorax, or pleural effusion, we recommend
 - Placement of the tube on -20 cm H_2O suction initially to facilitate lung reexpansion and/or evacuation of fluid.
 - Suction may not be required in some patient populations (i.e., those without underlying lung disease or who do not require mechanical ventilation).
 - Continue suction until the lung is reexpanded and there is no air leak. Then convert to water seal.
 - Obtain a radiograph on water seal to confirm lung expansion.
 - Remove when drainage is negligible (<150 - 200 mL per day).
 - For empyema, the infectious process must be resolved, there should be no residual empyema cavity on imaging studies, and drainage must be scant prior to removal.
 - It is common for empyema tubes to remain in place for weeks.
 - In lung resection patients, management is more complex because the routine use of suction may potentiate air leaks. We recommend consultation with the patient's surgeon regarding management of the tube(s).
 - The timing of chest tube removal relative to the respiratory cycle (i.e., end inspiration or end expiration) does not appear to be important, even in ventilator-dependent patients.
 - Although routine chest radiography after removal is not a universal practice, we recommend obtaining one within 4 hours of removal to confirm lung expansion.
 - Routine clamping of chest tubes should generally be avoided.
- Clinically more important that the tube reside in the pleural space rather than a specific location relative to the chest wall or lung parenchyma.
- Infectious
 - Insertion site (wound) infection
 - Pleural space infection (empyema) rates vary from 1% to 11%.
- Unresolved pneumothorax
- Persistent pleural fluid collection
- Infrequent
 - Injury to the lung
 - May manifest as hemothorax, persistent air leak, residual pneumothorax, or subcutaneous emphysema
 - Injury to the intercostal vessels
 - May manifest as hemothorax and occasionally requires surgery to achieve hemostasis
 - Chylothorax
 - Long thoracic nerve injury (winging of the scapula)
 - Intercostal neuralgia
 - Horner's syndrome
 - Phrenic nerve palsy
- Serious rare complications
 - Reexpansion pulmonary edema
 - Manifests as dyspnea (in the absence of lung collapse) following drainage of a large pneumothorax or hemothorax
 - Ipsilateral edema seen on chest radiograph
 - Treatment is supportive
 - Some recommend slow removal of large effusions (<1 L in the first 30 minutes) to minimize the risk.
 - Esophageal rupture
 - Perforation of the heart or great vessels
 - Laceration of the subclavian vessels
 - Injury to the diaphragm and/or upper abdominal structures (liver, spleen, stomach, colon)
 - Puncture of silicone breast implants (intrathoracic silicosis)

OUTCOMES AND EVIDENCE

- Few aspects of chest tube management have been subjected to rigorous study or are standardized.
- Patient outcomes following tube thoracostomy are related to their underlying condition(s).
 - Deaths due to the procedure itself are infrequent.
- No clear consensus exists regarding the role of prophylactic antibiotics for tube thoracostomy, but they may be of some benefit.
- Recent meta-analysis of studies performed in trauma patients revealed a reduction in the risk of posttraumatic empyema and pneumonia.
- If one elects to administer antibiotics, coverage against *Staphylococcus* should be chosen.

Complications

- Reported to be as low as 2% and as high as 30%
- Improper insertion technique, operator inexperience, and forceful use of sharp trocars are avoidable errors that account for many of the complications.
- Common
 - Malpositioning
 - Generally around 3%, though a recent study of critically ill patients who underwent CT following tube thoracostomy reported an incidence of 30%.

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■ PREPROCEDURE

Indications

- Diagnostic uses
 - To assess the patency and anatomy of the upper airway
 - To evaluate problems associated with endotracheal tubes and airway stents, such as tracheal damage, device malposition, or airway obstruction
 - To investigate lung abnormalities of unclear etiology on the chest x-ray
 - To investigate unexplained hemoptysis, cough, and localized wheeze or stridor
 - To obtain lower respiratory tract specimens by bronchoalveolar lavage (BAL) or protected specimen brushing (PSB) for cytologic or microbiologic analyses
 - To investigate the etiology of positive sputum cytology results
 - To determine the location and extent of respiratory tract injury after toxic inhalation or aspiration of gastric contents
 - To evaluate the airways for suspected tracheobronchial injury after thoracic trauma
 - To evaluate a suspected tracheoesophageal fistula
 - To perform endobronchial or transbronchial lung biopsies (TBLBs) and transbronchial needle aspirations (TBNAs) for histologic, cytologic, or microbiologic analyses
- Therapeutic uses
 - To remove retained secretions or mucous plugs not mobilized by physiotherapy
 - To retrieve foreign bodies (Videos E13-5 and E13-6)
 - To perform difficult tracheal intubations
 - To aid in performing percutaneous tracheostomies (Video E13-4)
 - To perform selective intubation of the main stem bronchus
 - To place airway stents
 - To perform airway balloon dilatation for the treatment of tracheobronchial stenosis
 - To remove abnormal endoluminal tissue from the trachea or bronchi through the use of forceps or laser techniques

Contraindications

- Absolute contraindications
 - Absence of consent from the patient unless a medical emergency warrants the procedure
 - Lack of trained personnel to perform or directly supervise the procedure
 - Lack of adequate personnel and facilities to manage possible life-threatening emergencies
 - Inability to adequately oxygenate the patient
 - Inability to normalize the platelet count and coagulation if biopsy is anticipated
 - Unstable hemodynamic status
 - Active uncontrolled bronchospasm
- Relative contraindications
 - Lack of patient cooperation
 - Unstable angina or recent myocardial infarction (within 6 weeks)

- Hypercapnia
- Brain injury (risk for increased intracranial pressure)
- Severe pulmonary hypertension and uremia (increased risk for serious hemorrhage following biopsy)

Equipment

- Fiberoptic bronchoscope, comprised of a few components that are incorporated into a functional unit (see Figs. E13-1 and E13-2)
 - Control handle: it contains
 - Body that fits into the hand
 - Eyepiece, to which video or photographic devices may be attached; just under the lens, a diopter adjustment ring is used to focus and adjust the eyepiece to fit each individual's eyesight; in some bronchoscopes, the top of the endoscopic view is marked by an indent or black triangle to assist in orientation
 - Bending lever; located on the back of the handle and used to activate the up and down movement of the last 2 to 3 cm of the insertion cord
 - Suction control valve
 - Suction connector
 - Access port to the working channel
 - Insertion cord: it is the flexible bronchoscopic element that hangs from the control handle and is introduced into the airways; within it are the viewing bundle, one to three light bundles, the working channel, and two wires to control the distal end of the scope.
 - Universal cord: it arises from the side of the control handle and transmits the light from the light source to the endoscope and then down to the insertion cord to illuminate the field of view. The light source is a metal box to which the universal cord attaches. In some types of bronchoscopes (portable scopes) the universal cord is not needed, as the light source is built into the control handle of the instrument and power is provided by a battery system. Modern digital flexible endoscopic systems use a charge-coupled device chip placed at the end of the scope to relay digitized information to the monitor via a processor. The venting connector is a component of the bronchoscope usually located on the universal cord. The ethylene oxide sterilization venting cap and leakage tester are attached to this connector. The ethylene oxide cap must be installed when the endoscope is subjected to gas sterilization and during transportation by air and must be removed before immersion or when the instrument is in use.
- Ancillary technical materials
 - Venous access equipment
 - Oxygen and related delivery equipment
 - Wall or portable vacuum systems and related suction supplies
 - Laser equipment, if applicable
 - Bite block, to be used in transoral procedures in awake patients
 - Sterile gauze, for clearing the tip of the bronchoscope during the procedure
 - Water-soluble lubricant
 - Antifogging systems, including warm water (max 60°C), weak soap solutions, and commercially available antifogging solutions;

when fogging occurs during the procedure, bringing the tip of the endoscope into contact with the mucosal surface may eliminate lens fogging

- Microbiology and cytology brushes, flexible forceps, retrieval valves, transbronchial aspiration needles, fixatives
- Specimen-collection traps, syringes for medication delivery, normal saline solution for bronchoalveolar lavage
- Laryngoscope
- Endotracheal tubes in various sizes
- Oral intubating airway that provides an open air space in the oropharynx and protects the endoscope from being bitten by the patient; it is useful if the oral route is chosen in patients under general anesthesia
- Endoscopy masks to assist fiberoptic intubation in patients being ventilated by a face mask provided with a rubber diaphragm that permits the passage of either the endoscope or the tracheal tube into the airways and prevents air leakage
- Endotracheal tube introducers of various sizes
- Cricothyroidotomy kit
- Laryngeal mask airway or other extraglottic devices of various sizes for ventilator support in emergency situations; laryngeal mask airway may also be used to aid the passage of the bronchoscope into the trachea
- An adapter for the insertion of the bronchoscope into the airways while preventing loss of the respiratory gases and maintaining ventilation and positive end-expiratory pressure throughout the procedure during either invasive or noninvasive ventilation (NIV)
- Self-inflating or anesthesia bag attached to a face mask by a T-adapter, for bag-mask ventilation in nonintubated, sedated patients undergoing bronchoscopy
- Resuscitation equipment
- Medications
 - Lidocaine for topical anesthesia; the minimum amount of lidocaine necessary should be used when installing through the endoscope; the total dose of lidocaine should be limited to

8.2 mg/kg in adults; great care must be given when administering lidocaine to patients with liver or cardiac failure

- Sedative agents (e.g., benzodiazepine and propofol)
- Synthetic narcotics (e.g., fentanyl or remifentanyl) to provide sedation and analgesia and to suppress the cough reflex
- Benzodiazepine and/or narcotic antagonists
- Epinephrine (usually 1 : 10,000 dilution), for bleeding control
- Nasal decongestants
- Emergency and resuscitation drugs
- Monitoring devices
 - Pulse oximeter
 - Continuous electrocardiogram
 - Continuous intraarterial blood pressure or intermittent cuff blood pressure measurement at least every 5 minutes
 - Intracranial pressure, essential in patients with serious brain injury
 - End-tidal carbon dioxide, useful in patients with brain injuries
 - Respiratory function monitoring of patients under mechanical ventilation, for ventilation parameters such as exhaled tidal volume and peak inspiratory pressure
 - Chest x-ray 1 hour after transbronchial biopsy to exclude pneumothorax
- Cleaning and sterilization equipment
 - Dedicated room for cleaning and manual or automated sterilization; automated washer disinfectors are recommended to minimize staff contact with disinfectant and their fumes
 - Soft nonabrasive cleaning cloth to gently wipe the external surfaces and components of the endoscope immediately after use
 - Water or neutral detergent solution to irrigate all accessible channels of the endoscope at the end of the procedure
 - Leak testing system
 - Cleaning brushes and neutral detergent solution for a thorough cleaning of the internal and external surfaces of the endoscope: cleaning brushes are passed through the working channel access port, the suction port opening, and the suction connector. They

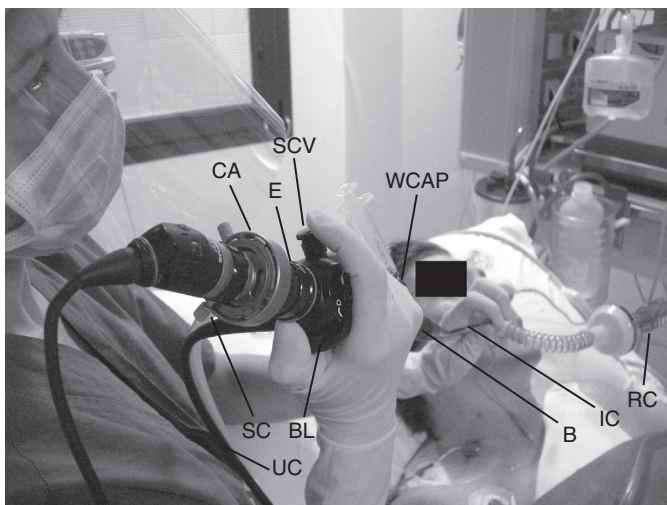


FIGURE E13-1 ■ Fiberoptic bronchoscopy in a patient under mechanical ventilation. Note how the operator uses her right hand to hold the handle of the instrument, with her thumb over the bending lever and her index finger over the suction control valve. B, body; BL, bending lever; CA, camera attachment; CH, control handle; E, eyepiece; IC, insertion cord; RC, respiratory circuit; SC, suction connector; SCV, suction control valve; UC, universal cord; WCAP, working channel access port.

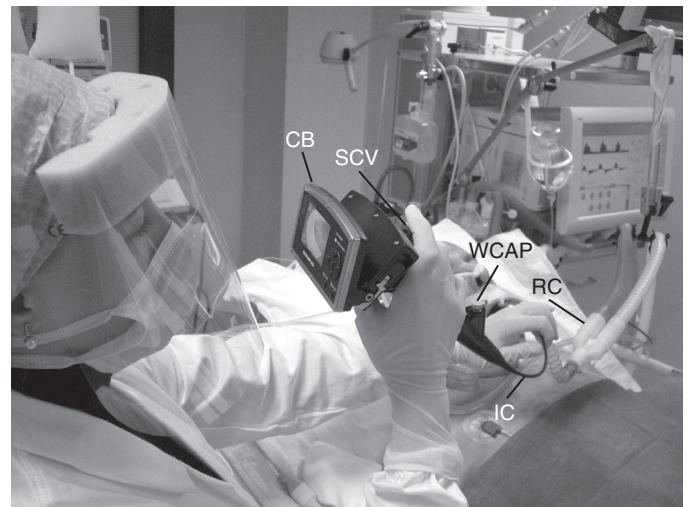


FIGURE E13-2 ■ Fiberoptic bronchoscopy in a patient under mechanical ventilation. The operator uses a recent model, battery-driven bronchoscope incorporating video camera, light source, and recording unit. The camera body of this bronchoscope can be rotated to the right and the left side by 90 degrees to either side, and the liquid crystal display panel can be tilted from 0 to 120 degrees. CB, camera body; IC, insertion cord; RC, respiratory circuit; SCV, suction control valve; WCAP, working channel access port.

are also used carefully to clean the distal end of the instrument; the brush head should be cleaned each time it emerges from the endoscope

- Protease enzymatic agent for cleaning and the removal of blood and protein residues
- High-level disinfection or sterilization agents (e.g., peracetic acid, glutaraldehyde, or ethylene oxide)
- Sterile water for rinsing the endoscope
- 70% ethyl or isopropyl alcohol to flush the external surfaces and inner channels of the endoscope, when the quality of the rinse water is in doubt or to assist in the drying process
- Cupboard to hang the endoscope

ANATOMY

- See Video E13-1 Trachea
- The trachea is a tube that passes from the larynx to the level of the fourth/fifth thoracic vertebra where it bifurcates into the two main bronchi (i.e., the left and the right) at the anatomic point known as the *carina*. The trachea has an inner diameter of about 21-27 mm and a length of about 10-16 cm. About 15-20 incomplete C-shaped cartilaginous rings reinforce the anterior and lateral sides of the trachea and main bronchi. The posterior wall, or membranous trachea, is free of cartilage and contains bundles of muscle fibers that are inserted into the posterior ends of the cartilage plates.
- Bronchi
 - The right main bronchus is wider, shorter, and more vertical than the left main bronchus. The cartilage and mucous membrane of the main bronchi are similar to those of the trachea. At the level where the main bronchi enter the lungs, the membranous region disappears, and the cartilage plates are no longer C-shaped but are smaller, more irregular, and arranged to surround the circumference of the airway. At this level, the muscle coat no longer inserts into the cartilage but forms a separate layer of interlacing bundles. Consequently, the airway lumen can be occluded by the contraction of the muscle.
 - The right main bronchus subdivides into three lobar bronchi, while the left main bronchus divides into two, although the lingula of the left lung is analogous to the right middle lobe. The lobar bronchi divide into segmental bronchi, each of which supplies a bronchopulmonary segment. The bronchopulmonary segments are the topographic units of the lung, and they are used to identify regions of the lung either radiologically or surgically. There are ten bronchopulmonary segments per lung, but, due to anatomic development, some of the segments in the left lung fuse, giving rise to eight segments. For counting orders or generations of airways, the main bronchi are usually counted as the first generation, the lobar bronchi as the second generation, and so on. Generally, in adult subjects, a bronchoscope with an outer diameter of 5 mm cannot be advanced farther than the fourth/fifth-order bronchi.
- Bronchioles
 - As the branching continues through the bronchial tree, the amount of hyaline cartilage in the walls decreases until it is absent in the bronchioles, which lie distal to the bronchi, beyond the last plate of cartilage. When any airway is pursued to its limit, the terminal bronchiole is reached. Each terminal bronchiole then gives rise to several respiratory bronchioles, which lead to the alveolar ducts and sacs. The alveolus is the basic anatomic unit of gas exchange in the lung.
- Nomenclature of peripheral bronchi
 - The nomenclature commonly used for the bronchial anatomy is that of Jackson and Huber. There are ten segments in the right lung and eight in the left. Subdivisions of the bronchial tree correspond to the anatomic segments and are named accordingly.

The right main bronchus gives rise to three lobar bronchi: upper, middle, and lower. The portion of the right main bronchus between the upper lobe bronchus and the origin of the middle and inferior lobe bronchi is known as the lower part of the right main bronchus, or bronchus intermedius. The right upper lobe bronchus is subdivided into three segmental bronchi: the apical, posterior, and anterior. The right middle lobe bronchus branches into two segmental bronchi: the lateral and medial. The right lower lobe bronchus gives rise to five segmental bronchi: the superior segmental bronchus, posteriorly directed and just below the orifice of the middle lobe bronchus, and more distally, four basal segmental bronchi: the medial, anterior, lateral, and posterior; occasionally, the medial basal bronchus is partially separated from the other basal segments by an extra fissure.

The left main bronchus subdivides into two lobar bronchi: the upper and lower. The left upper lobe bronchus subdivides into a superior division bronchus and a lingular division bronchus. The superior division has two segmental bronchi: the apical-posterior and anterior. The lingular division has two segmental bronchi: the superior and inferior. The anatomy of the left lower lobe bronchus is similar to that of the right lower lobe bronchus, except that there are usually only three basal segmental bronchi on the left: the anteromedial, lateral, and posterior; additionally, the left lower lobe bronchus has a greater distance between its superior segment and its basal pyramid bronchi, compared to the right side.

With the advent of fiberoptic bronchoscopy, Dr. Shigeto Ikeda introduced additional nomenclature for the fourth, fifth, and sixth divisions. According to this nomenclature, the segmental bronchi are numbered from 1 to 10 on each side and are identified with the capital letter "B" for bronchus and prefixed by the capital letter "R" for right or "L" for the left. This way, LB6 identifies the superior segmental bronchus of the left lower lobe. Subsegmental or fourth-order bronchi are designated by the lowercase letter "a" for posterior and "b" for anterior; the letter "c" may be used for additional bronchi. Fifth-order bronchi are identified by the Roman numerals "i" (posterior) and "ii" (anterior). Finally, "α" and "β" are used for sixth-order bronchi.

- Variations in the bronchial anatomy are not infrequent.
- Key bronchoscopic anatomic features as viewed by an operator positioned at the head end of a supine patient
 - Right lung. The orifice of the bronchus to the right upper lobe is in the 3 o'clock position, and its distance from the carina is quite variable. The arrangement of the three segmental bronchi of the right upper lobe bronchus is nearly symmetric. Just beyond the lower section of the right main bronchus, or bronchus intermedius, the typical anatomic configuration consists of the orifice of the middle lobe bronchus, anteriorly directed, in the 12-2 o'clock position; the orifice of the bronchus to the superior segment of the lower lobe, at the same level but in the 6-7 o'clock position; and, directly in front, the basal segmental bronchi of the right lower lobe.
 - Left lung. After entering the left main bronchus, the orifices of the upper and lower lobe bronchi generally lie in the top left and bottom right, respectively, of the bronchoscopic image. Within the orifice of the left upper lobe bronchus, the lingular division bronchus lies to the right of the superior division bronchus. Inside the entrance of the left lower lobe bronchus, the orifice of the superior segmental bronchus is in the 6-7 o'clock position, just as in the right lung.

PROCEDURE

- Define the indication for fiberoptic bronchoscopy.
- Choose the size of the bronchoscope according to the indication of procedure, the patient size, and the size of the endotracheal tube; a

large bronchoscope with a wide working channel provides excellent suction performance and permits the passage of large bronchoscopic tools. In adult patients with tracheal intubation, an outer diameter of the bronchoscope at least 1.5 mm narrower than the lumen of the endotracheal tube can prevent excessive increases in airflow resistance and decreases in the tidal volume.

- Assure the bronchoscope is in proper working order.
- Check any cameras and/or video equipment that may be used.
- Assess the patient's medical, physiologic, and psychologic status.
- Reassure the patient, if conscious.
- Prescribe appropriate premedication, if needed.
- Establish intravenous access.
- Connect the bronchoscope to the light source when it is present, turn on the light, adjust the focus (e.g., by looking at written material until a clear view is obtained), and obtain the white balance.
- Connect the suction catheter to the suction connector.
- Place the distal end of the insertion cord of the bronchoscope into warm water.
- Apply or check the monitoring.
- Place the patient in a supine, semirecumbent, or even sitting position, depending on the type of procedure.
- Start topical anesthesia, general anesthesia, or intravenous sedation, based on the needs of the patient.
- Stand behind or to the left or right side of the patient. If you stand to the side, you can approach the patient either from behind or the front; in the latter situation, once the bronchoscope has passed into the pharynx, the superior part of the endoscopic view will correspond to the inferior region of the patient.
- Lubricate the bronchoscope.
- Handling the bronchoscope. Right-handed users will find it easier to hold the handle of the instrument with their right hand, with the index finger over the suction valve and the thumb over the bending lever, and to use their left hand to hold the insertion cord. The black cursor in the viewfinder, when present, describes the plane of movement of the tip of the endoscope.
- The bronchoscopic procedure requires only three movements: (1) flexion of the tip of the bronchoscope along the plane of the cursor; (2) rotation of the entire endoscope to the left or right; and (3) the advancement or withdrawal of the instrument. The goal is to keep the point of interest (e.g., vocal cords, bronchial orifice, etc.) in the center of the field. When the bending lever is depressed, the tip rises, whereas when the lever is elevated, the tip points downward. The insertion cord should be kept as straight as possible to either prevent accidental damage to the bronchoscope or improve the control over the tip of the instrument. To look right, the tip of the bronchoscope may be turned upward while the control handle is twisted clockwise. Alternatively, the insertion cord may be rotated anticlockwise with the tip turned downward. To look left, the insertion cord is rotated clockwise or anticlockwise with the tip deflected downward or upward, respectively. The operator will decide which maneuvers to perform depending on the ease of obtaining the desired movements.
- The insertion cord should be able to rotate throughout its length when the handle is rotated axially, to avoid distortion of the image orientation. This orientation distortion resulting from the axial rotation usually occurs when the distal end of the bronchoscope is blocked by the air-tight rubber seal at the entrance of the endotracheal tube or even by the inside walls of the tube. In these circumstances, the tip of the bronchoscope fails to rotate synchronously with the proximal end of the instrument.
- When a camera attachment is used with the bronchoscope, the camera position relative to the bronchoscope needs to be calibrated by rotating the bronchoscope camera system until a certain movement inside the patient's airway corresponds with the proper motion on the monitor.
- The bronchoscope may be inserted into the airway through the nose or the mouth in spontaneously breathing patients or through the endotracheal tube in intubated patients. During NIV, the bronchoscope is passed through the NIV interface (Videos E13-2 and E13-3).
- The application of NIV during bronchoscopy may be useful either in at-risk hypoxemic patients who are initially breathing spontaneously and who start NIV to assist bronchoscopy or in patients who are already receiving NIV and scheduled to undergo bronchoscopy during NIV. When NIV is administered through a facial mask, a T-adaptor with a sealed connector is attached to the mask for insertion of the bronchoscope through the nose or the mouth.
- Fiberoptic intubation. The endoscope may be passed transnasally or transorally through the vocal cords into the trachea. Then the endotracheal tube is slipped over the instrument.
- Sampling techniques. Samples from the lower airways are commonly obtained by BAL, PSB, TBLB, and TBNA. When BAL or PSB is performed, the sampling area is selected based on the location of the new or progressive infiltrate on a chest x-ray or the segment visualized during bronchoscopy as having purulent secretions. Data are lacking for the optimal sampling site in patients with diffuse lung infiltrates.
- BAL. The tip of the bronchoscope is wedged as far as possible into a distal airway (generally a fourth- or fifth-order bronchus), and a sterile saline solution is instilled through the bronchoscope and then aspirated into a sterile trap. Aliquots of 20 to 60 mL are injected and aspirated back after each instillation. The total amount of fluid used to perform BAL ranges from 140 to 240 mL. In the supine patient, BAL fluid recovery is best from the right middle lobe or lingula. At least 5 mL of retrieved fluid is needed for adequate microbiologic analysis. The first aliquot of aspirated fluid is likely to contain a large amount of material from the proximal airway and must be analyzed separately from the rest. The recovery of more than 5% squamous epithelial cells in the BAL specimen indicates proximal tracheobronchial contamination. Since lidocaine has bacteriostatic properties, the use of this local anesthetic could alter the microbiologic results.
- PSB. This technique is performed using a retractable brush within a double-sheathed catheter device with a distal dissolvable plug occluding the outer catheter. First, the tip of the bronchoscope is positioned close to the sampling area. Next, the catheter is inserted through the working channel and advanced 1 to 3 cm beyond the distal end of the bronchoscope to avoid the collection of pooled secretions around the distal tip of the instrument. The inner catheter containing the brush is advanced to eject the distal plug into a large airway, and the brush is advanced under direct vision into the desired subsegment. Once the sample is obtained, the brush is retracted into the catheter, which is then withdrawn and removed from the bronchoscope. The brush is then advanced beyond the catheter, cut with sterile scissors, and placed into 1 mL of transport medium to avoid drying.
- TBLB. Histologic samples of the bronchial mucosa, bronchial wall, lung parenchyma, and alveoli may be obtained using TBLB. In diffuse lung disease, the biopsy specimen should be taken from a peripheral airway, preferably the lower lobe. In this way, the danger of significant bleeding may be reduced, owing to the smaller caliber of the distal bronchial vessels. The number of biopsies needed for TBLB is not standardized. However, seven to eight biopsy specimens have been proposed for localized lung lesions, whereas five TBLB samples from one lung seem to ensure a high diagnostic yield for most diffuse lung diseases.
- TBNA: TBNA may be used to obtain tissue samples from paratracheal, hilar, and peribronchial areas. For visible tumors, the yield of TBNA and forceps biopsy is similar. A protected transbronchial needle is passed through the working channel of the bronchoscope and positioned with the needle perpendicular to the endobronchial wall. The tracheal wall, carina, main stem bronchus, or major spur is pierced with a quick thrust. Suction is then applied to the proximal end of the needle sheath with a 20-mL syringe containing 2 mL

of saline solution. The needle and sheath are removed from the bronchoscope, and the specimen is collected into a container for cytologic analysis. If a dry syringe is used, the specimen is smeared on a glass slide before the examination. At each biopsy site, two or three punctures are commonly made, employing a new needle for each location.

- Recommendations for bronchoscopy during mechanical ventilation through the endotracheal tube. Insert a connection between the endotracheal tube and the ventilator tubing to slide the bronchoscope. Volume-controlled ventilation is usually preferred. Set the fraction of inspired oxygen (FiO_2) at 100%, and remove or reduce positive end-expiratory pressure, except in very severe respiratory failure. Increase respiratory frequency and decrease tidal volume; increase percent inspiratory time. Set the peak pressure alarm to a level to allow adequate ventilation. After the procedure, return all ventilator parameters to their initial values. Over the first 30 minutes after the termination of bronchoscopy, gradually reduce the applied FiO_2 to the prebronchoscopy requirements as long as the patient can maintain an arterial oxygen saturation of hemoglobin measured by a pulse oximeter (SpO_2) at $>92\%$.
- Other procedural considerations. Enteral feeding or oral food intake should be suspended for at least 4 hours before the procedure. Asthmatic subjects should be premedicated with a bronchodilator before the procedure. Platelet count and coagulation times should be checked before performing bronchoscopy in patients in whom a biopsy is anticipated.

AFTERPROCEDURE

Postprocedure Care

- Monitoring
 - Level of consciousness
 - Medications administered
 - Subjective responses (e.g., pain, discomfort, and dyspnea)
 - Blood pressure, heart rate, rhythm, and changes in cardiac status
 - SpO_2 and supplemental oxygen use
- Close surveillance to promptly detect and treat any new findings presenting over the first hours after the end of the procedure (see complications)
- Nothing by mouth for 2 hours

Complications

- Common
 - Hypoxemia; it commonly occurs during bronchoscopy; the insertion of a bronchoscope into the airways reduces the cross-sectional area available for airflow, thus increasing the airway resistance and the work of breathing. Continuous suctioning through the instrument evacuates respiratory gases and

decreases the residual functional capacity, leading to the development of hypoxemia. Hypoxemia may be more severe after BAL, owing to ventilation-perfusion abnormalities induced by the instillation of a saline solution; the decrease in arterial oxygen partial pressure resulting from bronchoscopy may last a few minutes to several hours after the removal of the bronchoscope

- Mild hypercapnia
- Increased airway resistance
- Modest alterations in systolic blood pressure, consisting of either a decrease (generally related to sedation) or an increase from the baseline
- Slight increase in heart rate
- Infrequent
 - Periprocedural adverse drug reactions
 - Bronchospasm or laryngospasm, particularly in patients with preexisting reactive airway disease
 - Major cardiac rhythm abnormalities; the risk of arrhythmias is the greatest during the passage of the bronchoscope through the vocal cords in nonintubated patients, especially if hypoxemia is present.
 - Bradycardia or other vagally mediated phenomena
 - Epistaxis, in transnasal procedures
 - Pneumothorax; it is very uncommon after bronchoscopy but has an increased incidence in patients undergoing TBLB
 - Significant bleeding, defined as more than 50 mL of blood loss; the likelihood of hemorrhage from bronchoscopy increases when biopsy or brushing procedures are performed; patients at a higher risk of bleeding include those with uremia, immunosuppression, pulmonary hypertension, liver disease, coagulation disorders, or thrombocytopenia
 - Fever and chills; fever rarely occurs after bronchoscopy (1.2%) but occurs more commonly (10% to 30% of cases) after BAL; fever is thought to be generally caused by the release of proinflammatory cytokines from alveolar macrophages
 - Nausea, vomiting
 - Cross-contamination of bronchoscopes
- Serious, rare complications
 - Death

OUTCOMES AND EVIDENCE

- Outcome after bronchoscopy depends on the patient's coexisting condition; flexible bronchoscopy is associated with a 0.3% incidence of major complications and a mortality rate of 0.02%; major complications requiring resuscitative measures are significantly more likely with rigid bronchoscopy as compared with flexible bronchoscopy.
- The most frequent life-threatening complications leading to death following bronchoscopy include airway problems, cardiovascular events, and bleeding.

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BEFORE PROCEDURE

Indications

- Diagnosis of pneumonia
 - Viral, bacterial, fungal, pneumonias
 - Quantitative cultures for ventilator-associated pneumonias
 - Infiltrates in an immunocompromised host
- Evaluation of diffuse lung infiltrates and evaluation of interstitial lung disease
- Suspected pulmonary hemorrhage
- Suspected malignancies
- Both bronchoalveolar lavage (BAL) and protected specimen bronchial brushing (PSB) use quantitative culture techniques to differentiate between airway colonization and true pulmonary infections.¹⁻⁴

Contraindications

- Acute respiratory distress syndrome with hypoxemia
 - May cause derecruitment in noncompliant severe air space disease
 - Cardiac arrhythmias, hypoxemia, bronchospasm
- Bronchopleural fistula
 - May not be able to return adequate specimen for analysis

Equipment

- Flexible fiberoptic bronchoscope
- Sterile saline
- Vacuum suction source
- Suction tubing
- Syringes: 10 mL, 20 mL, or 60 mL slip-tip
- Sterile collection trap
- Lidocaine, 1% to 2% for topical anesthesia, if needed
- Medications for procedural conscious sedation, if needed
- Burman airway or oral airway
- Supplemental oxygen
- Endotracheal bronchoscope attachment

ANATOMY

- If performed on native airways, the first structures to be identified are the epiglottis and the vocal cords.
 - Topical anesthesia using 1% to 2% lidocaine is administered through a bronchoscope to the vocal cords.
- Next landmark to be located is the trachea and the identification of the carina.
 - Additional administration of 1% to 2% lidocaine to the carina.
- Right and left main bronchi are identified, and location of desired BAL specimen is obtained at the site where purulent material is present or where infiltrate is visible on the chest x-ray.⁵
- If unsure as to which lobe needs to be sampled, the posterior portion of the right lower lobe should be sampled first. Autopsy

studies indicate that pneumonias in intensive care unit (ICU) patients often involve this lobe.⁶⁻⁹

- To obtain the BAL, the bronchoscope is advanced to the farthest segment of the affected bronchus until it cannot be advanced any farther.

PROCEDURE: BRONCHOALVEOLAR LAVAGE

See Video E14-1.

- Obtain informed consent, including for topical anesthesia of airways and/or conscious sedation.
- Prepare for conscious sedation, and use telemetry devices to monitor continuous pulse oximetry, intermittent blood pressure cuff measurement, and supplemental oxygen (via nasal cannula or non-rebreather mask or ventilator).
- For patients at risk of bronchospasm, premedicate with bronchodilators, and treat airways with 2% lidocaine via an atomizer.
- Review chest radiograph to identify ideal location for BAL. Right middle lobe or lingula is preferred in supine patients, with the right lower lobe also serving as a possible direct path for aspiration.
- Prepare the bronchoscope, collection trap, tubing, and sterile saline.
- Anesthetize vocal cords in nonintubated patients and carina in intubated patients with 2% lidocaine (5 mg/kg maximum).
- Avoid suctioning prior to obtaining BAL specimen to avoid specimen contamination.
- Advance the bronchoscope until wedged in the desired subsegmental bronchus.
- Flush 20 mL sterile saline through the wedged bronchoscope, watching for the flow of saline into distal airways and also for the blanching of tissues.
- Obtain sample immediately after the wash, ensuring the return of the lavage specimen into the collection trap.
- Slight repositioning of bronchoscope tip can allow for better fluid return.
- Intermittent pulsing of suctioning can reduce distal airway collapse.
- Repeat 20-mL sterile saline washes as necessary to obtain adequate sample (usually a total of 30-50 mL, which is usually 40%-70% recovery of total instilled volume).
- Larger volume aliquots for lavage can be used (as much as 50 mL per lavage, with total volume of 120 mL in 3 to 6 aliquots).^{5,10}
 - Estimated alveolar surface area distal to the wedged bronchoscope is 100 times greater than the peripheral airway.
- Fluid return of the BAL can affect the validity of results, and small returns may contain only diluted material from the bronchus rather than the alveoli, resulting in false negatives.¹¹
 - In patients with highly collapsible airways, including patients with chronic obstructive pulmonary disease (COPD), the amount of negative pressure applied via the bronchoscope to aspirate sample can limit the amount of sample returned and may give rise to a false negative result.
- Sensitivity of BAL is 73% and specificity is 82% in diagnosis of pneumonia.¹²⁻²³

PROCEDURE: PROTECTED SPECIMEN BRONCHIAL BRUSHING

- Same procedure as bronchoalveolar lavage except for the use of an endobronchial catheter wedged in the tracheobronchial tree.
- The brush is rubbed against areas of suspected infection and then removed from the procedure port of the bronchoscope.
- The brush is then aseptically cut into a measured volume of sterile diluent (usually 1 mL of preservative-free sterile saline).^{10,24}
- Double-lumen catheter brush systems with single-sheathed or telescoping plugged catheter tips with distal occluding plugs are used.²⁴⁻²⁶
- Quantitative cutoff is 10^3 colony-forming units per milliliter (CFU/mL).
- Sensitivity of protected specimen bronchial brushing for pneumonia is 89% (95% confidence interval [CI], 87%-93%) and specificity is 94% (95% CI, 92%-97%).^{13,27-33}

AFTER PROCEDURE

Postprocedure Care

- Patients are continuously monitored until full recovery from conscious sedation.
- Ventilated patients are placed on 100% FiO₂ during the procedure and weaned back to previous FiO₂ levels, as tolerated. Derecruitment is possible and may require recruitment maneuvers.
- Specimen handling
 - For PSB, the brush should be aseptically cut into 1 mL of preservative-free sterile saline.^{10,24}
 - For BAL, the specimen container should be sent for analysis within 30 minutes, although refrigeration can prolong transport and analysis.^{34,35}
- The specimen should be obtained before new antibiotics are administered.
 - Even a few doses of antibiotics can result in negative microbiological cultures.³⁶
 - Quantitative culture techniques of distal pulmonary secretions with minimal or no upper airway contamination.^{1,2}

- BAL and PSB culture sensitivities are lowered if antibiotic therapy has already been initiated.³⁷⁻³⁹
- These techniques do not retrospectively identify resolving pneumonia or assess the adequacy of therapy.^{9,40-43}

Complications

- Common
 - Cough
 - Transient infiltrates that typically resolve in 24 hours
 - Transient decrease in PaO₂
- Infrequent
 - Transient fever, chills, myalgias⁴⁴
- Serious, rare complications
 - Derecruitment and hypoxemia resulting in intubation and positive pressure ventilation or increase in ventilator requirements⁴⁵⁻⁴⁸
 - Pneumothorax

OUTCOMES AND EVIDENCE

- Quantitative culture techniques are necessary to differentiate infecting organisms from pharyngeal contaminants.⁴⁹⁻⁵³
 - Significant BAL culture concentrates are at least 10^5 to 10^6 CFU/mL.^{2,6,54-57}
 - Significant PSB culture concentrates are at least 10^3 bacteria.¹⁰
- A small number of false positive BAL and PSB results can be seen even when using strict criteria to distinguish between airway colonization and deep lung infections of 10^3 to 10^4 CFU/mL.⁵⁸
- False negative BAL and PSB results occur when
 - Bronchoscopy is performed at an early stage of infection, and bacterial load is not high enough to reach diagnostic significance.
 - Specimens are obtained from unaffected segments of lung.
 - Specimen processing errors occur.
 - Specimens are obtained after initiation of a new class of antibiotics.
- Consider repeat sampling for persistently symptomatic patients with initial negative quantitative concentrations.⁵⁹

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BEFORE PROCEDURE

Indications

- Requirement of a temporary or long-term artificial airway for prolonged mechanical ventilation
- Management of secretions
- Nonemergency airway obstruction

Contraindications

- Inability to clearly palpate and identify tracheal landmarks
- Enlarged thyroid or other neck mass
- Active infection at the site
- Emergency need for airway
- Positive end-expiratory pressure (PEEP) greater than 20 cm H₂O
- Previous surgical scar
- Bleeding
- Increased intracranial pressure
- Clinically significant coagulopathy
- Documented tracheomalacia
- Cervical irradiation
- Morbid obesity
- Maxillofacial or neck trauma
- Lack of cervical spine clearance
- Inability to extend the neck because of a cervical spine fracture
- In addition, we do not perform the procedure in patients younger than 16 years of age because of the scarcity of experience reported in pediatric patients.

Equipment

- Equipment required at the bedside to perform the percutaneous dilatational tracheostomy (PDT) procedure should include
 - PDT introducer set (Ciaglia Blue Rhino Percutaneous Tracheostomy Introducer Set #C-PTIS-100-HC, Cook Critical Care, Bloomington, Indiana)
 - Bronchoscope with video monitor display and bronchoscopy endotracheal tube adapter
 - Continuous electrocardiographic (ECG) monitor
 - Blood pressure monitoring device
 - Pulse oximeter
 - Free-flowing intravenous catheter
 - Mechanical ventilator
 - Suction
 - Resuscitation ("crash") cart
 - Open tracheostomy instrument tray (unopened)
- Supplies required at the bedside include
 - Chloroprep or other solution for skin preparation
 - 4 × 4-inch bandages
 - Syringes and needles
 - Sterile gowns and gloves
 - Shiley Percutaneous Dual Cannula Cuffed Tracheostomy Tube
 - Kelly clamp
 - Sterile saline solution

- Medications required at the bedside include
 - 1% Xylocaine with epinephrine 1 : 100,000
 - Midazolam, 1 mg/mL injectable or other appropriate sedative
 - Morphine, 10 mg injectable or another appropriate narcotic
 - Vecuronium, injectable, or other appropriate paralyzing agent
 - Sterile normal saline flush solution
 - Other medications at the discretion of the PDT operator
- The choice of a PDT introducer set may vary by institution; ours includes the set listed only because we have significant experience with it. However, it is critical that only one type of PDT introducer set be in use in an institution at any given time. To ensure maximum safety, every aspect of this procedure must be standardized, especially the equipment used.

ANATOMY

The thyroid notch and cartilage are palpated, followed by the cricothyroid membrane and cartilage and the tracheal rings. It is essential that the tracheal puncture be made inferior to the cricoid cartilage landmark. If the second and third tracheal rings cannot be distinctly identified, the procedure is aborted, and an open tracheostomy is performed.

PROCEDURE

See Video E15-1.

- A single tapered PDT dilator and kit with simultaneous intraoperative bronchoscopy is used.
- Two teams are used simultaneously. One team manages the endotracheal tube, and the other manages the placement of the tracheostomy tube.
- The patient's physiologic parameters, including arterial oxygen saturation, are monitored continuously throughout the procedure by the intensive care unit (ICU) nurses and a respiratory therapist.
- Intravenous sedation and paralytic agents are administered as required, and the patient is fully ventilated via an endotracheal tube.
- The patient is positioned with the neck slightly extended and a pillow under the shoulders.
- Under sterile conditions, the PDT dilators and tracheostomy tube must be prepared.
- The Blue Rhino tracheal dilator is water activated, so it is dipped in sterile saline or water to enhance its lubricant coating.
- The Shiley Percutaneous Dual Cannula Cuffed Tracheostomy Tube is designed specifically to be used with the Cook Percutaneous Tracheostomy Introducer Set. Depending on the size of the patient, it is prepared by inflating the balloon to ensure the integrity and then collapsing the balloon by withdrawing all air.
- The tracheostomy tube, with the cuff, completely deflated, is inserted over the introducer dilator as one unit, placed 2 cm from the tip of the dilator, and then lubricated with sterile gel. The Shiley's tapered distal tip and inverted cuff shoulder are specifically designed for easier insertion. It is important that the tracheostomy tube be placed exactly 2 cm from the tip. If it is placed more than 2 cm from the tip, it will likely not enter the trachea. If it is advanced too far and placed less than 2 cm from the tip, the trachea may be damaged upon insertion.

- The neck is prepared with Chloroprep.
- The dermis and subcutaneous tissues are infiltrated with 1% lidocaine with epinephrine.
- The upper airway endoscopist will then introduce the bronchoscope into the endotracheal tube.
- The endotracheal tube is untaped, the cuff deflated, and the tube is then withdrawn until the tip lies just below the vocal cords. The utmost care is taken to avoid withdrawing the endotracheal tube too far, which could result in extubation of the patient. We recommend that the bronchoscope remains near the tip of the endotracheal tube but entirely within it to prevent inadvertent puncture or spearing of the bronchoscope by the puncture needle.
- The PDT operator verifies the patient's neck anatomy, starting with palpation of the thyroid notch and cartilage and then moving down to the cricothyroid membrane and cartilage and the tracheal rings.
- The anatomy is reconfirmed with digital palpation of the cricoid cartilage because it is essential that the tracheal puncture is made inferior to this landmark. If the second and third tracheal rings cannot be distinctly identified, the procedure is aborted, and an open tracheostomy is performed.
- A 2-cm horizontal skin incision centered between the second and third tracheal rings is made, and the midline subcutaneous tissues are dissected bluntly with a hemostat until the pretracheal fascia is exposed.
- The PDT operator reconfirms the tracheal anatomy by direct palpation through the incision. The trachea is then punctured between the second and third tracheal rings with a 14-gauge cannula-over-needle from the PDT kit.
- Tracheal penetration is confirmed by visualization with the bronchoscope, as well as aspiration of air from the needle.
- The needle is removed, and a J-tip guide wire is then introduced into the trachea through the cannula and visualized with the bronchoscope. The puncturing cannula is then withdrawn.
- A small 14F dilator is then introduced over the guide wire to widen the tracheal opening. The dilator is then withdrawn.
- An 8F guiding catheter is introduced over the guide wire to the skin level mark on the guide wire. The guiding catheter and guide wire are introduced as a unit into the trachea until the safety ridge on the guiding catheter is at the level of the skin. The positioning of the guiding catheter is confirmed by aligning the proximal end of the catheter with the proximal gray mark on the guide wire. This positioning is critical to prevent displacement of the J-tip guide wire and possible trauma to the posterior tracheal wall during subsequent dilations.
- The lubricated Blue Rhino tracheal dilator is then passed over the cannula and guide wire and into the trachea to dilate the tract fully. This requires forceful pressure to accomplish smoothly.
- The tracheal dilator is then withdrawn, but the guiding catheter and guide wire remain in place.
- The tracheostomy tube and introducer dilator are threaded over the guide cannula and guide wire as one unit and inserted into the trachea under direct bronchoscopic visualization.
- The introducer dilator, guiding catheter, and guide wire are then withdrawn, leaving the tracheostomy tube in place.
- The inner cannula is then inserted, and the cuff is inflated.
- The PDT operator continues to hold the tracheostomy in place with one hand and never removes it until the tracheostomy tube is sutured in all four corners to ensure the tube is not inadvertently displaced.
- The bronchoscope is then inserted into the tracheostomy tube to confirm placement within the trachea.
- The ventilator tubing is then connected to the tracheostomy. The appropriate tidal volume and oxygen saturation are confirmed.
- The tracheostomy tube is sutured to the neck with 4-0 gauge nylon sutures placed in each corner.
- Once the tracheostomy tube is sutured in all four corners and also secured around the neck with umbilical tape, the endotracheal tube is removed. Make sure that the umbilical tape is not placed too tightly, as a skin breakdown can result. At least one finger should be able to fit between the umbilical tape and the skin.

AFTER PROCEDURE

Postprocedure Care

- A simple 4 × 4-inch gauze dressing is partially slit and placed between the tracheostomy wings and the skin.
- A chest radiograph is not indicated unless the procedure was complicated.
- A close observation by the nursing staff is required to detect bleeding externally at the tracheostomy site or internally into the airway. The bleeding must be immediately reported to the PDT operator and the ICU physician and must be carefully evaluated and controlled.
- Bleeding into the airway can lead to the formation of an obstructing clot at the carina, with fatal consequences.

Complications

- Common
 - Bleeding
 - Subcutaneous emphysema
 - Extratracheal cannulation
 - Brief episodes of hypoxia
 - Stomal infections
- Serious complications
 - Puncture or laceration of the posterior tracheal wall
 - Loss of airway
 - Conversion to open tracheostomy
 - Serious hemorrhage due to a severed blood vessel
 - Death

OUTCOMES AND EVIDENCE

- PDT is a safe procedure, with morbidity and mortality rates equivalent to or lower than those of an open tracheostomy.
- Numerous early studies reported the morbidity of PDT to be between 3% and 19%, compared with a complication rate of 26% to 63% for open tracheostomy.
- Recent studies have found the overall mortality for a tracheostomy to be 37%, with no statistically significant difference in mortality for PDT compared with an open tracheostomy.
- The incidence of wound infection has been reported to be 6.6%.
- One study compared PDT to surgical tracheostomy (ST) and found that PDT was associated with a significantly reduced risk of wound infection (OR, 0.28; 95% CI, 0.16-0.49; $P < 0.0005$).
- One report found the overall incidence of bleeding to be 5.7%, with no significant difference in incidence when comparing PDT to ST.

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BEFORE PROCEDURE

Indications

- Short-term hemostasis and stabilization of patients until definitive therapy can be arranged
- Failure to achieve hemostasis after endoscopic treatment of bleeding esophageal varices
- As a temporizing measure when endoscopic treatment is not immediately available or emergency transcatheter intrahepatic portosystemic shunt is being arranged

Contraindications

- Known or suspected esophageal tear
- Recent esophageal surgery
- Known esophageal stricture
- Use with caution in patients with a hiatal hernia

Equipment

- Minnesota tube (a modified Sengstaken-Blakemore tube with esophageal suction port above the esophageal balloon)
- Sengstaken-Blakemore tube (has a 250-cc gastric balloon and esophageal balloon and a single gastric suction port)
- Linton-Nachlas tube (has a single gastric 600-cc balloon)

PROCEDURE

See Video E16-1.

- If not already done, proceed with endotracheal intubation for airway protection.
- Ensure all equipment is available and ready.
 - Tube of choice
 - Large-volume syringe
 - A traction pulley system
 - Adequate suction
- Test the integrity of the gastric and esophageal balloon(s) of the tube by inflating them fully. Deflate the balloon(s), making sure all the air is out.
- Insert the tube transnasally, and advance it into the full length of the esophagus. If the transnasal route cannot be used, transoral insertion is also acceptable. Avoid transnasal placement in coagulopathic patients if possible.
- Put 30 to 50 mL of air through the gastric port, clamp it, and check for the correct placement. The partially inflated gastric balloon must be clearly seen below the diaphragm on a chest x-ray. Do not overinflate the gastric balloon during this step, as accidental full balloon inflation in the esophagus would likely lead to esophageal rupture.
- Once placement is confirmed, inflate the gastric balloon fully (500-700 mL).
- Pull the tube back slowly until meeting with resistance. Traction can then be applied in a number of ways: with an overhead frame pulley system (such as the one used for skeletal traction) or by securely taping the tube to the nose. More creatively, the patient can be fit with a football helmet or a catcher's mask, which are then used to stabilize the tube. The frame pulley system has the

advantage that the degree of traction can be accurately measured. A 1-kg weight is enough (a 1-L bag of a crystalloid solution can be conveniently used).

- Connect the suction ports to suction. If the tube used has a gastric and esophageal suction ports, place them to suction separately, and monitor the output. If the blood continues to come out of the esophageal port, inflate the esophageal balloon to 25 to 35 mm Hg (this is best achieved by attaching a three-way stopcock to the inflation port, with one of the limbs connected to a transducer for continuous pressure monitoring).

AFTER PROCEDURE

Postprocedure Care

- If inflated, monitor the pressure of the esophageal balloon at least once a day but preferably continuously.
- Monitor the angle of the tube with respect to the nose, and adjust accordingly to prevent pressure necrosis.
- The tube should be removed as early as possible. However, it is unknown how long a tube can safely remain in place, but it can be left in place 24-48 hours, and the gastric balloon should be deflated every 12 hours to check for rebleeding.
- To remove the tube, the steps are reversed. First, deflate the esophageal balloon (if using a tube that has one), keeping the gastric balloon on traction. If bleeding does not resume, one can proceed to discontinue the traction while keeping the gastric balloon fully inflated for an additional 24-48 hours. If there is no rebleeding, then the gastric balloon is deflated, and the tube is removed.
- If bleeding continues, then reinflate the appropriate balloon.

Complications

- The incidence of tube-related complications being the direct cause of death is 0%-20%.
- Common
 - Esophageal and fundal mucosal ulcerations
 - Pressure necrosis of the alae nasae
 - Nasopharyngeal bleeding
- Infrequent
 - Aspiration pneumonia
- Serious, rare complications
 - Esophageal perforation
 - Airway obstruction
 - Tube migration with laryngeal obstruction or tracheal rupture
 - Impaction of the balloon requiring surgery for removal

OUTCOMES AND EVIDENCE

- Primary hemostasis can probably be achieved in about 30%-90% of cases.
- The variability in success rates are due to patient selection, concomitant use of other therapies, and experience of staff using the tubes.
- The evidence is weak because most studies are at least two decades old, employed different types of tubes (e.g., Sengstaken-Blakemore, Linton, or Minnesota), and weren't likely randomized. This situation is unlikely to change, as balloon tamponade is seldom needed today.

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■ BEFORE THE PROCEDURE

Indications

- Inability to maintain adequate volitional intake in the setting of a functional gastrointestinal tract and/or
 - Acute critical illness expected to require more than 2-day intensive care unit (ICU) stay
 - Daily nutritional requirements are not met for more than 7 days in adults
 - Poor nutritional status and nutrient depletion
 - Unintentional weight loss of more than 5 lb or 5% of body weight over 1 month or body mass index (BMI) less than 18.5 kg/m²

Contraindications

- Inability to tolerate enteral nutrition
 - Mechanical bowel obstruction
 - Severe ileus
 - Short gut
 - High-output fistula
 - Peritonitis
 - Major gastrointestinal bleeding
- Hemodynamic compromise (e.g., starting or escalating dose of vasopressors in previously stable patient, large volume fluid or blood product resuscitation)
- Severe cranial or facial fractures
- Esophageal obstruction or recent surgery
- Esophageal or gastric varices
- Coagulopathy
- Patient not cooperative with nasoenteric feeding tube placement

Equipment

- Tube
 - Nasogastric sump tube (14F-18F)
 - Nasoenteric feeding tube with stylet and/or metal weighted tip
- Lubricant
- Gloves
- Gown with long sleeves
- Eye protection
- Emesis basin
- Syringe
 - 60-mL Toomey syringe if inserting a sump tube
 - 10-mL Luer-Lok syringe if inserting a nasoenteric feeding tube
- Stethoscope
- Adhesive device
 - Tape
 - Bridle
- Optional
 - Lidocaine jelly
 - Proton pump inhibitor (e.g., metoclopramide or erythromycin)
 - End-tidal CO₂ detector
 - pH testing strip

■ ANATOMY

The successful placement of the feeding tube requires that it pass through the nasal cavity, pharynx, esophagus, and into the stomach. The nasal cavity is the continuation of each nostril and is separated into halves by the nasal septum. The pharynx consists of a space that extends from the internal nares down to the inferior border of the cricoid cartilage. At this level, it divides into the esophagus and larynx. The esophagus continues until it terminates in a smooth muscle sphincter that separates the lower esophagus from the stomach. Typically, the lower esophageal sphincter lies 40 cm from the incisors. The pylorus lies approximately 60 to 65 cm from the incisors. Markers are inscribed on the feeding tube to facilitate tube advancement to the appropriate depth.

■ PROCEDURE

See Video E17-1.

- Position patient
 - If awake, place in a seated position.
 - If intubated or unable to comply with instructions, place supine, and elevate the head of the bed to 45 degrees.
- Coat tube with lubricant.
- Consider applying lidocaine jelly to the back of the nares.
- Insert tube into the nares.
- As the tube enters the hypopharynx, ask the patient to tilt head forward and swallow.
- Once inserted to 35 cm, tape the tube in place and confirm the intrasophageal position
 - Obtain a chest x-ray (CXR) or
 - Attach an end-tidal CO₂ detector to the end of the tube. If the indicator turns yellow (positive for CO₂), remove the tube and reposition. If the indicator remains purple (negative for CO₂), proceed.
- Advance the feeding tube to 55 cm, and tape in place if intending to initiate gastric feeding.
- If intending to initiate gastric feeding
 - Check the position of the tube.
 - Use a stethoscope to auscultate the left upper quadrant.
 - Insufflate air into the tube using a syringe.
 - If the passage of air into the stomach is heard, tape the tube in place. If unable to hear the passage of air, reposition the tube.
- If intending to initiate postpyloric feeding
 - Place the patient in the right lateral decubitus position.
 - Consider administering a prokinetic agent.
 - Advance the tube to 80 to 100 cm.
- Other adjuncts for assistance with the positioning of the tube
 - Magnets
 - Endoscopy
 - Bedside fluoroscopy

■ AFTER PROCEDURE

Postprocedure Care

- Obtain CXR to confirm the position of the tube.
- Remove the stylet.

- Attach the tube securely to the nose using tape.
- Consider placing a bridle.

Complications

- Common
 - Unplanned removal of the feeding tube
 - Tube obstruction
- Infrequent
 - Trauma from insertion of the tube
 - Bleeding from the nasal turbinates
 - Retropharyngeal hematoma
 - Gastrointestinal bleeding
 - Otitis media
 - Sinusitis
 - Arrhythmia
- Serious and/or rare
 - Placement into the cranium, trachea, and bronchus

- Perforation of the bronchus (pneumothorax), esophagus, stomach, and duodenum

OUTCOMES AND EVIDENCE

- Early nutrition support therapy, especially using the enteral route, may improve patient outcomes in the major elective gastrointestinal surgery and surgical critical care population by reducing infectious complications, length of stay in the ICU, and disease severity.
- Placement of the nasoenteric feeding tube results in complications in approximately 2% to 5% of cases. Experienced practitioners who verify the placement of the tube before initiating feeding can reduce the incidence of adverse sequelae resulting from the inadvertent insertion of tubes into unintended locations.
- The decision to initiate gastric versus postpyloric feeding remains controversial. Evidence of aspiration, history of gastric atony, or intolerance of gastric feeding should prompt physicians to consider placing a postpyloric feeding tube.

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BEFORE PROCEDURE

Indications

- Suspicion of a central nervous system (CNS) infection
- Suspicion of a subarachnoid hemorrhage
- The need to obtain cerebrospinal fluid to diagnose other inflammatory or degenerative CNS diseases
- Reduction of cerebrospinal fluid (CSF) pressure in pseudotumor cerebri

Contraindications

- Absolute
 - Intracranial or spinous (especially intramedullary) mass (e.g., tumor, abscess). If there is a concern, an imaging study should be performed before the procedure. A rapid decrease in intracranial pressure from the withdrawal of CSF could precipitate herniation or worsening of spinal cord function if a mass lesion is present.
 - Overlying skin infection
 - Lumbar spine disease
- Relative
 - Coagulopathy and/or thrombocytopenia, because an epidural hematoma can develop at the puncture site. Fresh frozen plasma and platelets should be infused to correct hematologic abnormalities before the procedure. If a coagulopathy is discovered after the procedure, therapy should still be administered, because bleeding can occur for many hours.
 - If a lumbar puncture is being performed to evaluate a patient with an aneurysmal subarachnoid hemorrhage, withdraw the smallest possible amount of CSF to obtain the necessary laboratory tests. Reducing the CSF pressure could precipitate rebleeding.
 - Uncooperative patient

Equipment

- Lumbar puncture tray or individual components (see later)
- Chlorhexidine or povidone-iodine prepping solution
- Sterile drape with a central opening
- 1% Lidocaine and a syringe with 25- and 22-gauge needles for local anesthesia
- 20- or 22-gauge spinal needle
- Manometer
- Tubes for CSF collection

ANATOMY

The site of the intended puncture is either the L4-5 or L5-S1 interspace. These can be determined as follows. The L3-4 interspace can be located by drawing an imaginary line between the posterior iliac crests. This is usually the most rostral space employed because the adult spinal cord ends at L2. Walk the fingers down the spinous processes to identify the L4-5 and L5-S1 interspaces, and mark them on the skin. Note that during lumbar spine disease, the question of a spinal mass or an overlying skin infection prevents the lumbar approach; a lateral

cervical approach can be performed by a physician trained in this technique. In cases of a difficult lumbar puncture in obese patients, a bedside ultrasound can be helpful.

PROCEDURE

See Video E18-1.

- Place the patient in the lateral decubitus position with knees flexed to the abdomen and head flexed with the chin toward the chest.
- Position the patient's back as close as possible to the edge of the bed nearest the examiner.
- Before preparing the skin, locate the L4-5 and L5-S1 interspaces and mark them.
- The skin should then be prepared with chlorhexidine or povidone-iodine. The preparation should proceed outward in a spiral and cover several interspaces in case multiple attempts are necessary.
- Drape the patient's back with a sterile sheet with an opening to the prepared area so that it covers the posterior iliac crest.
- Anesthetize the skin with 1% lidocaine using a 25-gauge needle, which may be exchanged for a longer 22-gauge needle to reach deeper tissues.
- Using a 20- or 22-gauge spinal needle, advance it with the stylet in place to avoid the introduction of epidermal cells into the subarachnoid space.
- Direct the bevel of the needle upward to separate the fibers of the ligamentum flavum. The angle of the needle 15 degrees cephalad and slightly downward toward the bed.
- When the dura is punctured, and a slight "pop" is felt, the stylet should be withdrawn.
- If a free flow of CSF does not occur, the needle can be rotated or may have to be advanced (after replacing the stylet).
- Once the free flow of CSF is obtained, attach a manometer to the spinal needle, usually by way of a stopcock. CSF should rise steadily in the manometer until the opening pressure is reached and respiratory fluctuation can be visualized in the fluid column.
- The patient's legs should be carefully extended and relaxed for an accurate pressure reading.
- Collect four tubes of CSF (3 mL of fluid in each) and send them for appropriate studies.
- In cases of pseudotumor cerebri in which a lumbar puncture has been chosen as a therapeutic modality to reduce the raised intracranial pressure, after quantifying the opening pressure, the removal of 20 mL of CSF is generally recommended and the closing pressure documented.
- Replace the stylet to minimize the possibility of pulling a nerve root through the dura as the needle is removed.
- Withdraw the needle and apply pressure to the puncture site.
- If the subarachnoid space cannot be entered with this technique or the patient cannot lie in the lateral decubitus position, a lumbar puncture can be performed with the patient sitting on the side of the bed leaning forward over a bedside table. However, once free CSF flow occurs, the patient should be returned to the recumbent position for accurate pressure measurements.
- If a patient is unable to bend one leg (e.g., after an angiographic procedure), a lumbar puncture can be attempted in the lateral position with the bottom leg held straight, and the top leg bent into the abdomen and supported with a pillow.

AFTER PROCEDURE

Postprocedure Care

- Allow the patient to lie flat for 1 to 3 hours after the procedure to minimize the risk of post–lumbar puncture headache. Argument persists regarding the value of prone versus supine positioning on the incidence of a headache and about the use of varying sizes and types of needles.

Complications

- Common
 - Headache
 - Bleeding from the puncture site
- Infrequent
 - CSF leak
 - Infection
 - Subarachnoid cyst

- Serious, rare complications
 - Epidural hematoma formation
 - Cerebral herniation
 - Aneurysmal rebleeding
 - Nerve root injury

OUTCOMES AND EVIDENCE

- To ensure an optimal diagnostic outcome when performing a lumbar puncture, it is wise to check with the laboratory before the procedure if any unusual tests are being performed, because an additional tube or larger volumes or special handling of CSF may be required. Regarding optimal patient outcomes, if a diagnostic lumbar puncture is delayed for imaging in a suspected case of bacterial meningitis, blood cultures should be obtained, and empiric antibiotics should be administered, as CSF cultures can be obtained up to 4 hours after starting treatment.

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Jugular Venous and Brain Tissue Oxygen Tension Monitoring

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ULTRASOUND-GUIDED INTERNAL JUGULAR VEIN OXYGEN SATURATION (Sjvo₂) CATHETER PLACEMENT: BEFORE PROCEDURE

Indications

- Severe traumatic brain injury
- Subarachnoid hemorrhage
- During neurosurgical and cardiovascular procedures in which, cerebral blood flow may be reduced
- Detection of arteriovenous fistulas
- To titrate hyperventilation in patients with increased intracranial pressure

Contraindications

- Absolute
 - Infection of the placement site
 - Suspected pathologic conditions affecting the internal jugular vein or superior vena cava
 - Severe coagulopathy
- Relative
 - Cervical spine injury
 - Tracheostomy
 - Recurrent sepsis
 - Hypercoagulable state
 - Sensitivity to heparin if a heparin-coated catheter is used
 - Distorted anatomic landmarks

Equipment

- Sterile gowns
- Sterile gloves
- Mask
- Betadine or chlorhexidine solution
- Commercially packaged catheterization kits are available; kits may include
 - Drapes
 - Disinfectant sponges
 - Gauze pads
 - Sutures with needles
 - Guide wire
 - Scalpel
 - Vein dilator
 - Penetration, guide, and anesthetic syringe, as well as a 1% or 2% lidocaine anesthetic solution
- Ultrasound machines with high-resolution vascular transducers are preferred for this procedure.
- Sterile transduction gel, acoustically transparent sterile transducer sheath, and sterile rubber bands or clips to secure sheath around transducer
- 5.5F fiberoptic intravascular catheter (Opticath catheter)

- The catheter contains the fiberoptics for light transmission, a distal lumen for pressure reading, sampling, or infusion, and a thermistor for temperature measurement.
- Optical module (to connect to bedside monitor)
- Introducer kit

ANATOMY

The venous sinuses of the brain drain out of the skull through the jugular foramina and into the internal jugular veins. Immediately distal to the jugular foramen, the vein dilates, forming the jugular venous bulb. The cerebral and cerebellar veins and the veins of the brainstem all open into major sinuses (e.g., superior sagittal, inferior sagittal, straight, right, and left transverse, and occipital sinuses); these terminate in the right and left sigmoid sinuses, which curve downward into a deep groove on the mastoid part of the temporal bone. Finally, they turn forward in the posterior aspect of the jugular foramen to become the jugular bulb of the internal jugular vein.

The trachea is in the midline descending to the sternal notch. The two heads of the sternocleidomastoid muscle and the clavicle form a triangle at the anterior neck. The internal jugular vein may be accessed through this triangle, approximately 2 to 3 cm above the clavicle. Performing a venous puncture higher in the triangle reduces the risk of pneumothorax and allows for better compression of the carotid artery in the case of an inadvertent carotid puncture.

PROCEDURE

See Video E19-1.

- Continuous electrocardiography (ECG) and pulse oximetry
- Place the patient in Trendelenburg position to increase jugular filling and reduce the possibility of an air embolism.
- Avoid this position in patients with increased intracranial pressure (ICP) or congestive heart failure.
- Rotate the patient's head slightly to the contralateral side of the chosen site.
- Perform an ultrasound survey to assess the location and patency of the jugular vein and to determine whether one side has dominant flow. Catheter placement is easier, and continuous oxygen saturation measurements will usually be better on the side with the greatest blood flow.
- The common carotid artery and the internal jugular vein should be easy to identify. You will see the common carotid artery as a pulsating image, and it will be difficult to compress. The internal jugular vein is larger, easily compressible, and nonpulsating. Ensure that the internal jugular vein is patent by gently compressing the vein with the transducer; slight pressure is sufficient to collapse the lumen of the internal jugular vein. Placing the transducer in a cross-sectional position during the ultrasound examination facilitates the interpretation of the resulting images. Many probes have a marker on one side that corresponds to the same side of the image on the screen. This helps the operator identify the correct orientation of the image.
- After you have identified an acceptable site for cannulation, you will need an assistant.

- Follow the Universal Precautions when placing a jugular venous line.
- Prepare the skin using a chlorhexidine-based antiseptic, and cover the area with a sterile fenestrated drape.
- To prepare the ultrasound probe, have the assistant dispense enough acoustic nonsterile gel into a sterile transducer sheath to cover the transducer surface inside the sheath.
- Have the assistant carefully feed the probe into the sheath and through the gel while extending the sterile sheath away from you over the length of the probe wire. Eliminate any wrinkles in the sheath and any air bubbles between the transducer and the sheath. Place the rubber bands to secure the cover sheath in place. To complete the acoustic coupling, apply a small amount of sterile ultrasound gel to the covered ultrasound probe or the patient's skin.
- Identify a convenient sterile area on which the probe can be placed when not in use.
- Position the transducer perpendicular to the skin so that the internal jugular vein is centered in the resulting ultrasound image and between the two heads of the sternocleidomastoid muscle. The ultrasound probe should be held in your nondominant hand.
- Gently palpate the skin to confirm that the puncture will be between the muscle heads and not through one of the heads.
- Using an 18-gauge needle, puncture the skin just below the transducer, being careful not to damage the sterile sheath.
- Slowly advance the needle at a 45-degree angle in an upward direction while watching the ultrasound screen. As you advance the needle, maintain negative pressure in the syringe until the vein is punctured. The needle will appear as a hyperechogenic shadow.
- If you do not aspirate blood as the needle is advanced, slowly withdraw the needle while maintaining negative pressure. The venous puncture may become evident as you withdraw the needle. Occasionally, pressure from the ultrasound probe may compress the vein, making it difficult to enter the vessel.
- As soon as the blood is freely aspirated, place the probe in the predetermined sterile area, stabilize the needle, and disconnect the syringe.
- Confirm that the blood flow is nonpulsatile.

Introducer Insertion

- Using the Seldinger technique, introduce a flexible guide wire through the needle and into the internal jugular vein. Direct the guide wire in an upward direction toward the jugular bulb.
- While holding the guide wire in place, remove the needle. The guide wire can be visualized in both cross-sectional and longitudinal views within the lumen of the internal jugular vein in the ultrasound screen.
- Use the scalpel to make a small incision in the skin to widen the opening.
- Thread the guide wire through the distal opening of the dilator until it exits through the proximal end of the dilator.
- Confirm that it has reached the proximal end of the dilator, hold the wire in place, and advance the dilator through the skin and into the vessel.
- Once the proper placement is achieved, remove the guide wire and the green dilator.
- Hold the proximal end of the guide wire at all times when advancing the dilator or catheter. This avoids complications from the unintended advancement of the guide wire.
- Bleeding frequently occurs after the dilator is withdrawn; minimize it by applying pressure until the bleeding subsides.

Opticath Intravascular Catheter Insertion

- Inspect the sterile package first; if damaged, DO NOT USE.
- Have an assistant remove the outer wrapping, and leave the catheter covered by the inner covering.

- Pass the optical connector to the assistant, who will connect it to the optical module and proceed with the preinsertion calibration. PLEASE NOTE that only *after* verifying with your assistant that the preinsertion calibration was successful should you proceed to the next step. Failure to do so will result in inaccurate readings.
- After a successful preinsertion calibration, the oximetry system is now ready for use. Prepare for the catheter insertion.
- Pull off the remaining inner catheter covering, and pull the red retainer tab to release the catheter.
- Grasp the catheter near the entrance of the black reference assembly, and gently pull it straight out. Care should be taken in removing the catheter, as the fiberoptics may be damaged if the catheter is withdrawn improperly.
- Flush the catheter with sterile solution, using the distal lumen to remove the remaining air.
- The catheter tip should be illuminated with a red light emission before insertion.
- The catheter should then be advanced until resistance is felt; this distance is usually about 13 to 15 cm and indicates the positioning in the jugular bulb.
- The catheter is then pulled back 0.5 to 1 cm to minimize cephalic vascular impact with head movement.
- Connect the distal lumen to a pressure monitoring line.
- When the catheter is in position and blood is flowing, the system will immediately provide SO₂ readings.
- At this time, ask the assistant to perform a light intensity calibration.
- Verify the position of the catheter tip, and secure the catheter to the patient. The optical module should be secured to or near the patient to avoid strain or tension on the catheter.
- Apply the dressing as per hospital protocol.

AFTER PROCEDURE

Postprocedure Care

- Lateral cervical spine x-ray should be used to confirm adequate catheter tip placement, which should be above the C1-C2 level to minimize contamination with blood coming from the facial vein.
- The Opticath intravascular catheter is removed by a physician. It is removed when ICP has been normal for 24 hours without specific treatment.
- The patient must be in the Trendelenburg position.
- Remove the sutures securing the catheter to the skin.
- Carefully pull out the Opticath intravascular catheter.
- Apply pressure to the site for a few minutes to prevent bleeding.
- Apply a sterile dressing.
- Assess for bleeding or signs of infection.
- Dispose of the Opticath intravascular catheter per hospital protocol.
- Clean the optical module and cable for storage.

Complications

- Carotid artery puncture
- Skin hematoma
- Pneumothorax
- Hemothorax
- Jugular vein thrombosis
- Nerve injury
- Catheter misplacement
- Infection

OUTCOMES AND EVIDENCE

- Normal jugular bulb oxygen saturation values are between 55% and 75%.
- <55% indicates relative cerebral hypoperfusion.

- >75% suggests luxury perfusion.
- Please refer to the standard critical care guidelines for management.

BRAIN TISSUE OXYGEN PROBE AND MICRODIALYSIS CATHETER PLACEMENT: BEFORE PROCEDURE

Indications

- Severe traumatic brain injury
- Aneurysmal subarachnoid hemorrhage
- Malignant stroke
- Vasogenic edema
- To assess brain tissue oxygenation, detect brain hypoxia, and for continuous monitoring of brain tissue chemistry (e.g., metabolites and drugs)

Contraindications

- Absolute
 - Infection and/or lack of skin at the site of planned insertion
 - Coagulopathy
- Relative
 - Incompatibility with available magnetic resonance imaging (MRI) system if an MRI of the brain is needed

Equipment

- Sterile gown pack
- Sterile gloves
- Sterile linen pack
- Sterile 4 × 4 gauze bandages
- Mask
- Shave prep kit
- Betadine bottle
- 16-gauge (orange) angiocatheter to tunnel the probe
- Cranial access tray
- One refrigerated combined LICOX probe box
- “Smart card” (enclosed in the sterile LICOX probe container)
- Note: Do not discard the probe packaging before the probe smart card has been removed from the packaging. Use only the smart card supplied with the probe (the serial number on probe should match the number on the smart card). Use of the wrong smart card can cause measurement errors. If the serial numbers do not match, use another LICOX probe box, and return the first one to the vendor.
- #11 blade
- Nylon 3-0 suture
- CMA 70 Brain Microdialysis catheter
- Central nervous system (CNS) perfusion fluid
- CMA 106 syringe
- Surgeon's head light
- Standard surgical suction
- LICOX monitor with a complete set of cables
- Module box and link box and cable (to attach LICOX monitor to bedside monitor)
- Power cord to red AC wall outlet
- CMA 106 Microdialysis Pump with battery

ANATOMY

Ideally, the probe should be placed in the area at risk for brain hypoxia. However, if a computed tomography (CT) scan reveals no areas at risk for hypoxia, the probe may be placed 2 to 4 cm off the midline just anterior to the coronal suture and at least 1 cm from the other probe when possible. Preparation must include shaving the patient's head to a diameter of approximately 2 to 4 cm off the midline just anterior to the coronal suture.

PROCEDURE

- Since these patients are critically ill, vital signs (e.g., invasive blood pressure, central venous pressure, ECG, pulse oximetry, and core temperature) must be continuously monitored.
- The patient must be under sedation throughout the procedure and have intravenous access and mechanical ventilatory support.
- Wash hands. All staff involved in the procedure should wear a surgical mask and gloves throughout the entire procedure.
- After reviewing the patient's CT head scan, the physician will determine the anatomic area for catheter placement.
- As noted earlier, the probe is placed in the area at risk for brain hypoxia, but if the CT scan does not show areas at risk for hypoxia (i.e., diffuse axonal injury), place the probe at least 1 cm from the intracranial pressure probe.
- This area will be prepped with Betadine. Strict sterile field and technique must be maintained throughout the procedure.
- Drape the patient with the sterile blanket.
- Place the patient in a semi-Fowler position, raising the head of the bed to the level of the physician's preference.
- If a ventriculostomy was previously placed, the same incision may be used for probe placement. If no incision exists, make a 3-cm linear incision, carrying it down to the bone.
- Infiltrate the incision with local anesthetic and epinephrine to help control the bleeding from the scalp incision.
- A self-retaining retractor is then inserted to provide good bone exposure.
- The blunt end of the forceps can be used to remove the periosteum.
- Drill the hole in the skull at the desired catheter insertion site, using a hand drill.
- Remove the drill, and rinse the hole with a sterile isotonic solution.
- Incise the dura carefully with a style or a #11 blade, securing hemostasis as necessary.
- Insert the sharp end of the 16-gauge angiocatheter needle from the inside out through the scalp, 5 cm distant from the burr hole.
- Remove only the needle, leaving the angiocatheter.
- Remove the LICOX catheter from its sterile package.
- Remove the probe from the humidity protection chamber.
- Insert the LICOX probe distal tip into the angiocatheter, and tunnel it below the scalp toward the burr hole.
- Pull the angiocatheter completely out of the scalp.
- Using forceps, insert the distal end of the probe into the brain parenchyma. Ensure that the catheter body is not damaged during insertion.
- If necessary, adjust the position of the probe to allow the distal tip of the catheter to be positioned correctly with respect to the insertion site.
- Use a single suture to secure the probe to the scalp near the insertion; this must be done carefully to avoid damaging or dislodging the catheter.
- To place the microdialysis catheter, insert the sharp end of the 16-gauge angiocatheter needle from the inside out through the scalp 5 cm distant from the burr hole and approximately 1 cm from the brain tissue PO₂ probe insertion site in the scalp.
- After removing the protection tube from the shaft, gently flush with the CNS perfusion fluid, both inlet and outlet tubes, and insert a sterile microvial into the microvial holder.
- Tunnel the microdialysis catheter as previously described for the brain tissue PO₂ probe.
- Grip the catheter shaft with the forceps, proximal to the distal end where the delicate membrane is located. An intact membrane is vital for microdialysate return.
- Insert the membrane into the brain tissue through the burr hole used to insert the brain tissue PO₂ probe.
- Fix the tubing to the scalp, using one suture around the catheter.
- Carefully remove the retractor.

- Make sure both probes remain in place.
- At the burr hole site, close the scalp incision using standard closure techniques; this must be done with extreme caution to avoid damaging any of the probes.
- Apply an extra transparent and soft-cloth adhesive dressing or any appropriate dry sterile occlusive dressing.
- Date and initial the dressing.
- Change the LICOX dressing every 48 hours or whenever saturated, using sterile technique including a mask and sterile gloves, and cleanse the insertion site with Betadine swabs from the central line dressing kit.

AFTER PROCEDURE

Postprocedure Care

- Securing of the LICOX cables
 - The cables should be taped to an arm board and then pinned to the patient's gown, allowing enough slack to accommodate movement of the patient for turning and transferring.
 - Plug in the connecting cable to the proximal end of the probe.
 - Connect both ends of the Y cable to the LICOX monitor. Insert the smart card in the card slot.
 - Power on the LICOX monitor.
 - Wait a few seconds for a stable reading; it may take up to 2 hours for reliable readings.
 - Connect the LICOX monitor to the bedside monitor, using the link box and cable.
 - Attach the Luer-Lok connector to the CMA 106 syringe filled with CNS perfusion fluid.
 - Place the CMA syringe in the CMA 106 pump, and close the lid.
 - Inspect the microvial after 6 minutes to see that the microdialysate flows through the catheter.
 - Replace the microvial every hour or as needed.
 - Discard the first two microvials, since this microdialysate is purely CNS perfusion fluid.
 - If the microdialysate contains blood, it may harm the CMA 600 microdialysis analyzer; if this occurs, the catheter must not be used.

- A CT scan of the head should be obtained after the procedure is complete to confirm the location of the probes.
- Discontinuation of the LICOX CMP system
 - It is recommended that LICOX probes not be left in tissue for more than 5 days.
 - The probes should be removed by a physician. Probes are removed after ICP has been normal for 24 hours without intervention.
 - Remove the sutures securing the probe to the scalp.
 - Carefully pull out the probes.
 - Suture the insertion site in the scalp with a single stitch.
 - Assess for bleeding, cerebrospinal fluid (CSF leak), and signs of infection.
 - Clean the skin and apply a sterile dressing.
 - Dispose of the probes per hospital protocol.
 - Clean the cables and attach to the monitor for storage. Blood and debris may be removed from the cables with a towel and aqueous soap solution that also may contain formaldehyde. Disinfectants containing a high percentage of alcohol or phenol will damage the cables.

Complications

- Common
 - Generally, there are no common complications.
- Infrequent
 - Infection and contusion in <2%
- Serious, rare complications
 - Thrombosis and hemorrhage

OUTCOMES AND EVIDENCE

- Normal brain tissue PO₂ values are between 25 and 50 mm Hg.
- <20 mm Hg indicates impending cerebral hypoxia.
- <10 mm Hg indicates critical hypoxia.
- Please refer to the standard critical care guidelines for the management of cerebral hypoxia.
- Normal values for microdialysate are less well defined; please refer to the textbook for further review.

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ULTRASOUND-GUIDED INTERNAL JUGULAR VEIN OXYGEN SATURATION (Sjvo₂) CATHETER PLACEMENT

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BEFORE PROCEDURE

Indications

- Common
 - Traumatic brain injury (TBI)
 - Subarachnoid hemorrhage
 - Intracranial hemorrhage (ICH)
 - Acute liver failure
 - Hydrocephalus
- Uncommon
 - Meningitis/encephalitis/brain abscess
 - Pseudotumor cerebri
 - Postoperative

Contraindications

- Absolute
 - Anticoagulation
 - Bleeding diathesis
- Relative
 - Scalp infection
 - Lack of specialized healthcare personnel

Equipment

- Flexible catheter or fiberoptic transducer
- Surgical scalpel
- Spinal needle
- Neurosurgical drill/saw
- Surgical scissors
- Retractors
- 14-gauge catheter

ANATOMY

- For brain monitoring, the entry point is located in the superiorly directed midpupillary line, 3 cm lateral to the sagittal suture and 2 cm anterior to the coronal suture on the right (frontal approach). This is the most commonly chosen site because it sits anterior to the motor strip, is lateral to both the superior sagittal sinus and the large bridging veins, and is on the nondominant hemisphere in most patients. If using a posterior approach, the entry point is 6 cm from theinion and 3 cm lateral to the midline. For lumbar monitoring, the L3-4 space is preferred.
- There are four main ways to monitor ICP
 1. Using an external flexible catheter inserted into the lateral cerebral ventricles (i.e., ventriculostomy) as the gold standard method.
 2. Using a catheter (fluid-coupled) or fiberoptic transducer (fluid-uncoupled) placed into the brain parenchyma (i.e., intraparenchymal catheter).
 3. Using a screw or bolt placed through the skull into the subarachnoid space.
 4. Using a sensor positioned in the epidural/subdural space beneath the skull.
- A lumbar drain can also be used to measure ICP and control the CSF outflow if zeroed at the level of the third ventricle.

PROCEDURE

- Ventriculostomy
 - Place the patient in a supine position with the head of the bed elevated to approximately 20 degrees.
 - Shave areas (frontal or posterior) bilaterally.
 - Prepare with a chlorhexidine-alcohol solution, and cover with a sterile drape.
 - Inject lidocaine solution (1%) into the skin and subcutaneous tissue.
 - Make a 1-cm incision with the scalpel and extend down to the bone. Hold the twist drill perpendicular to the skull to make a burr hole, avoiding the brain parenchyma.
 - Once the burr hole is irrigated, insert a spinal needle through the dura to verify that the incision is large enough to accommodate the catheter.
 - Advance the ventricular catheter through the burr hole perpendicular to the brain parenchyma, toward the inner canthus of the ipsilateral eye. Insert the catheter to a depth of approximately 6 cm to enter the frontal horn of the lateral ventricle. If the cerebrospinal fluid (CSF) is encountered before a depth of 6 cm, withdraw the stylet and advance the catheter the remaining distance. If CSF flow is not obtained at 6 cm, additional attempts should be made with the catheter tip directed more medially (i.e., toward the bridge of the nose or the inner canthus of the contralateral eye).
 - Tunnel the external end of the catheter under the scalp to exit through a separate incision approximately 5 to 6 cm from the entry point. Connect the distal end of the catheter to a pressure transducer and/or drainage system. Close the incision wound with sutures, and secure the catheter to the scalp with nylon suture. Apply a sterile nonocclusive dressing to minimize the risk of infection.
 - Zero the pressure transducer (fluid-coupled) at the level of the external auditory meatus.
- Intraparenchymal
 - The placement and tunneling of the device are similar to that of a ventriculostomy, but the depth of insertion depends on the compartment being monitored (e.g., subdural space, parenchyma, or ventricular system).
- Subarachnoid screw or bolt
 - The device is inserted using the same location and technique described earlier for burr hole placement. Once the burr hole is drilled, the dura and arachnoid are opened, and the threaded bolt is placed into the skull abutting the dura. Continuous fluid coupling between the subarachnoid space and an external pressure transducer are recorded through rigid tubing attached to the top of the bolt.
- Epidural/subdural sensor
 - This is inserted via the burr hole into the space between the skull and the epidural lining.
- Lumbar drain
 - Ensure that the patient has a functioning ventriculostomy in place and open cisterns on head CT scan
 - Place the patient in lateral decubitus.
 - Use the same preparation as for brain monitoring.
 - Insert a 14-gauge needle with 10 to 15 degrees of angulation in the cephalic direction, and once the lumbar cistern is entered,

rotate the needle 90 degrees, remove the obturator from the needle, and measure an opening pressure.

- Insert the catheter with a guide wire until the 15-cm mark on the catheter is reached. Remove the needle while maintaining the catheter in the same position. Remove the guide wire from the lumbar drain catheter, and connect the drain to the CSF collecting system.

AFTER PROCEDURE

Postprocedure Care

- If fluid-coupled systems are used, the pressure transducer must be adjusted to the head position to avoid errors in measurement.
- Check for air bubbles, blood clots, or other material occluding the tubing.
- Inspect the drain insertion site to ensure no leakage of CSF around the exit site.
- Sample the CSF daily to detect infection early.
- Normal ICP values are between 0 to 10 mm Hg (under resting conditions).
- *Intracranial hypertension* is defined as a sustained elevation of ICP above 20 to 25 mm Hg for more than 5 minutes.

Complications

- Common
 - Malpositioning
 - Erroneous values (subarachnoid catheters in case of swollen parenchyma and dural flap; epidural catheters when ICP exceeds 30 mm Hg)
 - Erroneous zeroing (intraparenchymal if monitoring more than 5 to 7 days)
- Infrequent
 - Overdrainage (lumbar drain)
 - Radiculopathy (lumbar drain)
- Serious rare complications
 - Infections (e.g., ventriculostomy)
 - Hemorrhage: 0.5% to 10%
 - Brain herniation (lumbar drain)

SUGGESTED READING

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Lavinio A, Menon DK. Intracranial pressure: why we monitor it, how to monitor it, what to do with the number and what's the future? *Curr Opin Anaesthesiol* 2011; Epub ahead of print.

OUTCOMES AND EVIDENCE

- Monitoring ICP is recommended in critically ill patients with coma (defined by a GCS < 9) after acute brain injury (e.g., trauma, intracranial hemorrhage, encephalitis) with abnormal noncontrast head CT scan (defined by the presence of intracerebral lesions and/or signs of brain edema, such as sulci or cisternal effacement) who are at risk for intracranial hypertension
- Monitoring ICP is useful in critically ill patients to manage intracranial hypertension, to guide ICP-targeted therapies, to calculate and monitor cerebral perfusion pressure, and to drain CSF.
- Intraventricular and intraparenchymal probes are equally effective in measuring ICP. Ventriculostomy must be continuously zeroed. Fiberoptic monitors are zeroed before insertion and are not affected by the patient position or bed height. The drift of measurements over time can be a problem, and intraparenchymal probes do not allow CSF drainage. ICP can also be measured via subarachnoid, epidural/subdural, or lumbar drains. Compared to intraventricular or intraparenchymal catheters, subarachnoid and subdural/epidural probes do not guarantee a reliable measure of ICP.
- The risk of hemorrhagic complications from the placement of an ICP monitor ranges from approximately 0.5% to 10%. The risk of a hemorrhage increases dramatically when coagulation abnormalities are present. The placement of intraparenchymal probes is easier than with intraventricular catheters, particularly in conditions of brain edema and ventricular effacement.
- The rate of infection associated with ICP monitors correlates with duration of placement, presence of a CSF leak, the frequency of CSF sampling, presence of intraventricular hemorrhage, and concurrent systemic infection. The utility of prophylactic antibiotics and daily surveillance of CSF cultures is highly controversial. The rate of catheter-related infection is lower with intraparenchymal than intraventricular catheters.

Stocchetti N, Maas AI. Traumatic intracranial hypertension. *N Engl J Med* 2014;370:2121-30.

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■ BEFORE PROCEDURE

Indications

- A need for estimating energy expenditure (EE) in critically ill patients in whom the EE is highly variable and difficult to predict by simple equations, such as
 - Patients with liver disease
 - Obese patients

Contraindications

- Absolute contraindications
 - Situations preventing a complete collection of expired gases
 - Leaks of gas from the ventilator circuit
 - Leaks around endotracheal tubes
 - Leaks through chest tubes
 - Instability of delivered oxygen concentration
 - Oxygen concentration above 65
- Relative contraindications
 - Ongoing hemodialysis
 - Hemodynamically unstable patient
 - Large bias flow
 - Extreme circuit flow rates

Equipment

- Indirect calorimeter

■ PROCEDURE

See Video E21-1.

- Select the patient.
- Connect the inspiratory sampling line tube to the water trap container.

ANNOTATED REFERENCES

Lev S, Cohen J, Singer P. Calorimetric measurements in the ICU. Facts and controversies. The heat is on. *Crit Care Clin* 2010;26:1e-9e.

A comprehensive review of calorimetric measurements in critically ill patients.

Loh NHW, Griffiths RD. The curse of overfeeding and the blight of underfeeding. In: Vincent JL, editor. *Yearbook of intensive care and emergency medicine*. Berlin: Springer-Verlag; 2009. p. 675-83. *This paper summarizes the various deleterious effects of overfeeding.*

- Switch on the monitor.
- Warm up for 30 minutes.
- Choose the correct respiratory mode.
- Perform gas calibration.
- Insert patient data.
- Connect the mixing chamber inlet to the expiratory outlet of the respirator.
- Place the inspiratory sampling line in the inspiratory tube of the respirator.
- Press start.
- Measure for at least 30 minutes.
- Get a report.

■ AFTER PROCEDURE

- Adjust metabolic care according to the metabolic measurements.

Complications

- Common
 - Inaccurate measurements due to equipment malfunction and methodologic problems
- Infrequent
 - Infections cross over.

MacDonald A, Hildebrandt L. Comparison of formulaic equations to determine energy expenditure in the critically ill patient. *Nutrition* 2003;19:233-9.

This paper summarizes the various equations available for predicting REE in critically ill patients and shows their limitations.

■ BEFORE PROCEDURE

Indications

- Venovenous extracorporeal membrane oxygenation (ECMO)
 - Inability to oxygenate and/or ventilate a patient due to the following
 - ARDS
 - Pneumonia
 - Lung Transplantation (Primary Graft Dysfunction)
 - Reperfusion ischemic injury
 - Rejection
 - Infection
 - Technical issues
 - Bridge to lung transplantation
 - Failure to achieve adequate PaO_2 (>50) on 100% FiO_2 or persistent shunt >25% despite an optimally tolerated PEEP through the following therapies
 - Failed trial of pressure control/inverse ratio
 - Trial of diuresis
 - Trial of paralytics
 - Trial of nitric oxide
 - Trial of high frequency of oscillator ventilation
 - Consider trial of prone positioning
- Venoarterial ECMO
 - Indication for ECMO in adult cardiac failure is cardiogenic shock: Inadequate tissue perfusion manifests as hypotension and low cardiac output despite adequate intravascular volume
 - Typical causes
 - Acute myocardial infarction
 - Myocarditis
 - Peripartum cardiomyopathy
 - Decompensated chronic heart failure
 - Postcardiotomy shock
 - Heart transplantation (primary graft dysfunction)
 - Ischemic reperfusion injury
 - Rejection
 - Pulmonary hypertension
 - Technique issues
 - Bridge to heart or heart-lung transplantation
 - Shock persists despite the following therapies
 - Volume administration
 - Inotropes and vasoconstrictors
 - Mechanical support with intraaortic balloon counterpulsation or impella if appropriate

Contraindications

- Absolute contraindications
 - Age greater than 65
- Significant life-limiting disease
 - Significant baseline lung disease including home O_2 dependence or heart disease
 - Not a transplant candidate
 - Encephalopathy
 - Cancer

- Cirrhosis
- HIV
- Recent stroke/intracranial hemorrhage
- Suspicion of anoxic brain injury
- Relative contraindications
 - Bleeding diathesis
 - Gastrointestinal bleed
 - Greater than 14 days of mechanical ventilation
 - Encephalopathy

Equipment

- Permanent equipment
 - 1—Centrifugal pump
 - Maquet Cardiohelp
 - Integrated pump and oxygenator
 - Provides real-time arterial and venous pressures, hemoglobin and SVO_2
 - Thoratec Centrimag
 - Magnetically levitated pump impella—contract free for less hemolysis
 - 1—ECMO cart (including instrument tray)
 - 1—Oxygenator bracket (Quadrox D)
 - 1—Pump external drive
 - 1—Heater/cooler with appropriate water lines and connectors (BioCal or Sarns) or heating blanket
 - 1—Oxygen/medical air blender with appropriate length (20 ft each) gas lines and connectors for all operating rooms and intensive care areas
 - 1—Cardiotomy reservoir holder
 - 1—Manifold for pressure readings on the BioPump 540 transducer, Medtronic DLP pressure display
 - 6—Tubing clamps and scissors
 - 1—Hand crank
 - 1—Bed plate with two long poles
 - 1—Blue roller clamp assembly for recirculation line (10 mm Keck roller clamp from Cole Parmer)
 - 2—Full 100% oxygen E cylinders with a tubing adaptor
 - 1—Set of each: four types of gas connectors
- Possible accessory equipment
 - 1—Hemoconcentrator bracket
- Disposable supplies
 - ECMO CARMEDA-bonded (CB) Medtronic custom tubing pack or a Maquet custom tubing pack—Quadrox Bioline or Levitronix pump head
 - Cardiotomy reservoir
 - Walrus extension connectors with high-flow stopcocks
 - Terumo extensions high flow (one positive and one negative for kidney)
 - Pressure veil and isolator tubings or DLP pressure display set
 - 3/16" to male connectors
 - Extra 3/8" CB straight connectors with a Luer-Lok
 - 3/8" non-Carmeda bonded connector
 - 3/8" perfusion adaptor
 - Plasmalyte-A pH 7.4—2000 mL (prime the circuit)
 - Sterile water for irrigation for BioCal or Sarns water heater (approximately 3 to 4 L)

- Syringes; 3 mL, 10 mL, and 60 mL
- Blood filter
- Extra supplies for ECMO site
 - CB BioMedicus cannulae
 - 50-cm venous: 29F; 27F; 25F;
 - 18-cm arterial: 23F (for venous insertion), 21F, 19F, 17F, and 15F
 - CB Medtronic DLP malleable venous cannulae: 32F, 36F, and 40F
 - CB EOPA cannulae: 20F; 22F; 24F
 - CB/non-CB right angle venous: 40F
 - CB Edwards RMI 36F RA
 - CB two-stage 36/46
- Avalon cannula (double lumen cannula): 23F, 27F, and 31F
- Insertion kits for cannulae (RMI PIKV for 23, 25, 27, and 29 venous)
- Extra oxygenator Quadrox D
- Fresenius hemoconcentration (with Terumo tubing assembly)
- SCUF custom tubing pack
- IV tubing for hemofiltration
- Extra CB VAD/liver pack
- Extra length CB 6-ft. $3/8" \times 3/32"$ tubing (sterile) and $1/4 \times 3/32"$ sterile tubing
- CB $3/8"$ connectors with Luer-Lok
- 8F pediatric arterial CB cannula with $1/4" \times 3/8"$ connector and $1/4"$ tubing CB (for distal femoral artery perfusion)
- Walrus large-bore stopcock and extension assemblies
- Terumo high-flow extension stopcocks
- Isolator (pressure veils), $3/16"$ male connectors, and stopcocks
- 3-mL, 10-mL, and 60-mL syringes
- 18-gauge needles and sterile safety blades or sterile scissors
- Plasmalyte-A pH 7.4
- Blood filter (40 microns)
- Heparin (1:1000 units/mL)
- 210-cm guide wire
- 100-cm guide wire
- Small biohazard bags
- Panduit ties and gun
- Appropriate charts, ECMO pre-bypass checklist, ECMO shift schedule, and a shift checklist

ANATOMY

For femoral cannulation should locate the femoral triangle of the patient. The femoral triangle is the name given to an area of the anterior aspect of the thigh formed as different muscles and ligaments cross each other producing an inverted triangular shape. Contained within this area, placed medially to laterally, are the femoral vein, artery, and nerve (remember "van"). The borders of the triangle are composed of the medial border of the sartorius that forms the lateral border of the triangle, while the inguinal ligament forms the superior border, and the medial border is formed by the medial border of the adductor longus. Within the triangle, the femoral artery lies at the midinguinal point, which is the midway point between the pubic symphysis and the anterior iliac spine. This midway point is an important landmark in locating the femoral artery. It is also an important landmark within the leg since medial to the femoral artery is the femoral vein. Thus, in effect, you can locate the femoral vein by palpating the femoral pulse and moving your needle medially.

The internal jugular vein lies within the triangle that is made up by the lateral head of the sternocleidomastoid muscle, medial head of the sternocleidomastoid muscle, and the clavicle inferiorly. Locate the apex of the triangle, and move inferiorly to the center to locate the internal jugular vein. The apex of this triangle is a good landmark in locating the internal jugular vein. The carotid artery lies lateral and inferior to the internal jugular vein.

In the anatomy for central ECMO cannulation, the ascending aorta located within the mediastinum is cannulated with the arterial

cannula, and the right atrium is cannulated with the venous cannula in venoarterial ECMO. In central venovenous ECMO, cannulas are placed in the right atrium (venous cannula) and pulmonary artery (arterial cannula).

PROCEDURE

• Venovenous percutaneous

Cannulation is usually performed at the patient's bedside with the assistance of nursing staff. Percutaneous venous cannulation for ECMO is achieved with the use of a modified Seldinger technique. The right neck and the appropriate groin region are prepared and draped in a sterile fashion, and anesthesia is achieved with a local anesthetic. Unless contraindicated by immediate postoperative status, all patients receive a bolus of 3000-5000 units of heparin (or 100 units/kg) for the cannulation procedure (percutaneous or open). The vein (e.g., femoral or jugular) is accessed at an angle of approximately 30 degrees with the skin, and the guide wire is passed through the needle. As for any percutaneous technique, the guide wire should pass unimpeded. Occasionally, the onset of cardiac ectopy provides evidence regarding the location of the wire's tip. We commonly temporarily replace the wire with an Angiocath or small dilator to verify that the access achieved is venous and not arterial. The wire is then replaced, and, using it as a guide, sequentially larger dilators are passed. Manual compression of the insertion site is used to prevent excessive bleeding as the dilators are sequentially removed and reinserted. It is very important to ensure that the wire moves freely during dilatation as well as cannula insertion. Free movement of the guide wire indicates that the dilator or cannula is following the path of the wire and not kinking and taking an alternative path, such as through the vessel wall. Kinking can be prevented by gentle traction on the wire applied by an assistant as the dilator or cannula is passed. Creation of a skin incision slightly smaller than the cannula being inserted facilitates passage of the cannula while still providing good hemostasis. Occasionally, difficulty is encountered with the passage of the cannula under the inguinal ligament or through the dilated opening in the vessel wall. Redilatation with a smaller dilator can facilitate passage. The preferred drainage site is the femoral vein, and the cannula is advanced to just below the caval-atrial junction. The flows are usually the maximum capable with consideration to negative inlet pressures, RPMs, and positive resistance. Inflow to the patient is usually the right internal jugular vein, using a CB arterial BioMedicus cannula (usually 17F, 19F, or 21F CB BioMedicus).

If a secondary site is needed, the femoral and internal jugular may be used and "Y'd" to the venous tubing for venoarterial ECMO.

The Avalon cannula can be inserted into the IJ using the 23F, 27F, or 31F. This cannula allows drainage from the cannula holes sitting in the IVC and SVC and return blood to the RA. A baffle in the cannula separates inflow from outflow.

After cannulation, it is important to assess the cannula position by obtaining a radiograph.

• Venoarterial percutaneous

See Video E22-1.

The preferred site is the femoral artery. Surgical (as well as percutaneous) insertion of arterial cannulas in the femoral artery can be complicated by malperfusion of the distal extremity. This complication may be addressed in several fashions but should be dealt with expeditiously to avoid severe injury. We prefer the insertion of a modified, cut high-pressure monitoring line (arterial line tubing) down the femoral artery of the affected limb. This can be achieved in the open wound just distal to the reinfusion cannula insertion site or, in the case of a percutaneous cannula, via an incision at a separate site. The tubing is connected to a CB $3/8 \times 3/8$ -inch connector with a Luer-Lok between the arterial cannula and the ECMO arterial pump tubing. If decreased heparinization and low flow in this system are concerns, heparin of 0.5 to 2 U/kg/hr may be infused by a pressure pump into this system for anticoagulation.

• Venovenous/venoarterial surgical cut-down

Using the same cannulas, when there is difficulty with percutaneous cannulation or the body habitus is not conducive surgical cut-down to gain access to the femoral vessels can be done either at the bedside or if time allows in the operating room cannulation.

- Central cannulation

ECMO may be performed with central cannulation with a CB Medtronic 35 cm DLP 32F, 36F, or 40F malleable venous, CB Medtronic DLP 2 stage 34/46, and DII 40F RA for right or left atrial cannulation. Inflow to the patient may be accomplished with Carmeda EOPA 22F or 24F or other appropriately coated cannula for a PA or aorta. The median sternotomy is the least favored as this site is associated with more bleeding complications. The cannulae may be tunneled inferior to the sternum and the chest then closed for hemostasis.

AFTER PROCEDURE

Postprocedure Care

- Daily patient and circuit management on ECMO including
 - Patient
 - Fluid
 - Electrolytes
 - Nutrition
 - Respiratory
 - Neurologic
 - Infection control
 - Sedation and pain control
 - Hematology
 - Cardiac
 - Psychosocial
 - Circuit
 - Aseptic technique
 - Pump/gas flow pressure monitoring
 - Blood product infusion techniques
 - Circuit infusions
 - Management of anticoagulation
 - Circuit checks
 - Hemofiltrations setup
 - Bedside care of the ECMO patient
- Weaning from venovenous ECMO is done by turning off the gases after placing the patient on reasonable ventilator settings and closely monitoring arterial saturations. The patient is decannulated after being maintained off of gases for 24 hours.
- Trial or wean with a VA system is very different. The arteriovenous bridge is used. The ventilator is set at the optimal setting. Additional heparin is given to achieve an ACT of 300 seconds. ECMO flows may be reduced by 1 L/min at intervals, and observations of the patient's hemodynamics and arterial saturation are critical. Echocardiogram imaging is also useful in determining when the patient may be ready to be cannulated.

Complications

- Medical
 - Intracranial and another hemorrhage
 - Pneumothorax/pneumopericardium
 - Cardiac arrest
 - Hypotension/hypovolemia
 - Severe coagulopathy/thrombocytopenia
 - Seizures
 - Hemothorax/hemopericardium
 - Uncontrolled bleeding
- Mechanical
 - Circuit disruption
 - System or component alarm/failure (e.g., pump, bladder, venous return monitor oxygenator, or heater)
 - Air embolus
 - Inadvertent decannulation
 - Clots

OUTCOMES AND EVIDENCE

- Patient outcomes after ECMO cannulation are very much dependent on the coexisting condition at the time of cannulation, as well as the clinical state of the patient on ECMO support.
 - Comorbidities precannulation
 - Organ dysfunction
 - Length of cannulation
 - Type of ECMO support
 - Venovenous vs. venoarterial
- Outcomes trial
 - CESAR trial
 - Of patients assigned to consideration for treatment by ECMO, 63% (57/90) survived to 6 months without disability vs. 47% (41/87) of those assigned to conventional management (relative risk: 0.69; 95% confidence interval [CI]: 0.05-0.97; $P = 0.03$).
 - ECMO in influenza H1N1 epidemic
 - The median duration of ECMO support was 10 (7-15) days. At the time of reporting, 48 of the 68 patients (71%; 95% CI: 60%-82%) had survived to ICU discharge, of whom 32 had survived to hospital discharge and 16 remained as hospital inpatients. Fourteen patients (21%; 95% CI: 11%-30%) had died, and six remained in the ICU, two of whom were still receiving ECMO.
 - Survival outcomes following the use of ECMO in patients with acute respiratory failure during the H1N1 influenza pandemic have validated the role of ECMO as an important management strategy in adults with severe respiratory failure.
- There is a lack of quality RCTs of ECMO outcomes in the adult population, especially venoarterial ECMO.

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Laparoscopy has proven itself an accurate diagnostic tool in a wide spectrum of clinical scenarios. More recently, it has been applied in the evaluation of both trauma and intensive care unit (ICU) patients. This chapter will focus on diagnostic laparoscopy for the critically ill patient in the ICU.

Acute intraabdominal pathologies remain a significant source of morbidity and mortality in the ICU. Etiologies include acalculous cholecystitis, intestinal ischemia, intestinal perforation, peptic ulcer disease complications, pseudomembranous colitis, diverticulitis, and pancreatitis, to name a few. Specifically, acalculous cholecystitis has been documented in 1% of surgical ICU patients and 0.5% of critically injured trauma patients. Likewise, intestinal ischemia is a significant risk following aortic procedures.

While those above occur relatively infrequently, associated morbidity and mortality are significant. If left undiagnosed and/or untreated, intraabdominal sepsis may lead to multiple organ failure (MOF), with mortality rates approaching 100%. The reported mortality rates specific to acalculous cholecystitis and mesenteric ischemia range from 50% to 100%.

A significant contributor to the high morbidity and mortality rates is a delay in diagnosis. Such delays are multifactorial and include failure to consider the diagnosis, difficulty in obtaining the diagnosis secondary to patient safety issues, and the lack of accuracy of the diagnostic modalities.

Critically ill patients also have numerous other potential sources of sepsis, further complicating the picture (e.g., central venous catheter infection, ventilator-associated pneumonia, and a urinary tract infection). As such, surgical consultations are often sought in these patients; indications include abdominal pain, abdominal distention, a fever of unknown etiology, sepsis of unknown etiology, inexplicable acidosis, enteral intolerance, and others. This often presents a diagnostic dilemma. Diagnostic modalities to assess the abdomen in this critically ill population include the physical examination, laboratory studies, plain radiography, computed tomography (CT) scans, ultrasound, diagnostic peritoneal lavage (DPL), exploratory laparotomy, and increasingly, diagnostic laparoscopy.

■ BEFORE PROCEDURE

Indications

Critical illness with suspicion for intraabdominal pathology with

- Inability to perform an exam (unreliable physical exam findings)
 - Altered mental status
 - Sedation
 - Paralysis
- Inability to transport for diagnostic radiologic imaging
 - Hemodynamic instability
 - Pulmonary instability
- Inability to make a diagnosis with given information
 - For example, radiologic imaging is equivocal or nondiagnostic
 - Other modalities unlikely to provide a diagnosis
 - For example, DPL is unable to diagnose a diaphragm injury

Contraindications

- Intraabdominal hypertension
- Open abdomen

- Recent abdominal wound dehiscence
- Previous laparotomy (relative contraindication)
- Recent laparotomy is not an absolute contraindication
- Hemodynamic instability (relative contraindication)

Equipment

- ICU equipment
- Monitoring
 - Continuous monitoring
 - Electrocardiogram (ECG)
 - SpO₂
 - Noninvasive blood pressure (NIBP) or arterial line
 - If NIBP record at least once every 3 minutes
 - End-tidal carbon dioxide (CO₂) monitor
 - Bispectral index (BIS) monitoring during administration of anesthesia (optional)
- Ventilator
 - Full ventilatory support may or may not be required based on patient condition.
 - If the patient is not intubated, the team should be fully prepared for endotracheal intubation.
- Laparoscopic equipment
 - Mobile laparoscopic cart with locking brakes and four antistatic rollers
- Optical equipment
 - Laparoscopic camera system
 - Laparoscopic light source
 - Video monitor
 - Only one monitor is necessary.
 - Ideally, the monitor should be able to tilt, swivel, and pivot on a boom.
 - A second monitor can be “slaved” from the main monitor and positioned for the assistant to see.
 - Video recorder (optional)
- Laparoscopic CO₂ insufflator system with a pressure monitor
- CO₂ gas tank with a backup tank and wrench tool
- Monopolar electrocautery generator with grounding pad
- Laparoscopic-specific set (sterilized)
 - Fiberoptic light cable
 - Telescopes
 - 10-mm scope (0- and 30-degree angles)
 - 5-mm scope (0- and 30-degree angles)
 - CO₂ insufflation hoses with a filter
 - Trocars/ports (surgeon specific)
- Entry technique
 - Open (Hasson method)
 - 12-mm Hasson port
 - Optiview visualizing trocar
 - 5-mm clear
 - Blind
 - Veress needle
 - 5- to 12-mm trocar
- Additional ports
 - Additional ports dictated by surgeon requirements
- Laparoscopic instruments (minimal necessary)
 - Ratcheted atraumatic graspers (×2)
 - Nonratcheted atraumatic graspers (×2)

- Maryland dissector
- Laparoscopic scissors
- Cauterization instrumentation with associated generators
 - Monopolar system
 - Other 5-mm cauterization systems can be used if necessary, such as
 - Harmonic
 - Ligasure
 - EnSeal
- Laparoscopic suction-irrigator
- Basic abdominal surgical set
 - Surgical sterile prep system
 - Laparotomy towels and drapes
 - Laparotomy sponges
 - Scalpel (#11 blade and/or #15 blade)
 - Suture
 - 0-polyglactin 910 suture on UR-6 needle (×2)
 - 4-0 polyglecaprone 25 suture on PS-2 needle (×2)
 - Surgical pickups
 - Adson tissue forceps (×2)
 - Rat-toothed, heavy forceps (×1)
 - Suture scissors
- Dressings
 - ¼-inch Steri-Strips
 - Surgical wound covers
 - Band-aids *or*
 - 2 × 2 sterile gauze with clear occlusive dressing

ANATOMY

Special considerations for patient selection and the entry technique need to be evaluated. Prior operations may preclude the ability to enter the abdomen safely or may obscure the clinician's ability to perform a complete visual inspection of its contents because of adhesive disease. In these cases, diagnostic laparoscopy may not be successful. Patients with portal hypertension are at an increased risk of bleeding due to the inadvertent injury of dilated venous collaterals that are not normally present within the abdominal wall. Finally, the inferior epigastric artery is at risk for injury during trocar placement, and careful attention should be paid to avoid its consistent location within the rectus sheath.

PROCEDURE

- The procedure can be performed safely with the following personnel
 - The surgeon (laparoscopist)
 - The intensivist/anesthesiologist for administration of sedation and analgesia, as well as for respiratory and hemodynamic monitoring
 - A scrub nurse to assist the surgeon
 - An ICU nurse (circulator) to obtain necessary equipment and medications
 - A respiratory therapist on standby to assist the intensivist/anesthesiologist
- The patient's position is neutral and supine.
- Complete prep and drape in standard fashion
- Monitoring should be continuous or at least every 3 minutes and include
 - Blood pressure, pulse rate, respiratory rate, tidal volume and peak inspiratory pressure, oxygen saturation (SpO₂), and end-tidal PCO₂
 - A bispectral index (BIS) monitor is optional.
- Sedation and analgesia provided intravenously
 - A narcotic (e.g., fentanyl, morphine)
 - A sedative
 - Benzodiazepines (e.g., midazolam, lorazepam)
 - Propofol
 - A paralytic (e.g., vecuronium, rocuronium, or cisatracurium)

- Diagnostic laparoscopy has been done successfully using only local anesthesia and a mild sedative.
 - For complex ICU patients with suspected intraabdominal pathology, using local anesthesia is not optimal.
- Decompression of the stomach with a nasogastric tube (NGT) and the bladder with a Foley catheter is advisable.
- A vertical incision is placed just cephalad or caudad to the umbilicus.
- This can be extended if a formal laparotomy is necessary.
- Open approach
 - Under direct vision, the fascia and peritoneum are opened through the linea alba.
 - Stay sutures (0-polyglactin 910) are placed (can be used to close fascia at the end of procedure).
 - The cannula is inserted, and the two facial sutures are looped around it in the provided grooves for stabilization.
- Blind techniques can be used if deemed safe and can minimize the incision necessary for peritoneal access.
- CO₂ is insufflated slowly to minimize adverse effects on respiratory function and hemodynamics.
- Some advocate lower insufflation pressures (8-12 mm Hg). No studies have been performed comparing different insufflation pressures.
- Angled scope is preferred for improved visualization.
- If the procedure is performed for a trauma patient, inspection of the diaphragm should be the first step (to reduce risk of tension pneumothorax if diaphragm injury).
- A quick inspection around the abdominal cavity for any obvious signs of peritonitis. If found, terminate the procedure and prepare for the formal therapeutic operation.
- Additional 5-mm ports can be placed under direct vision as necessary.
- Complete the inspection as you would with formal exploration, in an organized fashion, including all abdominal and pelvic viscera in addition to peritoneal surfaces.

AFTER PROCEDURE

Postprocedure Care

- Continuous monitoring with ECG, SpO₂ and NIBP as long as patient condition warrants
- Maintain NGT to suction and Foley to gravity.
- Check the arterial blood gas (ABG) for acidosis and hypoxemia.
- Optimize ventilation and oxygenation.
- If the laparoscopy was nondiagnostic, the surgeon should be prepared to perform a laparotomy, either at bedside if patient condition warrants or in the operating room if the patient is stable for transport.

Complications

- Common
 - Increased intraabdominal pressure, which may result in
 - Oliguria
 - Increased peak airway pressures and resistance
 - Decreased functional residual capacity and lung compliance
 - Increased difficulty with ventilation and/or oxygenation
 - Hypotension due to
 - Decreased venous return and/or increased systemic vascular resistance (afterload)
 - Hypercarbia with associated metabolic acidosis
 - Results from increased pulmonary dead-space and peritoneal absorption of insufflated CO₂
 - Usually transient
 - Can be corrected through increasing minute ventilation

- Infrequent
 - Intestinal injury due to
 - Trocar insertion
 - Manipulation of bowel or intestinal adhesiolysis
 - Use of electrocautery
 - Vascular injury due to
 - Trocar insertion
 - Manipulation of mesentery
 - Bladder injury due to
 - Trocar insertion
 - Deep venous thrombosis
 - Associated with prolonged procedures coupled with prolonged impaired venous blood return and perioperative hypercoagulability
- Serious, rare complications
 - Gas embolization from CO₂ pneumoperitoneum into the venous system, manifested by
 - Sudden hemodynamic collapse with precipitous drop in end-tidal CO₂ (not specific)
 - Positioning patient in steep Trendelenburg and rolled to the left may put gas embolism away from pulmonary outflow tract and restore blood flow out of the right heart.
 - Tension pneumothorax due to CO₂ tracking through gaps in the diaphragm into the pleural space
 - Acute volume overload and pulmonary edema
 - Can result after the release of pneumoperitoneum
 - Large amounts of intravenous fluids infused during the procedure to maintain a hemodynamic status
 - Elevated intracranial pressure (ICP)
 - Hypercarbia can result in cerebral vasodilation, with the concomitant potential for increased ICP.
 - Intraabdominal hypertension can impede venous flow from the periphery and increases the cerebrospinal fluid pressure.
 - Despite the significant advantages of laparoscopy, it is not without its disadvantages. The most concerning are potential

detrimental physiological effects, specifically to the cardiovascular and pulmonary systems. Experimental animal models demonstrate hemodynamic compromise in septic animals undergoing laparoscopy, usually secondary to the associated hypercarbia and acidosis. Others document temporary myocardial insufficiency, with decreases in cardiac output up to 80% after only 20 minutes of CO₂ insufflation. However, many studies report no hemodynamic alterations during laparoscopy. Means of avoiding such outcomes include slow CO₂ insufflation, lower intraabdominal pressures, using alternative gases for insufflation (e.g., nitrous oxide), and ultimately, desufflation if necessary.

OUTCOMES AND EVIDENCE

- Bedside laparoscopy in the ICU is safe and effective in diagnosing intraabdominal pathology in critically ill patients.
- Gagné et al. performed 20 bedside laparoscopic procedures on 19 patients, with a mean time of 21 minutes; 18 of 19 patients avoided nontherapeutic laparotomy as a result.
- Pecoraro et al. reported that 4 of the 11 patients had recent laparotomies. In 6 of the 11 patients studied, the use of bedside laparoscopy avoided nontherapeutic open laparotomy.
- Kelly et al. performed 17 cases, 16 completed. No complications, with 100% accuracy among the 16 completed procedures. Abdominal CT in 9 patients was accurate in only 33%.
- Hackert et al. studied 17 patients, revealing a 94% sensitivity for bedside laparoscopy.
- Peris et al. performed the largest (retrospective) study to date with 32 patients, a mean time of 40 minutes, and no complications; 15 (46.9%) of the patients had a pathologic finding necessitating intervention; 6 patients with sepsis, who had prior negative diagnostic peritoneal lavages, were found to have peritonitis via a diagnostic laparoscopy.

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■ INTUBATION: BEFORE PROCEDURE

Indications

- Airway patency
 - Anatomic obstruction
 - Congenital anomalies
 - Acquired obstruction
 - Infectious obstruction
 - Inability to functionally maintain airway (e.g., depressed level of consciousness)
 - Loss of airway cough and/or gag reflex
 - Neuromuscular weakness
- Lower respiratory failure
 - Inability to ventilate/exchange PCO_2
 - Inability to oxygenate
 - Relieve increased work of breathing
 - Neuromuscular weakness
 - Need for aggressive pulmonary toilet
- Hemodynamic instability
- Need for controlled ventilation
 - Pulmonary hypertension
 - Intracranial hypertension

Contraindications

- In emergent situations, there is no contraindication for endotracheal intubation.
- Relative contraindications
 - Abnormal anatomy; may require an alternative approach to airway management (e.g., cricothyrotomy with retrograde intubation or bronchoscopic intubation)
 - Profuse upper airway or lower airway bleeding
 - Increased intracranial pressure (ICP): requires rapid-sequence intubation
 - Cervical or suspected cervical spine injury: requires immobilization of the head and neck

Equipment

- Monitoring equipment: pulse oximeter, electrocardiogram (ECG), blood pressure
- Oxygen source: delivered by mask before intubation; if apneic, oxygenation to be used and then high-flow nasal cannula
- Bag for manual ventilation
 - Anesthesia-type bag: expands when connected to gas flow; various designs available but must have adequate flow through system to prevent rebreathing
 - Self-inflating bag: designs vary; many have pressure pop-off at 35 to 45 cm H_2O , so if lungs are severely noncompliant, may not adequately ventilate or oxygenate with this bag or may need to bypass the pop-off
- Laryngoscope
 - Check before use for adequate battery and bulb function.
 - Small handle and larger handle are available.
 - Bronchoscopic and video laryngoscopes are available.

- Laryngoscope blade
 - Various sizes and styles are available.
 - Size must be appropriate for child
 - Too short will not visualize the larynx.
 - Too long may apply too much pressure and take too much room in the mouth.
 - Width is also important
 - Wide blades will help manage the tongue, which can be disproportionately large in children.
- Endotracheal tubes (ETTs)
 - Appropriate estimated size tube: $(\text{Age} + 16)/4 = \text{Endotracheal tube size}$
 - Adjust for extremes in patient size or known abnormality of tracheal size.
 - Tubes are cuffed and uncuffed
 - Cuffed tubes are universally recommended above age 8 years.
 - Under age 8 years, most recent recommendations are that cuffed tubes may be used. In the past, cuffed tubes were thought to be unnecessary because of the narrow trachea at the level of the cricoid cartilage and potentially risky because of the risk of airway injury. Currently, the cuffs are high-volume, low-pressure cuffs that require lower pressure to be effective, therefore decreasing the risk of airway injury. For patients with noncompliant lungs requiring higher airway pressures, the presence of a cuff decreases the air leak, allowing for better lung inflation and recruitment. The cuff may not need to be inflated to adequately manage air leakage, thus decreasing the risk of airway injury.
 - Stylets: available in pediatric and adult sizes; may be needed to help strengthen the pliable ETT to assist in intubation; skill and experience of the operator will dictate its usefulness.
- Suction devices: must be sturdy enough to suction very thick secretions in even the smallest infant
- End-tidal CO_2 detector: disposable colorimetric CO_2 detectors are available in pediatric and adult sizes; the weight of the patient will determine the size of the device.
- Means for securing the ETT: either tape or an appropriately sized securement device
- Airway support devices: these may be useful depending on the stability of the airway
 - Oral airways: come in various sizes; poorly tolerated in a conscious patient; may be needed for airway maintenance before intubation
 - Nasopharyngeal airways: come in various sizes and can relieve nasal and pharyngeal obstruction in conscious patients, including children. The appropriate-sized airway extends from the nares to the tragus of the ear. The diameter should be large enough that it does not cause obstruction and not so large that it causes blanching of the alae nasi, which can lead to necrosis.
 - Laryngeal mask airway: can provide immediate airway access and should be available during even nonemergent intubation in the event the airway is difficult to intubate. They come in a variety of sizes appropriate for pediatric patients. The LMA consists of a wide-bore tube with a standard 15-mm adapter at

the proximal end for attachment to the circuit or resuscitation bag. The distal end is an elliptical mask that can be inflated and conforms to the shape of the larynx, providing a low-pressure seal for ventilation at the level of the larynx (see [Procedure](#)).

- Pharmacologic agents: various sedative and paralytic drugs are available for intubation. There are different conditions for intubation that require certain combinations of drugs for safest and most effective intubation. One must be familiar with the variety of drugs available, including side effects, indications, and contraindications.
 - Anticholinergic agents: prevent bradycardia during laryngoscopy and decrease oral secretions
 - Sedative agents: in choosing one of these agents, consideration should be given to hemodynamic status, the presence of increased ICP, age of patient, underlying chronic medical conditions, and the current disease process
 - Anxiolytics including benzodiazepines (e.g., midazolam or lorazepam)
 - Narcotics including opiates (e.g., fentanyl or morphine)
 - Anesthetics (e.g., ketamine, etomidate, or propofol)
 - Neuromuscular blockers
 - Nondepolarizing agents
 - Amino-steroid agents: vecuronium or rocuronium
 - Benzylquinolinium agents: atracurium or cisatracurium
 - Depolarizing agents: succinylcholine; there is a U.S. Food and Drug Administration (FDA) warning against its routine use in children because of the frequency and severity of side effects. Although its rapid onset of action in emergencies is thought to be useful, the onset of action is not significantly advantageous over rocuronium, which has fewer side effects.

■ ANATOMY

The pediatric airway changes with age and development and differs from the adult airway in many aspects. Understanding these differences and being aware of the age-related changes are important for optimal airway management. The larynx in children is located higher in the neck, with the epiglottis being at the level of C1 as a neonate and at the level of C3-4 by 6 months of age, as opposed to the adult, where the larynx is around C5. This more superior position of the larynx creates more acute angulation during laryngoscopy and can make the visualization of the glottic opening more difficult. Also, the tongue is located more superiorly and closer to the palate in children than in adults and is larger in relation to the bony structures of the cranium, potentially causing airway obstruction. The narrowest portion of a child's airway is the subglottic region, whereas the narrowest portion of an adult airway is the vocal cords. This difference has allowed for uncuffed tracheal tubes to be used in infants and young children. Another major difference is that children have a more protuberant occiput, which may cause excessive neck flexion. Finally, the infant's nares are smaller. Since infants are obligate nasal breathers for the first 6 months of life, occlusion of the nasal passages with secretions, edema, or blood can cause significant resistance to airflow and significantly increase the work of breathing.

■ BEFORE PROCEDURE

If time allows and the procedure is not emergent, then a preprocedure plan should be in place. A plan should include assessing the airway, risk for hypotension or hypoxemia during the procedure, and the risk of hypercarbia (is there increased intracranial pressure or pulmonary hypertension). A plan should include who is most appropriate to do the intubation (i.e., what skill level would be needed), for instance, a pediatric ICU fellow, PICU attending, anesthesiologist, or even ENT surgeon. The method of intubation should be discussed, including which medications would be appropriate and the indications for

intubation. A backup plan for airway support if the airway proves to be difficult should be conceived and in place.

■ PROCEDURE

- Evaluate the difficulty of airway intubation and risk for complications.
 - History of difficult airway
 - Physical examination with attention to size of mouth, size of tongue, small mandible, large head
 - Potential for hypoxemia or hypotension during procedure
 - Need to avoid hypercarbia via pulmonary hypertension, increased intracranial pressure
- Secure equipment and test functionality
 - Test patency of intravenous (IV) access.
 - Check bag and mask for adequate oxygen flow.
 - Check suction device for adequate suction.
 - Check laryngoscope handle and blade for the presence of bright light.
 - For cuffed ETT, check cuff for the ability to hold air.
 - Place stylet in ETT if desired.
 - Have ETT one size larger and smaller available.
- Have proper personnel available including nursing, respiratory therapy, and more experienced intubators if appropriate.
- Monitor the patient with pulse oximeter, ECG, blood pressure cuff (set to cycle frequently during procedure).
- Preoxygenate patient; if possible allow the patient to breathe spontaneously on FiO_2 1.0 or as much as can be delivered to maximally increase the patient's PaO_2 prior to the intubation attempt; apneic oxygenation using high-flow nasal cannula providing continuous oxygen flow even after paralytics are given may be helpful in preventing desaturation during intubation.
- Position the patient's head; the goal of head positioning is to align the oral, pharyngeal, and laryngeal axes.
 - Infants have a large occiput that puts them close to proper alignment, although they may need a roll under the shoulders; care should be taken to avoid overextension of the head, which also misaligns the airway.
 - Children should have a roll under the occiput to put the head in a "sniffing" position, which will better align the airway.
 - Head extension in both groups better aligns the airway.
- Administer pharmacologic agents.
 - Anticholinergic may be delivered first.
 - Sedatives are given next, observing closely for changes in respiration and hemodynamics; may need to have the airway and breathing supported just with sedative administration.
 - Neuromuscular blockade is delivered last and only after determining that the airway can be managed with a bag and mask; if not, the neuromuscular blocker should not be given and intubation attempted with the patient breathing spontaneously.
- Open the mouth using the thumb and finger in a scissor-like fashion between the teeth.
- Insert the laryngoscope.
 - Hold the laryngoscope in the left hand.
 - Place it in the right side of the mouth.
 - Sweep the tongue and laryngoscope toward the left.
 - Place the tip of the laryngoscope in the vallecula or onto the epiglottis itself.
 - Visualize the larynx by lifting the mandible with the laryngoscope blade toward the ceiling at a 45- to 60-degree angle to the child's chest. Avoid "cranking" the laryngoscope back as if on a fulcrum, as this can cause injury to the lips and teeth.
 - Visualize the cords, and then place the ETT in the right corner of the mouth beside the laryngoscope blade, and advance the tube through the vocal cords. Avoid passing the tube down the laryngoscope itself, as that blocks the view of the larynx and straightens the tube, making it difficult to pass through the vocal cords.

- The tube should be advanced with the vocal cord mark just past the vocal cords to avoid right main stem intubation.

AFTER PROCEDURE

Postprocedure Care

- Immediately ensure the correct position of the ETT.
 - Place the end-tidal CO₂ detector, noting appropriate color change depending on the brand of detector. A color change should occur within six breaths unless the patient is in cardiac arrest or impending arrest.
 - Observe equal bilateral chest excursion with bag ventilation.
 - Observe maintenance of appropriate oxygen saturation.
 - Auscultate bilateral breath sounds.
- If a cuffed ETT is used, inflate the cuff with the least amount of volume necessary to prevent a leak around the ETT; overinflation of the cuff may lead to injury of the tracheal mucosa and cartilage.
- Secure the ETT using tape or a securement device.
- Confirm the ETT position with a chest radiograph.
- Suction the ETT post procedure; secretions can obstruct the tube.

Complications

- Esophageal intubation: quickly determined by lack of CO₂ detection, lack of chest wall movement, and lack of breath sounds
- Malposition of the ETT most commonly into the right main stem bronchus; common in small infants owing to the short length of their trachea; detected by asymmetric chest rising and asymmetric breath sounds. If necessary, confirm the position radiographically.
- Wrong size ETT, most commonly a too-small uncuffed tube, allowing for excessive air leakage and the inability to ventilate and oxygenate the patient; requires reintubation with proper tube size
- Undiagnosed difficult airway resulting in loss of airway during procedure or the inability to place ETT; must be managed immediately either with laryngeal mask airway (LMA) or if necessary, cricothyroidotomy; may need fiberoptic bronchoscopy to visualize the airway or may need the creation of a surgical airway
- Hemodynamic instability during the procedure due to the cardiovascular depressant effects of sedatives, hypoxemia during the procedure, or the patient's underlying disease process. May need intravascular volume expansion or even chemical resuscitation if severe enough.
- Aspiration during intubation due to a full stomach at the time of intubation; the risk is decreased if the patient is placed nil per os (NPO) for at least 6 hours prior to intubation; however, aspiration is always a risk. Aspiration in patients known not to be NPO but who need urgent or emergent intubation is decreased with emptying the stomach with a large-bore nasogastric (NG) tube and with cricoid pressure maneuver during intubation.
- Patients with increased ICP may have sharp increase in ICP during intubation, resulting in deterioration or even cerebral herniation; use rapid-sequence intubation.
 - Sedation
 - If hemodynamically unstable, etomidate or midazolam and fentanyl
 - If hemodynamically stable, midazolam and fentanyl or morphine
 - Lidocaine
 - Paralytic: rocuronium
- Patients with increased intraocular pressure may have worsening of the pressure, even resulting in extrusion of the vitreous, so rapid-sequence intubation as with increased ICP is recommended.
- Oral injuries are possible
 - Tooth injury or loss; check for loose teeth prior to intubation if time allows.

- Lacerations, bruising to lips and oropharynx
- Damage to the tonsils, including avulsion
- Damage to vocal cords and laryngeal nerve, resulting in paralytic cord(s)
- Cervical spinal cord injury in patient with unstable cervical spine; the risk is decreased when head and neck are immobilized at the time of intubation.

OUTCOMES AND EVIDENCE

- Preliminary data suggest that the use of preprocedural planning and a checklist decreases the risk of tracheal intubation-associated events.
- Successful intubation in the pediatric patient depends on the length of training, the level of supervision, the ongoing experience of the practitioner, and the use of rapid-sequence intubation.
- Cuffed ETTs are as safe as uncuffed ETTs in the pediatric patient in a prospective data collection study in a pediatric intensive care unit (PICU).
- LMA can be successfully placed in pediatric patients but may be associated with an increased risk of complications in younger patients
 - In a randomized controlled study of children 3 to 10 years of age in the operating room, both LMA and ETT were successfully placed on the first attempt in all patients, with fewer complications such as a sore throat, coughing, vomiting, and hypoxia in the LMA group.
- Patients with multiple trauma and possible cervical spinal cord injuries who were intubated emergently had no further neurologic loss following intubation, according to a retrospective study of 237 injured patients; 21 patients (8.9%) had a cervical cord or bone injury; 213 patients were orally intubated.

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INTRASOSEOUS INFUSION: BEFORE PROCEDURE

Indications

- Life-threatening situations when rapid intravascular access cannot be obtained
- Cardiopulmonary arrest
- Severe shock from all causes
- Status epilepticus

Contraindications

- Bone fracture
- Previous unsuccessful attempt at that site
- Infected or burned areas; relative contraindication
- Vascular compromise to the extremity

Equipment

- Standard technique
 - Intraosseous needle
 - Needle with a stylet
 - Specially designed needles
 - Jamshidi-type needle
 - Butterfly or hypodermic needle (if that is all that is available)
 - Slip-tip syringe and tubing connector
- Powered insertion technique
 - Bone injection gun
 - Needle designed for the gun
 - Slip-tip syringe and tubing connector

ANATOMY

The preferable site for insertion is the anterior tibia, 1 to 2 cm below the tibial tuberosity on the medial aspect of the tibia. Other sites include the distal femur, medial malleolus, and anterior superior iliac spine. These sites are useful in pediatric patients from preterm neonates to adolescents. The proximal humerus is useful for adolescents and adult patients. A sternal access system is now available for adult-sized patients.

PROCEDURE

- Prepare the site using sterile technique.
- Identify landmarks.
 - Tibial tuberosity
 - Flat part of the tibia 1 cm to 2 cm below the tuberosity
- Needle entry technique
 - Standard
 - Advance the needle until a sudden decrease in resistance is felt, indicating that the bone marrow has been entered.
 - Powered insertion
 - Place the needle into powered injection gun.
 - Place the needle in the appropriate location on the patient.
 - Discharge the gun.
- Remove stylet and aspirate.
 - If the aspiration is successful, the needle should be flushed.
 - If aspiration is not successful, flush with 5 mL to 10 mL saline.
 - If it flushes easily, marrow has probably been entered.
- Attach the connector tubing, and begin infusion.

AFTER PROCEDURE

Postprocedure Care

- Careful stabilization of the intraosseous needle
- Close observation for evidence of extravasation

Complications

- Common
 - Extravasation of fluid
 - Due to the posterior penetration of the cortex
 - Due to the incomplete penetration of the cortex
 - Through a nutrient vessel foramen
 - Through a bony defect
 - Increased risk due to
 - Prolonged infusions
 - Infusions under pressure
 - Catecholamine infusions
 - Hypertonic solutions
- Infrequent
 - Compartment syndrome
 - Osteomyelitis

- Rare complications
 - Fat emboli
 - Tibial fracture

OUTCOMES AND EVIDENCE

- Intraosseous infusion
 - Easily and rapidly performed in emergency situations in both the prehospital and hospital environments
 - Effective in delivering fluids, blood, and medications in emergency situations
 - Safe but attention to the presence of infiltration or misplacement of the needle is important in preventing complications.
- Randomized controlled trial comparing standard bone marrow needle placement versus powered injector technique showed no significant difference with respect to the success rate of placement, adverse events, and time to a successful placement. Both techniques were successful about 80% of the time.

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CENTRAL VENOUS CATHETERIZATION: BEFORE PROCEDURE

Indications

There are many indications for the insertion of temporary central venous catheters (CVC) in pediatric patients, and often multiple indications coexist. Since there is risk associated with both insertion and maintenance of these catheters, it is imperative that a true indication for placement be met. If more than one indication exists, the risk/benefit ratio falls in favor of catheter placement.

- Monitoring of central venous pressure (CVP) and measurement of central venous oxygen saturation (ScvO₂) in hemodynamically compromised patients
- Delivery of hypertonic or sclerosing agents
 - Total parenteral nutrition
 - Chemotherapy
 - Pressor infusions
 - Electrolyte infusions
 - Multiple blood product transfusions
 - Other medications with the risk of venous infiltration
- Poor peripheral venous access
 - Patients who need multiple IV access or long-term venous access
 - Patients needing frequent phlebotomy
- Procedures
 - Continuous renal replacement therapy
 - Hemodialysis
 - Plasmapheresis
 - Plasma exchange

Contraindications

All contraindications are relative, but the risks and benefits of the procedure must be weighed carefully.

- Coagulopathy
 - Correction of the coagulopathy should be attempted prior to the procedure if the acuity of the situation allows.
 - Sites with more risk in coagulopathic patients include subclavian and internal jugular veins; topical pressure to decrease bleeding is more effective at the femoral site.

- Skin infection at site of insertion
 - Including diaper dermatitis for femoral vein catheterization
- Site-specific contraindications
 - Avoid femoral vein catheterization in patients with abdominal catastrophes because the patency of more central veins cannot be assured.
 - Avoid internal jugular catheterization in patients with increased ICP.
 - Patients with hyperinflated lungs are at an increased risk of pneumothoraces with subclavian or internal jugular catheterization.
- Patients with active bacteremia are at risk for colonizing the CVC, so ideally the CVC would not be placed until the blood cultures are negative. That is not always possible, depending on the acuity of the patient and the patient's peripheral venous access.

Equipment

Proper insertion technique using full sterile barrier precautions and chlorhexidine prep of the skin have been shown to decrease infections associated with CVCs. Additionally, having the equipment including sterile gloves and drapes together in one location (e.g., a cart) increases the compliance with sterile technique by the insertion practitioner and makes insertion more efficient. A checklist of insertion practice also improves the compliance of proper technique.

- Sedation appropriate for age and condition of the patient with appropriate monitoring
- Local analgesia
 - 1% lidocaine with a sterile syringe and narrow-gauge needle for infiltration
 - Topical analgesia may be used prior to sterilely preparing the skin for adding analgesia.
- Sterile gloves, caps, masks, and sterile drapes
- Skin preparation antiseptic
 - 2% chlorhexidine-alcohol based skin prep is recommended.
 - Alternatives include 70% alcohol, tincture of iodine, iodophor.
- Central venous catheter: choice of catheter depends on the use of the catheter, the condition of the patient, the site of insertion, and how long the catheter is expected to be in place.
 - Various materials
 - Polyurethane or polytetrafluoroethylene catheters are associated with fewer infections compared with polyvinyl chloride and polyethylene.
 - Multiple sizes appropriate for infants and children
 - Different diameters
 - Varying lengths
 - Varying number of ports from one to three
 - Impregnated catheters
 - Antiseptics such as chlorhexidine-silver sulfadiazine
 - Antibiotics such as minocycline-rifampin
 - Heparin
 - Specialized catheters for dialysis and pheresis that are relatively short and have two large-bore ports for optimal blood flow
- Bedside ultrasound (US), sterile protection sleeve, packet of sterile gel if the US is to be used
- Steel hollow needles, guidewire, dilator appropriately sized for patient and catheter; kits containing the catheter, needles, guidewire, vessel dilator, and other equipment necessary for insertion are commercially available.
- Slip-tip syringes
- Heparinized saline flush
- Tubing connectors
- Dressing
 - Sterile, transparent, and semipermeable dressing
 - Sterile gauze dressing if area is bleeding or wet
- Antiseptic disk is optional
 - Chlorhexidine impregnated
 - Silver or calcium alginate impregnated

ANATOMY

The selection of the site for insertion is based on the skill and experience of the operator and the patient's condition and size. The femoral veins are relatively easy to access in nearly all pediatric patients. Although a risk with any site, bleeding is more easily controllable with femoral catheterization. As opposed to adults, the risk of femoral catheterization in infants and children does not appear to present a greater risk of infection than other sites. Use of the internal jugular vein is also relatively safe in most patients. The right internal jugular is associated with fewer complications than the left. Subclavian venous access is noted to have higher complications at the time of insertion, but the catheter is more easily secured and more comfortable for a mobile patient.

Access to the femoral vein in pediatric patients is similar to that in adults. The pulsations of the femoral artery are located below the inguinal ligament, and the vein is accessed medial to the artery about 1 cm below the inguinal ligament. If pulsations are not palpable, the site can be located halfway between the symphysis pubis and the anterior superior iliac spine. The right femoral vein is the preferred site because entry into the inferior vena cava is straighter, with the catheter less likely to enter other minor veins. For right-handed operators, there is more success of entry. Left-handed operators may choose the left femoral vein for easier access. The patient should be supine with legs positioned slightly frog-legged. Often a rolled towel or small blanket is needed underneath the buttocks to elevate and straighten the femoral vessels, allowing easier access.

For internal jugular access, the patient is placed supine in the Trendelenburg position about 30 degrees head down if tolerated. The head is turned away from the side to be catheterized. The right side is preferable because of decreased complications and minimal manipulation to enter the superior vena cava. There are three techniques for entry to the internal jugular veins in children. Become proficient at one rather than attempting all three. The anterior approach is most common. First, identify the carotid artery and the anterior border of the sternocleidomastoid muscle. The insertion site is at the midpoint of this anterior border. The needle should be introduced at a 30-degree angle and aimed at the ipsilateral nipple. The patient is placed in the same position for the subclavian approach, with the head turned away from the site of insertion. The suprasternal notch and the clavicle are identified. The needle is inserted below the lateral two-thirds of the clavicle and aimed at the suprasternal notch.

For subclavian access, a roll is placed between the shoulders and the patient positioned slightly in the Trendelenburg position. The site of entry is just inferior to the lateral and middle junction of the clavicle. The needle is directed to the suprasternal notch and passes underneath the clavicle to enter the subclavian vein.

PROCEDURE

The Seldinger technique is the most common for placing CVCs in infants and children. With ultrasound guidance, this technique is associated with decreased complications and decreased number of attempts in pediatric patients. In extreme circumstances, direct visualization of the vein by cutdown technique may be necessary.

- Seldinger technique
 - Wash hands and put on a sterile gown and gloves.
 - Sterilely prepare the skin with 2% chlorhexidine scrub for at least 30 seconds, with at least 30 seconds of drying time for the chlorhexidine. For the groin, a 2-minute scrub with a 30-second dry time is recommended.
 - Sterilely drape the area using full barrier precautions.
 - If using US guidance, drape the US probe with a sterile US sleeve and secure to the bed.
 - Numb the skin and underlying tissues.
 - Using sterile US gel and the sterilely covered probe, identify the vein.
 - Pass the introducer needle into the vein, aspirating with a slip-tip syringe. The needle can be advanced into the vein after

identifying it with the probe (static guidance) or while the probe is in place (real-time guidance).

- When venous blood enters the syringe easily, disconnect the syringe and pass the guidewire through the needle.
 - The wire must pass easily and without resistance.
 - The patient should be monitored for possible cardiac arrhythmias if the wire enters the heart and causes ectopy.
- Make a small incision at the site of the needle entry as large as the diameter of the vessel dilator.
- Remove the needle, taking care to keep the guide wire in position in the vessel, and then pass the vessel dilator over the guide wire to dilate the vein.
- Remove the vessel dilator, again taking care to leave the guide wire in place.
- Pass the catheter over the wire and into position; then remove the guide wire.
- Aspirate blood and any air from the catheter, and flush with heparinized saline; repeat for all ports.
- Secure the catheter with suture.
- Dress the catheter with the antiseptic-impregnated disk if desired, and then place the transparent dressing.
- Confirm position with a radiograph prior to using the catheter.
 - For subclavian and internal jugular catheters: chest radiograph
 - For femoral catheters: lateral abdominal radiograph to ensure catheter has entered the IVC

AFTER PROCEDURE

Postprocedure Care

Sterile insertion practices as already described and bundled maintenance care have been shown significantly to decrease the risk of CVC-associated bloodstream infections.

- Hand hygiene: prior to manipulating or accessing the CVC, proper hand hygiene should be performed to decrease the risk of pathogen transmission.
 - Wearing clean gloves is also recommended for accessing the CVC to prevent the further transmission of pathogens but to also protect the caregiver from contamination.
- Checklists and CVC kits
 - Providing a checklist of CVC maintenance procedures aids in reminding caregivers of all the steps involved in CVC care.
 - Kits of equipment needed for maintenance procedures, complete with all necessary materials and readily available in one place, aid in ensuring the complete and appropriate performance of routine care.
- The catheter and catheter site must be assessed regularly
 - Daily assessment of the need of the catheter should be reviewed by the healthcare team, including nurses and physicians, and the catheter should be removed if the indications for placement no longer exist.
 - The site should be examined for evidence of infection, such as redness at the site, drainage, swelling, or pain,
 - The catheter should be examined for positioning, especially how much catheter is outside of the skin and whether the securing maneuvers (e.g., suture or device) are still in place.
- The catheter should regularly be assessed (i.e., each nursing shift) for patency. If unable to aspirate and/or flush the catheter, attempts at opening up the lumen with thrombolytics such as TPA should be attempted.
 - The quality of the dressing should be noted: whether it is still occlusive, the presence of wetness under the dressing, and so forth.
- Dressing
 - Catheter site should be cleaned with an antiseptic agent, preferably 2% chlorhexidine-alcohol combination.

- Chlorhexidine has not been labeled for patients younger than 2 months old; however, there are extensive literature and experience showing its safe use in infants as young as immediately following birth.
 - Povidone iodine may be used in patients with a sensitivity to chlorhexidine.
 - The use of iodine ointment is not recommended because of the increased risk of fungal overgrowth.

Types of dressings

- Transparent, semipermeable dressing: allows visualization of the site and does not have to be changed as frequently.
- Gauze and tape: best used when the site is wet from blood, other fluid, or sweat; requires more frequent changes.
- Other dressings such as a silver-impregnated foam dressing may be useful for wet areas or macerated and burned skin.

Dressing change

Frequency

- For transparent, semipermeable dressing: once a week if the site remains clean and dry
- For gauze and tape dressing: no less than every 48 hours
- Dressing should be changed whenever the site is wet.

Procedure

- Caregiver should wear a cap, mask, and sterile gloves.
- Site should be cleaned as it was when the catheter was inserted, most commonly with 2% chlorhexidine-alcohol.
- Antiseptic device replaced if being used
- Catheter resecured with a suture or securement device if needed
- Dressing reapplied and labeled as to when to change again

Infusion tubing: various tubing systems are unit-specific.

- Tubing should be changed regularly but not excessively
 - Administration sets no more than every 72 hours unless soiled
 - Tubing that has administered blood, blood products, or lipids within 24 hours
 - Change caps (if used in the system) no more than every 72 hours and when the administration set is changed.
- Access points must be cleaned with an antiseptic (chlorhexidine or alcohol) by scrubbing and allowing the antiseptic to dry before entering for infusing or aspirating blood.
- Stopcocks are discouraged because of the difficulty in maintaining antisepsis.
- Tubing should be assembled using aseptic or sterile technique.
- Flushing is performed for multiple reasons
 - Check patency of the line.
 - Clear the line of medications or blood products that may cause precipitation if in contact with other medications.
 - Clear the line with heparin-containing fluid to prevent thrombosis.
 - Lock the line or port that is not being used with concentrated heparin or antibiotic/heparin flush.
- Routine replacement of the catheter is not recommended, especially rewiring the catheter, as this is associated with increased risk of infection. Since there is limited venous access, a routine rotation of the CVC in children is not recommended.

Complications

Insertion complications

- Bleeding due to arterial puncture, venous perforation, or coagulopathy
 - External bleeding at the site
 - Hematoma: mostly minor but can be significant, such as neck hematoma from internal jugular placement, causing airway compression or retroperitoneal hematoma from femoral placement

- Hemothorax from internal jugular or subclavian placement
- Hemopericardium rarely occurs.
- Pneumothorax: increased risk with internal jugular and subclavian placement
- Maintenance complications
 - Infection
 - At the site
 - Bloodstream infection is a significant, costly complication that results in morbidity and increases mortality in some patients, but with attention to insertion and maintenance practices can be significantly decreased.
 - Catheter occlusion due to thrombosis or precipitate
 - Vascular thrombosis in vessel; more common with chronic catheters; may be more common than recognized and often results in occlusion and loss of vessel patency, often permanent, and may predispose to infection
 - Catheter erosion can result in pleural effusions or cardiac tamponade.

OUTCOMES AND EVIDENCE

- Measurement of CVP allows the calculation and maintenance of perfusion pressure (mean arterial pressure minus CVP), which provides better tissue perfusion in shock states.
- In a prospective randomized trial comparing pediatric patients with septic shock treated with and without ScvO₂ goal-directed therapy, patients treated with ScvO₂ goal-directed therapy had a significantly lower 28-day mortality (11.8% vs. 39%) and less organ dysfunction than patients without.
- In a prospective study of a planned transition in pediatric ICU patients from the landmark technique for the use of ultrasound guidance, the use of ultrasound to guide placement of CVC was associated with decreased complications and fewer access attempts.
- In a multi-institutional, interrupted time-series design with historical control data in 29 PICUs, utilizing two CVC care practice bundles, an insertion bundle, and a maintenance bundle, the rate of catheter-associated bloodstream infections decreased by 43% from 5.4 to 3.1 infections per 1000 central line days.
- To prevent catheter-associated thrombosis, preventive measures including routine flushing with heparinized saline, the use of heparinized infusion fluids, and the early treatment of a possible occlusion with thrombolytics may decrease rates.
 - A randomized controlled trial comparing a heparinized fluid infusion to nonheparinized in infants with peripherally placed central lines showed a significant decrease in thrombosis requiring catheter removal in the heparinized fluid group (6% vs. 31%).
- The use of US for the percutaneous placement of CVC has been shown in pediatric patients to improve cannulation success and decrease both the number of attempts at cannulation and the time to cannulation.

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PULMONARY ARTERY CATHETERIZATION: BEFORE PROCEDURE

Indications

- Pulmonary hypertension, either primary or secondary
- Severe shock unresponsive to fluid resuscitation and vasoactive infusions
- Severe respiratory failure requiring high positive airway pressures with associated hemodynamic compromise

Contraindications

- No absolute contraindications
- Relative contraindications
 - Coagulopathy, which may cause a vascular hemorrhage
 - Tricuspid or pulmonary insufficiency may make bedside placement difficult.
 - Atrial or ventricular arrhythmias may deteriorate owing to the presence of the intracardiac line.
 - Intracardiac shunts, tricuspid insufficiency, or pulmonary insufficiency may make a measurement of cardiac output by the thermodilution method uninterpretable.

Equipment

- For percutaneous placement (not the operative placement of single-lumen catheters), multiple types are available but should be narrow gauge (e.g., 20 gauge) to decrease the risk of intrapulmonary artery thrombosis.
- Sedation and analgesia appropriate for age and condition of the patient
- Skin preparation antiseptic
 - 2% chlorhexidine-based skin prep is recommended.
 - Alternatives include 70% alcohol, tincture of iodine, iodophor.
- Sterile gloves, caps, masks, sterile drapes (large enough for full sterile barrier)
- Swan-Ganz–type pulmonary artery catheter
 - Components
 - Proximal port for CVP
 - Distal port (end hole) for pulmonary arterial and pulmonary occlusion pressure measurement
 - Balloon tip
 - Thermistor at tip of catheter
 - Sizes
 - 5F for patients less than 15 kg
 - 7F for larger patients
 - Variable distance between the ports
 - The proximal port should be in the right atrium (RA).
 - Distal port in the pulmonary artery (PA)
 - Distance between RA and PA in various pediatric patients has been determined and can be used to determine which catheter is appropriate.
- Introducer sheath: one French size larger than the catheter, with a sterile sleeve to cover the catheter
- Heparinized saline flush

- Pressure tubing with a transducer connected to a monitor so pressure tracings can be monitored during catheter placement

■ ANATOMY

The site of placement depends on many factors, including the skill of the operator, size of the patient, presence of coagulopathy, medical condition of the patient, and accessibility of the vein. The sites most commonly used are the femoral veins, internal jugular veins, and subclavian veins. Although any of these sites will allow passage of the catheter into the right atrium and on into the right ventricle and pulmonary artery, less manipulation of the catheter is needed using the right internal jugular vein or the left subclavian vein. However, the right femoral vein also requires less manipulation and is very commonly used because of its easier accessibility and fewer complications in patients with bleeding diatheses, and there is essentially no risk of pneumothorax in patients with severe lung disease. Other veins at these locations can also be used, but more manipulation may be necessary for bedside placement.

■ PROCEDURE

- Single-lumen pulmonary arterial catheter is placed with direct visualization in the operating room.
- The Swan-Ganz–type PA catheter is placed percutaneously.
 - Using sterile technique and full barrier precautions, as in the placement of a central venous catheter, the introducer sheath is placed using the Seldinger technique.
 - The catheter is passed through the introducer sheath and the sterile sleeve. During insertion, the balloon is inflated to allow the catheter to follow the blood flow, and the distal port is transduced so the pressure tracing can be monitored. The tracing is noted to be that of a right atrial trace initially. Then, as the catheter passes the tricuspid valve, the tracing becomes that of a ventricular pressure trace with a low diastolic pressure. The catheter is then allowed to flow into the pulmonary artery, and the tracing is that of an arterial trace, with the systolic pressure being the same as the right ventricle, but the diastolic pressure being higher. The catheter, still with the balloon inflated, is then advanced into the pulmonary arterial occlusion position, and again the trace is that of an atrial trace but with slightly higher values than the right atrial trace. The balloon is then deflated, and the pulmonary arterial trace should recur. If not, the catheter should be pulled back until a good pulmonary artery trace is seen, and then the balloon is reinflated to confirm the catheter will “wedge” or float into the occlusion position. As the catheter is advanced, attention must be paid to the ECG, as atrial or ventricular ectopy may occur. The major difference in passing the catheter in pediatric patients is that the turns and torques of the catheter must be made with more finesse than in adults because the distances are shorter, and the cavities of the right atrium and ventricle are smaller.
- Bedside ultrasound may be useful when passing the catheter to confirm the location.
 - After the catheter is stable in a good position, it should be secured within the sterile sleeve. The introducer sheath should be secured with a suture and the site dressed as with a central line.
 - A chest radiograph should be performed to confirm proper positioning.
- Measurement of thermodilution cardiac output
 - A known volume of fluid at a lower temperature than blood (either iced or room temperature) is injected into the proximal port of the catheter, and the temperature change at the thermistor is noted. The amount of heat loss allows for the calculation of flow.
 - A smaller volume of injectate is used in the 5F catheter to avoid fluid overload of the patient.

- Iced injectate is not recommended in pediatrics because repeated measures may result in hypothermia for small infants and children.
- Room temperature injectate is recommended for smaller pediatric patients.
- The type of fluid injected also must be taken into consideration for the pediatric patient if repeated measures are to be made (usually should be normal saline).
- Generally, three injections should be made during each measurement period, and with repeated measurements, that volume can potentially affect the electrolytes of the pediatric patient.
- The cardiac output measured in this way is reported and divided by the patient's body surface area as the cardiac index.

■ AFTER PROCEDURE

Postprocedure Care

- Catheter care and dressing as for the central venous line
- Balloon is never left inflated because of the risk of pulmonary infarction
- Continuous monitoring of both the right atrial (proximal) port and the pulmonary arterial port (distal) to ensure that the catheter stays in the proper location
- Regular chest radiographs to confirm the catheter position

Complications

- At the time of accessing the vein
 - Bleeding
 - Pneumothorax when the internal jugular or subclavian veins are used
- During catheter placement and positioning
 - Arrhythmias are most common.
- Prolonged use
 - Infection at the site or in the bloodstream
 - Rarely, endocarditis
 - Trauma to the tricuspid or pulmonary valve is usually clinically insignificant but may predispose the patient to endocarditis
 - Arrhythmias
 - Thrombosis of the vein of entry or the pulmonary artery
- Rare
 - Pulmonary infarction
 - Rupture of the pulmonary artery with balloon inflation

■ OUTCOMES AND EVIDENCE

- Monitoring PA pressure in the postoperative period in infants undergoing cardiac surgery has been shown to help guide therapy in prospective descriptive studies but not randomized controlled studies.
- Using cardiac output as measured by thermodilution has been helpful when guiding resuscitation during shock in pediatrics.
- Studies showing an improved outcome using the PA catheter are not available.

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INTRAARTERIAL CATHETER: BEFORE PROCEDURE

Indications

- Continuous measurement of the arterial blood pressure
 - Hemodynamic instability with real or potential hypotension
 - Severe hypertension requiring continuous vasoactive infusions
 - Measurement of cerebral perfusion pressure in patients with increased ICP
- Frequent assessment of arterial blood gases
- Rarely, frequent blood sampling in patients who have relative contraindications to central venous access (e.g., diabetic ketoacidosis)

Contraindications

- Perfusion of the extremity distal to the arterial catheterization would be compromised by the catheter placement.
- Skin disruption at the site of insertion
- Coagulopathy is a relative contraindication.

Equipment

- Seldinger technique
 - Butterfly catheter and small-gauge wire: 0.15 or 0.18 cm
 - Steel needle or butterfly catheter, small-gauge wire (0.15 or 0.18 cm), and small peripheral vascular catheter or 2.5F single-lumen catheter
 - Peripheral vascular catheter size can vary from a 24 gauge in small infants to 20 gauge in adolescents; larger catheters are not indicated.
- Sterile site preparation
 - Skin preparation pads, either 3% chlorhexidine or alcohol
 - Sterile gloves
 - Sterile towels
 - Sterile drapes
- Analgesic agents
 - 1% lidocaine local with a 25-gauge needle and syringe
 - Topical anesthetic such as EMLA
- Heparinized saline flush solution
- Tubing set
 - Luer-Lok tubing to attach to the catheter: type depends on PICU nursing standards
 - Pressure tubing to extend to the pressure transducer
 - Pressure transducer connected to monitor
- Securement equipment: tape, suture, and/or clear adherent dressing

ANATOMY

Arterial catheterization is performed in pediatric patients using the peripheral and femoral arteries. For neonates, the umbilical artery is used. The peripheral arteries most commonly used in pediatrics are the radial, dorsalis pedis, and posterior tibial arteries. Ulnar arteries can also be used, but attention should be paid to the patency of the radial artery prior to accessing the ulnar artery. The femoral artery is also accessible in pediatric patients.

PROCEDURE

- Apply topical analgesic in patients who are conscious or minimally sedated.
- Prepare the skin and drape for the sterile procedure.
- Inject 1% lidocaine local in the skin and around the artery, taking care to aspirate to avoid intraarterial injection.
 - Ultrasound may be used to locate the artery and facilitate successful catheter insertion using a static or real-time technique.

- For direct insertion
 - Direct catheter toward artery, and when arterial blood flows back into the catheter, carefully advance catheter about 1 to 2 mm, and then remove stylet.
 - Attach the connecting tubing and aspirate blood, removing air bubbles, and then inject heparinized saline. Blood should be easily aspirated into the syringe.
- Using the Seldinger technique (the most common technique for femoral arterial access but can be used for any commonly used artery)
 - Using a steel or butterfly needle with the tubing detached, direct the needle toward the artery.
 - When arterial blood is obtained and flowing freely, advance the guide wire through the needle; it should pass easily with no resistance.
 - Then remove the needle and pass the catheter over the wire and into the artery.
 - Remove the wire and attach the connecting tubing; aspirate blood, removing air bubbles, and then flush with heparinized saline. The blood should be easily aspirated into the syringe.
 - Attach the connecting tubing to the high-pressure tubing and transducer, allowing the arterial waveform to be visualized.

AFTER PROCEDURE

Postprocedure Care

- Continuous blood pressure monitoring with appropriate alarms
- Continuous fluid delivery, most commonly with heparin-containing fluid to prevent clot formation in the catheter
- Frequent evaluation of the system to detect any disruption of the catheter system
- Frequent evaluation of perfusion to the extremity distal to the catheter and the skin in the area around the catheter
- Evaluation of the securement of the catheter to prevent inadvertent dislodgment
- Dressing changes, including cleaning of the site to prevent infection

Complications

- Bleeding at the site
 - At the time of insertion, this can be minor.
 - If the patient is coagulopathic, bleeding may be more of a concern.
- Ischemia distal to the catheter
 - Due to compromise of arterial flow
 - Embolic
 - Thrombotic
 - Injuries may be severe, including the loss of toes, fingers, feet, hands, or even legs.
- Infection is rare with percutaneous catheters.
- Exsanguination
 - May occur if any part of the arterial catheter system becomes disconnected
 - Prevented by continuous monitoring with appropriate alarms that can immediately detect a loss of blood pressure
 - Frequent observation and checking of the system are also necessary.

OUTCOMES AND EVIDENCE

- No randomized controlled studies on the use of arterial monitoring and outcome are available in pediatrics.
- In a data analysis of a pediatric prospective data registry with more than 10,000 patients with arterial lines, 10.3% exhibited complications associated with arterial catheters.
 - Complications are more common in younger patients, patients with catheters placed later in the hospital course, and certain procedures

- Cardiac surgery, dialysis, and bone marrow transplantation
 - Most common associated complications were catheter-related infections, mechanical complications, and arterial thromboembolism.
 - Serious complications such as amputation were rare (0.6%).

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DEFIBRILLATION: BEFORE PROCEDURE

Indications

- Documented or suspected ventricular fibrillation (VF) or pulseless ventricular tachycardia
 - VF in pediatrics is associated with multiple clinical scenarios.
 - Dilated cardiomyopathy
 - Myocarditis
 - Drug intoxication
 - Underlying congenital heart disease
 - Prolonged QT syndrome
 - Sudden blow to the chest (e.g., a baseball)
 - Electric shock
 - Severe electrolyte abnormalities (e.g., hyperkalemia)

Contraindications

- No contraindications in a patient with proven or suspected VF

Equipment

- Defibrillator
 - Monophasic type: older
 - Biphasic type: requires lower energy
 - Automatic external defibrillators (AEDs)

ANATOMY

The placement of the pads or paddles is essentially the same as for adults. One is placed on the upper right side of the chest and the other at the apex of the heart, directly over the heart and to the left of the left midclavicular line. For some infants, because their chest is so small, the pads/paddles may still touch in this location. In this case, the pads/paddles may be placed in an anterior/posterior position with one placed on the chest to the left of the sternum and another on the back below the scapula.

PROCEDURE

- Follow Pediatric Advanced Life Support (PALS) defibrillation sequence recommendations.
- Place pads or paddles in the proper location.
- Manual defibrillation: useful in all ages and sizes of pediatric patients
 - Select energy
 - 2 J/kg for the first shock
 - 4 J/kg for subsequent attempts
- Automatic external defibrillation
 - Different brands of AEDs have varying ability to defibrillate pediatric patients. It is best to use a device with pediatric attenuation ability and one that can recognize pediatric shockable rhythms (PALS).

- Apply patches and follow instructions given by AED if a shockable rhythm is present.

AFTER PROCEDURE

Postprocedure Care

- Determine the treatable causes of VF and treat.
- Start antiarrhythmic agents to prevent recurrence.

Complications

- Major complication is inability to convert to perfusing rhythm or deterioration into asystole; may be converted into another arrhythmia
- Skin burns are the most common complication and rarely are clinically significant.
- Myocardial damage can occur, but using doses of more than 4 J/kg have been reported to have few adverse effects.
- Blood clots have been reported in adults.

OUTCOMES AND EVIDENCE

- Defibrillation using a dose of 2 J/kg was successful in 91% of shocks in a retrospective study of children.
- Out-of-hospital pediatric patients with ventricular fibrillation had a 20% chance of surviving to discharge from a secondary analysis of data from a randomized controlled study of out-of-hospital airway management.
- In hospitalized pediatric patients with cardiac arrest whose initial rhythm was ventricular fibrillation or ventricular tachycardia, a survival-to-discharge rate of 35% was reported in a National Registry of Cardiopulmonary Resuscitation prospective data analysis.
- AEDs have been shown to be effective for pediatric patients older than 1 year of age in multiple studies; use of AEDs in high-risk patients younger than 1 year has been shown to be effective.

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CARDIOVERSION: BEFORE PROCEDURE

Indications

- Hemodynamically unstable atrial tachycardias
 - Supraventricular reentry tachycardia
 - Atrial flutter
 - Atrial fibrillation
- Atrial tachycardias that have failed medical management

Contraindications

- Ectopic tachycardias will not be converted
 - Atrial ectopic tachycardia
 - Junctional ectopic tachycardia
- Unstable ventricular tachycardia or VF, which need to be defibrillated
- Patients on digoxin will have a lowered VF threshold and may develop VF with cardioversion.
- Patients with chronic atrial fibrillation or atrial flutter are at risk of embolism from atrial thrombi and should not be cardioverted until a transesophageal echocardiogram shows no evidence of thrombus.

Equipment

- Defibrillator with the ability to synchronize the discharge with ECG
- Sedation and analgesia should be provided following safe sedation guidelines.

ANATOMY

The placement of the pads or paddles is essentially the same as for defibrillation. One is placed on the upper right side of the chest and the other at the apex of the heart, directly over the heart and to the left of the left midclavicular line. For some infants, because their chest is so small, the pads/paddles may still touch in this location. In this case, the pads/paddles may be placed in an anterior/posterior position with one pad on the chest to the left of the sternum and one pad on the back beneath the left scapula.

PROCEDURE

- Apply appropriately sized pads or paddles to the chest.
- Attach the ECG pads for the defibrillator or position the paddles such that a good ECG trace is obtained.
- Turn the defibrillator setting to synchronous mode.
- Set the energy to 0.5 to 1 J/kg.
- Hold the discharge button down until the dose of energy is delivered, which will occur after the defibrillator has detected two to three complexes.

AFTER PROCEDURE

Postprocedure Care

- Observe the rhythm for recurrence.
- Begin antiarrhythmic therapy based on the original rhythm and the presence of an underlying heart disease.
- Observe the skin for evidence of burns.

Complications

- Other abnormal rhythms can occur
 - If VF occurs, change the mode to asynchronous, and immediately defibrillate with 2 J/kg and follow the PALS VF sequence.
 - Bradycardias may occur and are usually transient, but if persistent may administer atropine.
- Thromboembolism may occur if atrial thrombi are present and may result in stroke or limb ischemia.
- Skin burns may occur but are rare with the low dose of energy.
- Myocardial injury is possible but rare at this low dose of energy.

OUTCOMES AND EVIDENCE

- Cardioversion was known to be effective in atrial arrhythmias more than 80% of the time in a prospective observational study.

- Blinded randomized trials of cardioversion versus other methods of converting atrial arrhythmias have not been done in children.

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TEMPORARY CARDIAC PACING: BEFORE PROCEDURE

Indications

- Symptomatic bradycardia
 - Sinus bradycardia not usually symptomatic or improves with adequate oxygenation and ventilation
 - Other bradydysrhythmias will often respond to atropine or β -adrenergic agonists
- Symptomatic advanced-grade heart block may require temporary or permanent pacing
 - Congenital complete atrioventricular block
 - Postoperative heart block
- Ingestion of medications often require only temporary pacing until the drug effect resolves.
 - Beta-blockers
 - Digoxin
 - Calcium channel blockers
- Pace termination of tachydysrhythmias such as intraatrial reentrant tachycardia (IART)

Contraindications

- Absolute contraindications
 - Temporary transvenous ventricular pacing
 - Presence of a prosthetic tricuspid valve
 - Epicardial pacing
 - No absolute contraindications
 - Transesophageal pacing
 - AV block, because the ventricle cannot be reliably paced from the esophagus
 - Esophageal abnormalities such as tracheoesophageal fistula or recent esophageal surgery
 - Transcutaneous pacing
 - Severe chest trauma that prohibits the application of patches
 - Transthoracic pacing
 - Indicated only in extreme circumstances, no absolute contraindications
- Relative contraindications
 - Temporary transvenous ventricular pacing
 - Severe hypothermia, secondary to risk of fibrillation during rewarming
 - Digitalis toxicity, secondary to the risk of ventricular dysrhythmias
 - Coagulopathy
 - Epicardial pacing
 - Dense fibrous scar around the heart may make placement difficult or lead to high thresholds.
 - Transesophageal pacing
 - Postorthotopic heart transplant, because the tissue near the esophagus is recipient left atrial tissue and electrically isolated from the donor's heart.

- Transcutaneous pacing
 - Capture may be impossible in extreme obesity, pericardial effusion, or increased thoracic capacity.
- Transthoracic pacing
 - Indicated only in extreme circumstances
 - Pacing during cardiac arrest is typically futile.

Equipment

- Bipolar transvenous pacing catheters, active fixation (must be placed under fluoroscopy) or balloon-tipped, commercially available in size 3F and larger
- Temporary pacing box (ensure adequate battery supply) with connection cables
- Long introducer needle or commercially available kit as needed if a transthoracic puncture intended
- External pacing pads and unit; suggest a defibrillation unit and paddles or pads, also available
- Temporary pacing wires per surgeon preference at the time of sternotomy

PROCEDURE

First, establish a stable airway and adequate ventilation and oxygenation, and consider atropine or β -adrenergic agonists.

Temporary Transvenous Ventricular Pacing

- Choice of vein dependent on operator comfort and skill (frequently right internal jugular; may also use femoral). It may require fluoroscopy to manipulate into right ventricle or subclavian veins. Consider avoiding the left subclavian vein if the patient is a candidate for a permanent transvenous system, usually greater than 20 kg.
- Bedside placement typically requires a balloon-tipped catheter; consider placement under fluoroscopic guidance if time permits.
- Under sterile conditions, the introducer sheath is placed in the central vein by a modified Seldinger technique; consider the use of ultrasound guidance.
- If the vein diameter permits the placement of a sheath one French size larger than necessary for the pacing catheter, then the side-arm of the sheath may be used for central venous access as well.
- Catheter is advanced under sterile procedure from the central vein through the sheath to right atrium and across the tricuspid valve into the right ventricle. The position is confirmed by attaching the catheter leads either to the ECG and noting intracardiac electrograms (sharp spikes that correspond to surface P waves when the catheter tip is in the atrium or to surface QRS when the catheter tip is in the ventricle) or by attaching the catheter leads to a pacing box and noting atrial or ventricular capture.
- Threshold testing is performed as follows: pacemaker output is decreased incrementally until a loss of capture is noted, then the output is increased to double the pacing threshold to ensure an adequate safety margin.
- A temporary pacing lead is secured in place, typically with sutures and/or clear adhesive dressing, and the position is confirmed by chest x-ray or echocardiogram.
- Pacing mode depends on the clinical circumstance. Ideally, this would be a demand mode such as VVI or DDD to inhibit pacemaker output when the intrinsic beat is sensed, thus preventing pace induction of tachydysrhythmias or ventricular fibrillation. However, when the sensing thresholds are marginal, asynchronous pacing may be necessary.
- Pacing and sensing thresholds should be determined at least daily while the patient requires a temporary pacemaker.

Epicardial Pacing

- Temporary pacing wires may be placed by the cardiothoracic surgeon at the time of sternotomy, typically one bipolar lead on the

atrium (commonly placed to the right of the sternum) and one bipolar lead on the ventricle (commonly placed to the left of the sternum). Wires are then tunneled through the anterior chest wall and secured in place.

- Pacing wires may be connected to a temporary pacing box if clinically needed.
- Threshold testing and the selection of a pacing mode is performed as detailed earlier.
- Removal of temporary pacing wires occurs with gentle traction.

Transesophageal Pacing

- Relatively easy technique for pacing atrium, especially “overdrive” pacing of atrial tachydysrhythmias; not useful for pacing the ventricle and typically uncomfortable
- A standard transvenous pacing catheter is lubricated and advanced through the nose into the distal esophagus to the approximate level of the atrium.
- As the catheter is passed, it may be helpful to connect leads to the ECG. The location where the ECG signal voltage is the greatest should be the position where pacing will be the most effective.
- Catheter is connected to the pacing box.

Transcutaneous Pacing

- Very painful, best reserved for unconscious or heavily sedated patients
- Two sizes of pacing patches available: pediatric size for patients up to 15 kg, adult size recommended for patients over 15 kg
- Patches are placed on the patient's chest, labeled front (negative electrode) and back (positive electrode); may also be placed on the right chest and apex of the left ventricle
- Since the current must traverse the chest wall, the output required is typically large, up to 200 milliamps, with a wider pulse width of 20 to 40 msec. Once ventricular capture is achieved, the output is decreased as much as possible.

Transthoracic Ventricular Pacing

- Rarely indicated in desperate situations, when other access to ventricular pacing has failed
- Requires long introducer needle or a commercially available kit
- Skin is prepped and draped under sterile precautions.
- Introducer needle attached to a slip-tip syringe is advanced from the left xiphocostal angle 30 degrees to skin, directed toward the left shoulder while aspirating. Aspiration of blood confirms needle placement in the right ventricle.
- Pacing catheter or wire is advanced into the right ventricle and secured in place; the position is confirmed by x-ray or echocardiogram.

AFTER PROCEDURE

Postprocedure Care

- Continuous monitoring of cardiac rhythm through telemetry
- Sedation and/or analgesia as warranted
- Conversion of the pacing mode as feasible to temporary transvenous or permanently implanted device if clinically indicated
- Routine reevaluation of pacing and sensing thresholds at least daily, and the reassessment of underlying cardiac rhythm and the need for continued pacing

Complications

- Temporary transvenous ventricular pacing
 - Complications of venous access (failure to gain access, bleeding, pneumothorax, and infection)

- Complications of pacing leads (dysrhythmias, cardiac perforation, and a loss of capture)
- Epicardial pacing
 - Rarely, bleeding or infection
- Transesophageal pacing
 - Chest pain is common and typically requires analgesia or sedation.
 - Esophageal perforation (rare)
- Transcutaneous pacing
 - Pain
 - Failure to capture
- Transthoracic pacing
 - Cardiac tamponade is common.
 - Injury to the heart or great vessels, pneumothorax or hemothorax, coronary artery laceration, liver, or lung laceration

OUTCOMES AND EVIDENCE

- Patient outcomes after temporary cardiac pacing primarily related to the underlying condition
 - Outcome following cardiac surgery in most centers is excellent. The majority of patients requiring postoperative pacing will not require a permanent implanted pacemaker.
 - Outcome of temporary pacing performed during cardiopulmonary resuscitation is poor.
- There is current debate regarding the prophylactic placement of temporary pacing wires in all pediatric patients undergoing heart surgery. Perhaps lower risk patients do not need empiric pacing wires placed in the operating room (OR).
- Temporary pacing wires placed in the OR may be used in up to 30% of postoperative congenital heart patients, with half of those uses for diagnostic rather than pacing purposes. The need to use temporary wires is higher if the patient has decreased cardiac function, a need for multiple catheters, or required cardioversion in the operating room.

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TRANSESOPHAGEAL ECHOCARDIOGRAPHY: BEFORE PROCEDURE

Since the transthoracic echocardiographic windows of pediatric patients are often superior to those of adults, the development of transesophageal echocardiography (TEE) in children initially lagged behind its development in adults. Presently, however, TEE has assumed a critical role in the evaluation of children with congenital and acquired heart disease.

Indications

- Need for echocardiographic evaluation in patients with inadequate or nondiagnostic transthoracic windows
 - Patients with intraatrial baffles
 - Suspected thrombus or vegetation on intravascular devices or heart valves
 - Aortic dissection
 - Recent postoperative patient with poor transthoracic windows
- Perioperatively at the time of cardiac surgery
 - Preoperatively
 - Specifically characterize congenital heart disease prior to planned surgical intervention
 - Postoperatively
 - Evaluate for intracardiac air prior to weaning from cardiopulmonary bypass.
 - Evaluate for residual defects such as shunts, valvular insufficiency, residual obstruction, and myocardial dysfunction.
 - 2% to 15% of planned cardiac surgical procedures significantly changed based on the results of the intraoperative TEE.
- Cardiac catheterization laboratory
 - During interventions, such as atrial and ventricular septal defect occluder devices, balloon valvuloplasty procedures, stenting procedures, and endomyocardial biopsies

Contraindications

- Relative contraindications
 - Unrepaired tracheoesophageal fistula
 - Recent esophageal surgery
 - Esophageal obstructive lesions
 - Active gastrointestinal bleeding
 - Perforated viscus
- Other considerations
 - Since neck flexion and extension are frequently required for probe placement, cervical spine abnormalities should be ruled out prior to the procedure.
 - For patients who require anticoagulation, parameters should be maintained at the lower end of the therapeutic range.

Equipment

- Appropriately sized TEE probe
- Echocardiogram (ultrasound) machine

PROCEDURE

Since the size of the probe relative to the size of the esophagus and adjacent structures is larger in pediatric patients, and because patients must be cooperative for the procedure to be performed safely. TEE in pediatric patients is performed under deep sedation or, more commonly, general anesthesia. Endotracheal intubation for airway protection and controlled ventilation is recommended for smaller patients at an increased risk of mechanical airway compromise—for example, children with systemic illnesses that increase their risk of respiratory depression with sedation, children at an increased risk of aspiration or impaired airway control, and children with poor underlying cardiopulmonary status such as severe cyanosis or poor ventricular function. The TEE probe is lubricated and advanced through the oropharynx into the esophagus. The passage of the probe into the esophagus may be facilitated by flexion of the patient's neck or a jaw lift maneuver. A complete two-dimensional color Doppler and pulsed-wave and continuous-wave Doppler interrogation of the cardiac chambers, valves, and great vessels is then performed as clinically indicated.

The greatest strength of TEE lies in its ability to image the heart and great vessels not adequately accessible through transthoracic windows, especially the more posterior cardiac structures. These include the delineation of atrial anatomy, pulmonary veins, and systemic venous

return, both in patients with unrepaired congenital heart disease and in patients post intraatrial baffle procedures. TEE may also be useful in examining the atrioventricular valves, the left ventricular outflow tract, levels of pulmonary outflow tract obstruction, the pulmonary artery confluence, and proximal branch pulmonary arteries. Limitations to TEE include imaging structures obstructed by bronchial air and limited imaging planes available from the esophageal window.

As technology has progressed, miniaturization of echocardiographic probes has permitted transesophageal imaging with increasingly greater resolution even in smaller patients. A commercially available 8F (2.5-mm diameter) probe designed for intracardiac echocardiography (ICE) may be used off-label for monoplane transesophageal imaging, even in neonates less than 2 kg. Also recently available are the first real-time three-dimensional TEE probes, which permit the accurate evaluation of three-dimensional cardiac structures and may prove valuable in TEE-guided catheter-based interventions.

AFTER PROCEDURE

Postprocedure Care

- After removal, the TEE probe should be examined for evidence of blood, suggesting pharyngeal or esophageal injury.
- Post-TEE airway management as clinically indicated

Complications

- Common
 - Mild mucosal injury
- Infrequent
 - Inability to successfully intubate the esophagus
 - Airway compromise likely related to compression of the membranous trachea
 - Compression of posterior vascular structures such as the descending aorta or pulmonary veins
- Serious, rare complications
 - Significant injury to the pharynx, esophagus, or stomach

OUTCOMES AND EVIDENCE

- Outcomes in pediatric TEE depend largely on the surgical or catheter-based interventions performed at the time of the echocardiographic exam.
- Intraoperative TEE has been shown to impact decision making in approximately 2% to 15% of cardiopulmonary bypass cases.

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FLEXIBLE BRONCHOSCOPY: BEFORE PROCEDURE

Indications

Under most circumstances, flexible airway endoscopy in critically ill children should be undertaken by an experienced pediatric bronchoscopist.

- Airway evaluation
 - Smoke inhalation
 - Airway trauma
 - Stridor (acute, postextubation)
 - Suspected airway lesion
 - Wheezing unresponsive to medical therapy
 - Localized hyperinflation
 - Suspected congenital anomalies
 - Hemoptysis*
 - Detection of suspected foreign body*
 - Postoperative evaluation of anastomotic sites
- Airway management
 - Difficult intubation
 - Facilitate extubation
 - Evaluation of the position of the ETT
- Collection of samples for diagnostic purposes
 - Persistent pulmonary infiltrate
 - Aspiration
 - Immunocompromised host with pulmonary infiltrate
 - Endobronchial and transbronchial biopsy of a mass
- Therapeutic indications
 - Selective bronchial intubation
 - Removal of large mucous plugs and respiratory secretions
 - Removal of bronchial casts
 - Instillation of surfactant in acute lung injury
 - Instillation of mucolytic agents in refractory atelectasis
 - Fibrin glue therapy for the treatment of bronchopleural fistula

Contraindications

- Absolute contraindications
 - Airway size too small for the available bronchoscope
 - Massive hemoptysis
 - Severe cardiovascular instability
 - Lack of trained personnel, inadequate equipment
 - The procedure will elicit no information of value.
- Relative contraindications
 - Bleeding diathesis
 - Severe pulmonary arterial hypertension
 - Profound hypoxemia despite 100% oxygen supplementation
 - Significant risk of cerebral herniation
 - Unstable arrhythmia
 - PEEP greater than 10 cm H₂O
 - Active bronchospasm
 - Mean arterial pressure less than 65 mm Hg on vasopressor therapy

Equipment

- A number of directable, flexible bronchoscopes are available for pediatric use, and each instrument has unique characteristics and limitations
 - The 2.2-mm ultrathin bronchoscope does not have a suction channel, but it may pass through ETTs with internal diameters as small as 2.5 mm, and therefore, it is extremely useful in the neonatal ICU.
 - In nonintubated infants and children intubated with 3.5- to 4.5-mm ETTs, the 2.7- to 2.8-mm bronchoscopes are especially useful and less prone to obstruct the airway than larger instruments.
 - A 3.4- to 3.8-mm bronchoscope is the most commonly used endoscope that can be used in nonintubated children aged 2 to 10 years or in children intubated with 5.0- to 6.0-mm ETTs.

*Rigid rather than flexible airway endoscopy by an experienced pediatric otolaryngologist or airway surgeon should be considered in critically ill children with massive hemoptysis or a suspected foreign body.

- The instrument most commonly used in adults and larger children is 4.7 to 4.9 mm in outside diameter and has a 2-mm suction channel.
- Topical lidocaine solution 2% for the nose and larynx, 1% for the lower airway (maximum dose should not exceed 5-7 mg/kg)
- Oxygen source and tubing
- Bag and mask, laryngoscope, and ETTs
- 1:10,000 epinephrine for management of airway bleeding (0.1 mL epinephrine in 5-10 mL NS)
- Two wall-mounted suction units (one for the bronchoscope)
- Resuscitation drugs and equipment
- Clear airway endoscopy mask in nonintubated children allows simultaneous insertion of the bronchoscope through a side port and delivery of continuous positive airway pressure.
- An adapter attached to the ventilator circuit and ETT, with an aperture that seals around the bronchoscope
- Specimen traps and syringes
- Sterile normal saline to be used for instillation
- Lidocaine jelly to anesthetize the nasal passage in nonintubated patients
- Water-soluble lubricant for the bronchoscope
- Video camera, recorder, and high-resolution television monitor placed on a mobile cart

ANATOMY

In addition to obvious size differences between pediatric and adult airways, there are anatomic differences that predispose the infant and young child to an airway obstruction with respiratory illness or manipulation. Thus, in nonintubated children, specific techniques that take into account these anatomic differences may be required to maintain airway patency and prevent airway injury.

- The tongue: relatively larger in proportion to the oral cavity
- The posterior pharynx: on the posterior wall, and often extended into the choana, adenoid tissue can be seen in young children.
- The larynx: the infant larynx lies nearly two vertebral bodies higher in the neck than that of the adult and is located more anteriorly; laryngeal structures are more compliant.
- The epiglottis has a much more pronounced curvature (omega-shaped) that is angled away from the tracheal axis.
- The arytenoid cartilages may be very prominent in the infant.
- The first tracheal ring (i.e., the cricoid cartilage) is the smallest cross-sectional area of the airway in young children.
- The normal shape of the trachea in children is nearly round, with cartilages extending visibly through an arch approximately 320 degrees. The membranous portion of the trachea is more mobile in the upper third of the trachea.
- The carina is very sharp in adults, but it is often blunted in children. The right main stem bronchus is immediately seen upon peering down the trachea.
- The right lung
 - The right upper lobe takes off just beyond the carina, and the lobar bronchus is very short and has three segmental bronchi including the anterior, posterior, and apical.
 - The right middle lobe takes off at an acute angle anteriorly and divides into lateral and medial segments.
 - The basilar segments of the lower lobe may be variable and include apical, medial, anterior, lateral, and posterior segments.
- The left lung
 - The left upper lobe divides into the apical posterior and anterior segments and lingular segments.
 - The lower lobe bronchi are variable and include apical, antero-medial, lateral, and posterior segments
 - In pediatric practice, as opposed to adult practice, it is rarely useful specifically to identify bronchi smaller than the segmental branches.

Procedure-Related Considerations

- Communication between the critical care team and bronchoscopist is essential to establish whether flexible airway endoscopy is the most appropriate approach for the evaluation and/or management of the patient's airway or pulmonary problem, what procedure should be performed, and what additional preprocedural evaluation of the patient is required.
- In general, the bronchoscopist should evaluate the patient's cardiopulmonary stability; review metabolic, hematologic, and coagulation laboratory results; review chest radiographs; and determine the size, if present, of any artificial airways.
- Patients who are known to be at risk for bronchospasm should be given preprocedure bronchodilators and steroids.
- Even intubated patients may aspirate around a cuffed ETT when the tube is moved during manipulation of the bronchoscope; therefore, the stomach should be emptied prior to the procedure (fasting 4-6 hours for milk and solids and 3 hours for water).
- In the child with a brain injury, flexible airway endoscopy should be performed with caution because the ICP may transiently but significantly increase during the procedure.

PROCEDURE

- Sedation and monitoring
 - In children undergoing flexible airway endoscopy, sedation is almost always required to obtain useful information and avoid discomfort and airway trauma.
 - Appropriate monitoring of critically ill children undergoing flexible airway endoscopy includes the presence of a second physician (intensivist preferred).
 - Continuous monitoring of oxygen saturation, respiratory rate, and cardiac rate and rhythm, as well as intermittent (or continuous) monitoring of blood pressure
- Oxygenation and ventilation
 - Although the bronchoscope may occupy 10% of the tracheal lumen in a nonintubated patient, the instrument takes up a larger percentage of available space in an ETT.
 - The presence of a bronchoscope in the airways results in physiologic alteration including increased airway resistance associated with decreased minute ventilation. In spontaneously breathing patients, expiratory resistance will increase more than inspiratory resistance; in intubated patients, gas exchange may be dramatically altered.
 - Positive end-expiratory pressure (PEEP) should be reduced to avoid large, inadvertent increases in PEEP due to increased expiratory resistance.
 - Patients undergoing bronchoscopy are always at risk for hypoxia. Therefore, supplemental oxygen should be given, and Sao_2 should be maintained above 90% throughout the procedure.
 - Suctioning should be limited to the shortest possible time because it removes gas from the lungs and may cause hypoxemia.
- Diagnostic/therapeutic techniques
 - Bronchoalveolar lavage (BAL)
 - Contamination from the upper airway occurs, because the bronchoscope traverses either the upper airway or ETT.
 - The procedure for BAL in children is not standardized.
 - The number and size of non-bacteriostatic saline aliquots instilled remains controversial, but typically 2 to 5 aliquots of 0.5 to 1 mL/kg, usually not exceeding 20 mL/aliquot, are utilized.
 - The usual return of BAL fluid is 40% to 60%. In most clinical laboratories, a minimum of 5 to 10 mL of BAL fluid is usually required to perform total cell and differential counts, as well as standard pathologic and microbiologic studies.
 - The importance of total and differential cell counts and a pathologic evaluation of BAL fluid should not be

underestimated. Consultation with an infectious disease specialist, pathologist, and/or the microbiology laboratory may be helpful in prioritizing studies and improving the diagnostic yield of BAL fluid studies.

- The position of the ETT should be checked at the end of the procedure.
- Protected specimen brush (PSB)
 - Brush is protected from upper airway contamination by an outer catheter and occluding plug.
 - While passed through the instrument channel of the bronchoscope, the sheathed brush does not come into contact with the upper airway or ETT secretions.
 - Once the catheter is in the distal airway, the plug is removed and the sample is collected.
- Bronchoscopic needle aspiration (BNA)
 - Used for sampling of lymph nodes located in the paratracheal, subcarinal, and perihilar areas
 - Can be used in the diagnosis of endobronchial lesions
 - Used mostly in adults for the diagnosis and staging of thoracic malignancies
- Endobronchial ultrasound (EBUS)
 - Enables the visualization of extra-airway structures that cannot be seen through the bronchoscope
- Laser bronchoscopy
 - In patients with an airway obstruction due to surgically unresectable malignancies
 - Preparation of airways for insertion of airway stents
 - Exclusively used in adults

AFTER PROCEDURE

Postprocedure Care

- Careful monitoring should be continued after the procedure, at least until the child has returned to pre-flexible airway endoscopy neurologic and cardiopulmonary status.
- The ability to rapidly reintubate the patient is essential.
- Chest x-ray indicated in patients whose respiratory status does not return to preprocedure status for the evaluation of complications

Complications

- Physiologic complications (more common)
 - Hypoxemia
 - Hypercapnia
 - Increase in ICP
 - Arrhythmias
 - Vagal stimulation related to inadequate topical anesthesia
 - Myocardial sensitization due to hypoxemia
 - Inadequate sedation may cause excessive catecholamine release.
 - Direct mechanical stimulation of the airway
 - Laryngospasm, bronchospasm, and a cough can induce arrhythmia.
 - Laryngospasm may occur even under general anesthesia.
- Mechanical complications (rare)
 - Pneumothorax
 - Bleeding (epistaxis is relatively common after the transnasal procedure)
 - Upper airway trauma in nonintubated patients
- Bacteriologic complications (rare)
 - 20% to 30% of patients will develop a transient fever following BAL (always self-limited).
 - Spreading infection from one area of the lung to another is possible.
 - Spilling of local pus into other airways
 - Bacterial endocarditis prophylaxis should be undertaken in patients with congenital heart defects.

OUTCOMES AND EVIDENCE

- Flexible bronchoscopy is an important tool in diagnosing and managing various pulmonary conditions in critically ill patients. Although special challenges exist for performing bronchoscopy in mechanically ventilated patients, if proper preprocedural training and planning are done and the patient is monitored carefully during the procedure, bronchoscopy can be performed quickly and safely at the bedside in most critically ill patients.
- Flexible bronchoscopy has a high diagnostic yield in immunocompromised patients with pulmonary infiltrates.
- Bronchoscopy has been shown to be effective in removing retained secretions and improving atelectasis.

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THORACENTESIS AND THORACOSTOMY: BEFORE PROCEDURE

Indications

- Thoracostomy
 - Symptomatic pleural effusion
 - Large effusion
 - Respiratory compromise
 - Purulent effusion
 - Pneumothorax
 - Tension pneumothorax
 - Pneumothorax in a patient on positive ventilation with concern that the pneumothorax can develop tension
- Needle thoracocentesis
 - Emergent drainage of tension pneumothorax
 - Diagnosis of type of pleural effusion

Contraindications

- No absolute contraindications
- Small effusions may be too difficult to drain without risking injury to the lung
- Coagulopathy; relative contraindication; should be corrected prior to chest tube placement if the time allows

- Abnormal anatomy, such as scoliosis, may make the procedure riskier
- Overlying skin infection

Equipment

- For either procedure
 - 1% lidocaine local analgesia
 - Skin preparation, preferably with 2% chlorhexidine
 - Sterile towels and gloves
 - Syringes: slip tip for aspiration and with needles for lidocaine injection
 - Sterile container to receive pleural fluid sample
 - Bedside ultrasound, sterile sleeve, sterile ultrasound gel if ultrasound is to be used
- Thoracentesis
 - Styleted needle
 - Such as an IV catheter, which has the advantage that once the stylet is removed, the catheter remaining in the chest is soft and pliable
 - Gauge of the catheter depends on size of patient and viscosity of the fluid
 - For purulent fluid, a larger bore catheter is needed.
 - Length depends on the size of the patient.
 - Small infants and children: a catheter longer than 2 inches in length is rarely indicated.
 - Larger adolescents or obese children may need catheters 3 to 4 inches in length.
- Thoracostomy
 - Chest tube of appropriate size
 - Depending on the patient size and size of intercostal space
 - A larger chest tube is necessary for blood or purulent fluid
 - Smaller tube or pigtail-type catheter can be used if draining pneumothorax, transudative, or chylous fluid
 - Soft multiholed pigtail catheters are useful for draining transudative or chylous pleural effusions and simple pneumothoraces not associated with bronchopleural fistulae.
 - Connecting tubing
 - Drainage system
 - Pleur-Evac system with suction if draining a pneumothorax or a complex effusion or blood
 - Simple collection bag if transudative or chylous fluid
 - Steel needle, guide wire, and a dilator if using Seldinger technique

ANATOMY

For either procedure in any location, the needle should be advanced over the top of the rib and into the pleura to avoid injuring the intercostal vessels that run along the inferior aspect of each rib. For emergent needle drainage of a pneumothorax, the patient should be lying supine and the needle placed in the second or third intercostal space in the midclavicular line. For chest tube placement for pneumothoraces, it is preferable to use the fourth intercostal space in the midaxillary line. For drainage of effusions, the needle should be placed either along the midaxillary line or infrascapular where the fluid is greatest. Determining the optimal location for drainage of complex effusions that may be loculated is best done using ultrasound guidance. For the placement of the chest tube for large pleural effusions and pneumothoraces, the fourth intercostal space in the midaxillary line is also used.

The position of the patient for needle thoracentesis again depends on the location of the fluid and the age, size, and stability of the patient. An older child who is stable and cooperative can be seated during the procedure, allowing a posterior approach, which for most nonloculated effusions is optimal. However, unstable children, smaller infants, or any child who needs sedation should be placed in a supine or a slight decubitus position.

Ultrasound of the chest can be performed to identify the best location for draining the fluid, particularly if the fluid may be loculated,

either due to the fluid being purulent or the patient having had previous chest surgery or chest tubes. The ultrasound can be used just to “mark” the best location for drainage or can be used to guide the needle insertion.

PROCEDURE

- Sedation and analgesia: chest tube placement is particularly painful, and sedation and analgesia must be provided that are appropriate for the age and condition of the patient.
- Skin is prepared for the sterile procedure.
- A 1% lidocaine local analgesic is infiltrated using a small-gauge needle into the skin over the intercostal space to be used. Then, using a longer but still narrow-gauge needle, lidocaine is infiltrated into the subcutaneous tissue, intercostal muscle, and pleura. Care is taken to aspirate as the needle is advanced to avoid intravascular injection of the lidocaine.
 - Perform bedside ultrasound of the chest to evaluate fluid, noting the type of fluid (presence of fibrinous or bloody material) and the best location for insertion; ultrasound may be used for static determination of fluid or real-time guidance of needle insertion
- Needle thoracentesis
 - The catheter is then advanced through the numbed tissue using a slip-tip syringe to aspirate as the needle is advanced. When the needle passes through the pleura, there usually is a pop, as the pleura is a tougher tissue. Air or fluid is then able to be aspirated. The stylet in the needle can then be removed and the most supple catheter left in the pleura for further aspiration of either the tension pneumothorax or the effusion.
- Tube thoracostomy; two techniques are used
 - Standard cutdown technique
 - After instillation of the local analgesic, a small incision is made that will be slightly larger than the diameter of the chest tube.
 - Mosquito-type forceps are inserted through the incision and tunneled up one rib space and then rotated so that the points of the forceps are aimed toward the pleura.
 - They are then advanced over the superior aspect of the rib and through the pleura. Generally, the pleura will give, often with a pop.
 - The chest tube is then guided through the defect in the pleura and into the pleural space. Posterior placement of the chest tube is optimal for the drainage of fluid. Anterior placement, in a patient lying supine, is optimal for the drainage of a pneumothorax. Occasionally for patients with severe ongoing air leaks requiring prone and supine positioning, placement of anterior and posterior chest tubes may be needed to provide adequate continuous drainage of the pneumothorax.
 - The chest tube is secured with a suture and the incision closed with a purse-string closure, with the suture wrapped and tied around the chest tube.
 - The tube should also be secured to the child's side with either tape or a chest-tube-securing device (commercially available) to prevent the tube from being pulled out when the child becomes more active.
 - A clean dressing may be applied, but if the site is wet from ongoing drainage, a dressing need not be placed; the area can simply be kept clean and dry.
 - Seldinger technique
 - After instillation of local analgesia, a hollow needle is introduced into the pleural space while aspirating with a slip-tip syringe.
 - When air (in the case of a pneumothorax) or fluid (in the case of an effusion) is aspirated, the syringe is carefully removed, and the guide wire is passed into the pleural space. The wire should advance easily.

- Once the wire is in place, a small nick in the diameter of the chest tube is made in the skin at the needle entry point.
- The needle is removed, and the dilator passed over the wire and through the pleura; then the dilator is removed.
- The chest tube or pigtail catheter is then passed over the wire. The chest tube may need progressively larger dilators and should have a trocar in it to better advance the tube through the pleura. The wire and trocar are then removed.
- The tube or catheter is connected to the drainage system, sutured into place, and a dressing applied.

AFTER PROCEDURE

Postprocedure Care

- A postprocedure chest x-ray should be performed to document the chest tube location, resolution of the pneumothorax or effusion, and note any new problems related to the tube.
- If using a closed suction system, patency of the chest tube should be regularly assessed. Regular documentation of the amount of fluid removed should occur. The pigtail catheters may have to be flushed with heparinized saline to maintain patency.
- The dressing should remain dry or be replaced if not.

Complications

- Bleeding from the chest wall or lung can occur with or without coagulopathy.
- Intrapulmonary placement of the chest tube or lung laceration may occur with any technique.
 - Bronchopleural fistula may occur if the lung is punctured.
- Mechanical problems with the tube
 - Side holes being outside the pleural space
 - The tube itself being placed into the subcutaneous tissue and not the pleural space
 - Kinking of the tube
 - Occlusion of the tube with fluid or pus
- Failure of the drainage system, resulting in the reaccumulation of a pneumothorax
- Laceration of the heart, pulmonary artery, diaphragm, liver, or spleen

OUTCOMES AND EVIDENCE

- Thoracentesis is a safe, traditional means of removing pleural fluid for diagnosis and drainage.
- Thoracostomy can be safely performed in patients of any age and size.
- The Seldinger technique with the placement of a pigtail catheter can be used to drain either pneumothoraces or pleural effusions effectively.
 - In a retrospective review of chest tube placement in pediatric patients in an emergency department, it was noted that the pneumothoraces were all drained in both the pigtail group and the large-bore chest tube group. The patients in the pigtail group appeared to have less pain than the patients with standard chest tubes.
 - In another retrospective chart review of pediatric inpatients who had chest tubes placed, pigtails were noted to be as efficacious in draining serous and chylous pleural as standard chest tubes but less effective in the drainage of hemothoraces and not effective in draining purulent effusions.

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PERICARDIOCENTESIS AND PERICARDIOSTOMY: BEFORE PROCEDURE

Indications

- Cardiac tamponade or impending tamponade due to a pericardial effusion or rarely, in small infants, pneumopericardium
- Rarely for the diagnostic drainage of a pericardial effusion

Contraindications

- When a cardiac tamponade is present, there is no contraindication.
- Relative contraindications
 - Coagulopathy
 - Inexperience of the operator
 - Loculation of the effusion
 - Loculation of the effusion where it cannot be reached percutaneously
 - Abnormal patient anatomy
- Certain situations may be better treated with open pericardiectomy and tube placement, such as the hemopericardium, particularly from penetrating trauma, purulent pericarditis, or loculated pericardial effusions with localized tamponade. However, if the patient is acutely in cardiac tamponade, pericardiocentesis can be performed while surgical pericardiectomy is being arranged.

Equipment

- Sedation: patient should be sedated for both comfort and safety to avoid inadvertent movement that could result in injury to the heart.
- Skin preparation
- Sterile gloves and towels
- 1% lidocaine local analgesia
- Hollow introducer needle
- Slip-tip syringe
- Flexible J guide wire that fits through the needle
- Dilator
- Pigtail catheter
- Connecting tubing, stopcock, collection bag
- Echocardiography equipment

ANATOMY

The patient is placed with the head elevated 30 degrees. The safest and easiest approach is the subxiphoid approach, although other approaches have been described. The needle is inserted at the junction of the xiphoid and the left costal margin and is directed toward the left shoulder.

PROCEDURE

- For emergent cardiac tamponade with or without cardiac arrest, blind needle aspiration with or without tube insertion is indicated.
- In less acute situations, echocardiographic assessment and direction are indicated
 - The pericardium is scanned to note the size and location of the fluid, presence or absence of loculated fluid, quality of fluid (whether there is evidence of blood or pus), and the presence of cardiac tamponade. Cardiac tamponade is diagnosed by the

collapse of the right atrial wall, diastolic compression of the right ventricle, abnormal tricuspid and mitral flow velocities with inspiration, and dilated inferior vena cava with the lack of a collapse during inspiration.

- The patient is placed on a cardiac monitor to watch for arrhythmias.
- The skin is sterilely prepped and draped.
- Lidocaine 1% local analgesia is infiltrated in the skin subxiphoid and then directed toward the lower left costal margin, being careful to aspirate prior to injection.
- The needle is then advanced from the subxiphoid position toward the left costal margin and the left shoulder, aspirating as the needle is advanced.
 - When fluid is obtained, the needle is no longer advanced.
 - If the fluid is bloody, place some of the fluid on a sterile gauze.
 - If the fluid clots, it is likely that the heart has been entered.
 - If the fluid does not clot, the fluid is likely a hemorrhagic effusion from the pericardial sac.
 - The echocardiogram may be used to note the position of the needle. Additionally, a small amount of saline can be injected through the needle, and microbubbles will be detected in the pericardial space if the needle is in a good position.
- The syringe is carefully removed, and the J-type wire is passed through the needle; its position in the pericardium is confirmed with the echocardiogram.
- A small nick is made in the skin the diameter of the catheter.
- The needle is removed, leaving the wire in the pericardial space, and the dilator is passed over the wire. Again, the wire position is confirmed with the echocardiogram.
- The dilator is then removed, and the catheter is passed over the wire; the position is again confirmed echocardiographically.
- The wire is removed and the stopcock and tubing connected to the catheter. The catheter is then aspirated.
- The catheter is secured with a suture, and the site sterilely dressed.

AFTER PROCEDURE

Postprocedure Care

- The catheter should be allowed to drain passively into a collection bag. The patency of the catheter should be checked, and if determined not to be patent, a small amount of sterile heparinized saline can be injected into the catheter to clear any clots or fibrin debris.
- The dressing should be changed according to the CVL dressing standard.

Complications

- Myocardial perforation may occur but may not result in any significant injury if the ventricle is entered. However, a laceration can occur, resulting in bleeding into the pericardial sac, causing or worsening tamponade.
- Coronary laceration is a rare occurrence and can result in acute cardiac ischemia and may require emergent operative intervention. It can be associated with death.
- Entering the pleural space can occur and thus a risk of pneumothorax or hemothorax.
- Injury to the diaphragm and abdominal viscera can occur, as well as pneumoperitoneum or hemoperitoneum.

OUTCOMES AND EVIDENCE

- Percutaneous drainage of pericardial effusion can be safely performed in children.
- Echocardiographic guidance improves both the success and safety of the procedure.

- In a data analysis of a prospective echocardiography database of adults, pericardiocentesis performed for tamponade was successful in relieving tamponade in 99% of patients and was the definitive therapy in 82%, with only a 3% incidence of complications.
- Similar studies in pediatric patients are not available.

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INTRACRANIAL PRESSURE MONITORING: BEFORE PROCEDURE

Indications

- Cerebral edema
- Traumatic brain injury (TBI)
- Glasgow Coma Scale (GCS) score less than 8
- May be indicated in patients with evidence of TBI and a better GCS if they will not be able to have their neurologic exam followed; for example
 - During anesthesia for another procedure
 - If the patient must be kept sedated for other reasons (e.g., severe lung injury with high ventilator settings)
- Medical causes
 - Medical encephalopathies (e.g., diabetic ketoacidosis and Reye syndrome)
 - Meningitis or encephalitis with evidence of cerebral edema
- The use of ICP monitoring in global hypoxic-ischemic injury (e.g., near-drowning after prolonged cardiac arrest) is less useful and may not be indicated.

Contraindications

- Coagulopathy is thought to be an absolute contraindication.
- Massive cerebral edema with slit-like ventricles may not allow the placement of an intraventricular device but will allow a tissue pressure monitor.

Equipment

- The available monitoring systems are discussed in detail in Chapter E20 of the textbook on the central nervous system monitoring in adults. Specific pediatric data on the advantages or disadvantages of these systems are lacking.

ANATOMY

Refer to Chapter E20; same landmarks as an adult.

■ PROCEDURE

- Should be performed by a neurosurgeon skilled in pediatric care
- Sedation and analgesia should be provided that is appropriate for the patient's age and clinical condition.
- Preparation and procedure guidelines are the same as adult placement.

■ AFTER PROCEDURE

Postprocedure Care

- With the head of the patient elevated at 30 to 45 degrees, the zero reference point for the particular ICP monitoring system should be placed at the outer canthus of the patient's eye.
- The ICP monitor must be transduced at all times. Tissue monitors can only be zeroed at the time of insertion. Intracranial monitors can regularly be zeroed and should be zeroed at least every 12 hours.
- The drip chamber of the ICP monitors will be at the level designated by the physician for optimal CSF drainage. For patients with increased ICP, some CSF should drain, but too rapid drainage can result in ventricular collapse and herniation.
- For pressure readings, the system must be off for drainage and open to the patient.
- Components of the system should not be replaced unless a new ICP system is placed or if the components become contaminated.

Complications

- Intracranial infection; most common but still relatively uncommon
- Intracerebral hemorrhage, especially if coagulopathy exists or develops with a monitor in place; may occur at the insertion or over time; may be intraparenchymal or intraventricular
- CSF leakage
- Blockage of pressure monitoring with blood or tissue

■ OUTCOMES AND EVIDENCE

- Increased ICP is associated with decreased survival and poor neurologic outcome. It may be difficult to diagnose in pediatric patients, especially the extent of the increased pressure, so monitoring is warranted.
- Multiple studies, as well as consensus practice, have shown that aggressive management of increased ICP after TBI may reduce secondary brain injury in both adults and pediatric patients.
- Since the widespread use of ICP monitoring, no randomized controlled trial in patients with TBI would be possible.
- In a study comparing the Camino tissue monitor with intraventricular pressure monitor in pediatric patients, there was a good correlation between the two measurements in the same patient on the same day.
- In a prospective uncontrolled study of complications of tissue pressure monitors in pediatric patients, 7% developed positive tip cultures (risk increased with length of monitoring), and 13% developed loss of waveform, but overall the monitors were safe, especially when used for less than 7 days.

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| <i>Test</i> | <i>Formula</i> | <i>Normal Values*</i> |
|--|---|--|
| Cardiac Index CI, expressed as L/min/M ² | $\frac{\text{Cardiac Output (CO) in L/min}}{\text{Body Surface Area (BSA) in M}^2}$ | 2.5-3.5 L/min/M ² |
| Stroke Index SI, expressed as mL | $\frac{\text{Cardiac Index (CI)} \times 1000}{\text{Heart Rate (HR)}}$ | 30-50 mL |
| Systemic Vascular Resistance Index SVRI, expressed as dynes · sec · cm ⁻⁵ | $\frac{(\text{Mean Arterial Pressure} - \text{Right Atrial Pressure}) \times 79.9}{\text{Cardiac Index}}$ MAP, RAP, mm Hg Cl, L/min/M ² | 900-1200 dynes · sec · cm ⁻⁵ Normal values for infants and children are age dependent. |
| Pulmonary Vascular Resistance Index PVRI, expressed as dynes · sec · cm ⁻⁵ | $\frac{(\text{Mean Pulmonary Arterial Pressure} - \text{Pulmonary Artery Occlusion Pressure}) \times 79.9}{\text{Cardiac Output}}$ MAP, PAP, mm Hg CO, L/min | 120-160 dynes · sec · cm ⁻⁵ Normal values for infants and children are age dependent. |
| Alveolar Oxygen Partial Pressure P _A O ₂ , expressed as mm Hg | $(\text{P}_{\text{bar}} - 47) \times \text{Fractional Inspired Oxygen Concentration} - (\text{PaCO}_2 \times 1.25)$ P _{bar} , PaCO ₂ , mm Hg FiO ₂ , 0.21-1.0 normal | Depends on FiO ₂ (100 mm Hg on room air at sea level) |
| Alveolar—arterial Oxygen Tension Delta (A—a) PO ₂ , expressed as mm Hg | P _A O ₂ —PaO ₂ P _A O ₂ , PaO ₂ , mm Hg | Depends on FiO ₂ |
| Oxygen Content in Pulmonary Capillary Blood CcO ₂ , expressed as mL/dL | $(\text{Hb} \times 1.34) + 0.0031 \times \text{P}_{\text{A}}\text{O}_2$ Hb, g/dL P _A O ₂ , mm Hg | 15-20 mL/dL |
| Arterial Oxygen CaO ₂ , expressed as mL/dL | $(\text{Hb} \times 1.34 \times \text{SaO}_2) + 0.0031 \times \text{PaO}_2$ Hb, g/dL SaO ₂ , PaO ₂ , mm Hg | 14-19 mL/dL |
| Oxygen Content in Mixed Venous Blood CvO ₂ , expressed as mL/dL | $(\text{Hb} \times 1.34 \times \text{SvO}_2) + 0.0031 \times \text{PvO}_2$ Hb, g/dL SvO ₂ , PvO ₂ , mm Hg | 9-14 mL/dL |
| Systemic Oxygen Delivery DO ₂ , expressed as mL/min/M ² | $\text{CaO}_2 \times \text{CI} \times 10$ CaO ₂ , mL/dL Cl, L/min/M ² | 400-650 mL/min/M ² |
| Systemic Oxygen Uptake VO ₂ , expressed as mL/min/M ² | $(\text{CaO}_2 - \text{CvO}_2) \times \text{CI} \times 10$ CaO ₂ , CvO ₂ , mL/dL Cl, L/min/M ² | 125-175 mL/min/M ² |
| Systemic Oxygen Extraction O ₂ extr, expressed as % | $\frac{(\text{CaO}_2 - \text{CvO}_2)}{\text{CaO}_2} \text{ or (simplified) } \frac{(\text{SaO}_2 - \text{SvO}_2)}{\text{SaO}_2}$ CaO ₂ , CvO ₂ , mL/dL | 20%-30% |
| Intrapulmonary Shunt Qs/Qt, expressed as % | $\frac{\text{CcO}_2 - \text{CaO}_2}{\text{CcO}_2 - \text{CvO}_2}$ | <5% |

*“Normal” values can vary depending on a variety of factors, including the laboratory running the test and the equipment or method used; patient age or gender; and the time of day when the sample was taken.

The Pediatric Risk of Mortality (PRISM III)

Cardiovascular, Neurologic, Vital Signs

| | | | |
|---|-----------------------------------|-------------------|------------------|
| Systolic Blood Pressure (mm Hg) | Score = 3 | Score = 7 | |
| Neonate | 40-55 | <40 | |
| Infant | 45-65 | <45 | |
| Child | 55-75 | <55 | |
| Adolescent | 65-85 | <65 | |
| Temperature | Score = 3 | | |
| | <33°C (91.4°F) or >40°C (104.0°F) | | |
| Mental Status | Score = 5 | | |
| | Stupor/coma or GCS < 8 | | |
| Heart Rate (beats per minute) | Score = 3 | Score = 4 | |
| Neonate | 215-225 | >225 | |
| Infant | 215-225 | >225 | |
| Child | 185-205 | >205 | |
| Adolescent | 145-155 | >155 | |
| Pupillary Reflexes | Score = 7 | Score = 11 | |
| | One fixed | Both fixed | |
| Acid-Base, Blood Gases | | | |
| Acidosis (pH or Total CO₂) | Score = 2 | Score = 6 | |
| pH or | 7.0-7.28 | <7.0 | |
| Total CO ₂ | 5-16.9 | <5 | |
| pH | Score = 2 | Score = 3 | |
| | 7.48-7.55 | >7.55 | |
| PCO₂ (mm Hg) | Score = 1 | Score = 3 | |
| | 50-75 | >75 | |
| Total CO₂ (mmol/L) | Score = 4 | | |
| | >34 | | |
| PaO₂ (mm Hg) | Score = 3 | Score = 6 | |
| | 42-49 | <42 | |
| Chemistry Tests | | | |
| Glucose | Score = 2 | | |
| | >200 mg/dL or >11 mmol/L | | |
| Potassium (mmol/L) | Score = 3 | | |
| | >6.9 | | |
| Blood Urea Nitrogen (BUN) | Score = 3 | | |
| Neonate | >11.9 mg/dL or >4.3 mmol/L | | |
| All other ages | >14.9 mg/dL or >5.4 mmol/L | | |
| Creatinine | Score = 2 | | |
| Neonate | >0.85 mg/dL or >75 µmol/L | | |
| Infant | >0.90 mg/dL or >80 µmol/L | | |
| Child | >0.90 mg/dL or >80 µmol/L | | |
| Adolescent | >1.30 mg/dL or >115 µmol/L | | |
| Hematology Tests | | | |
| White Blood Cell Count (cells/mm³) | Score = 4 | | |
| | <3,000 | | |
| Platelet Count (× 10³ cel ls/mm³) | Score = 2 | Score = 4 | Score = 5 |
| | 100-200 | 50-99 | <50 |
| Prothrombin Time (PT) or Partial Thromboplastin Time (PTT) | Score = 3 | | |
| Neonate | PT > 22.0 or PTT > 85.0 | | |
| All other ages | PT > 22.0 or PTT > 57.0 | | |

Other Factors: Nonoperative cardiovascular disease, chromosomal anomaly, cancer, previous PICU admission, pre-ICU CPR, postoperative, acute diabetes (e.g., DKA), admit from inpatient unit.

From Pollack MM, Patel KM, Ruttimann EU: PRISM III: An updated pediatric risk of mortality score. Crit Care Med 1996;24:743-752.

The Sequential Organ Failure Assessment (SOFA) Score

| Score | 0 | 1 | 2 | 3 | 4 |
|--|----------------|-------------------|--|---|--|
| Respiration | | | | | |
| PaO ₂ /FiO ₂ , mm Hg | >400 | ≤400 | ≤300 | ≤200 ——with respiratory support—— | ≤100 |
| Coagulation | | | | | |
| Platelets × 10 ³ /mm ³ | >150 | ≤150 | ≤100 | ≤50 | ≤20 |
| Liver | | | | | |
| Bilirubin, mg/dL (µmol/L) | <1.2 (<20) | 1.2-1.9 (20-32) | 2.0-5.9 (33-101) | 6.0-11.9 (102-204) | >12.0 (>204) |
| Cardiovascular | | | | | |
| Hypotension | No hypotension | MAP <70 mm Hg | dopamine ≤5 or dobutamine (any dose)* | dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1* | dopamine >15 or epinephrine >0.1 or norepinephrine >0.1* |
| Central nervous system | | | | | |
| Glasgow coma score | 15 | 13-14 | 10-12 | 6-9 | <6 |
| Renal | | | | | |
| Creatinine, mg/dL (µmol/L) | <1.2 (<110) | 1.2-1.9 (110-170) | 2.0-3.4 (171-299) | 3.5-4.9 (300-440) | >5.0 (>440) |
| OR urine output | | | | <500 mL/d | <200 mL/d |

*Adrenergic agents administered for at least one hour (doses given are in mcg/kg/min).

Metric Unit Conversions

| | |
|------------------------|-------------------|
| 1 cm = 0.3937 in | 1 kg = 2.2 lb |
| 1 in = 2.54 cm | 1 lb = 0.4545 kg |
| °C = [(°F - 32) × 5]/9 | 1 gm = 0.03527 oz |